Antibakteriyel Kombinasyonlar Ne Zaman? Nasıl?

Gram-Pozitif Bakteri İnfeksiyonlarında Kombinasyon

E. Ediz Tütüncü

XIX. Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Kongresi

29 Mart 2018, Antalya

Kombinasyon tedavisi

Birden fazla sayıda antimikrobiyalin eşzamanlı olarak kullanılması

- Artmış güvenlik duygusu,
- Artmış güvenlik kaygısı

Antimikrobiyal kombinasyon kullanımı endikasyonları

I- Kritik hastaların ampirik tedavisinin düzenlenmesi,

II- Polimikrobiyal infeksiyonlar,

III- Direnç gelişiminin önlenmesi,

IV- Toksisitenin azaltılması,

V- Antimikrobiyal sinerjizm

I- Kritik hastaların ampirik tedavisi

- Kritik hastalarda olası patojenlere karşı geniş spektrumlu bir kapsama sağlamak ve (en az) bir etkin antimikrobiyal ajanın en kısa sürede verilmesi olasılığını arttırmak

  - MRSA ile birlikte fakültatif gram negatif ya da anaerob etkenlerin kapsanması,

  - Kültür sonuçları çıkana dek gram negatif etkenlerde optimal etkinlik sağlamak için iki ajanın birlikte kullanımı

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2010, p. 4851–4863 Vol. 54, No. 11
0066-4804/10/$12.00 doi:10.1128/AAC.00627-10

Systematic Review and Meta-Analysis of the Efficacy of Appropriate Empiric Antibiotic Therapy for Sepsis▽†

Mical Paul,[1]* Vered Shani,[2] Eli Muchtar,[2] Galia Kariv,[2] Eyal Robenshtok,[2] and Leonard Leibovici[2]

Unit of Infectious Diseases[1] and Department of Medicine E,[2] Rabin Medical Center, Beilinson Hospital, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Received 6 May 2010/Returned for modification 6 July 2010/Accepted 14 August 2010

Kritik hastalarda etken mikroorganizmayı hedefleyen etkin antimikrobiyal tedavi daha iyi klinik sonuçlarla koreledir.

Paul M et al. Antimicrob Agents Chemother 2010;54:4851

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 1742–1748 Vol. 54, No. 5
0066-4804/10/$12.00 doi:10.1128/AAC.01365-09

Empiric Combination Antibiotic Therapy Is Associated with Improved Outcome against Sepsis Due to Gram-Negative Bacteria: a Retrospective Analysis▽

Scott T. Micek,[1] Emily C. Welch,[1] Junaid Khan,[2] Mubashir Pervez,[2] Joshua A. Doherty,[3] Richard M. Reichley,[3] and Marin H. Kollef[2]*

Pharmacy Department, Barnes-Jewish Hospital, St. Louis, Missouri[1]; Pulmonary and Critical Care Division, Washington University School of Medicine, St. Louis, Missouri[2]; and Hospital Informatics Group, BJC Healthcare, St. Louis, Missouri[3]

Received 28 September 2009/Returned for modification 29 December 2009/Accepted 6 February 2010

Ampirik antimikrobiyal tedaviye ikinci ajanın eklenmesi, olası etkenlere yönelik uygun kapsamın sağlanması ve daha iyi klinik sonuçlarla ilişkilidir.

Micek ST al. Antimicrob Agents Chemother 2010;54:1742

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 1742–1748 Vol. 54, No. 5
0066-4804/10/$12.00 doi:10.1128/AAC.01365-09

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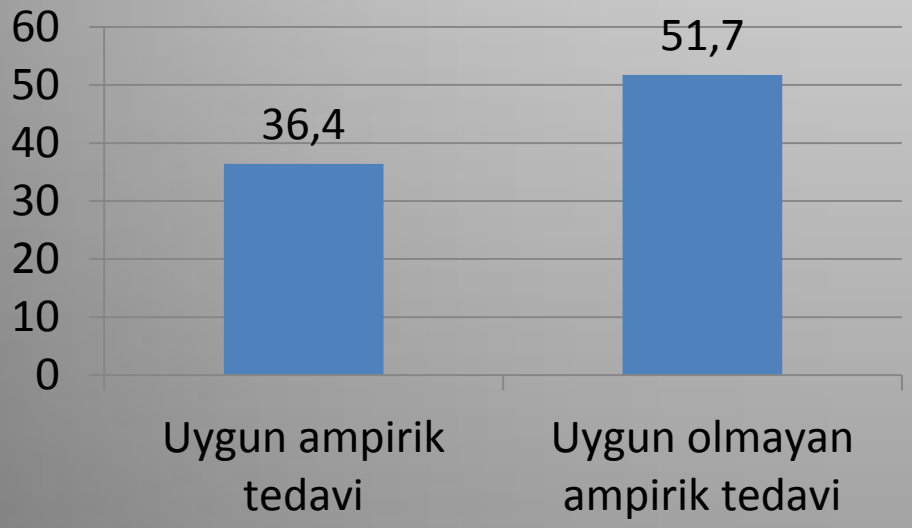
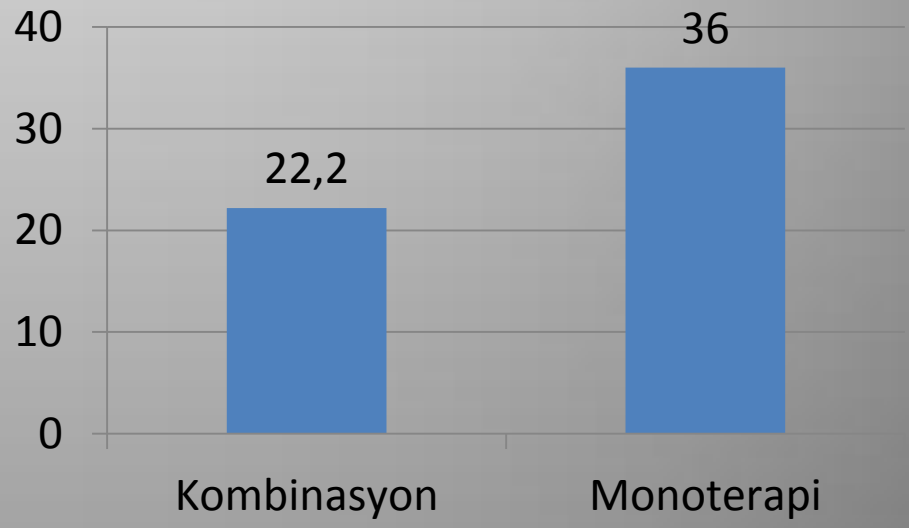
Received 28 September 2009/Returned for modification 29 December 2009/Accepted 6 February 2010

Mortalite (%)



Uygun olmayan ampirik tedavi



Micek ST al. Antimicrob Agents Chemother 2010;54:1742

II- Polimikrobiyal infeksiyonlar

- Farklı etkenlerin rol alabildiği infeksiyonlarda uygun kapsamın sağlanması adına
  - İntraperitoneal infeksiyonlar,
  - Pelvik infeksiyonlar,
  - Diyabetik ayak infeksiyonları,

II- Polimikrobiyal infeksiyonlar

Sağladıkları geniş spektrumlu kapsama sayesinde pek çok polimikrobiyal infeksiyonda karbapenemler, beta laktam-beta laktamaz inhibitörleri, kinolonlar, glisilsiklin antibiyotikler etkin “monoterapi” biçiminde kullanılabilirler.

III- Direnç gelişiminin önlenmesi

- Farklı etki yolları ile direnç gelişimi mekanizmalarına sahip ilaçların kombine kullanımı, etken mikroorganizmanın dirençli subpopülasyonlarının seçilmesini engeller.
  - Tüberküloz tedavisi,
  - Antiretroviral tedavi,
  - Protez materyal varlığında rifampisin kullanımı

Drug Resistance Updates 14 (2011) 107–117

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Conserving antibiotics for the future: New ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective

Johan W. Mouton[a,b,c,*], Paul G. Ambrose[d], Rafael Canton[e], George L. Drusano[f], Stephan Harbarth[g], Alasdair MacGowan[h], Ursula Theuretzbacher[i], John Turnidge[j]

Bakteriyel infeksiyonların antibiyotik kombinasyonlarıyla tedavi edilmesi, antimikrobiyallerin etkinliğinin korunmasını sağlayabilir.

Mouton JW al. Drug Resist Updates 2011;14:107

OPEN ACCESS Freely available online

PLoS one

The Impact of Different Antibiotic Regimens on the Emergence of Antimicrobial-Resistant Bacteria

Erika M. C. D'Agata[1☯], Myrielle Dupont-Rouzeyrol[2☯], Pierre Magal[3], Damien Olivier[4], Shigui Ruan[5*]

1 Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, United States of America, **2** Laboratoire d'Ecotoxicologie des Milieux Aquatiques, Université du Havre, Le Havre, France, **3** Laboratoire de Mathématiques Appliquées, Université du Havre, Le Havre, France, **4** Laboratoire d'Informatique, de Traitement de l'Information et des Systèmes, Université du Havre, Le Havre, France, **5** Department of Mathematics, University of Miami, Coral Gables, Florida, United States of America

Antibiyotik direnç gelişimini değerlendirmek üzere tasarlanmış matematiksel modeller, kombinasyon tedavisinin direnç gelişimini önleyebileceğini düşündürmektedir.

D'Agata EMC et al. PLoS ONE 2008;3:e4036

OPEN ACCESS Freely available online

PLoS one

The Impact of Different Antibiotic Regimens on the Emergence of Antimicrobial-Resistant Bacteria

Erika M. C. D'Agata[1☯], Myrielle Dupont-Rouzeyrol[2☯], Pierre Magal[3], Damien Olivier[4], Shigui Ruan[5]*

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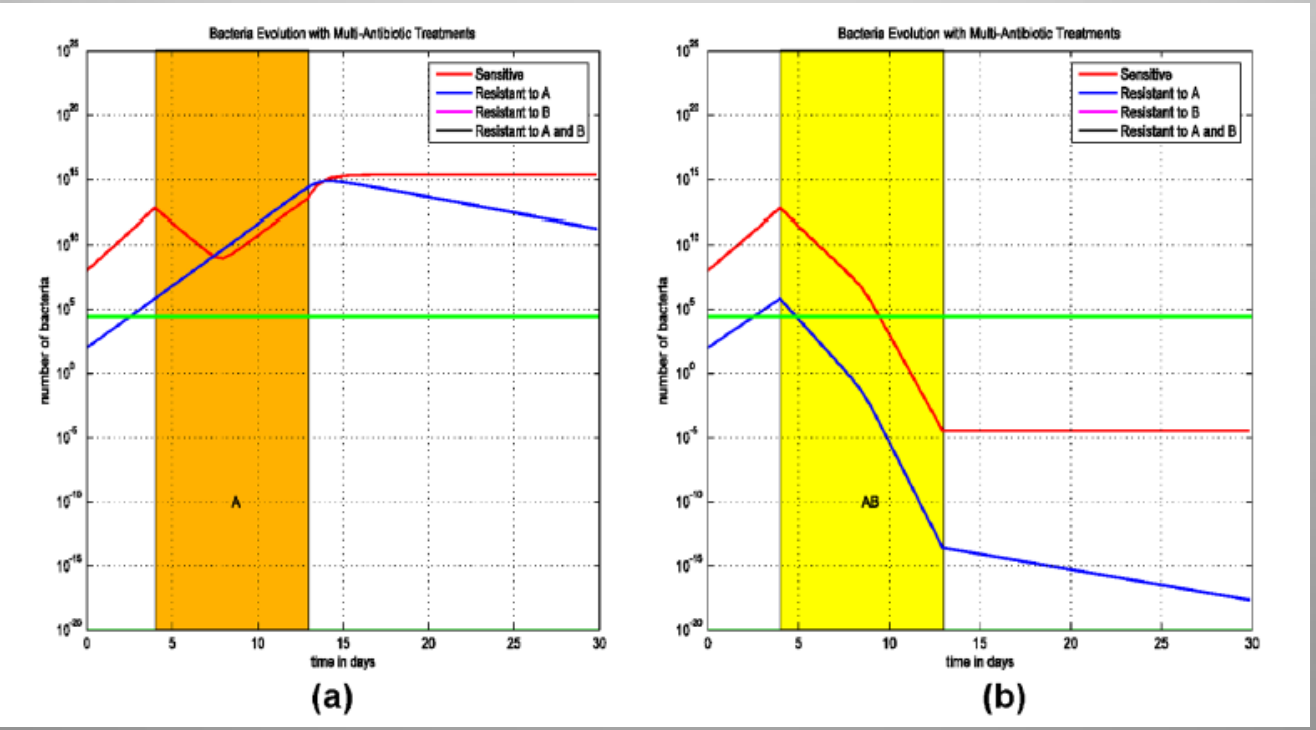

D'Agata EMC et al. PLoS ONE 2008;3:e4036

Journal of Antimicrobial Chemotherapy
DOI: 10.1093/jac/dkg269

JAC

The mutant selection window and antimicrobial resistance

Karl Drlica*

Public Health Research Institute, 225 Warren Street, Newark, NJ 07103, USA

The mutant selection window is an antimicrobial concentration range extending from the minimal concentration required to block the growth of wild-type bacteria up to that required to inhibit the growth of the least susceptible, single-step mutant. The upper boundary is also called the mutant prevention concentration (MPC). Placing antimicrobial concentrations inside the window is expected to enrich resistant mutant subpopulations selectively, whereas placing concentrations above the window is expected to restrict selective enrichment. Since window dimensions are characteristic of each pathogen–antimicrobial combination, they can be linked with antimicrobial pharmacokinetics to rank compounds and dosing regimens in terms of their propensity to enrich mutant fractions of bacterial populations. For situations in which antimicrobial concentrations cannot be kept above the window, restricting the enrichment of mutants requires combination therapy.

"Mutant selection window" / "Mutant seçimi penceresi" kavramı, kombinasyon tedavisinin ilaç direnci gelişimini önlemedeki rolü konusunda bir çerçeve sağlamaktadır.

Drlica K et al. J Antimicrob Chemother 2003;52:11

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- MIC: Kültür ortamında mikroorganizmaların çoğunun üremesini inhibe eden antibiyotik konsantrasyonu,
- MIC, dirençli subpopülasyonların çoğalmasını engellemez ve bu dirençli mutantlar zaman içinde "seçilirler".

Drlica K et al. J Antimicrob Chemother 2003;52:11

Journal of Antimicrobial Chemotherapy
DOI: 10.1093/jac/dkg269

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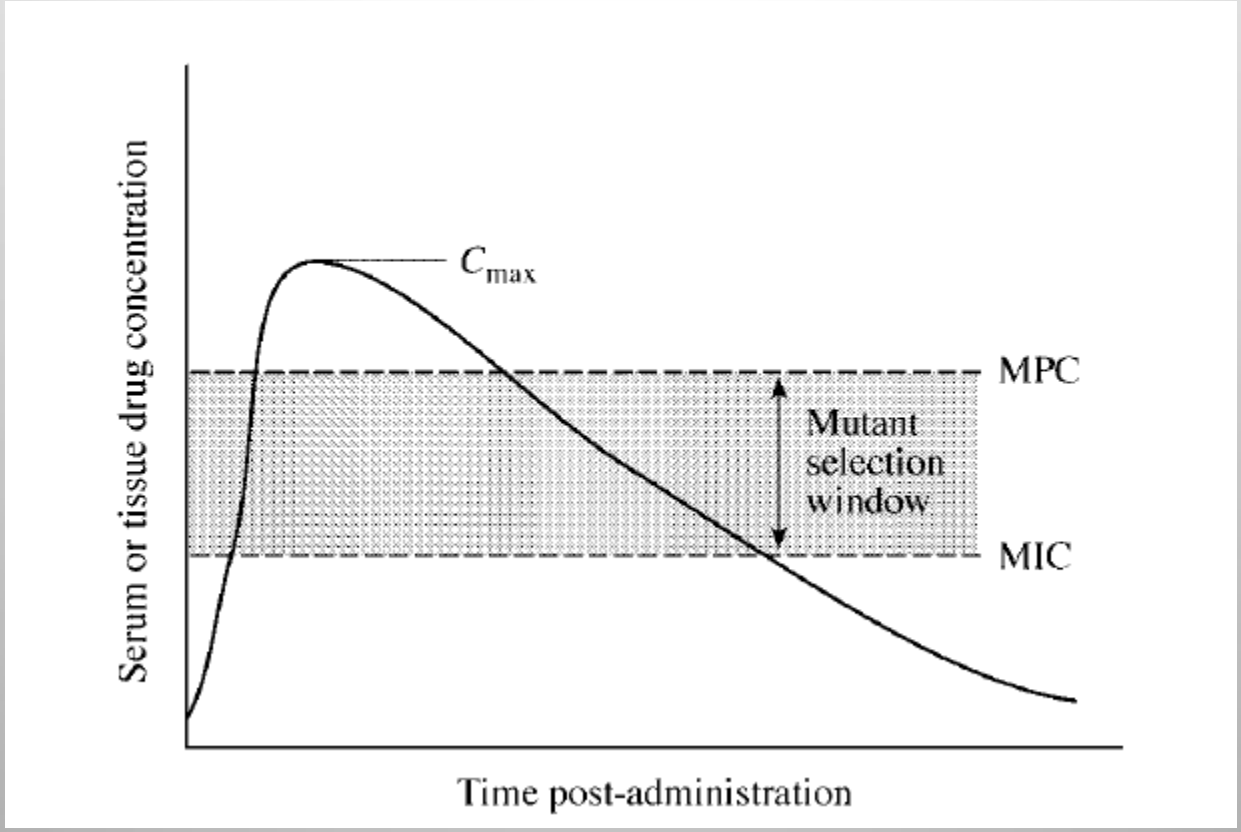
- Bakteriyel infeksiyonlarda mikroorganizma sayısı 10^{10}
- Antibiyotik direnç mutasyonlarının olasılığı 10^{-6} -10^{-8}
- Antibiyotik kullanımından önce binlerce dirençli mikroorganizma var olabilir.

Drlica K et al. J Antimicrob Chemother 2003;52:11



- MPC “Mutant prevention concentration” dirençli subpopülasyonların da inhibe olduğu antibiyotik konsantrasyonları

Drlica K et al. J Antimicrob Chemother 2003;52:11

Journal of Antimicrobial Chemotherapy
DOI: 10.1093/jac/dkg269

JAC

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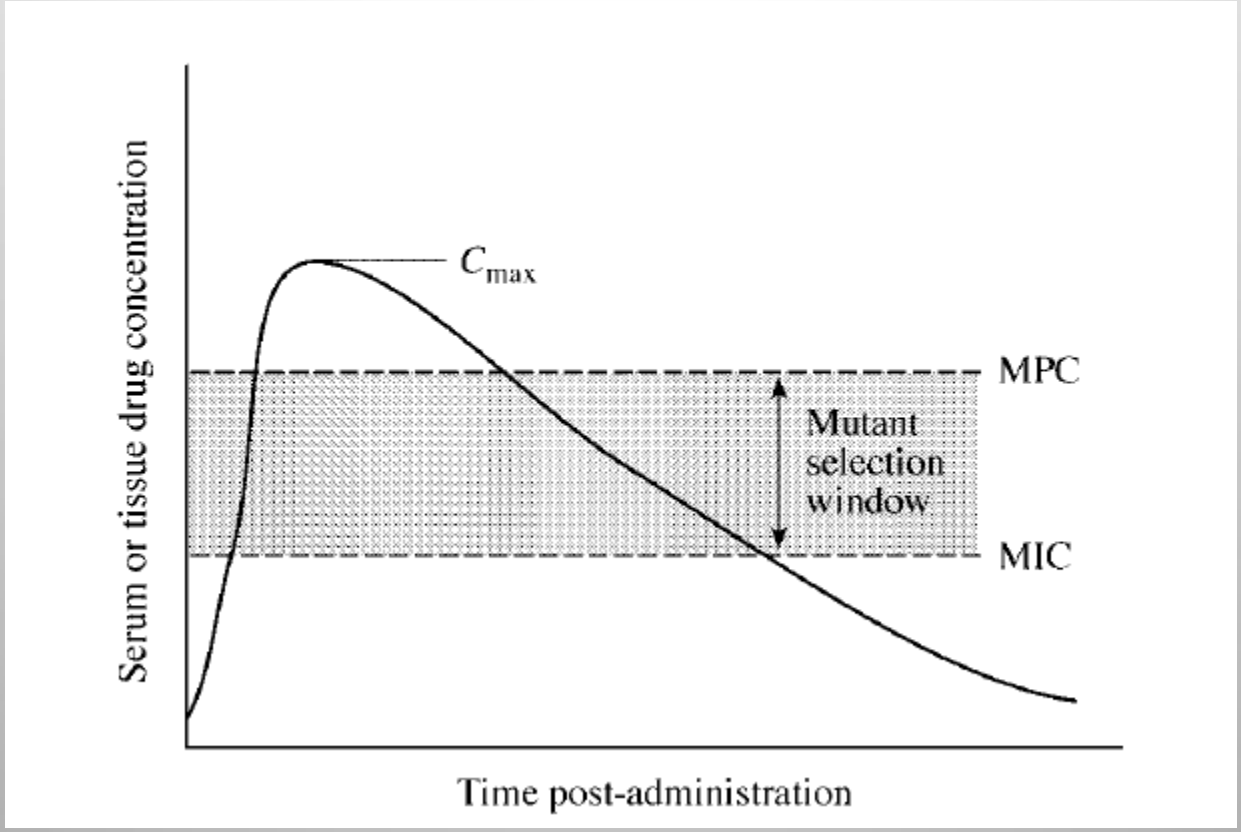
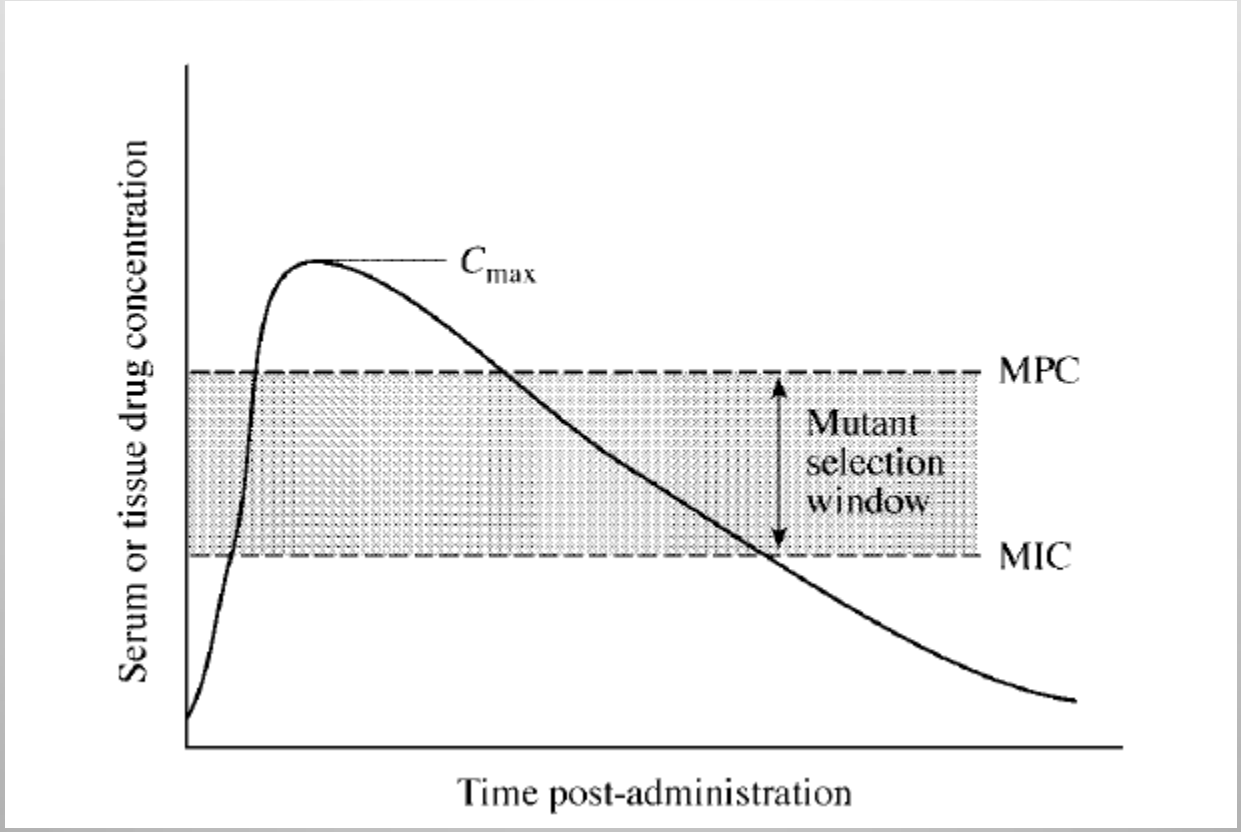
MPC, popülasyondaki en az duyarlı mutantın üremesine engel olacak antibiyotik konsantrasyonudur.

Drlica K et al. J Antimicrob Chemother 2003;52:11



$MIC_{(99)}$ ile MPC arasındaki antibiyotik konsantrasyonları “Mutant seçimi penceresi” dirençli mutantların seçilebildiği konsantrasyonlardır.

Drlica K et al. J Antimicrob Chemother 2003;52:11



Prensip olarak, antibiyotiklerin kombine kullanımı “Mutant seçimi penceresi” içerisinde dirençli mutantların gelişimini önleyebilir.

Drlica K et al. J Antimicrob Chemother 2003;52:11

Infection. 1999;27 Suppl 2:S24-8.

Combination therapy as a tool to prevent emergence of bacterial resistance.

Mouton JW[1].

Author information

Abstract

Emergence of resistance is an ever increasing problem. One of the methods by which emergence of resistance may possibly be prevented, or at least delayed, is the use of combination therapy. Since the emergence of resistant mutants is a direct result of selective pressure by antimicrobial therapy, the chance of mutants resistant to two antimicrobials in the parent population being present is a product of mutation frequencies, provided that resistance mechanisms are independent. Comparative studies in in vitro pharmacokinetic models and in vivo indicate that emergence of resistance is less common when combination therapy is used. This is particularly true for microorganisms known to develop resistance relatively quickly, such as Pseudomonas aeruginosa, and resistance mechanisms which occur at a relatively high frequency.

Kombinasyon tedavisinin direnç gelişimini önlediğini gösteren preklinik çalışmalar vardır…

Mouton JW et al. Drug Resist Updat 2011;14:107

Journal of Antimicrobial Chemotherapy (2008) **61**, 629–635
doi:10.1093/jac/dkm542
Advance Access publication 1 February 2008

JAC

Selection of linezolid-resistant *Enterococcus faecium* in an *in vitro* dynamic model: protective effect of doxycycline

Stephen H. Zinner[1], Deborah Gilbert[2], Irene Yu. Lubenko[3], Kenneth Greer[2] and Alexander A. Firsov[3]*

[1]*Mount Auburn Hospital, Harvard Medical School, Cambridge, MA, USA;* [2]*Roger Williams Medical Center, Providence, RI, USA;* [3]*Department of Pharmacokinetics and Pharmacodynamics, Gause Institute of New Antibiotics, Russian Academy of Medical Sciences, 11 Bolshaya Pirogovskaya Street, Moscow 119021, Russia*

- *E. faecium* MIC 1,8 mg/L, MPC 7 mg/L
- "Mutant seçimi penceresi" konsepti çerçevesinde, doksisiklin kombinasyonu, linezolid dirençli enterokokların gelişimini önlemiştir.

Zinner SH et al. J Antimicrob Chemother 2008;61:629

AAC
Journals.ASM.org

β-Lactams Increase the Antibacterial Activity of Daptomycin against Clinical Methicillin-Resistant *Staphylococcus aureus* Strains and Prevent Selection of Daptomycin-Resistant Derivatives

Shrenik Mehta, Christopher Singh, Konrad B. Plata, Palas K. Chanda, Arundhati Paul, Sarah Riosa, Roberto R. Rosato, and Adriana E. Rosato

Department of Pathology and Genomic Medicine, Center for Molecular and Translational Human Infectious Diseases Research, The Methodist Hospital Research Institute, Houston, Texas, USA

Daptomisin betalaktam kombinasyonu klinik MRSA izolatlarında daptomisin dirençli varyantların gelişimini önlemiştir.

Mehta S et al. Antimicrob Agents Chemother. 2012;56:6192

MAJOR ARTICLE

Effect of Aminoglycoside and β-Lactam Combination Therapy versus β-Lactam Monotherapy on the Emergence of Antimicrobial Resistance: A Meta-analysis of Randomized, Controlled Trials

Ioannis A. Bliziotis,[1] George Samonis,[3] Konstantinos Z. Vardakas,[1] Stavroula Chrysanthopoulou,[1] and Matthew E. Falagas[1,2,4]

Direnç gelişimi açısından BL+AG kombinasyonu vs BL monoterapisi

- 8 RCT

Bliziotis IA et al. Clin Infect Dis. 2005;41:149

MAJOR ARTICLE

Effect of Aminoglycoside and β-Lactam Combination Therapy versus β-Lactam Monotherapy on the Emergence of Antimicrobial Resistance: A Meta-analysis of Randomized, Controlled Trials

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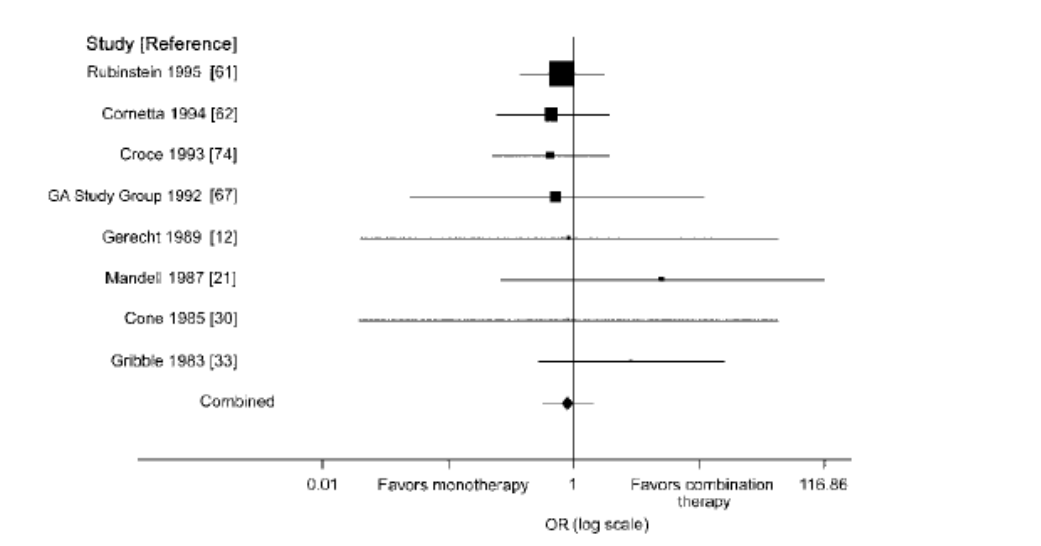


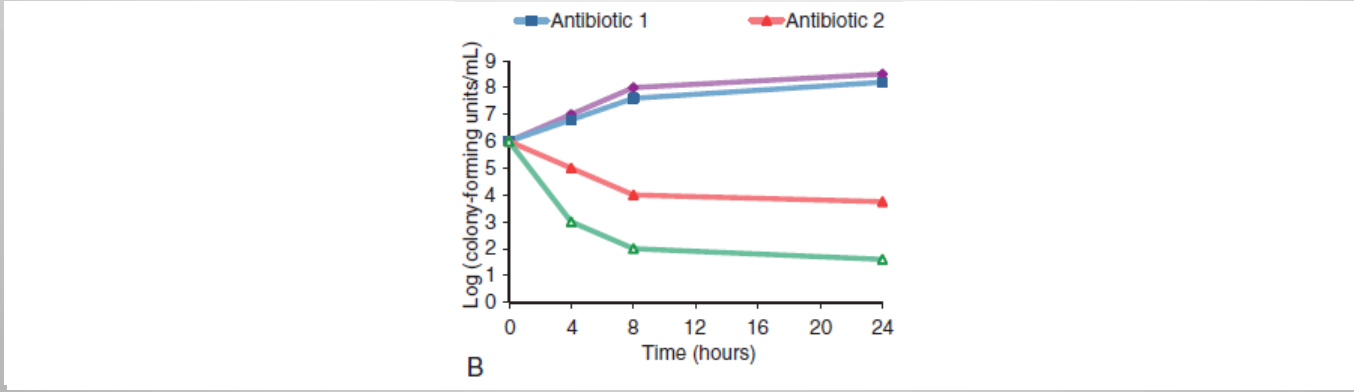
BL monoterapisi direnç gelişimi ile ilişkili değildir (OR:0,90)

Bliziotis IA et al. Clin Infect Dis. 2005;41:149

IV- Toksisitenin azaltılması

- Aditif etkinliğe sahip iki antibiyotiğin normalden düşük dozlarda kombine kullanımının toksisiteyi azaltabileceği teorik olarak öngörülmüşse de pratikte örneği yoktur…

V- Antimikrobiyal sinerjizm



Sinerjizm: İki antibiyotiğin birlikte kullanılmaları ile ayrı ayrı kullanıldıklarındaki etkilerinin toplamından daha fazla etki sağlanması

V- Antimikrobiyal sinerjizm

- Sinerjistik antimikrobiyal ajanların kombine kullanımı, in vitro çalışmalarda pek çok kombinasyon için gösterilmiş olsa da, klinik pratikte az sayıda klinik durumda yararlıdır.

  - Antimikrobiyal kombinasyonun sinerjik etkisi için en iyi örnek enterokokal endokardit tedavisidir.

Antimikrobiyal kombinasyon kullanımı endikasyonları

I- Kritik hastaların ampirik tedavisinin düzenlenmesi,

II- Polimikrobiyal infeksiyonlar,

III- Direnç gelişiminin önlenmesi,

IV- Toksisitenin azaltılması,

V- Antimikrobiyal sinerjizm

I- Kritik hastaların ampirik tedavisinin düzenlenmesi

Q J Med 2005; **98**:291–298
doi:10.1093/qjmed/hci047

Advance Access publication 10 March 2005

Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis

N. PROULX[1], D. FRÉCHETTE[2], B. TOYE[2], J. CHAN[2] and S. KRAVCIK[2]

From the [1]Department of Medicine, University of Western Ontario, London, and [2]Department of Medicine, Ottawa Hospital/University of Ottawa, Ottawa, Ontario, Canada

- Olgu fatalite %13

➢ Mortalite için OR;

- Antibiyotik başlanmasına kadar geçen süre >6 saat (OR:8,4)
- Diğer bir merkezden antibiyotik tedavisi başlanmaksızın transfer (OR:21,8)
- Tanı-tedavi sıralaması / BT, LP, tedavi (OR:5,6)

Proulx N et al. QJM 2005;98(4):291

ORIGINAL ARTICLE

ESCMID guideline: diagnosis and treatment of acute bacterial meningitis

D. van de Beek[1], C. Cabellos[2], O. Dzupova[3], S. Esposito[4], M. Klein[5], A. T. Kloek[1], S. L. Leib[6], B. Mourvillier[7], C. Ostergaard[8], P. Pagliano[9], H. W. Pfister[5], R. C. Read[10], O. Resat Sipahi[11] and M. C. Brouwer[1], for the ESCMID Study Group for Infections of the Brain (ESGIB)

1) Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands, 2) Department of Infectious Diseases, Hospital Universitari de Bellvitge, Barcelona, Spain, 3) Department of Infectious Diseases, Charles University, Third Faculty of Medicine, Prague, Czech Republic, 4) Pediatric Highly Intensive Care Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy, 5) Department of Neurology, Klinikum Großhadern, Munich, Germany, 6) Institute for Infectious Diseases, University of Bern, Bern, Switzerland, 7) Department of Intensive Care Medicine, Groupe Hospitalier Bichat-Claude Bernard, Paris, France, 8) Department of Clinical Microbiology, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark, 9) Department of Infectious Diseases, "D. Cotugno" Hospital, Naples, Italy, 10) Department of Infectious Diseases, Southampton General Hospital, Southampton, United Kingdom and 11) Department of Infectious Diseases and Clinical Microbiology, Ege University, Izmir, Turkey

van de Beek D et al. Clin Microbiol Infect 2016; 22: S37

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment: Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Standard treatment: *S. pneumoniae* susceptible to penicillin	Intravenous dose[a]
Neonates <1 month old	Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside		Age <1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h)
Age >18 and <50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h
Age >50 years, or Age >18 and <50 years plus risk factors for *Listeria monocytogenes*[a]	Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G	Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/ penicillin G	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing immunocompromise.

- Yaş >18 ve <50

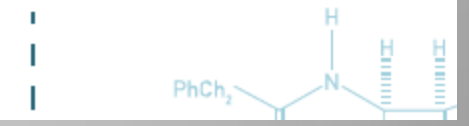
  - Seftriakson/sefotaksim ile vankomisin ya da rifampisin

van de Beek D et al. Clin Microbiol Infect 2016; 22: S37

World Health Organization
REGIONAL OFFICE FOR Europe

Central Asian and Eastern European Surveillance of Antimicrobial Resistance

Annual report 2017



- Türkiye

  2016 verileri 67 laboratuvardan gelen verilerin toplanmasıyla elde edilmiştir.

http://www.euro.who.int/__data/assets/pdf_file/0005/354434/WHO_CAESAR_AnnualReport_2017.pdf

Table 5.48 Percentage of resistance for *S. pneumoniae* among blood and CSF isolates in Turkey in 2016

Antibiotic (group)	*S. pneumoniae*	
	N	Resistance (%)
Penicillins (R)	174	16
Penicillins (I+R)	174	47
Third-generation cephalosporins (R)	113	7
Third-generation cephalosporins (I+R)	113	29
Fluoroquinolones (R)	130	5
Norfloxacin (R)	0	–
Macrolides (R)	163	39
Macrolides (I+R)	163	42
Multidrug resistance (I+R)	155	30

- *S. pneumonia* kan ve BOS izolatları
- Penisilin direnci menenjit dışı duyarlılık kırılım noktalarına göre raporlanmıştır.

http://www.euro.who.int/__data/assets/pdf_file/0005/354434/WHO_CAESAR_AnnualReport_2017.pdf

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment: Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Standard treatment: *S. pneumoniae* susceptible to penicillin	Intravenous dose[a]
Neonates <1 month old	Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside		Age <1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h)
Age >18 and <50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h
Age >50 years, or Age >18 and <50 years plus risk factors for *Listeria monocytogenes*[a]	Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G	Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/ penicillin G	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing immunocompromise.

- Yaş >18 ve <50

  - Seftriakson/sefotaksim ile vankomisin ya da rifampisin

van de Beek D et al. Clin Microbiol Infect 2016; 22: S37

MAJOR ARTICLE

Listeria monocytogenes Sequence Type 6 and Increased Rate of Unfavorable Outcome in Meningitis: Epidemiologic Cohort Study

Merel M. Koopmans,[1] Matthijs C. Brouwer,[1] Merijn W. Bijlsma,[1] Sandra Bovenkerk,[2] Wendy Keijzers,[2,3] Arie van der Ende,[2,3,a] and Diederik van de Beek[1,a]

Departments of [1]Neurology and [2]Medical Microbiology, Academic Medical Center, University of Amsterdam, Center of Infection and Immunity Amsterdam, and [3]Netherlands Reference Laboratory for Bacterial Meningitis, Amsterdam, The Netherlands

- *L. monocytogenes* yetişkinlerde en sık karşılaşılan üçüncü etken,
- Risk faktörleri

  - Yaş>60 ya da

  - DM, kanser, immün sistemi bozan durumlar ya da ilaç kullanımı

Koopmans MM et al. Clin Infect Dis 2013;57:247

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment: Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Standard treatment: *S. pneumoniae* susceptible to penicillin	Intravenous dose[a]
Neonates <1 month old	Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside		Age <1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h)
Age >18 and <50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h
Age >50 years, or Age >18 and <50 years plus risk factors for *Listeria monocytogenes*[a]	Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G	Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/ penicillin G	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 µg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing immunocompromise.

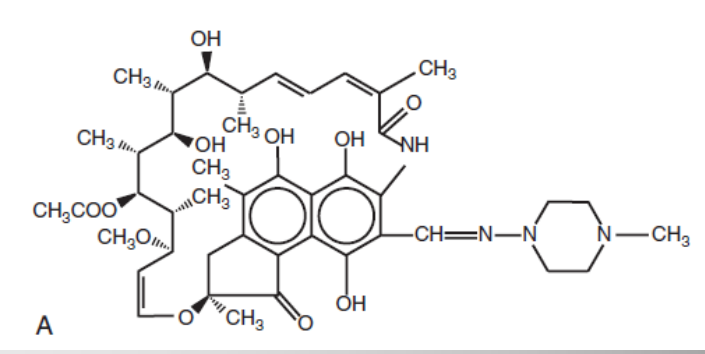
- Yaş>50 ya da yaş >18 ve <50 ve *L. monocytogenes* için risk faktörleri (DM, immün sistemi bozan durumlar ya da ilaç kullanımı)

  - Seftriakson/sefotaksim ile vankomisin/rifampisin ile ampisilin/amoksisilin/pen G

van de Beek D et al. Clin Microbiol Infect 2016; 22: S37

III- Direnç gelişiminin önlenmesi

Rifampisin



- Rifampisin *S. aureus* ve koagülaz negatif stafilokoklara karşı bakterisidal etkinlik gösterir.

- Özellikle biyofilm formasyonunun söz konusu olduğu durumlarda, lipid çözünürlüğü ve nötrofillerde birikimi biyofilm içindeki mikroorganizmalara etkinliğini sağlamaktadır.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1999, p. 2813–2816 Vol. 43, No. 11
0066-4804/99/$04.00+0

Molecular Characterization of *rpoB* Mutations Conferring Cross-Resistance to Rifamycins on Methicillin-Resistant *Staphylococcus aureus*

THOMAS A. WICHELHAUS,* VOLKER SCHÄFER, VOLKER BRADE, AND BORIS BÖDDINGHAUS

Institute of Medical Microbiology, University Hospital of Frankfurt, Frankfurt am Main, Germany

Received 1 February 1999/Returned for modification 24 May 1999/Accepted 25 August 1999

- Rifampisin direncinden RNA polimeraz β alt ünitesini kodlayan "rpoB geni"ndeki nokta mutasyonları sorumludur.
- Mutasyon yeri ve buna bağlı aminoasit değişiklikleri rifamisinlere direnç düzeyiyle ilişkilidir.

Wichelhaus TA et al. Antimicrob Agents Chemother 1999;43:2813

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2010, p. 14–34 Vol. 23, No. 1
0893-8512/10/$12.00 doi:10.1128/CMR.00034-09

Rifampin Combination Therapy for Nonmycobacterial Infections

Graeme N. Forrest[1,2]* and Kimberly Tamura[1]

Portland Veterans Affairs Medical Center[1] and Oregon Health and Science University,[2] Portland, Oregon

INTRODUCTION 14
BACKGROUND 15
Rifampin Resistance 15
PHARMACOLOGY 15
Pharmacokinetics 15
Side Effects 15
Drug Interactions 16
RIFAMPIN COMBINATION THERAPY 16

- Rifampisinin kullanıldığı ilk tüberküloz dışı hastalıklar stafilokokla infeksiyonlar olmuştur,
- Rifampisin dirençli izolatların gelişiminin önlenmesi için en az bir diğer antimikrobiyalle kombine edilmesi gereklidir.

Forrest GN et al. Clin Microbiol Rev 2010;23:14

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2010, p. 14–34 Vol. 23, No. 1
0893-8512/10/$12.00 doi:10.1128/CMR.00034-09

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- *S. aureus* suşlarında 10^{-6}-10^{-7} sıklıkla rifampisin dirençli mutantların varlığı, tedavi sırasında mutantların seçilmesi ve hızlı direnç gelişimiyle sonuçlanmaktadır.

Forrest GN et al. Clin Microbiol Rev 2010;23:14

CLINICAL MICROBIOLOGY REVIEWS, Jan. 2010, p. 14–34 Vol. 23, No. 1
0893-8512/10/$12.00 doi:10.1128/CMR.00034-09

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RIFAMPIN COMBINATION THERAPY 16

- Özellikle apse ya da endokardit gibi bakteriyel yükün fazla olduğu infeksiyonlarda direnç gelişimi çok hızlıdır ve bu nedenle kombinasyon rejimlerinin bir parçası olarak kullanılmalıdır.

Forrest GN et al. Clin Microbiol Rev 2010;23:14

European Heart Journal (2015) **36**, 3075–3123
doi:10.1093/eurheartj/ehv319

ESC GUIDELINES

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Habib G et al. Eur Heart J 2015;36:3075

Table 17 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Prosthetic valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin or oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses	≥ 6	I	B	6,8, 135, 136	Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric doses:[g] Oxacillin and (flu)cloxacillin as above Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses					
Penicillin-allergic patients[a] and methicillin-resistant staphylococci						
Vancomycin[b] with Rifampin[e] and Gentamicin[f]	30–60 mg/kg/day i.v. in 2–3 doses	≥ 6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis. Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric dosing:[g] As above					

- Stafilokok türlerinin etken olduğu protez kapak İE

Habib G et al. Eur Heart J 2015;36:3075

Table 17 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Prosthetic valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin or oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses 900–1200 mg i.v. or orally in 2 or 3 divided doses 3 mg/kg/day i.v. or i.m. in 1 or 2 doses	≥ 6 ≥ 6 2	I I I	B B B	6,8, 135, 136	Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
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	Paediatric dosing:[g] As above					

- "Rifampisinin tek başına kullanımı sıklıkla direnç gelişimiyle sonuçlanır ve önerilmez"

Habib G et al. Eur Heart J 2015;36:3075

Table 17 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Prosthetic valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin or oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses	≥ 6	I	B	6,8, 135, 136	Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
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	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric doses:[g] Oxacillin and (flu)cloxacillin as above Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses					
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	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric dosing:[g] As above					

- "Rifampisin 3-5 günlük etkin antibiyotik tedavisi sonrası, bakteriyemi sonlandıktan sonra, eklenmesi önerilir"

Habib G et al. Eur Heart J 2015;36:3075

AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

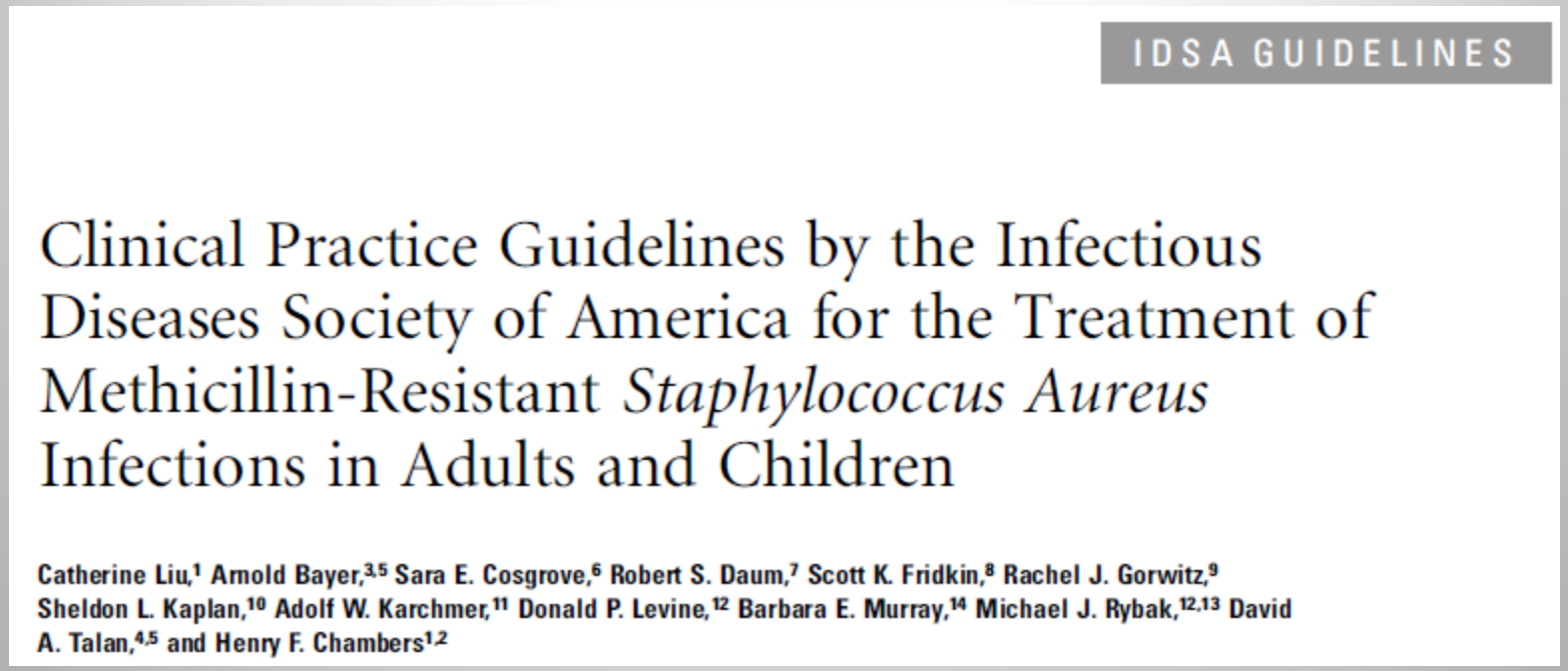
Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD;

Table 11. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 6 equally divided doses	≥6	*Class I; Level of Evidence B*	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 5 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins.
Plus				
Rifampin	900 mg per 24 h IV or orally in 3 equally divided doses	≥6		
Plus				
Gentamicin†	3 mg/kg per 24 h IV or IM in 2 or 3 equally divided doses	2		
Oxacillin-resistant strains				
Vancomycin	30 mg/kg 24 h in 2 equally divided doses	≥6	*Class I; Level of Evidence B*	Adjust vancomycin to a trough concentration of 10–20 μg/mL. (see text for gentamicin alternatives)
Plus				
Rifampin	900 mg/24 h IV/PO in 3 equally divided doses	≥6		
Plus				
Gentamicin	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		

32:1435



- MRSA osteomyeliti

  Cerrahi debridman ve IV/po antibiyotik tedavisi

  "Vankomisin, daptomisin, linezolid, klindamisin, TMP/SMX ve rifampisin"

- "Rifampisin bakteriyeminin sona ermesinden sonra eklenmelidir"

Liu C et al. Clin Infect Dis 2011;1:38

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

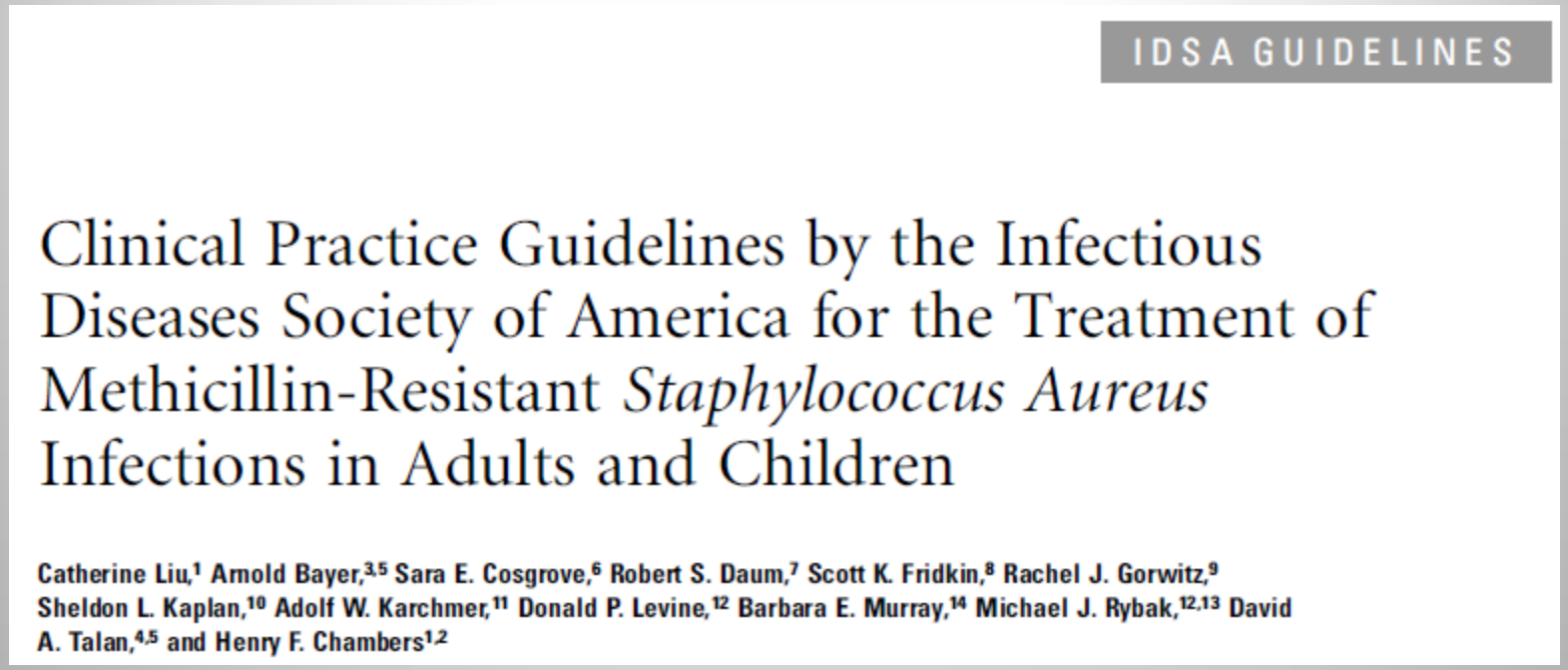
- Optimal tedavi süresi ?

  - Minimum 8 hafta

  - Ek olarak 1-3 ay süreyle “rifampin bazlı kombinasyon tedavisi” önerilmektedir.

    “TMP/SMX, doksi, klinda, kinolon”

Liu C et al. Clin Infect Dis 2011;1:38



- MRSA protez infeksiyonları

  - IV antibiyotik tedavisi, 2 hafta

    "Vankomisin, daptomisin, linezolid, klindamisin, TMP/SMX ve rifampisin"

  - Ek olarak kalça için 3, diz için 6 ay süreyle "rifampin bazlı kombinasyon tedavisi" önerilmektedir.

    "TMP/SMX, doksi, klinda, kinolon"

Liu C et al. Clin Infect Dis 2011;1:38

Original Contribution

May 20, 1998

Role of Rifampin for Treatment of Orthopedic Implant-Related Staphylococcal Infections

A Randomized Controlled Trial

Werner Zimmerli, MD; Andreas F. Widmer, MD, MSc; Marianne Blatter, MD; et al

JAMA. 1998;279(19):1537-1541. doi:10.1001/jama.279.19.1537

- Kanıtlanmış stafilokokal ortopedik implant infeksiyonlarında randomize, plasebo kontrollü çalışma
- 2 hafta IV flukloksasilin ya da vankomisin,

  Siprofloksasin + rifampisin (n=18)

  Siprofloksasin + plasebo (n=15)

Zimmerli W et al. JAMA 1998;279:1537

Original Contribution

May 20, 1998

Role of Rifampin for Treatment of Orthopedic Implant-Related Staphylococcal Infections

A Randomized Controlled Trial

Werner Zimmerli, MD; Andreas F. Widmer, MD, MSc; Marianne Blatter, MD; et al

JAMA. 1998;279(19):1537-1541. doi:10.1001/jama.279.19.1537

- ITT kür
  - CIP + RIF %89 (16/18)
  - CIP + PLS %60 (9/15)
- Tedavi sonu kür
  - CIP + RIF %100 (12/12)
  - CIP + PLS %58 (7/12)

Zimmerli W et al. JAMA 1998;279:1537

Original Contribution

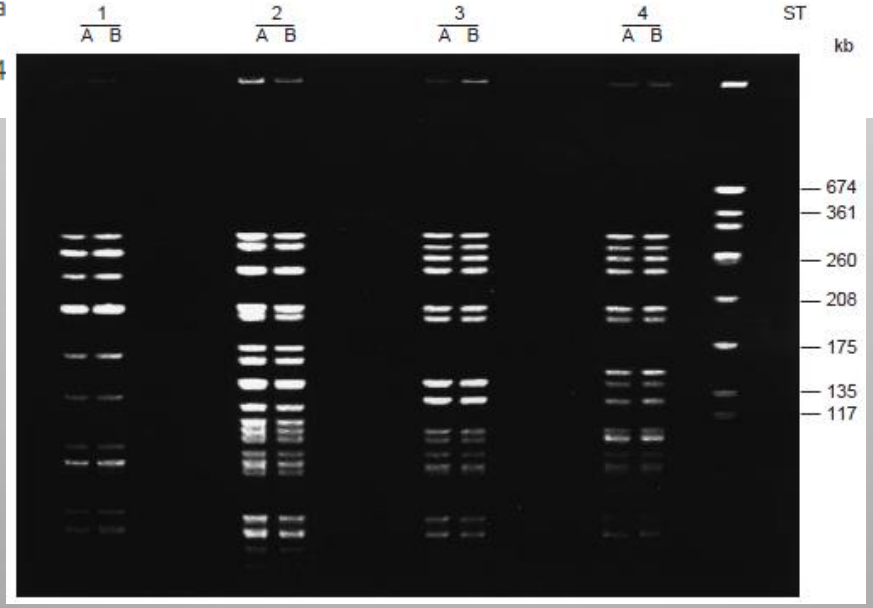
May 20, 1998

Role of Rifampin for Treatment of Orthopedic Implant-Related Staphylococcal Infections

A Randomized Controlled Trial

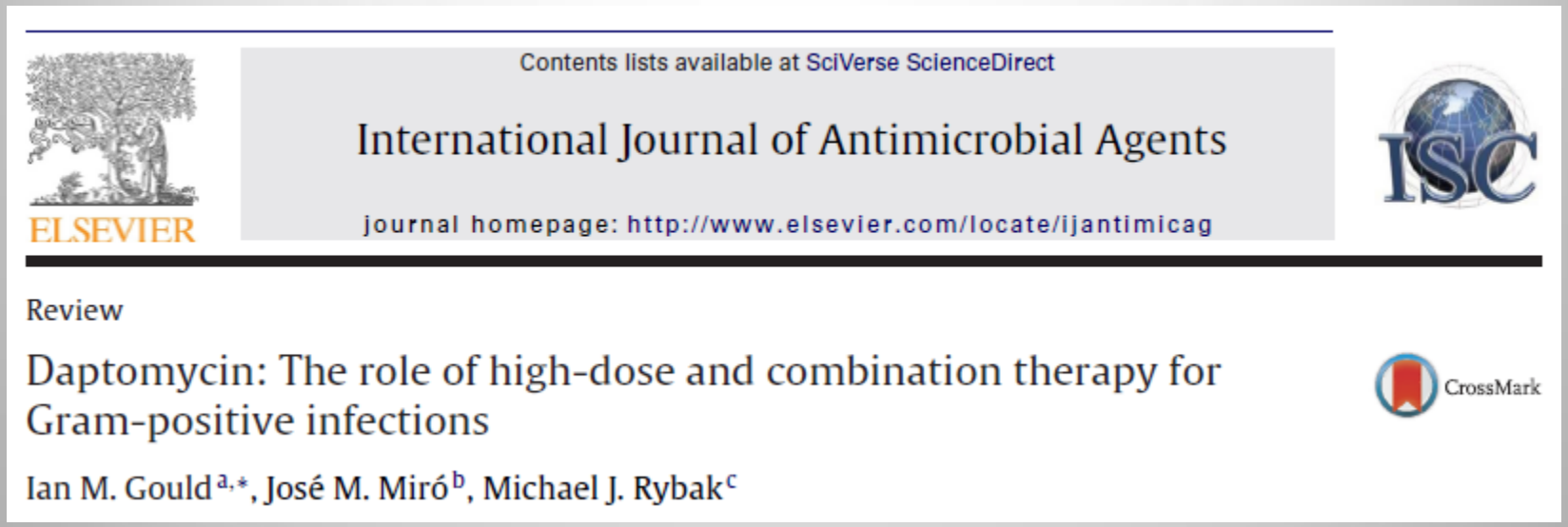
Werner Zimmerli, MD; Andrea

JAMA. 1998;279(19):1537-154



Siprofloksasin monoterapisi alan dört hastada kinolon direnci

Zimmerli W et al. JAMA 1998;279:1537



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journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Daptomycin: The role of high-dose and combination therapy for Gram-positive infections

Ian M. Gould[a,*], José M. Miró[b], Michael J. Rybak[c]

- Tedavisi güç durumlarda direnç olasılığını azaltmak ve klinik başarıyı artırmak adına daptomisinin yüksek doz ve kombine kullanımı önerilmektedir.
  - Tedavi süresinin uzatılması gereken durumlar,
  - Suboptimal kaynak kontrolü,
  - Önceki antibiyotik tedavisine yanıtsızlık

Gould IM et al. Int J Antimicrob Agents 2013;42:202

V- Antimikrobiyal sinerjizm

- İn vitro sinerjizmle ilgili çok sayıda çalışma bulunmasına karşın sinerjistik antimikrobiyal kombinasyonların monoterapiden daha etkin olduğuna dair az sayıda klinik durum tanımlanmıştır.

Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses	4–6	I	B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
	3 mg/kg/day i.v. or i.m. in 1 dose	2–6**	I	B		
	Paediatric doses:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses					
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses	6	I	B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis. This combination is not active against *E. faecium*
	4 g/day i.v. or i.m. in 2 doses	6	I	B		
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses	6	I	C		
	3 mg/kg/day i.v. or i.m. in 1 dose	6	I	C		
	Paediatric doses:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above					

Sinerjistik antimikrobiyal kombinasyon tedavisi için en iyi bilinen uygulama enterokokal endokardit tedavisidir.

Habib G et al. Eur Heart J 2015;36:3075

Enterokokal İE

- Enterokokal İE

  E. faecalis %90-97

  E. faecium %2-5

- Enterokoklar antibiyotik aracılı öldürmeye oldukça dirençlidir, betalaktamlar ya da vankomisin ile monoterapi bakteriyostatiktir.
- Tedavide sinerjistik bakterisidal kombinasyonların uzun süre kullanımına gereksinim vardır.

Enterokokal İE

- Enterokoklar çok sayıda ilaca dirençlidir.

  Penisilin, ampisilin, vankomisin duyarlılığı ile aminoglikozidlere yüksek düzey direnç belirlenmelidir

- Enterokokal İE'te hücre duvarına etkili bir ajanla bir aminoglikozidin kombinasyonu standart yaklaşımdır.

  - Daha düşük relaps,
  - Daha yüksek klinik iyileşme

SPECIAL SECTION: ANTIMICROBIAL RESISTANCE

George M. Eliopoulos, Section Editor

Aminoglycoside Resistance in Enterococci

Joseph W. Chow

Infectious Disease Section, John D. Dingell Veterans Affairs Medical Center, Wayne State University School of Medicine, Detroit, Michigan

High-level aminoglycoside resistance in enterococci is mediated generally by aminoglycoside-modifying enzymes, which eliminate the synergistic bactericidal effect usually seen when

- Tüm enterokoklarda AG'e karşı intrinsik düşük düzey direnç vardır. (Gentamisin MIC 6-48 g/L)
- Enterokokların fakültatif anaerobik metabolizması, ilacın hücre içine geçişini kısıtlayarak düşük düzey dirence yol açar.

Chow JW. Clin Infect Dis 2000;31:586

SPECIAL SECTION: ANTIMICROBIAL RESISTANCE

George M. Eliopoulos, Section Editor

Aminoglycoside Resistance in Enterococci

Joseph W. Chow

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- Hücre duvar sentezine etki eden antibiyotikler (ampisilin/vankomisin), AG'in hücre içine geçişini kolaylaştırarak mikroorganizmanın öldürülmesini sağlar.

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- Kazanılmış direnç genleri tarafından kodlanan farklı AG modifiye edici enzimler, “yüksek düzey AG direnci”ne yol açarak (MIC>2000 g/L) sinerjistik etkiyi ortadan kaldırır.

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	Aminoglycoside							
Resistance gene	Gentamicin	Tobramycin	Amikacin	Kanamycin	Netilmicin	Dibekacin	Streptomycin	Arbekacin
aac(6′)-Ie-aph(2″)-Ia	R	R	R	R	R	R	S	S[a]
aph(2″)-Ib	R	R	S	R	R	R	S	S
aph(2″)-Ic	R	R	S	R	S	S	S	S
aph(2″)-Id	R	R	S	R	R	R	S	S
aph(3′)-IIIa	S	S	R	R	S	S	S	S
aac(6′)-Ii	S	R	S	R	R	NT	S	NT
ant(3″)-Ia	S	S	S	S	S	S	R	S
ant(4′)-Ia	S	R	R	R	S	NT	S	S
ant(6′)-Ia	S	S	S	S	S	S	R	S

Klinik olarak en önemli bifonksiyonel enzim aac (6')-Ie-aph(2')-Ia, streptomisin hariç tüm AG'e direnç sağlar.

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Gentamisin MIC>500 g/L ⇨ aac (6')-Ie-aph(2')-Ia

Sadece streptomisin seçenek olarak kalır…

Chow JW. Clin Infect Dis 2000;31:586

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	Aminoglycoside							
Resistance gene	Gentamicin	Tobramycin	Amikacin	Kanamycin	Netilmicin	Dibekacin	Streptomycin	Arbekacin
aac(6′)-Ie-aph(2″)-Ia	R	R	R	R	R	R	S	S[a]
aph(2″)-Ib	R	R	S	R	R	R	S	S
aph(2″)-Ic	R	R	S	R	S	S	S	S
aph(2″)-Id	R	R	S	R	R	R	S	S
aph(3′)-IIIa	S	S	R	R	S	S	S	S
aac(6′)-Ii	S	R	S	R	R	NT	S	NT
ant(3″)-Ia	S	S	S	S	S	S	R	S
ant(4′)-Ia	S	R	R	R	S	NT	S	S
ant(6′)-Ia	S	S	S	S	S	S	R	S

Tüm *E. faecium* suşlarında kromozomal olarak kodlanan asetiltransferaz Aac (6')-Ii vardır.

Chow JW. Clin Infect Dis 2000;31:586

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High-level aminoglycoside resistance in enterococci is mediated generally by aminoglycoside-modifying enzymes, which eliminate the synergistic bactericidal effect usually seen when

- Enterokok izolatlarının ≥3 farklı AG modifiye edici enzim kodlaması nadir değildir.

Chow JW. Clin Infect Dis 2000;31:586

Journal of Microbiology and Infectious Diseases / JMID

2013; 3 (3): 100-103
doi: 10.5799/ahinjs.02.2013.03.0090

ORIGINAL ARTICLE

High-level resistance to aminoglycoside, vancomycin, and linezolid in *enterococci* strains

Gülçin Baldır[1], Derya Öztürk Engin[2], Metin Küçükercan[1], Asuman İnan[2], Seniha Akçay[1], Seyfi Özyürek[2], Sebahat Aksaray[1]

[1]*Department of Clinical Microbiology, Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey*

[2]*Department of Infectious Diseases and Clinical Microbiology Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey*

100 VRE, 100 VSE

VSE izolatlarında

HLGR %42, HLSR %48, HLAR %36

VRE izolatlarında

HLGR %83, HLSR %89, HLAR %78

Baldır G et al. J Microbiol Infect Dis 2013;3:100

Çift betalaktam tedavisi

- Seftriakson ve ampisilin kombinasyonu, farklı PBP’lerin saturasyonu yoluyla sinerjistik etki sağlar.

Annals of Internal Medicine®

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ARTICLES | 17 APRIL 2007

Brief Communication: Treatment of *Enterococcus faecalis* Endocarditis with Ampicillin plus Ceftriaxone

Joan Gavaldà, MD; Oscar Len, MD; José M. Miró, MD; Patricia Muñoz, MD; Miguel Montejo, MD; Aristides Alarcón, MD; Julián de la Torre-Cisneros, MD; Carmen Peña, MD; Xavier Martínez-Lacasa, MD; Cristina Sarria, MD; Germán Bou, MD; José M. Aguado, MD; Enrique Navas, MD; Joan Romeu, MD; Francesc Marco, MD; Carmen Torres, MD; Pilar Tornos, MD; Ana Planes, MD; Vicenç Falcó, MD; Benito Almirante, MD; Albert Pahissa, MD

HLAR +/- *E. faecalis* İE, CTR/AMP kombinasyonu

21 HLAR, 22 non-HLAR

Klinik başarı

HLAR %71,4, non-HLAR %72,7

Gavalda J et al. Ann Intern Med 2007;146(8):574

MAJOR ARTICLE

Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating *Enterococcus faecalis* Infective Endocarditis

Nuria Fernández-Hidalgo,[1] Benito Almirante,[1] Joan Gavaldà,[1] Mercè Gurgui,[2] Carmen Peña,[3] Arístides de Alarcón,[4] Josefa Ruiz,[5] Isidre Vilacosta,[6] Miguel Montejo,[7] Nuria Vallejo,[8] Francisco López-Medrano,[9] Antonio Plata,[10] Javier López,[11] Carmen Hidalgo-Tenorio,[12] Juan Gálvez,[13] Carmen Sáez,[14] José Manuel Lomas,[15] Marco Falcone,[18] Javier de la Torre,[16] Xavier Martínez-Lacasa,[17] and Albert Pahissa[1]

- Gözlemsel, non-randomize, kohort

  AMP/CTR (n=159) vs AMP/GEN (n=87)

- Mortalite, tedavi başarısızlığı, relaps açısından fark yok,

Fernandez Hidalgo N et al. Clin Infect Dis 2013;56:1261

MAJOR ARTICLE

Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating *Enterococcus faecalis* Infective Endocarditis

Nuria Fernández-Hidalgo,[1] Benito Almirante,[1] Joan Gavaldà,[1] Mercè Gurgui,[2] Carmen Peña,[3] Arístides de Alarcón,[4] Josefa Ruiz,[5] Isidre Vilacosta,[6] Miguel Montejo,[7] Nuria Vallejo,[8] Francisco López-Medrano,[9] Antonio Plata,[10] Javier López,[11] Carmen Hidalgo-Tenorio,[12] Juan Gálvez,[13] Carmen Sáez,[14] José Manuel Lomas,[15] Marco Falcone,[18] Javier de la Torre,[16] Xavier Martínez-Lacasa,[17] and Albert Pahissa[1]

E. faecalis İE tedavisinde AMP/CTR kombinasyonu HLAR direncinden bağımsız olarak AMP/GEN kombinasyonu kadar etkilidir.

Fernandez Hidalgo N et al. Clin Infect Dis 2013;56:1261

Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses	4–6	I	B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
	3 mg/kg/day i.v. or i.m. in 1 dose	2–6**	I	B		
	Paediatric doses:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/					
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses	6	I	B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis. This combination is not active against *E. faecium*
	4 g/day i.v. or i.m. in 2 doses	6	I	B		
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses	6	I	C		
	3 mg/kg/day i.v. or i.m. in 1 dose	6	I	C		
	Paediatric doses:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above					

CTR/AMP kombinasyon enterokokal endokardit tedavisinde ilk seçenek tedavi önerileri arasındadır.

Habib G et al. Eur Heart J 2015;36:3075

Table 12. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Susceptible to Penicillin and Gentamicin in Patients Who Can Tolerate β-Lactam Therapy*

Regimen	Dose† and Route	Duration, wk	Strength of Recommendation	Comments
Either			*Class IIa; Level of Evidence B*	Native valve: 4-wk therapy recommended for patients with symptoms of illness <3 mo; 6-wk therapy recommended for native valve symptoms >3 mo and for patients with prosthetic valve or prosthetic material. Recommended for patients with creatinine clearance >50 mL/min.
Ampicillin sodium	2 g IV every 4 h	4–6		
Or		4–6	*Class IIa; Level of Evidence B*	
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6		
Plus				
Gentamicin sulfate‡	3 mg/kg ideal body weight in 2–3 equally divided doses			
Or				
Double β-lactam Ampicillin	2 g IV every 4 h	6	*Class IIa; Level of Evidence B*	Recommended for patients with initial creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during therapy with gentamicin-containing regimen.
Plus				
Ceftriaxone	2 g IV every 12 h	6		

Penisilin S, gentamisin S

Ampisilin ve gentamisin ya da

Ampisilin ve seftriakson

Baddour LM et al. Circulation 2015;132:1435

Table 13. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* species Caused by a Strain Susceptible to Penicillin and Resistant to Aminoglycosides or Streptomycin-Susceptible Gentamicin-Resistant in Patients Able to Tolerate β-Lactam Therapy*

Regimen	Dose† and Route	Duration, wk	Strength of Recommendation	Comments
Double β-lactam	2 g IV every 4 h	6	*Class IIa; Level of Evidence B*	Double β-lactam is reasonable for patients with normal or impaired renal function abnormal cranial nerve VIII function or if the laboratory is unable to provide rapid results of streptomycin serum concentration; native valve infection with symptoms of infection <3-mo duration may be treated for 4 wk with the streptomycin-containing regimen. PVE, NVE with symptoms >3 mo, or treatment with a double β-lactam regimen require a minimum of 6 wk of therapy.
Ampicillin				
Plus				
Ceftriaxone	2 g IV every 12 h			
Alternative for streptomycin susceptible/gentamicin resistant				
Either		4–6	*Class IIa; Level of Evidence B*	Use is reasonable only for patients with availability of rapid streptomycin serum concentrations. Patients with creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during treatment should be treated with double–β-lactam regimen. Patients with abnormal cranial nerve VIII function should be treated with double–β-lactam regimen.
Ampicillin sodium	2 g IV every 4 h			
Or				
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses			
Plus				
Streptomycin sulfate‡	15 mg/kg ideal body weight per 24h IV or IM in 2 equally divided doses			

Penisilin S, gentamisin R, streptomisin S

Ampisilin ve streptomisin

Ampisilin ve seftriakson

Baddour LM et al. Circulation 2015;132:1435

Table 14. Vancomycin-Containing Regimens for Vancomycin- and Aminoglycoside-Susceptible Penicillin-Resistant *Enterococcus* Species for Native or Prosthetic Valve (or Other Prosthetic Material) IE in Patients Unable to Tolerate β-Lactam

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Unable to tolerate β-lactams				
Vancomycin†	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin‡	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		
Penicillin resistance; intrinsic or β-lactamase producer				
Vancomycin plus aminoglycoside	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIb; Level of Evidence C*	For β-lactamase–producing strain, if able to tolerate a β-lactam antibiotic, ampicillin-sulbactam§ plus aminoglycoside therapy may be used.

Penisilin R, aminoglikozid S

Vankomisin ve gentamisin

Baddour LM et al. Circulation 2015;132:1435

Table 15. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Linezolid	600 mg IV or orally every 12 h	>6	*Class IIb; Level of Evidence C*	Linezolid use may be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions. Patients with IE caused by these strains should be treated by a care team including specialists in infectious diseases, cardiology, cardiac surgery, clinical pharmacy, and, in children, pediatrics. Cardiac valve replacement may be necessary for cure.
Or				
Daptomycin	10–12 mg/kg per dose	>6	*Class IIb; Level of Evidence C*	

Penisilin R, aminoglikozid R, vankomisin R

Linezolid ya da

Daptomisin

Baddour LM et al. Circulation 2015;132:1435

Summary of clinical studies on combination therapy for *Staphylococcus aureus* bacteremia[a].

	Author	Combination therapy	Study design	Outcome	Potential clinical role
MSSA	Sakoulas et a (Sakoulas et al., 2016)	Cefazolin + ertapenem	Single case study	Clearance of refractory bacteremia in a single case	Refractory MSSA bacteremia despite monotherapy and appropriate source control
	Moise et al. (Moise et al., 2013)	Daptomycin + beta-lactam	Multicenter, retrospective, observational study	8/8 patients successfully treated with combination therapy versus 12/16 patients treated without beta-lactams	Deep-seated infections, including endocarditis, joint/bone infections, and suspected endovascular sources
MRSA	Dilworth et al. (Dilworth et al., 2014)	Vancomycin + beta-lactam for at least 24 h	Retrospective cohort of 50 patients treated with combination therapy vs. 30 patients with monotherapy	Improved rate of microbiological clearance	Refractory MRSA bacteremia despite monotherapy with vancomycin Monitor for renal toxicity depending on beta-lactam used
	Davis et al. (Davis et al., 2016)	Vancomycin + flucloxacillin	Multicenter, randomized trial of 60 patients receiving vancomycin + flucloxacillin vs. vancomycin alone	Decreased duration of bacteremia by 1 day Potential for increased renal toxicity	Refractory MRSA bacteremia despite monotherapy with vancomycin Monitor for renal toxicity
	Gritsenko et al. (Gritsenko et al., 2017)	Ceftaroline + vancomycin	Case series of five patients	Clearance of refractory bacteremia in all patients	Refractory MRSA bacteremia despite monotherapy with vancomycin
	Dhand et al. (Dhand and Sakoulas, 2014)	Daptomycin + nafcillin or oxacillin	Case series of seven patients	Clearance of refractory bacteremia in all patients within 24–48 h of combination therapy	Refractory MRSA with high MIC to vancomycin despite monotherapy
	Sakoulas et a (Sakoulas et al., 2014a)	Daptomycin + ceftaroline	Case series of 26 patients with staphylococcal bacteremia of which 22 patients had MRSA or VISA	23/26 resulted in clearance of bacteremia within 1–6 days	Refractory MRSA with high MIC to vancomycin, VISA, or VRSA despite monotherapy
	Moise et al. (Moise et al., 2013)	Daptomycin + beta-lactam	Multicenter, retrospective, observational study	18/22 patients successfully treated with combination therapy versus 27/34 patients treated without beta-lactams	Deep-seated infections, including endocarditis, joint/bone infections, and suspected endovascular sources

Tedavi başarısızlıkları, relaps, mortalite ve ilaç direncinin artması gibi komplikasyonlar, tedavisi güç infeksiyonlar için yeni potansiyel tedavi yaklaşımları gerektirmekte,

Yeni ajanların geliştirilmesindeki tıkanıklık dikkate alındığında, var olan antibakteriyellerle kombinasyonlar yeni tedavi seçenekleri yaratacaktır.