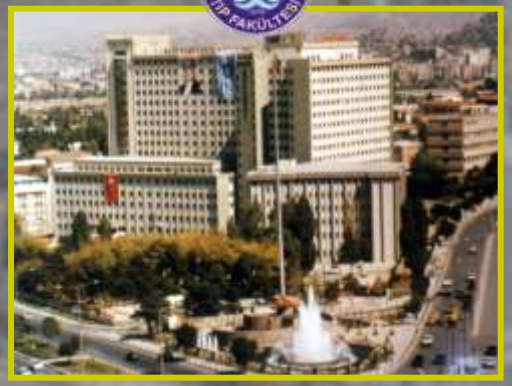
GRAM-POZİTİF ENFEKSİYONLARIN TEDAVİSİNDE YENİ BİR YOL: KLİNİK YAKLAŞIM

Esin ŞENOL

G.Ü.T.F. İNFEKSİYON HASTALIKLARI VE KLİNİK MİKROBİYOLOJİ ANABİLİM DALI



Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

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The Infectious Diseases Society of America (IDSA) continues to view with concern the lean pipeline for novel therapeutics to treat drug-resistant infections, especially those caused by gram-negative pathogens. Infections now occur that are resistant to all current antibacterial options. Although the IDSA is encouraged by the prospect of success for some agents currently in preclinical development, there is an urgent, immediate need for new agents with activity against these panresistant organisms. There is no evidence that this need will be met in the foreseeable future. Furthermore, we remain concerned that the infrastructure for discovering and developing new antibacterials continues to stagnate, thereby risking the future pipeline of antibacterial drugs. The IDSA proposed solutions in its 2004 policy report, "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates,

"ESKAPE" PATHOGENS

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumonia*
- *Acineobacter baumanii*
- *Pseudomonas aeruginosa*
- *Enterobacter spp*

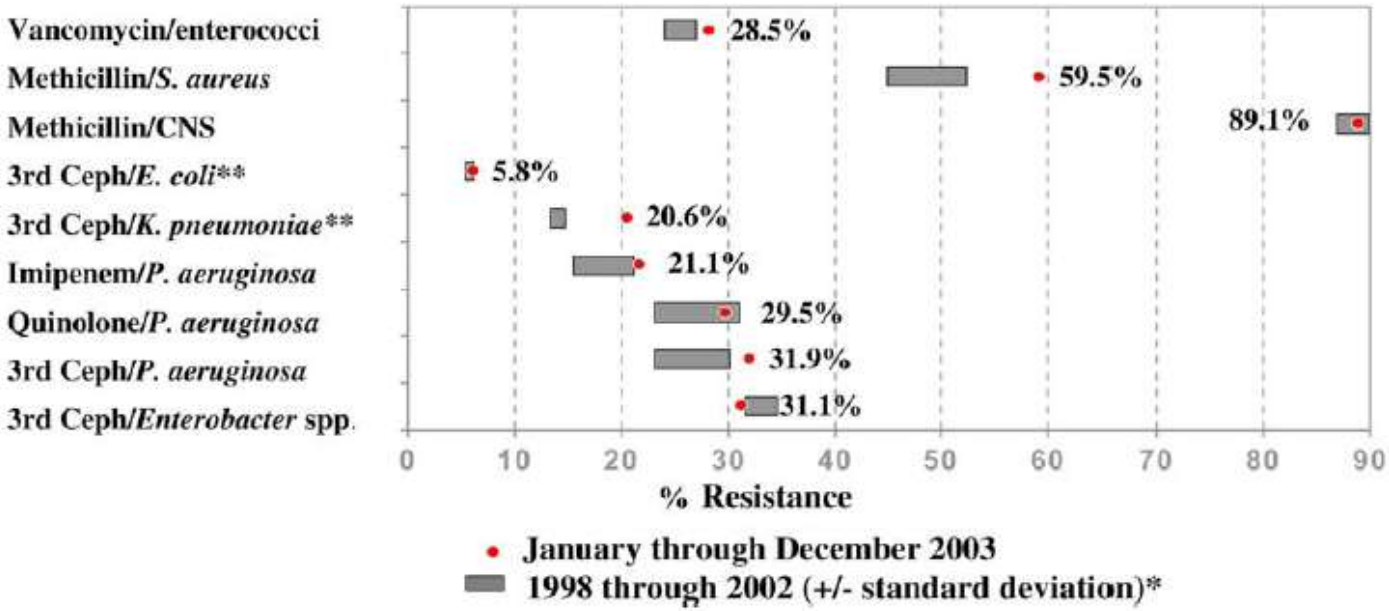
Rice LB. J Infect Dis 2008;197:1079-1081

21.YÜZYILDA ÖNEMLİ DİRENÇ SORUNLARI

- MRSA
- MRCoNS
- VRE

- ESBL VE KARBAPENEMAZ YAPAN *Enterobacteriaceae*
- MDR/PANREZİSTAN *P. aeruginosa* ve *Acinetobacter*

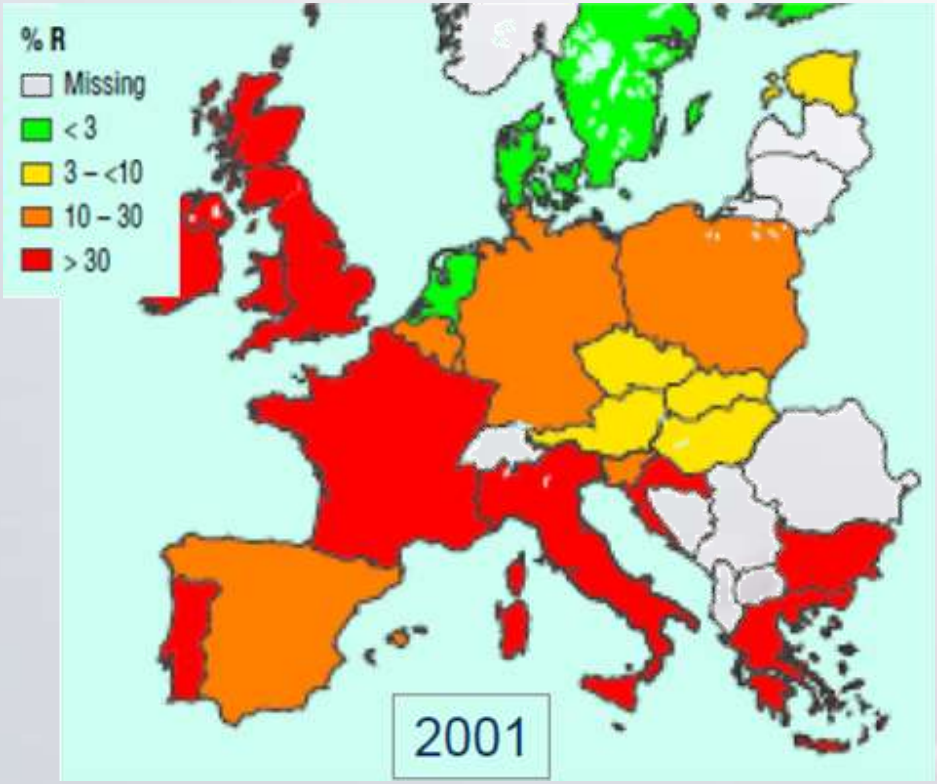
NNIS Data on Resistance 1998-2002 vs 2003

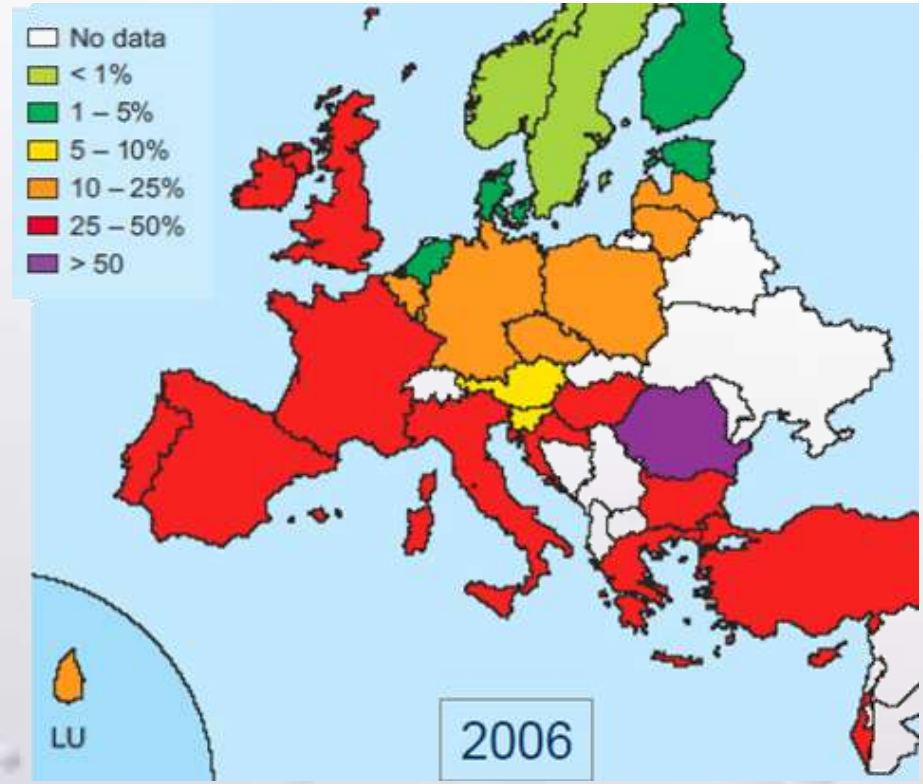


Jan–Dec 2003 No. of Isolates	% increase in resistance (2003 vs 98-02*)
2048	12%
4100	11%
3336	1%
1355	0%
1068	47%
1392	15%
1825	9%
2119	20%
1411	–6%

NNIS report. Am J Infect Control 2004

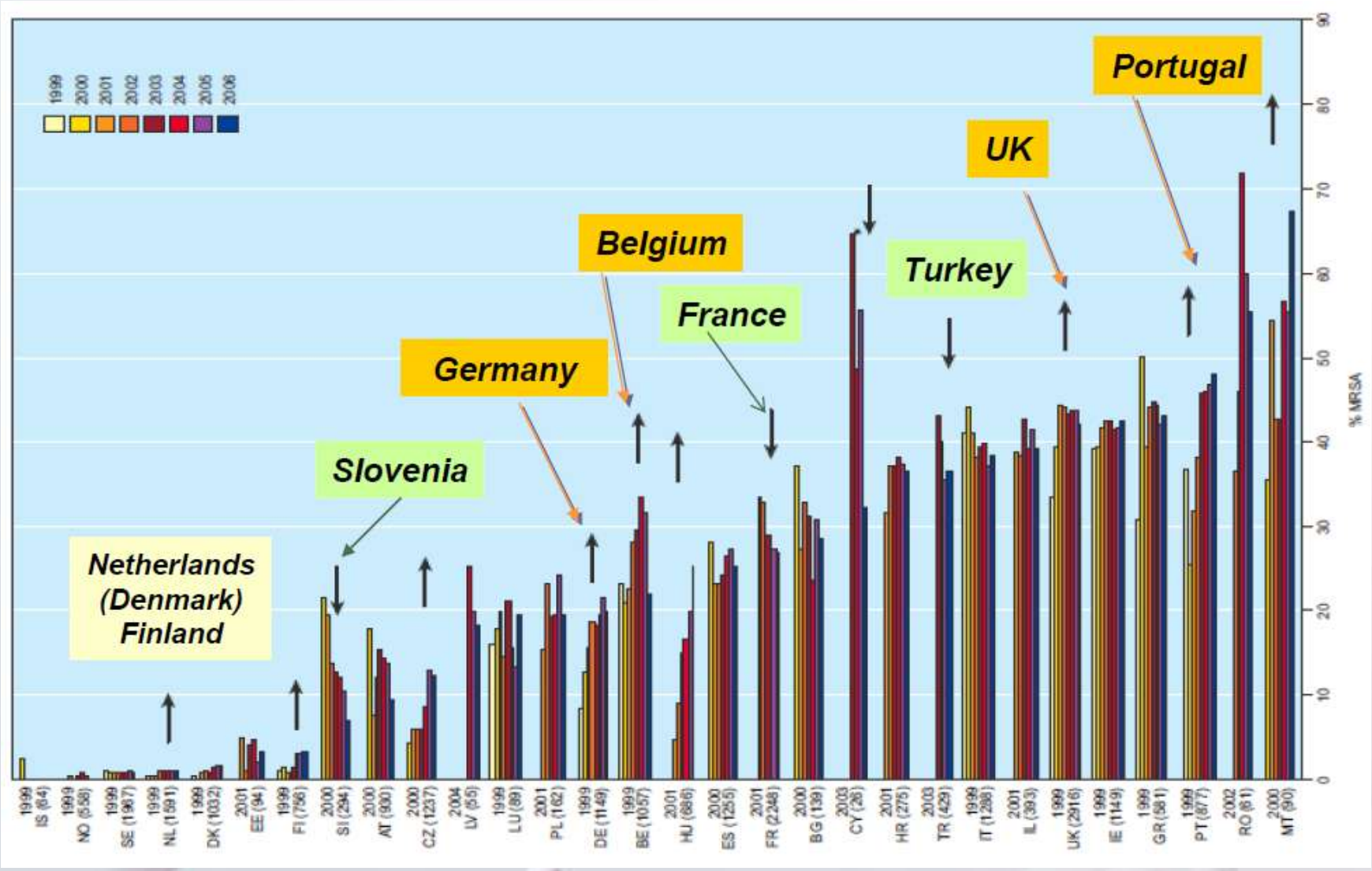
MRSA – Avrupa:
İnvazif *S.aureus* izolatları





EARSS Annual Report 2006 - http://www.earss.rivm.nl.

MRSA (%R), EARSS, 1999-2006



EARSS Annual Report 2006 - http://www.earss.rivm.nl.

Device-associated hospital-acquired infection rates in Turkish intensive care units. Findings of the International Nosocomial Infection Control Consortium (INICC)

H. Leblebicioglu [a], V.D. Rosenthal [b,*], Ö.A. Arıkan [c], A. Özgültekin [d], A.N. Yalcin [e], I. Koksal [f], G. Usluer [g], Y.C. Sardan [h], S. Ulusoy [i], the Turkish Branch of INICC [1]

Table III Overall susceptibility of micro-organisms (percentage resistant)

Micro-organisms	Antibiotic to which micro-organism is resistant	Percentage resistant
Staphylococcus aureus (MRSA)	Meticillin	89.2
Enterobacteriaceae	Ceftriaxone	48.2
Enterobacteriaceae	Ceftazidim	52.0
Enterobacteriaceae	Piperacillin–tazobactam	33.2
Pseudomonas aeruginosa	Ciprofloxacin	51.1
P. aeruginosa	Ceftazidim	50.7
P. aeruginosa	Imipenem	38.7
P. aeruginosa	Piperacilin–tazobactam	30.0
Enterococci	Vancomycin	1.9
Acinetobacter	Piperacilin–tazobactam	87.1

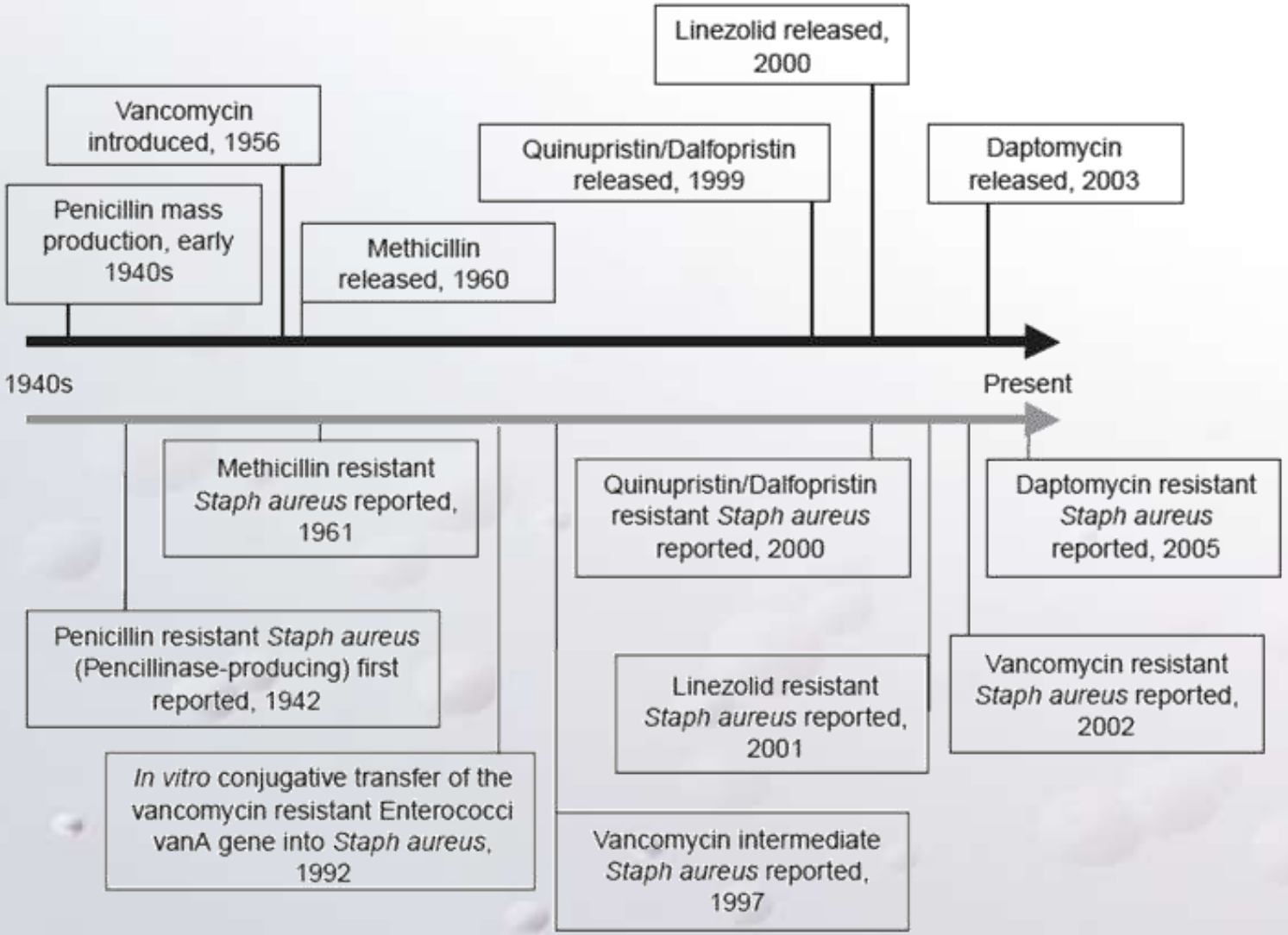
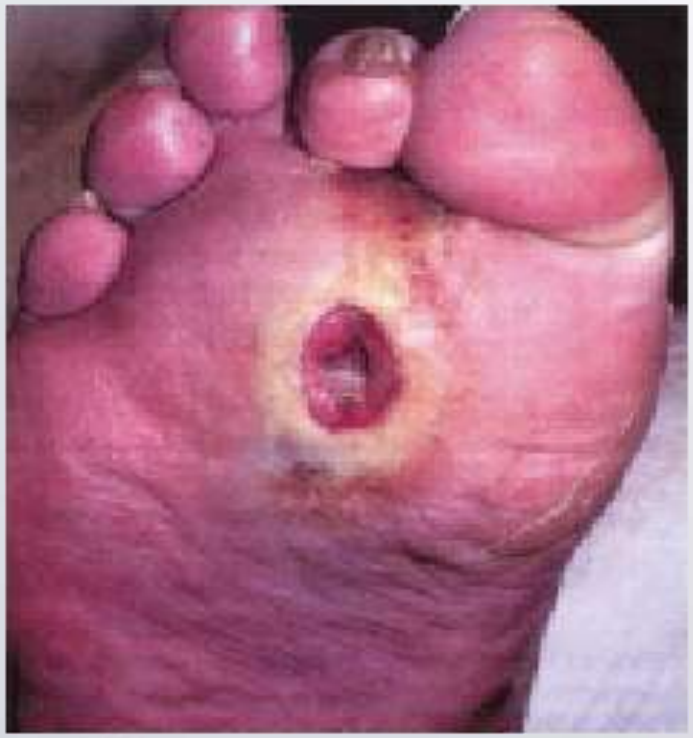
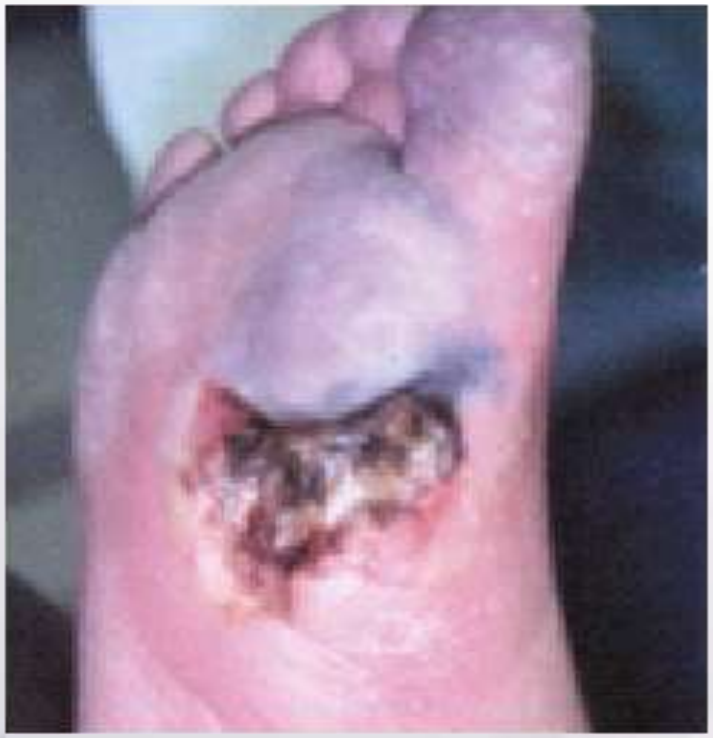


Figure 9.1 New drug development and the emergence of antibiotic-resistant *Staphylococcus aureus*. Reproduced from Low (2005), with permission.

Diabetik Ayak İnfeksiyonları



(a)

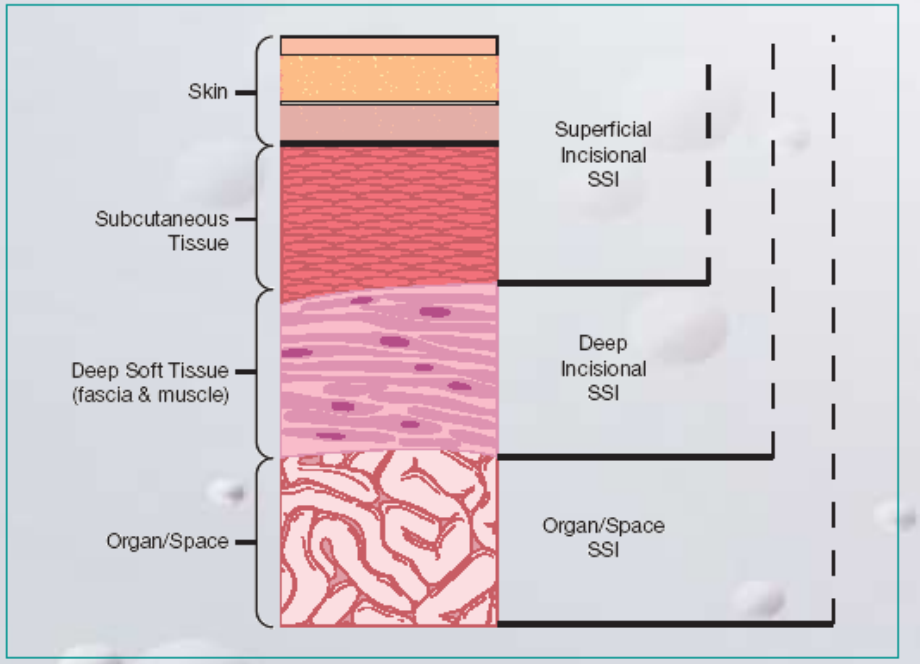


(b)

Cerrahi Alan İnfeksiyonları

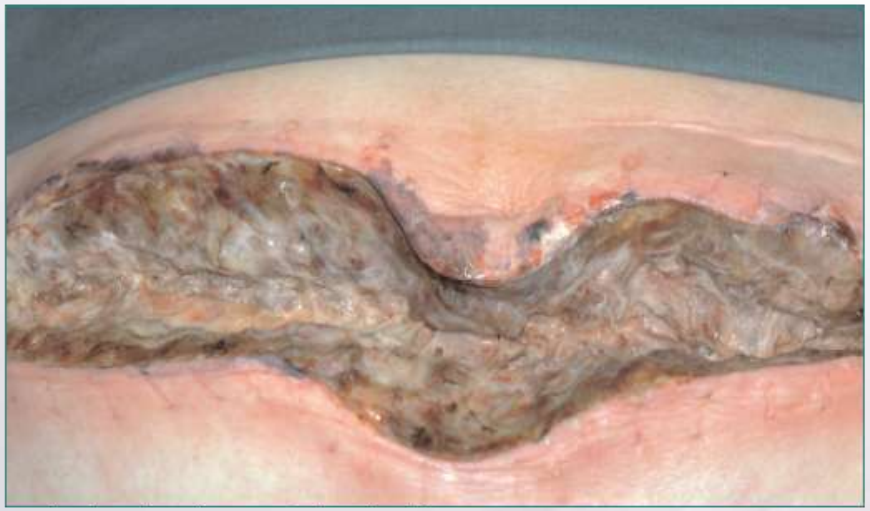
- Tüm cerrahi girimlerin %2-5
- CAİ'ları en sık görülen 2. sıklıktaki NKİ

Figure 1. CDC Classification of SSIs



Adapted from: Mangram AJ et al. Guideline for Prevention of Surgical Site Infection, 1999. Infect Control Hosp Epid 1999;20:247-278.

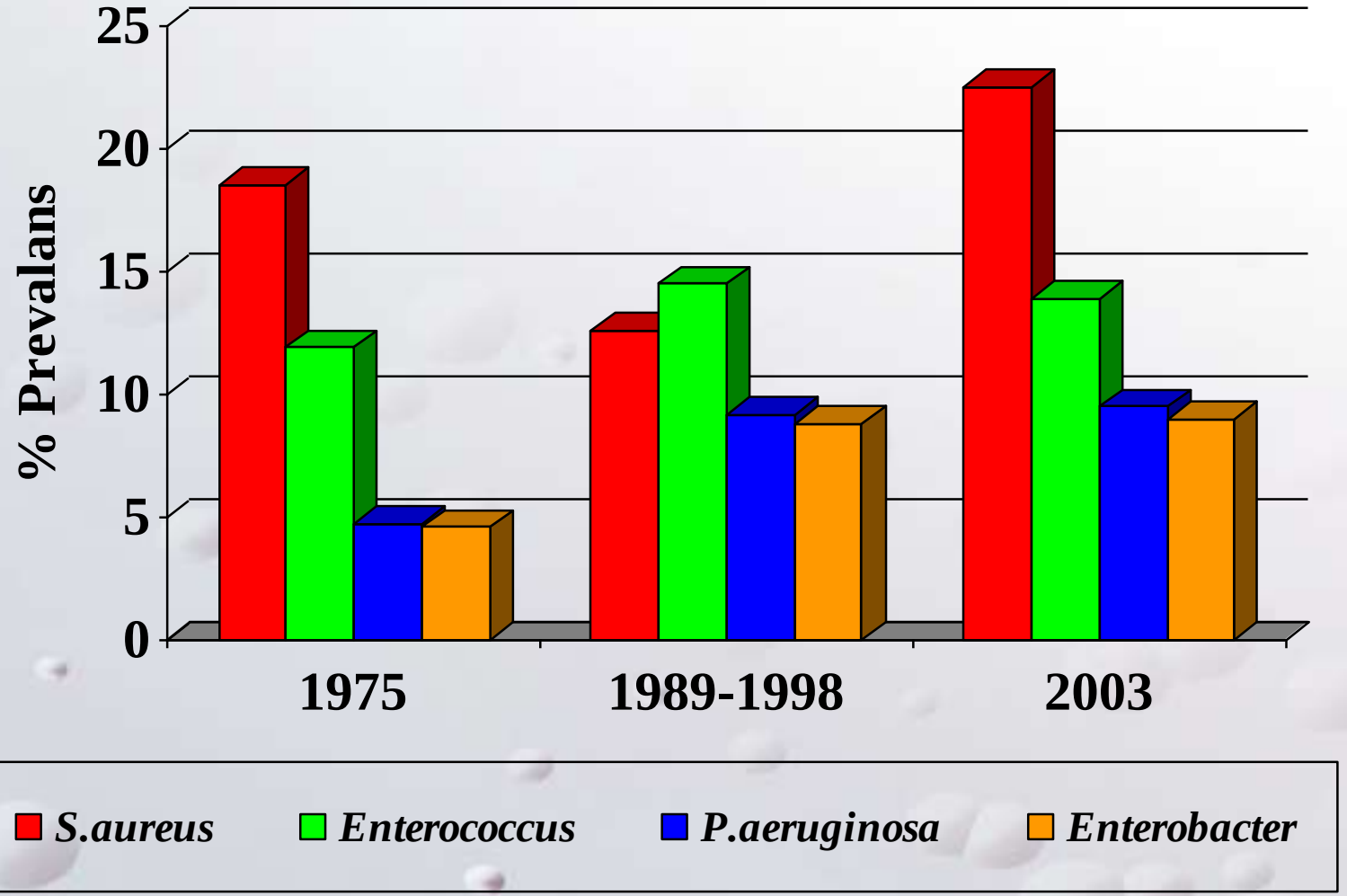
Figure 5. Infected Open Abdominal Incision



Visuals Unlimited, Inc. (www.visualsunlimited.com)

NNIS VERİLERİ: 1975-2003

Nozokomiyel CYDİ



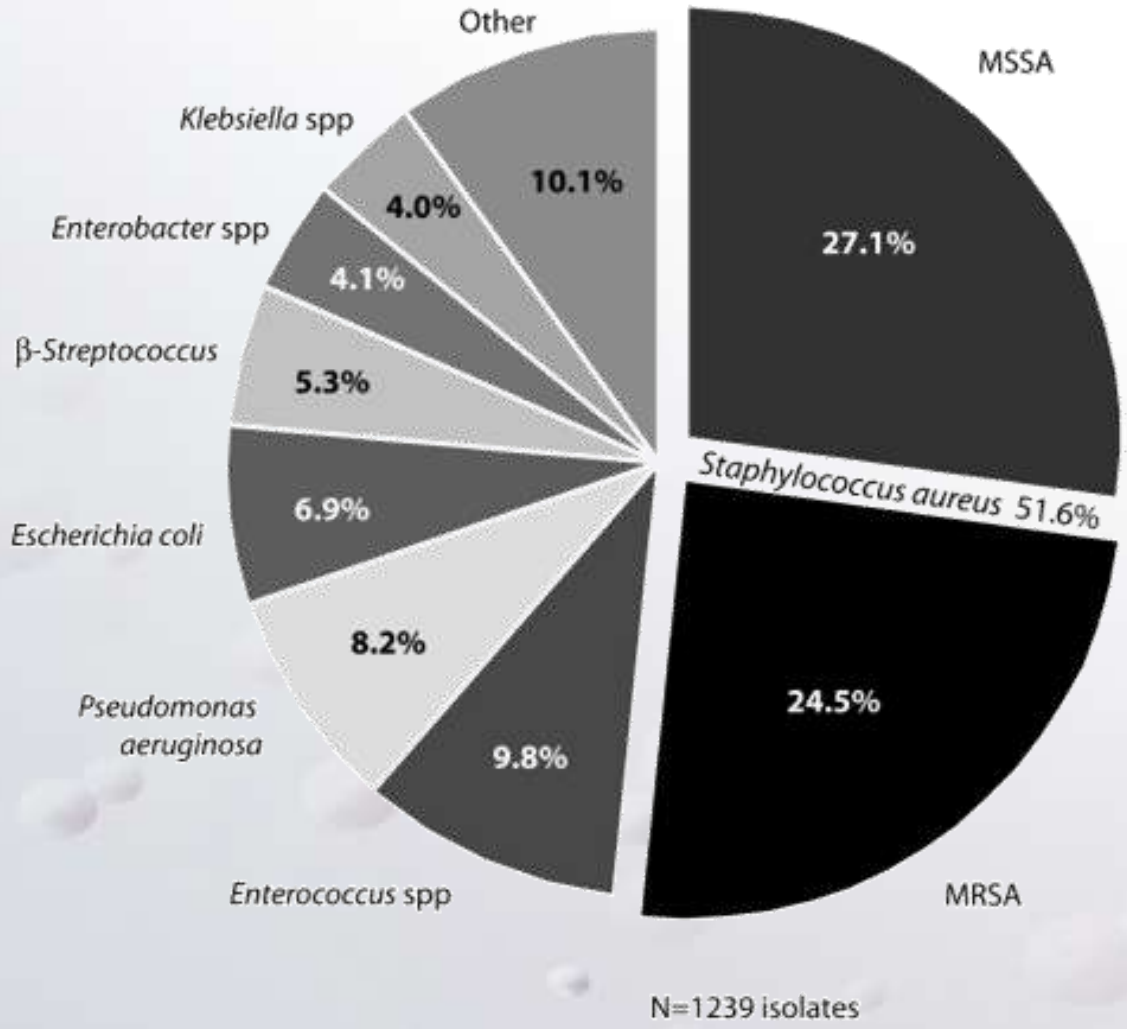
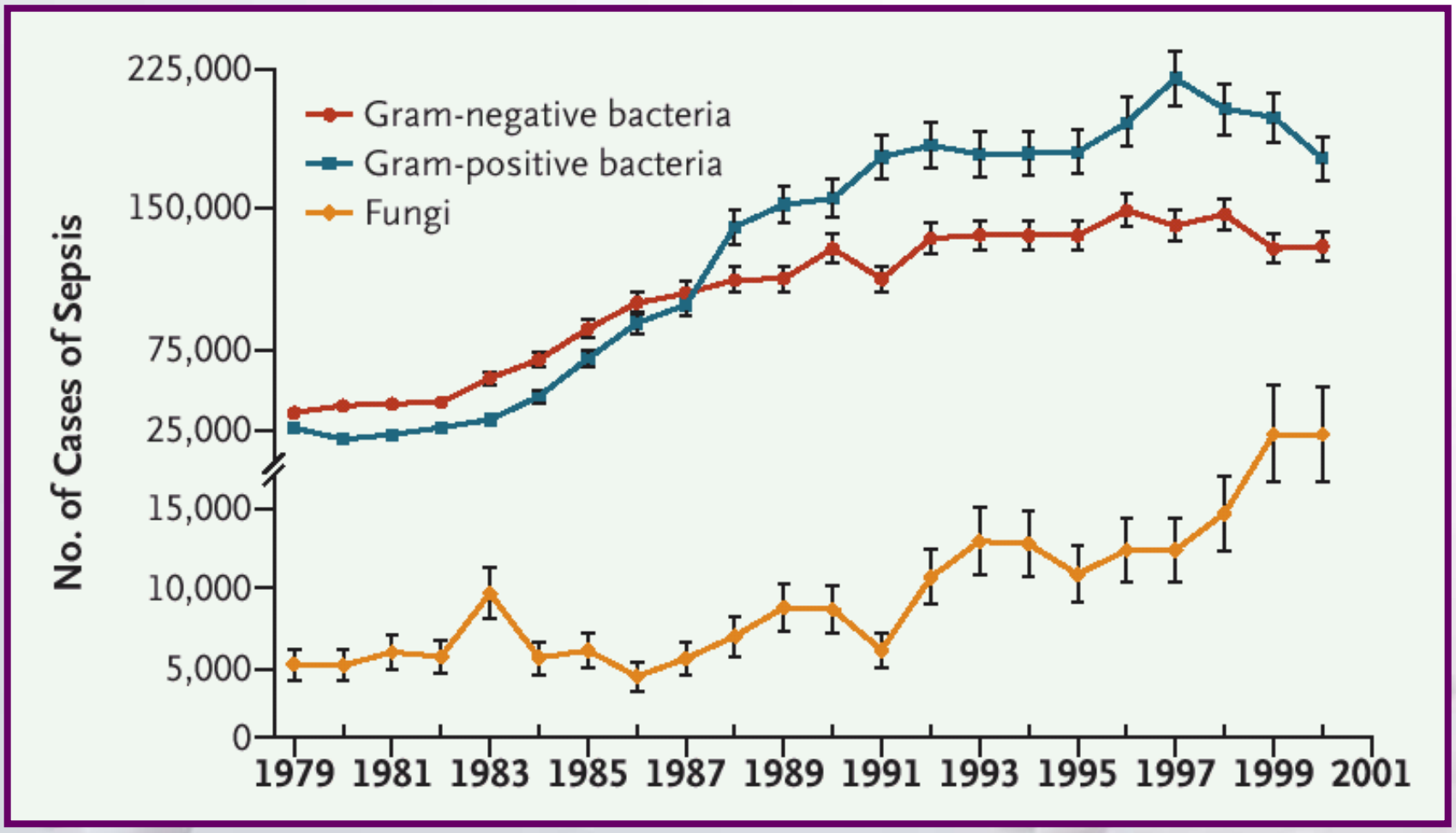


FIG. 1. Microbiology of skin and soft tissue infection isolates from SENTRY Antimicrobial Surveillance Program. Data are from U.S. and Canada, 2004 [10]. MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *S. aureus*.

Sepsis Nedeni Olan Etkenler



Martin GS, et al. N Engl J Med, 2003

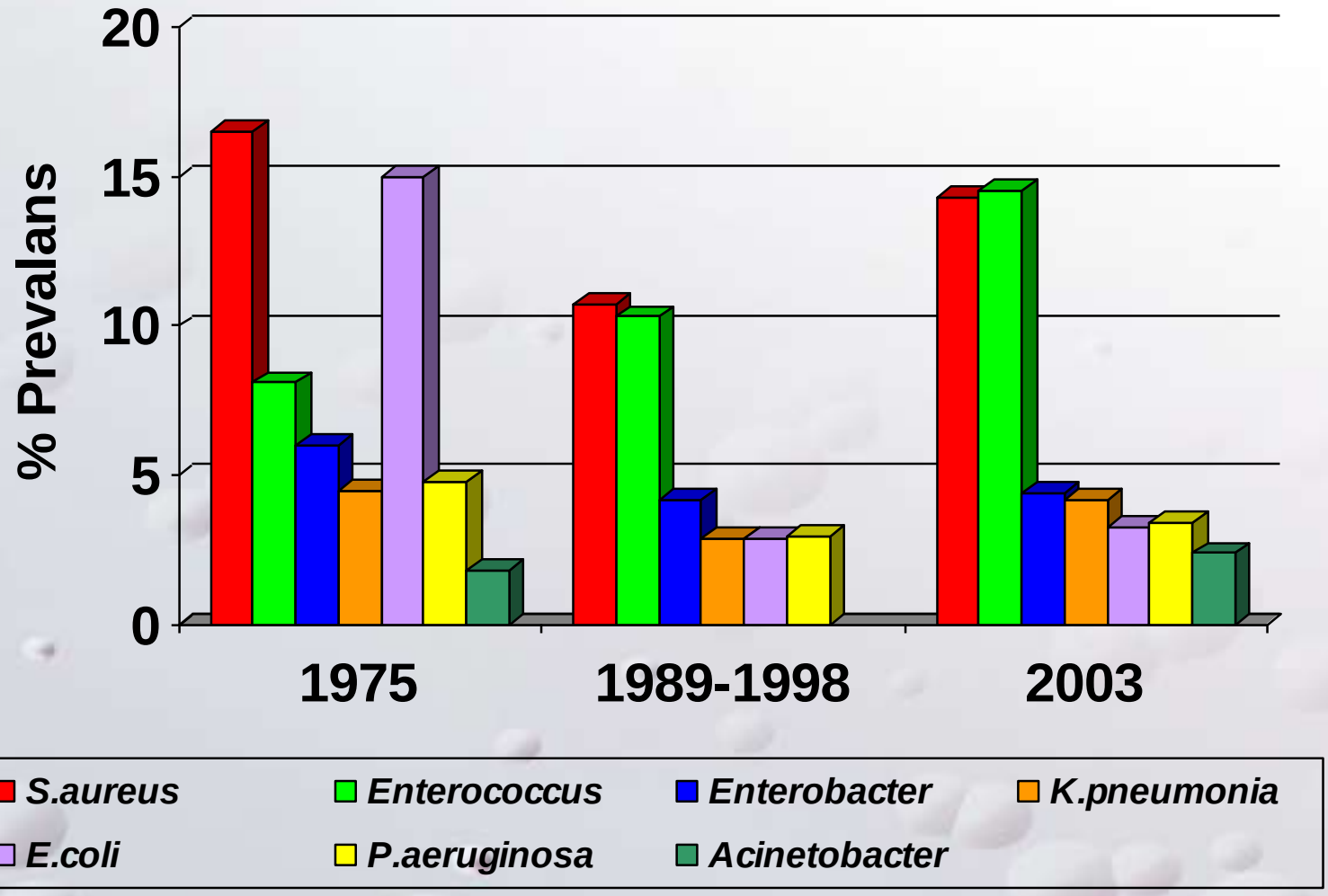
NOZOKOMİYAL KAN İNFEKSİYONLARININ İNSİDANSI VE DAĞILIMI

	İnsidans(%)	Mortalite
Koag(-)stafilokoklar	32	21
Staphylococcus aureus	16	25
Enterokoklar	11	32
Candida türleri	8	40
Escherichia coli	6	24
Klebsiella türleri	5	27
Enterobacter türleri	5	28
Pseudomonas türleri	4	33
Serratia türleri	1	26
Viridans streptokoklar	1	23

- *Edmond et al. Clin Infect Dis 1999*

NNIS VERİLERİ: 1975-2003

Nozokomiyel KDİ Etkenler



TK-MRSA

- TK-infeksiyonlarla ilişkili
- Hastanede yatan hastalarda yayım, NK-MRSA ilişkili KDİ'larının %40
- En sık CYDİ, nekrotizan pnömoni
- Risk Faktörleri
  - Yakın temas
  - Klasik risk faktörlerinin olmaması; yakın zamanlı antibiotik kullanımı, yakın zamanlı hastaneye yatış veya sağlık personeli teması, girişimsel uygulamalar; kateter, hemodializ, önceden MRSA kolonizasyonu
- Nekrotizan infeksiyona ilerleyebilir
- Şiddetli olmayan durumlarda
  - Eritromisin, klindamisin siprofloksasin, T/S

Kobayashi SD. Curr Opin Pharmacol 2009;9:545-51

Seybold U et al. Clin Infect Dis 2006;42:647-56

SENTRY-NK-CYDİ etkenleri

- En sık;
  - *S. aureus* %45.9 (TK-MRSA-%58-70)
  - *P. aeruginosa* %10.8
  - *Enterococcus* spp. %8.2
  - *E. coli* %7.0
  - *Enterobacter* spp. %5.8
  - *Klebsiella* spp. %5.1

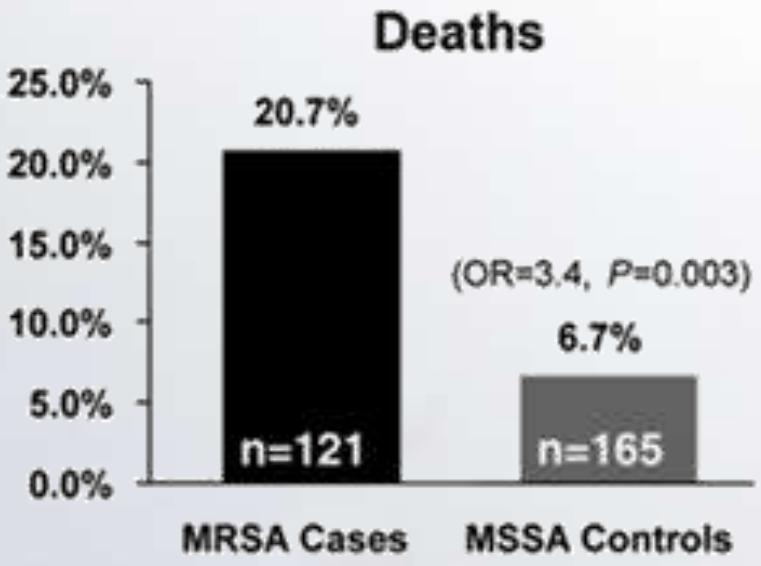
Rennie et al. Diagn Microbiol Infect Dis 2003;45:287-293.

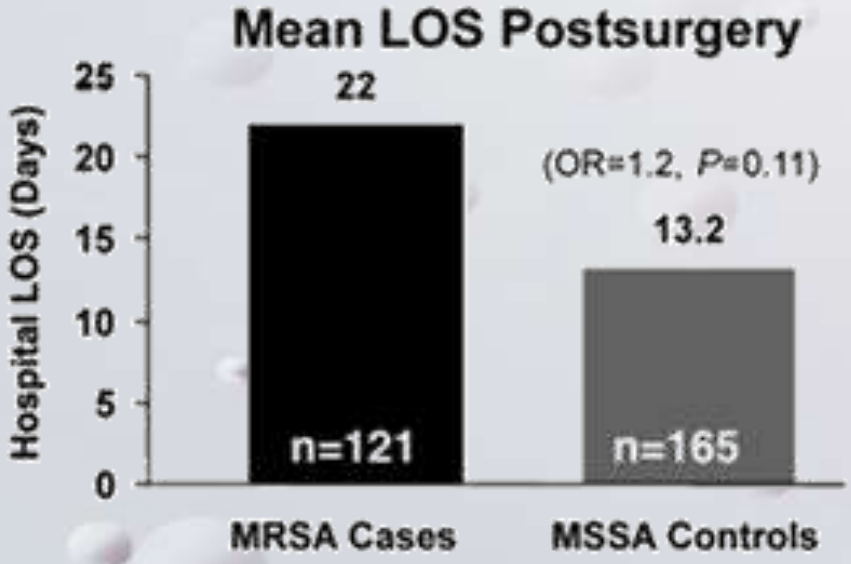
CYDİ-YAKLAŞIM
Önemli Adımlar

- Tanı ve tedavideki gecikmeleri önlemek
- Değerlendirmeler: Hastaneye yatırmak, antimikrobiyel tedavi başlamak, cerrahi konsultasyon
- Tedavi seçiminde: MRSA-ilişkili risk faktörleri (TK-MRSA artan önemi)

Merlino JI. Cleveland Clinic J Med 2007

Dryden MS. J Antimicrob Chemother 2010;65:35-44





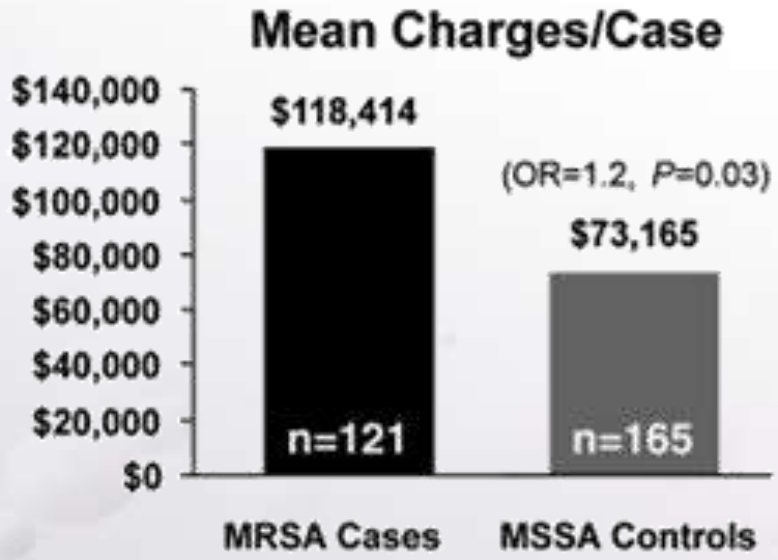


FIG. 3. Surgical site infections with methicillin-resistant *Staphylococcus aureus* (MRSA) are associated significantly with increased mortality rate, length of stay (LOS), and costs [44]. ME = multiplicative effects; MSSA = methicillin-sensitive *S. aureus*; OR = odds ratio.

GRAM-POZİTİF İNFEKSİYON TEDAVİSİNDE - GÜNCEL DURUM

- Lokal duyarlılıklar ve epidemiyoloji biliniyor
- Özel bir PK/PD profili gerekmiyor
- Nekrotizan olmayan ve toplumsal kökenli infeksiyonlarda

ANTİSTAFİLOKOKAL PENİSİLİN

Ne Zaman MDR – Stafilokokal İnfeksiyon?

- Pnömoni
- Nekrotizan yumuşak doku infeksiyonları
- Kronik osteomiyelit
- Bakteriyel endokardit + β-laktam allerjisi
- Yabancı cisim infeksiyonları
- β-laktam allerjisi


VANCOCIN
VANCOCIN HCl
500 mg

Stafilokoklarda glikopeptid direnci

- VRSA
- VISA
- GISA
- hVISA

Hepsi MRSA

Japonya 1996

ABD 1997

İngiltere, Fransa'da birkaç izolat

Vankomisin - Sorunlar

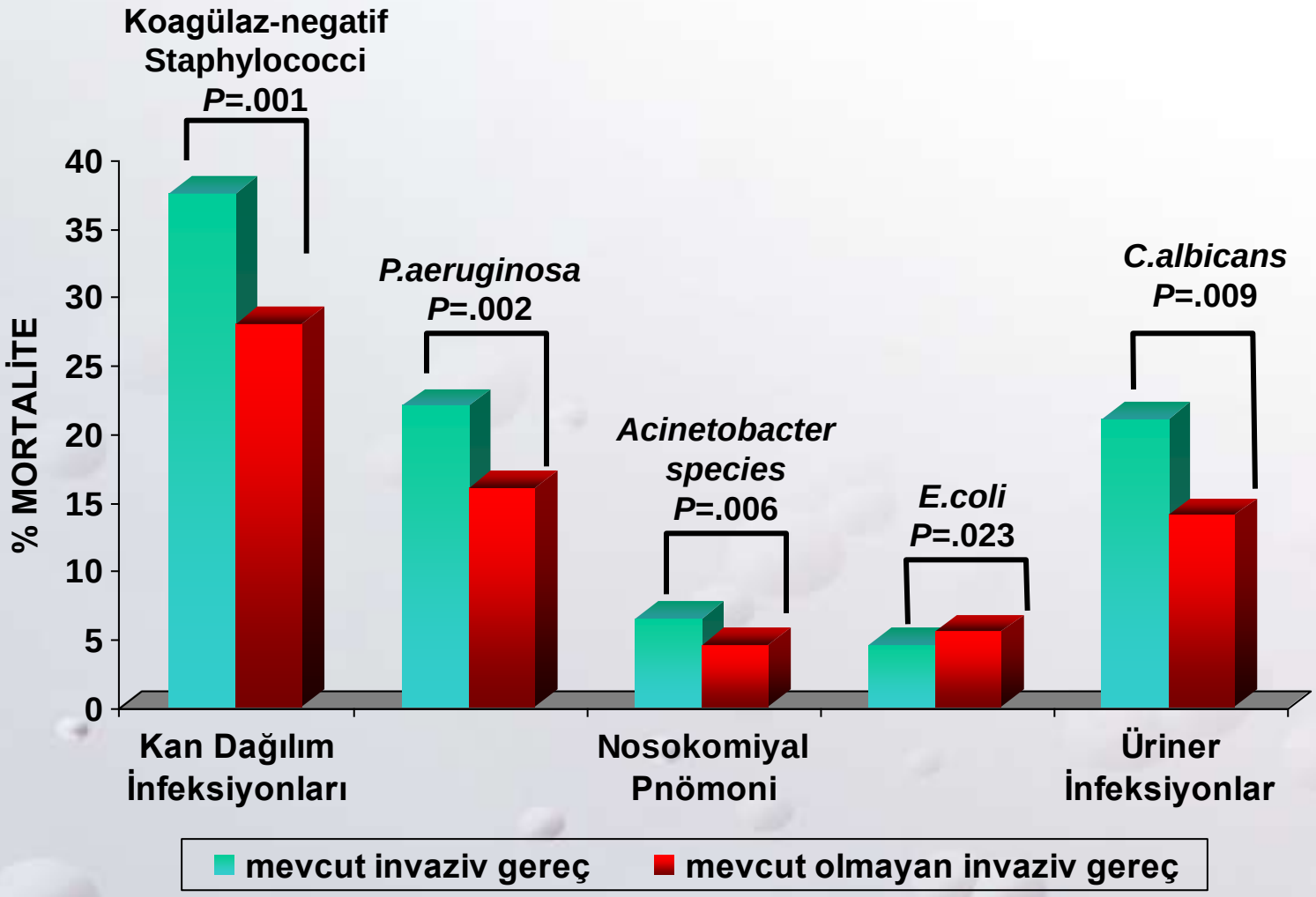
- Klinik başarısızlık
- Tembel antibiyotik → öldürmedeki gecikme / tolerans
- MIK'ler yükseliyor: CYDİ etkeni MRSA; 2003 %100 vs 2006 %62 MIC ≤ 0.5 mg/ml (%31 MIC ≤ 2 mg/ml)
- hVISA ve VISA suşlarında ↑
- PK/PD iyi değil: %10-20 doku konsantrasyonu ve gecikmiş geçiş

Levine D. Clin Infect Dis 2006;42
Napolitano LM. Surg Infect 2008:9

Table 4. Vancomycin and MRSA bacteraemia: MIC distribution of vancomycin for MRSA from bacteraemias in the UK, from the BSAC bacteraemia surveillance, 2001–06[60]

MIC (mg/L)	*n*	%
0.5	56	9.1
1	390	63.6
2	166	27.1
4	1	0.2

İnfeksiyon Bölgesi ve İnvazif Gereç Türüne Göre Spesifik Etkenler



Kolef M. CID 2000:31 (Suppl 4):131-8

Febril Nötropenik Hastalardan Kateterle İlişkili Kan Dolaşımı İnfeksiyonu Etkeni Olarak İzole Edilen Koagülaz-Negatif Stafilokok Türlerinin Teikoplanine Duyarlılıkları

Susceptibility to Teicoplanin among Coagulase-Negative Staphylococci Isolated from Catheter Related Bloodstream Infections in Febrile Neutropenic Patients

Özlem Güzel-Tunçcan, Derya Tozlu-Keten, Murat Dizbay, Esin Şenol
Gazi Üniversitesi, Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Ankara, Türkiye

Özet

Amaç: Febril nötropeni (FN) hastalarında özellikle koagülaz-negatif stafilokokların (KNS) etken olduğu kateterle ilişkili kan dolaşımı infeksiyonları (KİKDİ) sık görülmekte ve ampirik tedavide glikopeptidler sık kullanılmaktadır. Ancak son yıllarda glikopeptidlerin yoğun kullanımı nedeniyle başta *Staphylococcus haemolyticus* ve *S. epidermidis* olmak üzere KNS'ler arasında teikoplanine duyarlılığı azalmış suşlar bildirilmektedir. Bu çalışmada Hematoloji Servisi ve Kök Hücre Nakil (KHN) Birimi'nde üç yıl boyunca takip edilen hastalarda gelişen KİKDİ'lerden izole edilen KNS'lere karşı teikoplaninin minimal inhibitör konsantrasyon (MİK) düzeylerini araştırmayı amaçladık.

Yöntemler: Çalışmamızda 2007-2009 yılları arasında, Hematoloji ve KHN Birimi'nde takip edilen FN hastalarında gelişen KİKDİ'lerden izole edilen KNS izolatları yer almıştır. Oksasilin duyarlılığı disk difüzyon yöntemiyle, teikoplanin duyarlılıkları ve MİK düzeyleri ise E-test® yöntemiyle belirlenmiştir.

Bulgular: Otuz dokuz hastanın farklı FN ataklarından KİKDİ etkeni olarak izole edilmiş 96 KNS izolatı çalışmaya alınmıştır. Çalışmada en sık izole edilen KNS türü *S. epidermidis* (%46) olup ikinci sıklıkta *S. haemolyticus* (%39) tespit edilmiştir. Çalışılan suşlarda teikoplanin direnci saptanmamıştır. Ancak izolatların %10'unda orta düzeyde duyarlılık tespit edilmiştir. *S. haemolyticus* suşlarında teikoplanin MİK düzeyleri ve metisiline direnç oranı *S. epidermidis*'e göre daha yüksek saptanmıştır.

Sonuçlar: FN hastalarında KİKDİ'lerden izole edilen KNS'ler tür düzeyinde tanımlanmalı; klinik yanıtsızlık varsa, tedavi MİK düzeyi saptanarak düzenlenmelidir. *S. haemolyticus* başta olmak üzere KNS izolatları arasında teikoplanin MİK düzeylerinin yakın takibi gerekmektedir. *Klimik Dergisi 2010; 23(2): 44-7.*

Anahtar Sözcükler: Febril nötropeni, kateterle ilişkili kan dolaşımı infeksiyonu, koagülaz-negatif stafilokoklar, teikoplanin.

Abstract

Objective: Catheter related bloodstream infections (CRBSI) caused by coagulase-negative staphylococci (CNS) are frequent in patients with febrile neutropenia (FN) and glycopeptides are used empirically in the treatment of these infections. Recently, decreased susceptibility to teicoplanin among CNS has been reported, especially in *Staphylococcus haemolyticus* and *S. epidermidis*, due to excessive use of glycopeptides. In this study, we aimed to determine the minimal inhibitor concentrations (MICs) of teicoplanin and to compare its activity with other antibiotics on CNS isolated from CRBSI in patients with hematological malignancies and hematopoietic stem cell transplantation.

Methods: The study was performed on CNS strains isolated from CRBSI of FN patients during the period between 2007 and 2009. Susceptibility to oxacillin was tested by disk diffusion method, and teicoplanin MICs were determined by using E-test® method.

Results: A total of 96 CNS strains causing CRBSI, isolated from different FN attacks of 39 patients were analyzed. Among them, *S. epidermidis* (46%) and *S. haemolyticus* (39%) were the most frequent CNS species. Although teicoplanin resistance was not detected in the CNS isolates, 10% of the isolates revealed decreased susceptibility to teicoplanin. Teicoplanin MICs and methicillin resistance rates were found to be statistically higher among *S. haemolyticus* strains than those of *S. epidermidis*.

Conclusions: CNS isolated from CRBSI in FN patients should be identified to the species level, and the change of therapy in case of clinical failure should be made according to the MICs of antibiotics. Teicoplanin MICs among CNS, especially in *S. haemolyticus*, should be closely monitored. *Klimik Dergisi 2010; 23(2): 44-7.*

Key Words: Febrile neutropenia, catheter related bloodstream infection, coagulase-negative staphylococci, teicoplanin.

VANKOMİSİN-TEDAVİ BAŞARISIZLIĞI

- MSSA bakteremisi
  - Vankomisin %20
  - Nafsilin %4
- MRSA infeksiyonları
  - İnfektif endokardit: %10-31
  - Bakteremi: %40-58
  - Nozokomiyel pnömoni: %35.5

- *Chang FY. Medicine 2003;82:333*
- *Fowler Jr VG, et al. NEJM 2008;355:653*

VANKOMİSİN TEDAVİ BAŞARISIZLIKLARI

- Cr.Cl <10 ml/dk, %20 tedavi başarısızlığı
- Hemodializ hastalarında-Vanko vs β-laktam, Vanko-MSSA infeksiyonlarında daha başarısız
- hVISA,VISA, tedavi başarısızlığı %76
- MIC>1 mg/L, bakteremi tedavisinde, empirik vankomisin ile mortalite yüksek
- Yüksek infeksiyon yükü; endokardit, derin apse, protez infeksiyonu

Mosa-Broader PA. Clin Infect Dis 2004:38:1700-5

Stryjewski ME. Clin Infect Dis 2007;44:190-6

Soriano A. Clin Infect Dis 2008;46:193-200

TABLE 1. SITUATIONS IN WHICH THE USE OF VANCOMYCIN SHOULD BE DISCOURAGED.*

Routine prophylaxis
Surgical patients without life-threatening allergy to beta-lactam antibiotics[34]
Low-birth-weight infants[35]
Patients on dialysis[36,37]
Patients with neutropenia
Patients with central venous catheters[36,38-43]
Empirical treatment
Febrile patients with neutropenia who are not at high risk for resistant gram-positive infection[44-50]
Febrile low-birth-weight infants
Decontamination of the digestive tract
Treatment based on indications
Patients with single blood cultures positive for coagulase-negative staphylococci[51-53]
Patients colonized with methicillin-resistant *S. aureus*[54,55]
Patients with *Clostridium difficile* colitis (first-line therapy)[56]
Patients on dialysis for whom convenience in treating infections is desirable[57-60]
Patients with gram-positive infections not due to resistant organisms

*Data are from the Hospital Infection Control Practices Advisory Committee.[33]

VANKOMİSİN-OPTİMAL KULLANIM

- Serum düzeyleri; >10mg/L, MIC >1mg/l ise >15-20 mg/l
- Vücut ağırlığı ile hesaplama; 15-20 mg/kg 8 saatte bir
- MIC >2 mg/L ise olağan dozlarla tedavi başarısızlığı
- İnfeksiyon yükü: endokardit, osteomyelit, menenjit

Rybak MJ. Clin Infect Dis 2009;49:3:325-7

Medscape

Source: Expert Rev Clin Pharmacol © 2009 Expert Reviews Ltd

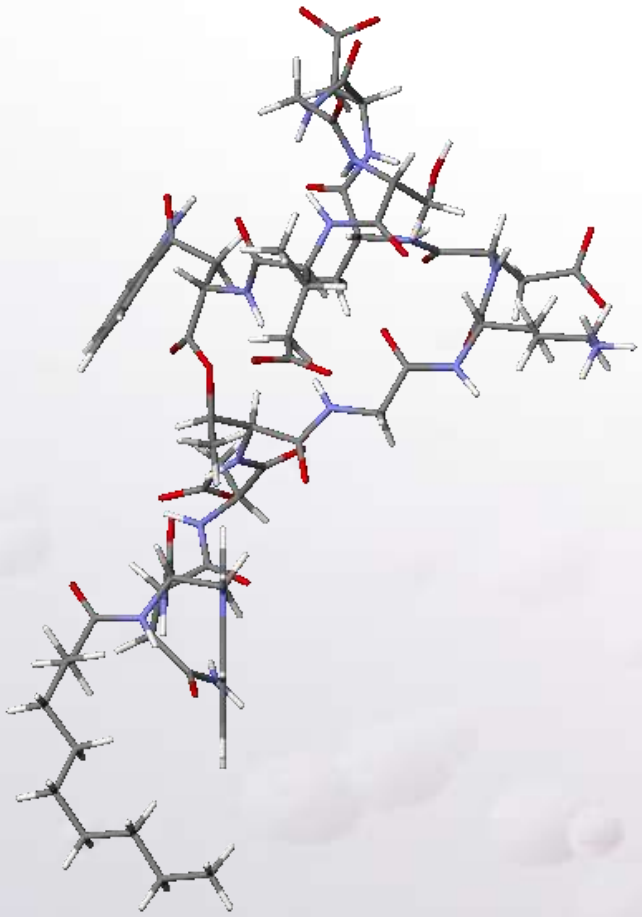
TABLE 4
Pros and cons of drugs active against MRSA

Drug	Pros	Cons
Trimethoprim-sulfamethoxazole (various)	High efficacy, oral form, inexpensive	
Tetracycline (various)	High efficacy, oral form, inexpensive	Contraindicated in pregancy
Clindamycin (various)	Oral form, inexpensive	Effective vs community-acquired strains only, *Clostridium difficile*–associated colitis
Vancomycin (various)	High efficacy	IV only, ototoxicity, nephrotoxicity, expensive
Linezolid (Zyvox)	High efficacy, oral form	Myelosuppression (reversible), expensive
Daptomycin (Cubicin)	High efficacy, bactericidal	IV only
Gentamicin (various)		Moderate efficacy vs hospital-acquired strains, IV only, nephrotoxicity, ototoxicity
Tigecycline (Tygacil)	Active vs both gram-positive and gram-negative bacteria	IV only, expensive, contraindicated in pregnant women and children

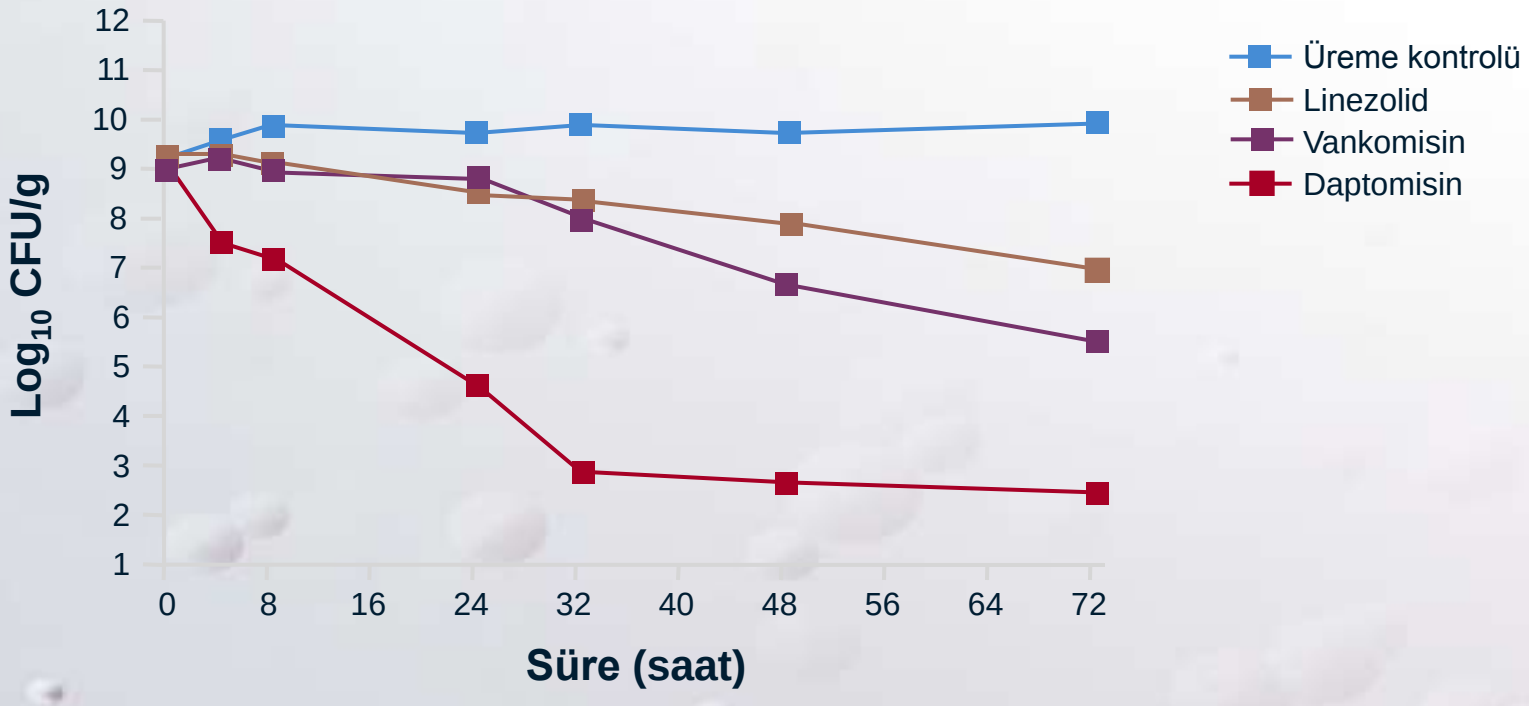
MRSA = methicillin-resistant *Staphylococcus aureus*; IV = intravenous

DAPTOMİSİN

- *Streptomyces roseosporus*
- 1985-Lilly
- 1997 yeniden,tek doz
- Lipopeptid
- Hızlı bakterisidal
- Durağan fazdaki bakterilere etkili



Daptomisinin *in vitro* olarak vankomisin ve linezolidle karşılaştımalı bakterisidal etkinliği

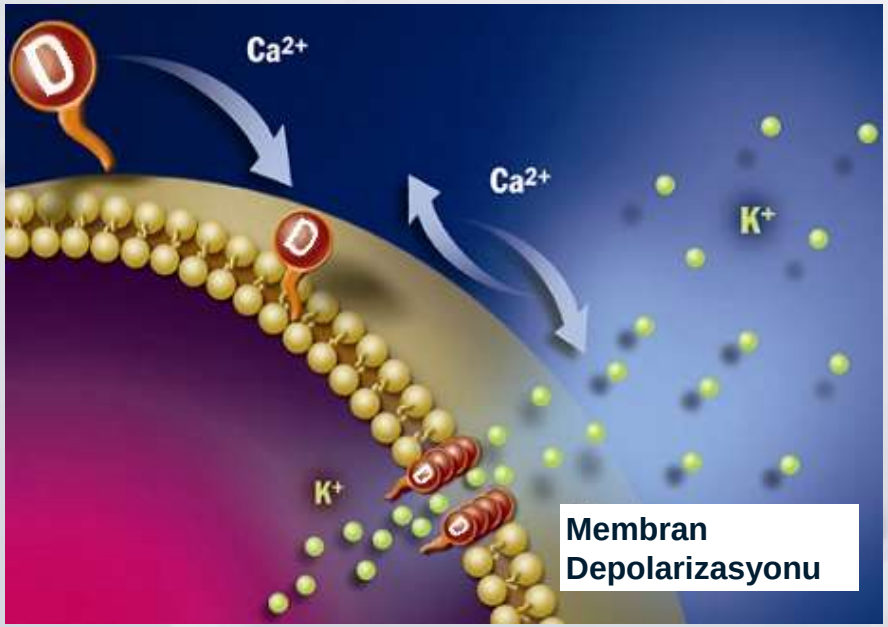


Yüksek inokulumlu MRSA kullanılmıştır

LaPlante KL & Rybak MJ. Antimicrob Agents Chemother 2004;48:4665–4672

DAPTOMİSİN-ETKİ MEKANİZMASI

- Bakteri hücre membran depolarizasyonu-Ca bağımlı bir etki
- Lizis olmadan hızlı hücre ölümü
- Konsantrasyona bağlı; AUC/MIC ve Cmax/MIC önemli



DAPTOMİSİN PK/PD ÖZELLİKLER

- Lineer PK, Y.Ö.: 8-9 saat, PAE ~5 sa
- 4-6 mg/kg, tek doz, 30 dk'lık infüzyon
- 8-10 mg/kg güvenli
- %80 idrarla atılım
- %90 proteine, geri dönüşümlü bağlanma
- Surfaktan ile inaktive
- C-P450 etkileşimi yok
- Dağılım hacmi düşük; 0.1 L/kg

Farmakokinetik parametreler[1]

12 mg/kg'a kadar lineer bir farmakokinetik gösterir.[2]

Cubicin® Dozu (i.v.)	C_{max} (mg/l)	$AUC_{0-\infty}$ (mg-s/ml)	T_{max} (s)	$T_{1/2}$ (s)
4 mg/kg	54.6	425.3	0.5	7.4
6 mg/kg	86.4	705.4	0.5	7.8

1. EMEA 2006 Scientific Discussion
2. Cubicin Kısa Ürün Bilgisi

Daptomisin - Endikasyonlar

- Komplike cilt ve yumuşak doku enfeksiyonları (kCYDİ) - 2003
- *Staphylococcus aureus* bakteriyemisi (SAB)
- Sağ kalp infektif endokarditi - 2006

TABLE 3. CLINICAL TRIAL RESULTS FOR TREATMENT OF COMPLICATED SKIN AND SOFT TISSUE INFECTIONS CAUSED BY METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Antibiotic	*Comparator*	*Experimental design*	*Total patients*	*No. of patients*	*Outcome in MRSA patients: agent vs. comparator*	*Outcome in all patients: agent vs. comparator*
Linezolid[42a]	Vancomycin	Open-label	1,180	285	Clinical cure[43]: 94.0% vs. 83.6% Microbiol. cure: 88.6% vs. 66.9%	Clinically evaluable: 94.4% vs. 90.4%
Daptomycin[55a]	Vancomycin	Double-blind	1,092	64	75.0% vs. 69.4%	Clinically evaluable: 83.4% vs. 84.2%
Tigecycline[61a]	Vancomycin	Double-blind	1,116	65		Clinically evaluable: 86.5% vs. 88.6%
Dalbavancin[68b]	Linezolid	Double-blind	854	278	91% vs. 89%	88.9% vs. 91.2%
Telavancin[72b]	Vancomycin	Double-blind	1,867	579	Clinical cure: 90.6% vs. 86.4% Microbiol. cure: 90% vs. 85%	Clinically evaluable: 88% vs. 87%
Ceftobiprole[64b]	Vancomycin	Double-blind	784	121	91.8% vs. 90.0%	Clinical cure ITT: 77.8% vs. 77.5% Clinically evaluable: 93.3% vs. 93.5%
Ceftobiprole[62b]	Vancomycin + ceftazidime	Double-blind (included diabetic foot infections)	828	123	89.7% vs. 86.1%	Clinical cure ITT: 81.9% vs. 80.8% Clinically evaluable: 90.5% vs. 90.2%
Iclaprim[80b]	Linezolid	Double-blind	497	70% of pathogens were *Staphylococcus aureus*, 25% of which were MRSA		Clinical cure ITT: 85.5% vs. 91.9% Clinically evaluable: 93.8% vs. 99.1% Microbiol. cure: 93.8% vs. 98.8%
Iclaprim[80b]	Linezolid	Double-blind	494	~60% of pathogens were *S. aureus*, 50% of which were MRSA	Microbiol. cure MRSA: 77.0% vs. 80.0%	Clinical cure ITT: 84.9% vs. 87.2% Clinically evaluable: 89.6% vs. 96.4% Microbiol. cure: 83.5% vs. 84.7% MSSA 77% vs. 80% MRSA

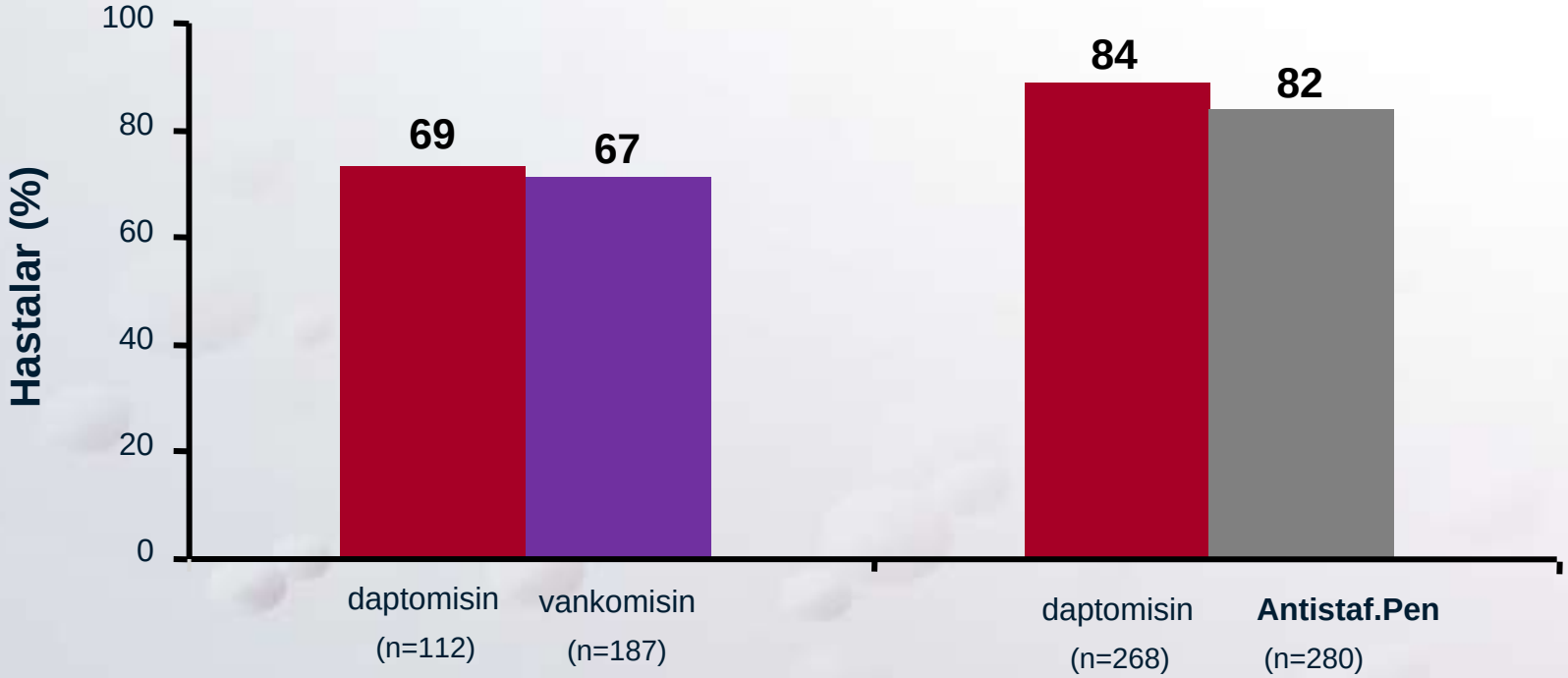
[a]Food and Drug Administration–approved for treatment of cSSTI caused by MRSA.
[b]Investigational agent.
Microbiol. = microbiological; MRSA = methicillin-resistant *Staphylococcus aureus*; ITT = intent to treat; MSSA = methicillin-sensitive *S. aureus*; cSSTI = complicated skin and soft tissue infection.

CYDİ - DAPTOMİSİN

- Dapto vs Vanko/Antistafilokokal Penisilin
- Daptomisin ile daha hızlı tedavi yanıtı elde edilmiştir
- Çok çeşitli kCYDİ larının tedavisinde karşılaştırma ilaçları kadar etkilidir
- Yan etki profili karşılaştırma ilaçlarına benzerdir

Arbeit et al. Clin Infect Dis 2004;38 (12);1673-81

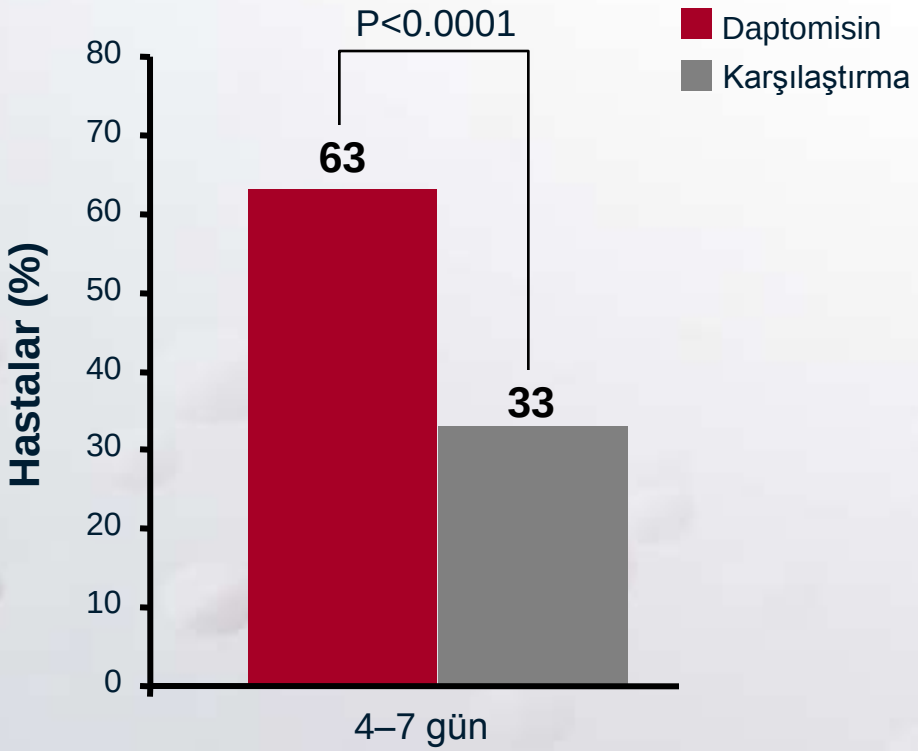
kCYDİ - faz III çalışma: Klinik başarı



***İyileşme testi değerlendirmesinde (son çalışma ilacı dozunun alınmasından 6-20 gün sonra) antibiyotik tedavisini durduracak düzeyde iyileşme ya da düzelme**

Arbeit RD et al. Clin Infect Dis 2004;38:1673–1681

kCYDİ faz III çalışma:

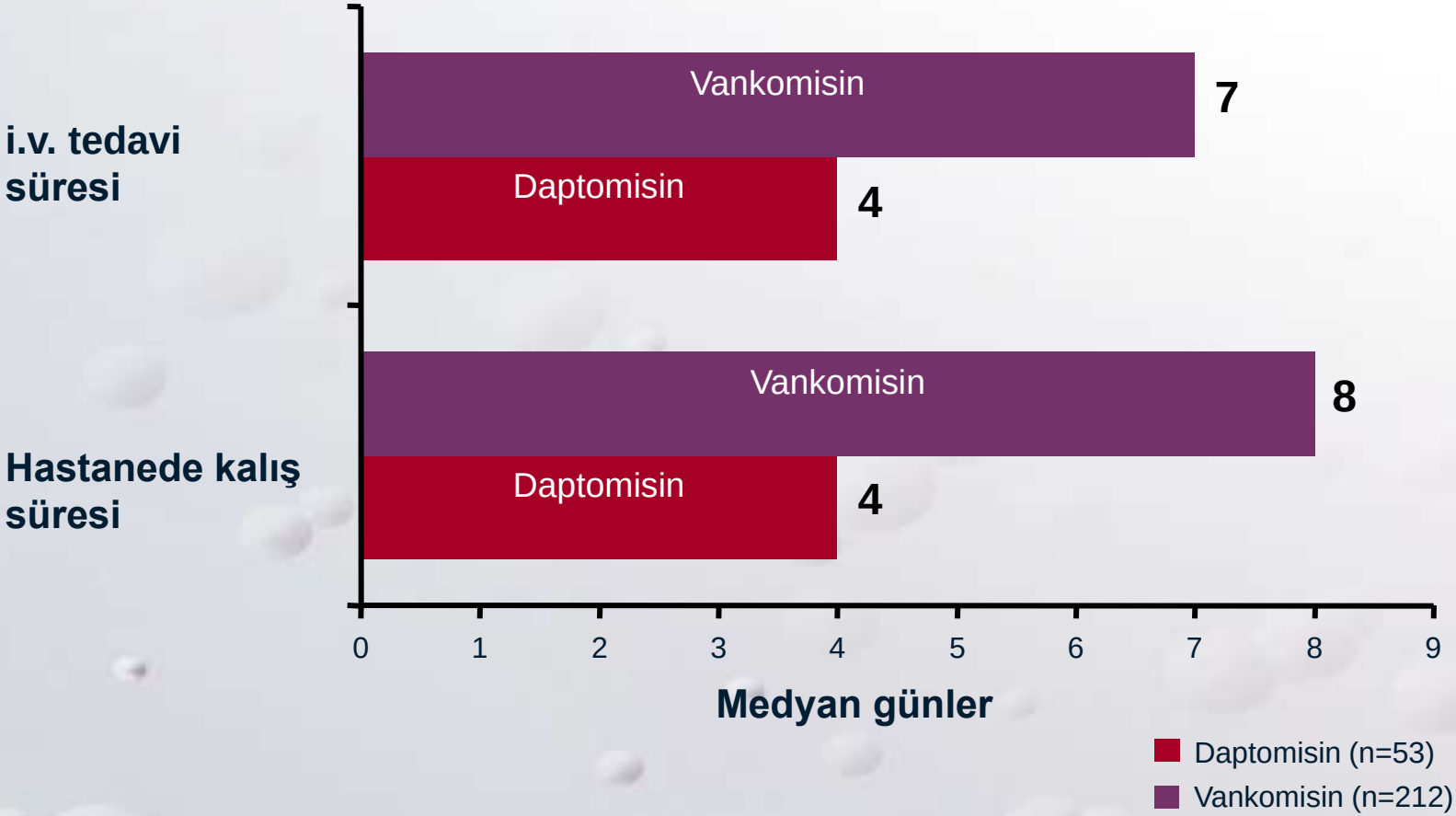


***Tek başına i.v. tedaviyle başarılı biçimde tedavi edilen hastalar (ITT popülasyonunun %89.8'i)**

Arbeit RD et al. Clin Infect Dis 2004;38:1673–1681

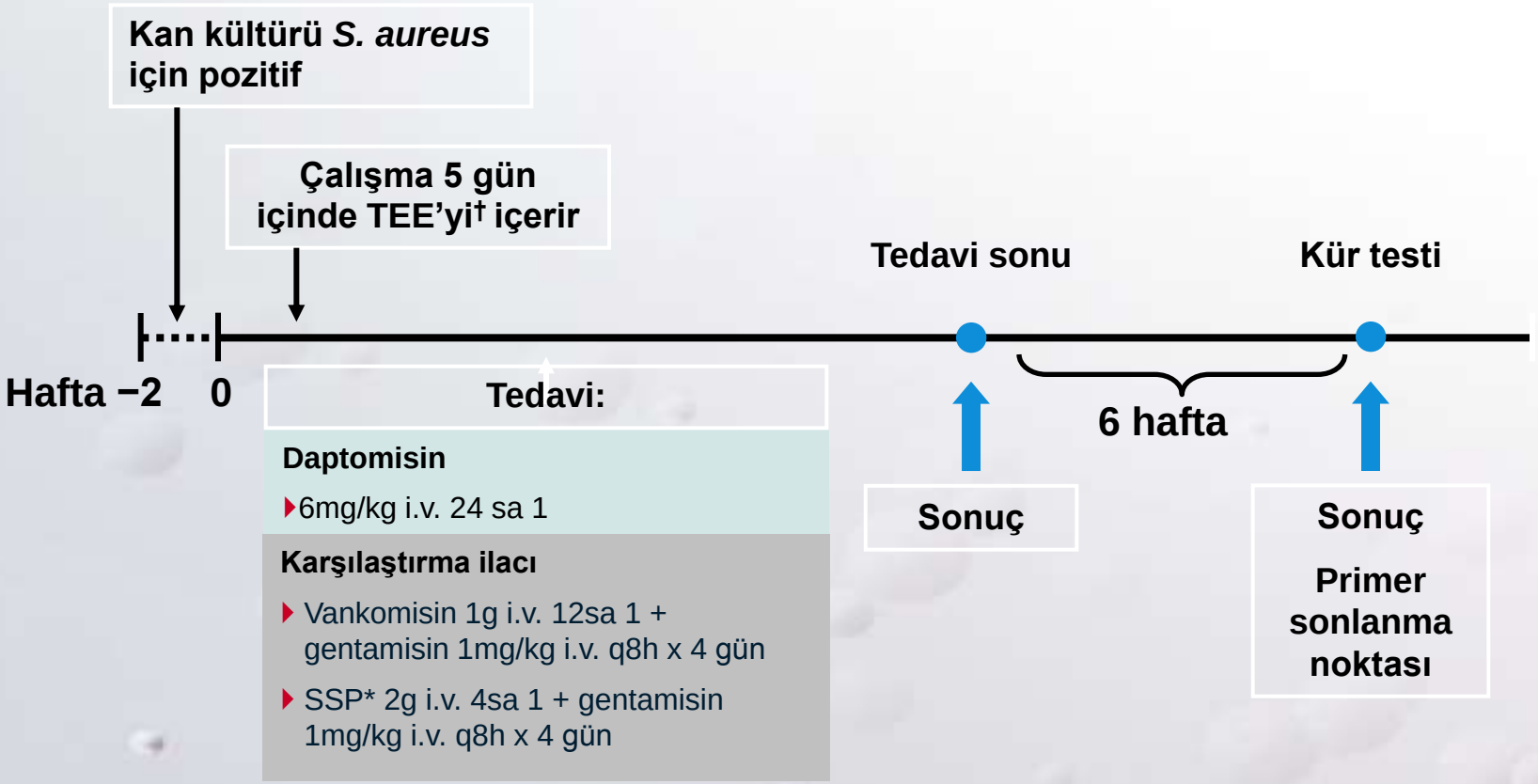
kCYDE'da tedavi ve hastanede kalış sürelerinin karşılaştırılması

MRSA bulunan 265 hasta ile vaka-kontrol çalışması



Davis SL et al. Pharmacotherapy 2007;27:1611–1618

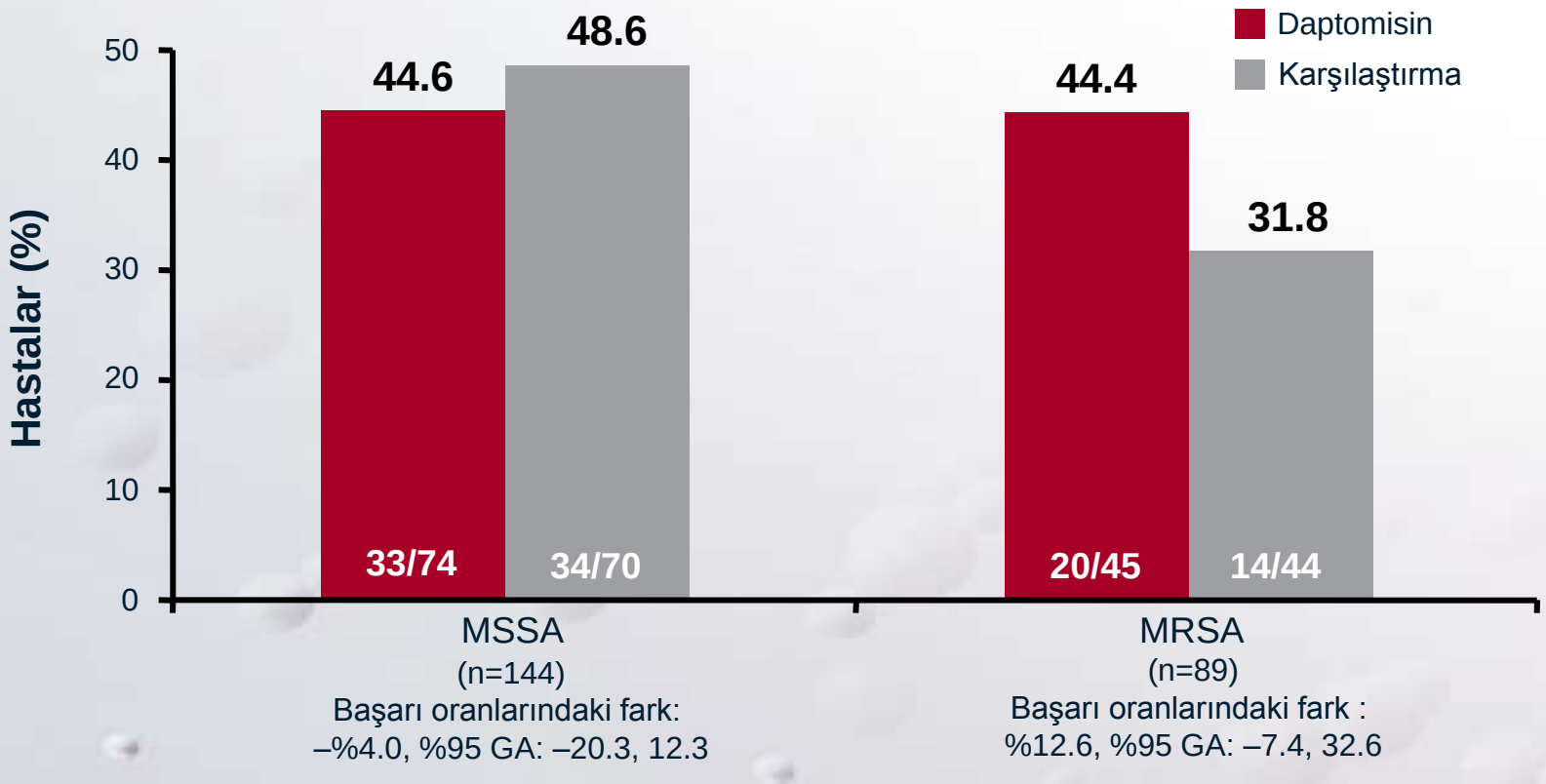
Faz III SAB/EE
Dört ülkede 44 merkez, 2002-2005



*Nafsilin, oksasilin ya da flukloksasilin, †TEE: transözofageal ekokardiyogram

Fowler VG et al. N Engl J Med 2006;355:653–665

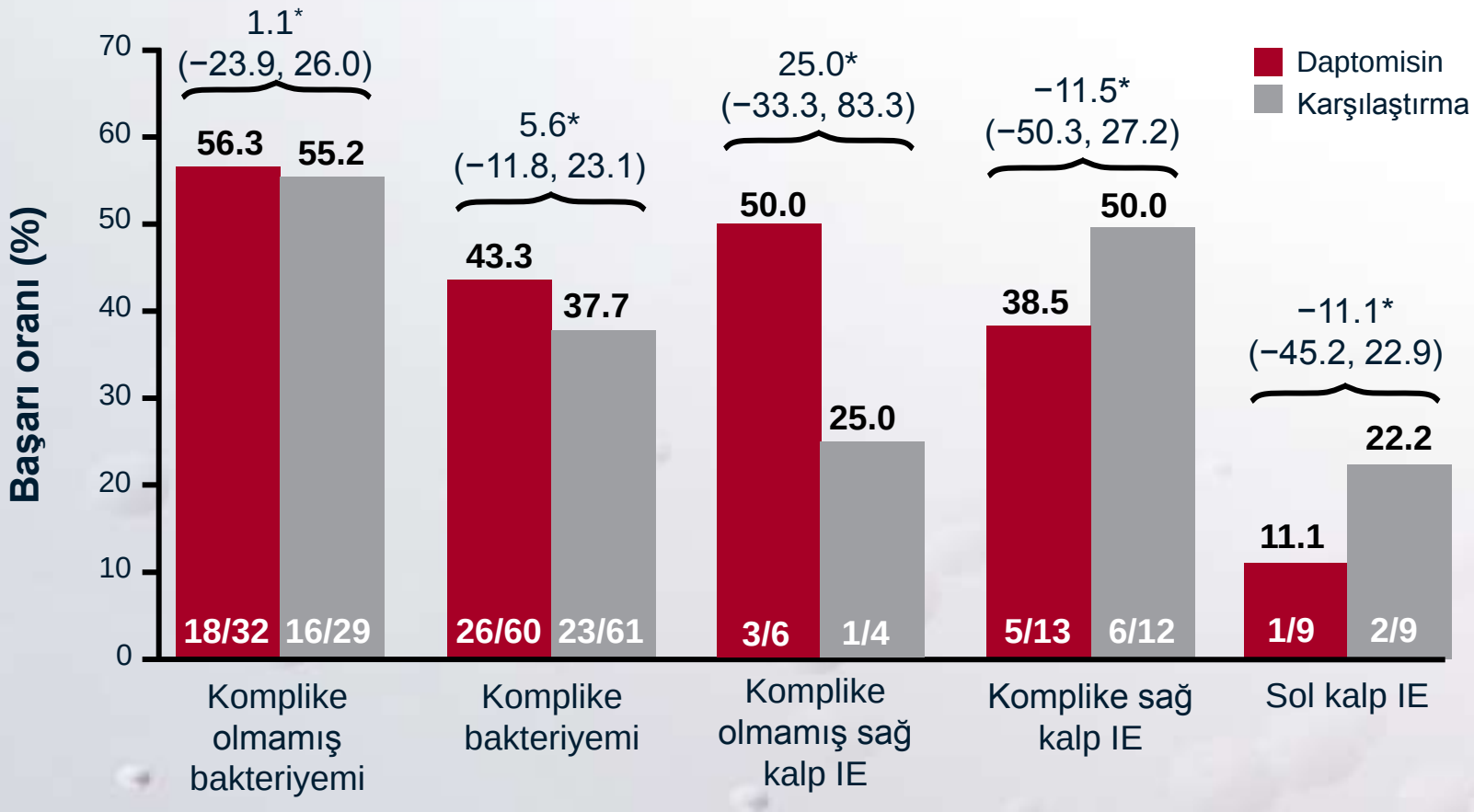
Faz III SAB/EE çalışması: klinik başarı*



***Çalışmanın sona ermesinden 6 hafta sonraki vizitte klinik başarı. Başarısızlık, klinik başarısızlık, mikrobiyolojik başarısızlık, ölüm, kan kültürü elde edilememesi, potansiyel olarak etkili olabilecek olan çalışma dışı antibiyotikler alınması ya da çalışma ilacının erken bırakılması şeklinde tanımlanmıştır.**

Fowler VG et al. N Engl J Med 2006;355:653–665

Faz III SAB/EE çalışması: son tanıya† göre MRSA'da 6 haftalık kür testinde başarı oranları



†Son tanı şu şekildedir: %26 komplike olmamış bakteriyemi; %51 komplike bakteriyemi, %15 sağ-taraflı IE, %8 sol-taraflı IE

***Başarı oranlarındaki fark (%95 GA)**

Fowler VG et al. N Engl J Med 2006;355:653–665

Host defence mechanisms

Lowered phagocytosis

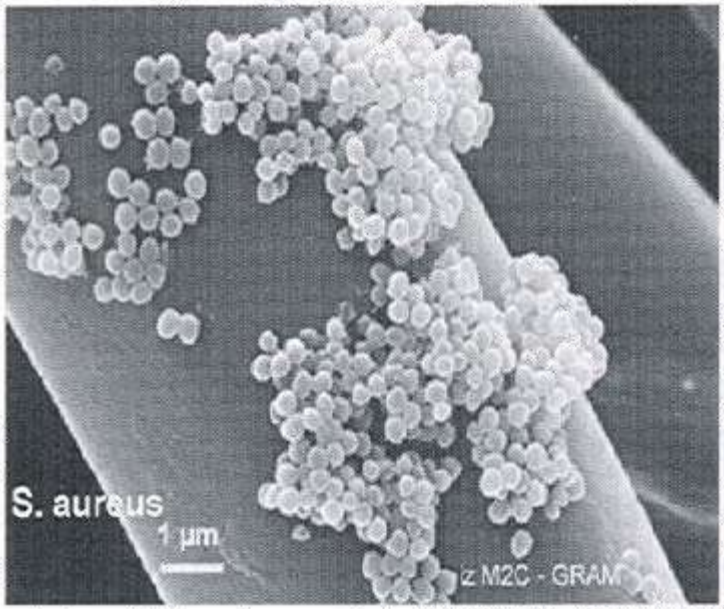
uneffective

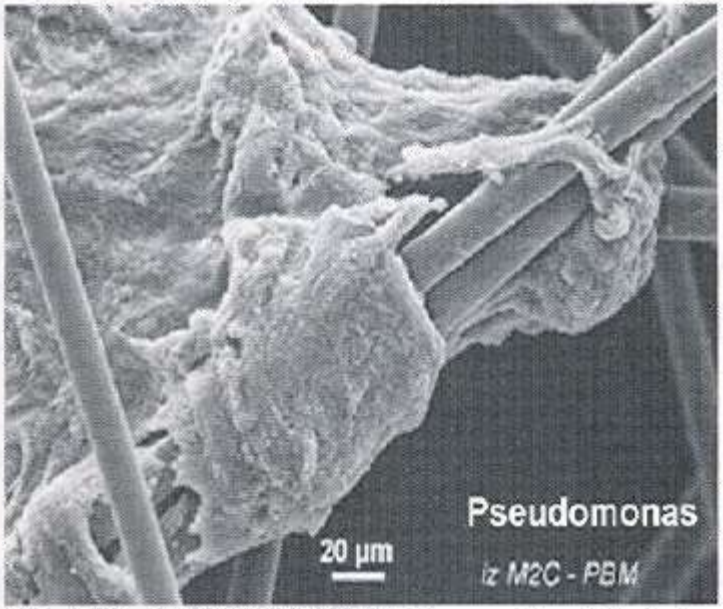
Antimicrobials

less active

10 –1000 times less susceptible to antimicrobials than planktonic cells

Bacterial biofilm on infected device





Altered pharmacodynamic parameters

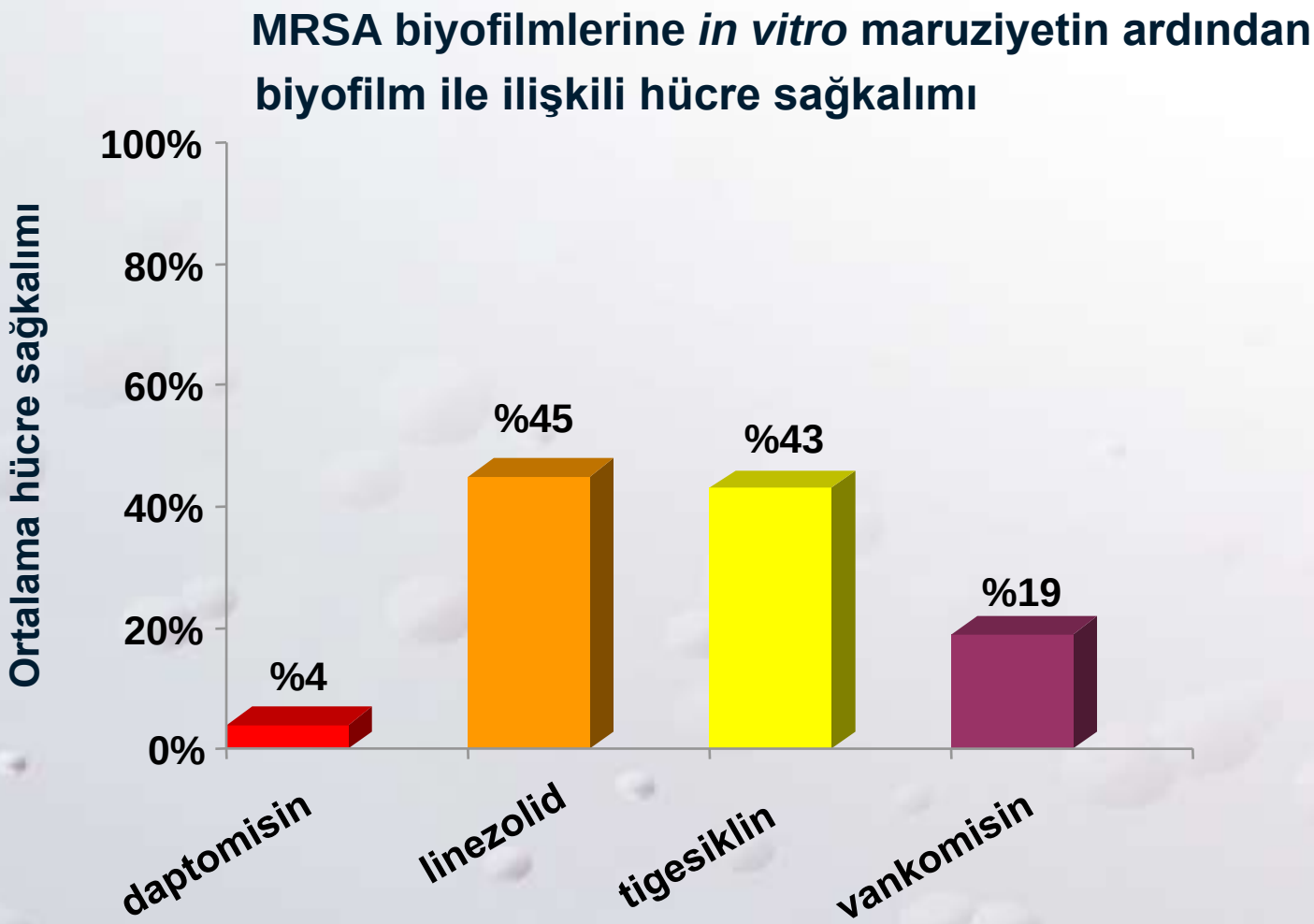
Resistance of bacterial biofilms to phagocytes and antimicrobials

Stafilokokal Biofilm Varlığında Antimikrobiyal Ajanların Etkinliğinde Azalma

Antimikrobiyal ajan	Etkinlikte azalma (%)
Clindamycin	1,4
Rifampin	0,99
Fusidic acid	4,4
Trimethoprim-sulfamethoxazole	4,8
Doxycycline	10
Gentamicin	9,8
Netilmicin	11
Ofloxacin	13
Ciprofloxacin	9,5
Daptomycin	9,1
Teicoplanin	52
Vancomycin	63

Souli M, et al. AAC 1998;42:939

Daptomisinin biyofilm etkinliği



Smith et al. Int J Antimicrob Agents 2009;33:374–378

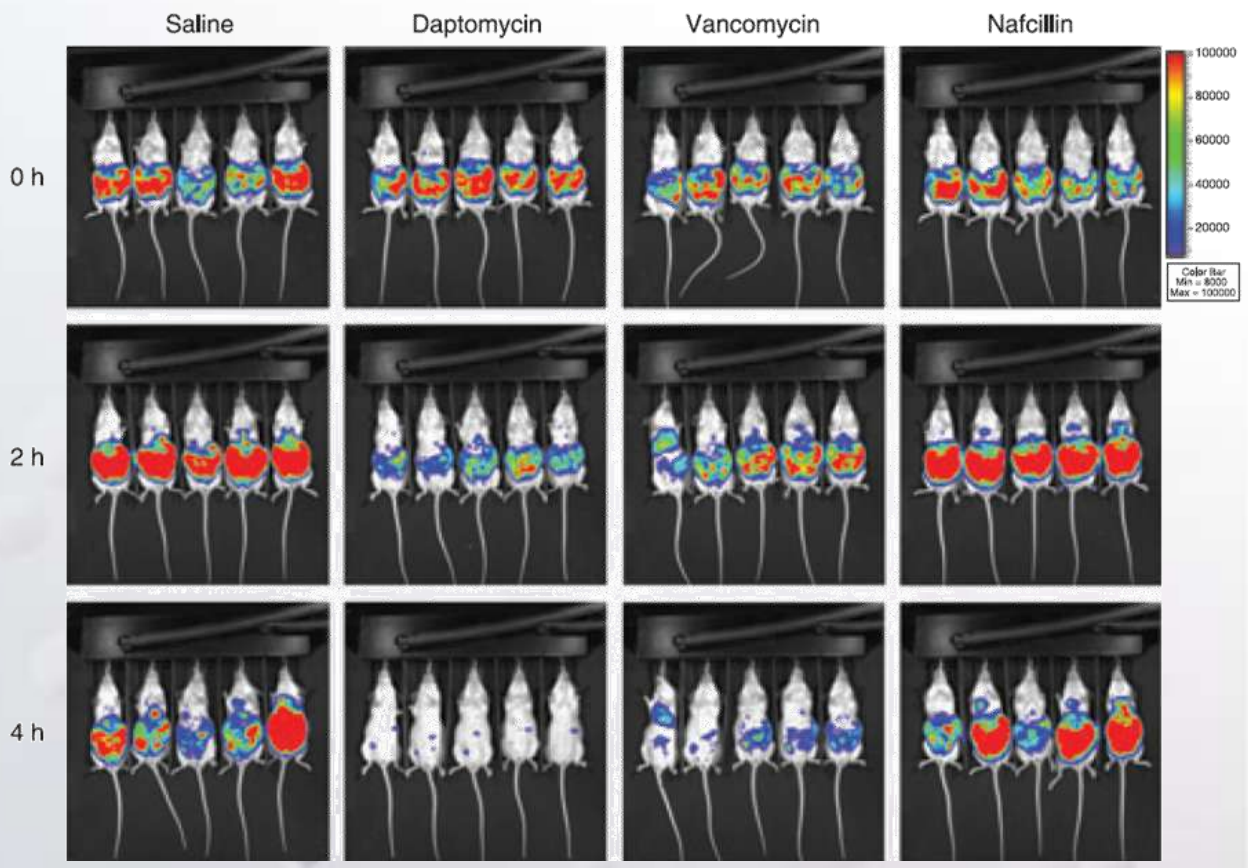
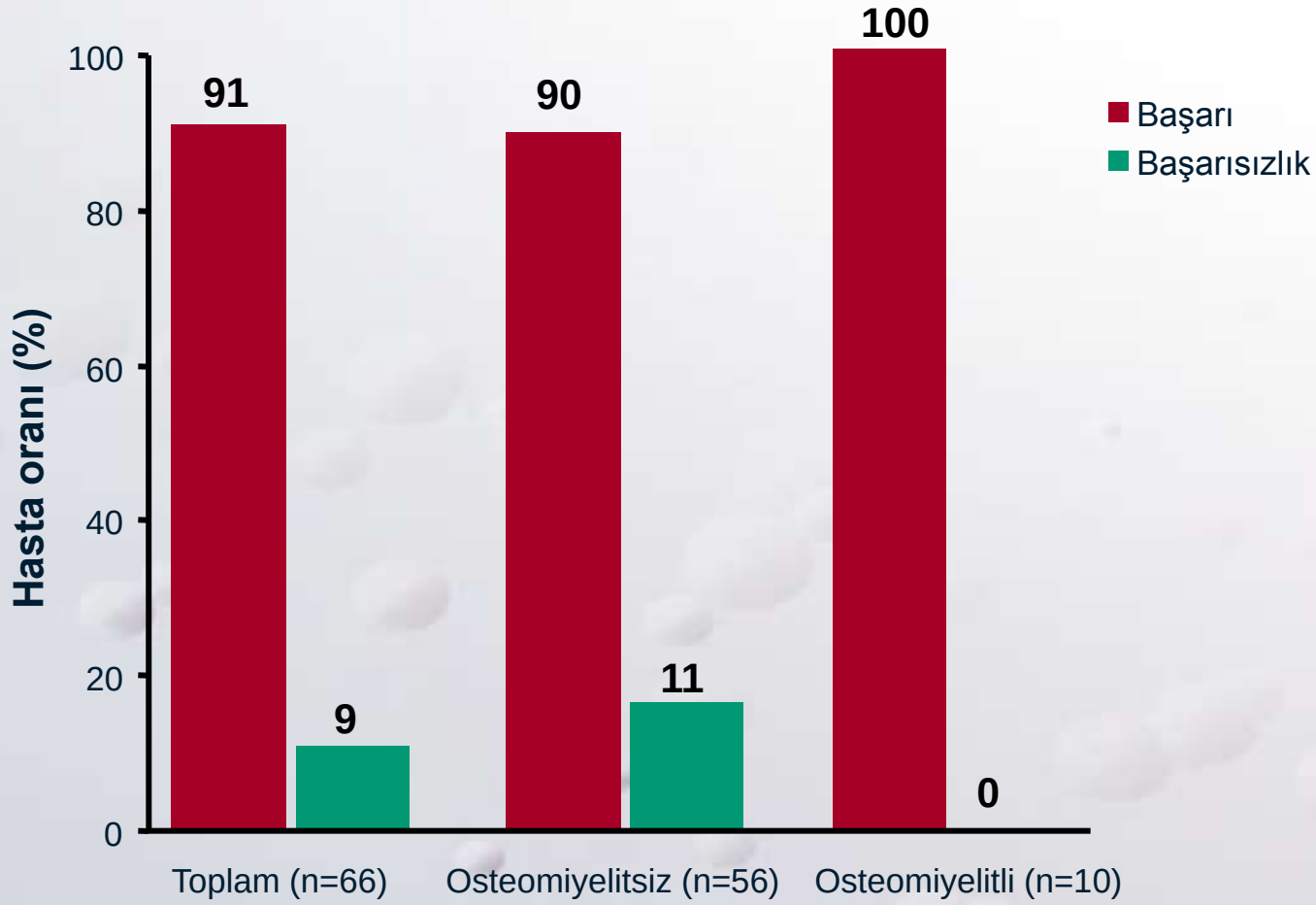


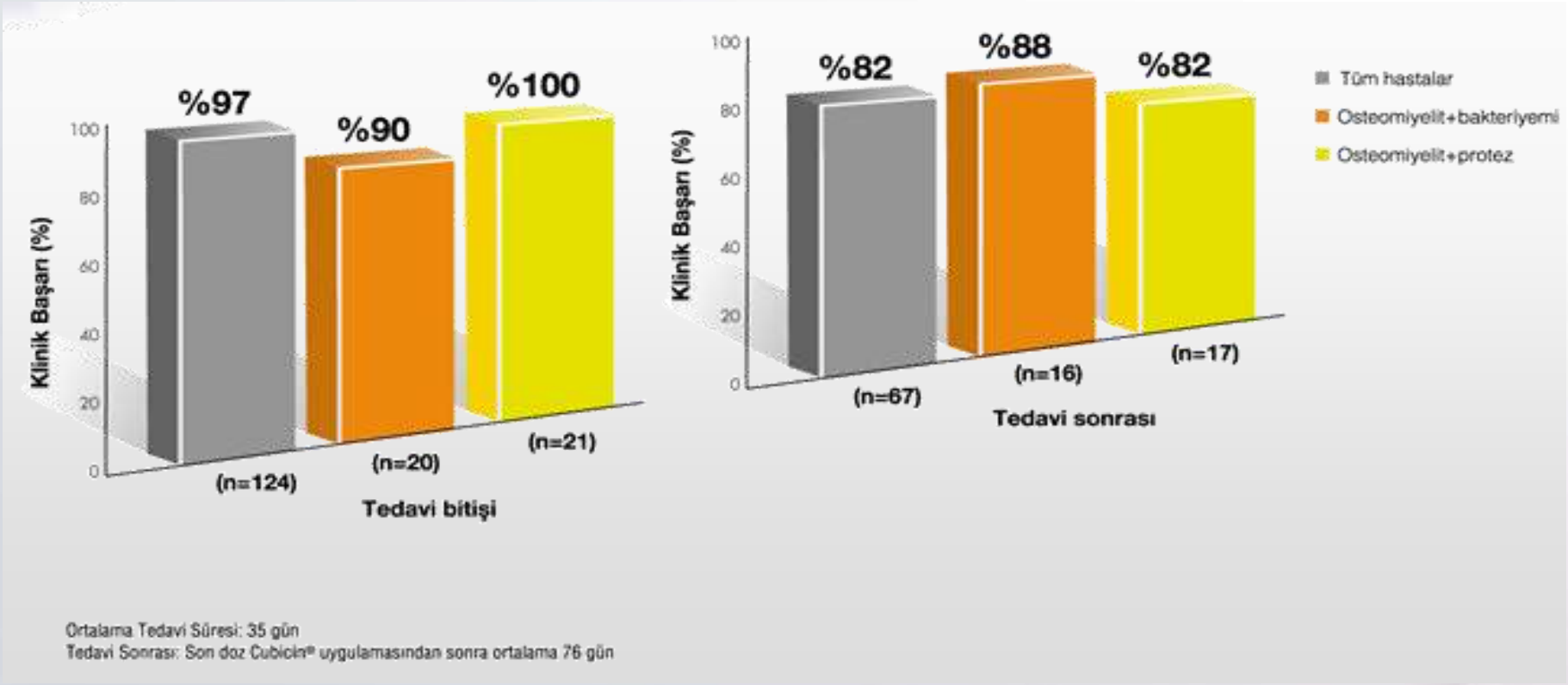
FIG. 3. *In vivo* activity of daptomycin, vancomycin and nafcillin against methicillin-resistant *Staphylococcus aureus* (MRSA) peritonitis in healthy rats. Luminescent images of MRSA (Xen-1) peritonitis in healthy rats. Groups of mice (n = 5/group) were anaesthetized with isoflurane and imaged for 3 min at 0, 2 and 4 h after being dosed with 10 mL/kg saline, 50 mg/kg daptomycin, 100 mg/kg vancomycin or 100 mg/kg nafcillin. Reproduced from reference [38], with permission from the American Society for Microbiology.

Diyabetik ayak infeksiyonlarında daptomisin: CORE çalışması 2005-2006



Johnson K et al, ICAAC 2007, Abstract L -490

Osteomiyelitte Etkinlik



Lamp et al. Am J Medi 2007;120(10A):S13-S20

Faz III SAB/EE çalışması: En yaygın advers olaylar (her iki grupta ≥%10 insidans)

Olay	Daptomisin (n=120)	Karşılaştırma (n=116)	P Değeri*
Anemi	15 (12.5)	18 (15.5)	0.58
Diyare	14 (11.7)	21 (18.1)	0.20
Kusma	14 (11.7)	15 (12.9)	0.84
Konstipasyon	13 (10.8)	14 (12.1)	0.84
Bulantı	12 (10.0)	23 (19.8)	0.04
Hipokalemi	11 (9.2)	15 (12.9)	0.41
Böbrek bozukluğu‡	8 (6.7)	21 (18.1)	0.009
Baş ağrısı	8 (6.7)	12 (10.3)	0.36
Periferik ödem	8 (6.7)	16 (13.8)	0.09
Artralji	4 (3.3)	13 (11.2)	0.02

*P değeri Fisher's exact testine göre hesaplanmıştır.

‡Böbrek bozukluğu kategorisi, interstisyel nefrit, toksik nefropati, akut prerenal yetersizlik, akut ya da kronik böbrek yetmezliği, böbrek bozukluğu ve renal tübüler nekrozu içermektedir.

TABLE 9. Common (1–10%) adverse events with daptomycin, linezolid and tigecycline as detailed in the European Summary of Product Characteristics [23–25]

Daptomycin [24]	Linezolid [23]	Tigecycline [25]
Fungal infections	Fungal infections	Abscess, infections
Headache	Vaginal/oral candidiasis	Prolonged aPTT, prolonged PT
Nausea, vomiting, diarrhoea	Headache	Dizziness
Rash	Nausea, vomiting, diarrhoea	Phlebitis
Infusion site reactions	Taste alteration	Nausea, vomiting, diarrhoea
Abnormal liver function tests	Tongue discoloration	Abdominal pain, dyspepsia, anorexia
Increased CPK	Abnormal liver function tests	Pruritis, rash
	Haematological disturbance (increased neutrophils/ eosinophils; anaemia)	Headache
		Abnormal liver function tests

aPTT, activated partial thromboplastin time; CPK, creatine phosphokinase; PT, prothrombin time.

E. Barton and A. MacGowan. Clin Microbiol Infect 2009; 15 (Suppl. 6): 17–25

APAT - DAPTOMİSİN

- CORE - Veri Tabanı
- 949 hasta; %60 APAT
- Tedavi başarısı %95 vs %85

Martone WJ. Int J Clin Pract 2008;6:8:1183-7

KOMBİNE KULLANIM

- MRSA-in-vitro sinerji
  - Gentamisin
  - Rifampisin
  - Beta-laktamlar
- Enterokok için
  - Rifampisin
  - Ampisilin

DAPTOMİSİN - ÇALIŞMALAR

- Cerrahi profilaksi (uzun y.ö., hızlı sidal etki): Koroner bypass ve kalça, diz artroplasti
- Protez infeksiyonları
- Kateter ilişkili bakteremi
- Nötropenik hasta (sidal, iyi gr (+) etkinlik), empirik tedavi, gram (+) bakteremi
- Enterokokal endokardit

www.clinicaltrials.gov


Teşekkürler