Gülhane Mikrobiyoloji Günleri

20 - 22 Nisan 2010

Antimikrobik Kemoterapi
Laboratuvar Uygulamaları ve Yenilikler

KLİMUD

GÜLHANE ASKERİ TIP AKADEMİSİ 1898

TÜRK MİKROBİYOLOJİ CEMİYETİ 1931

Gülhane Mikrobiyoloji Günleri: “Antimikrobiyal Direnç”

Nisan 2010 İstanbul

Dirençli Bakterilerde Tedavi Yaklaşımları; Gram-pozitifler

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Hacettepe Üniversitesi Tıp Fakültesi

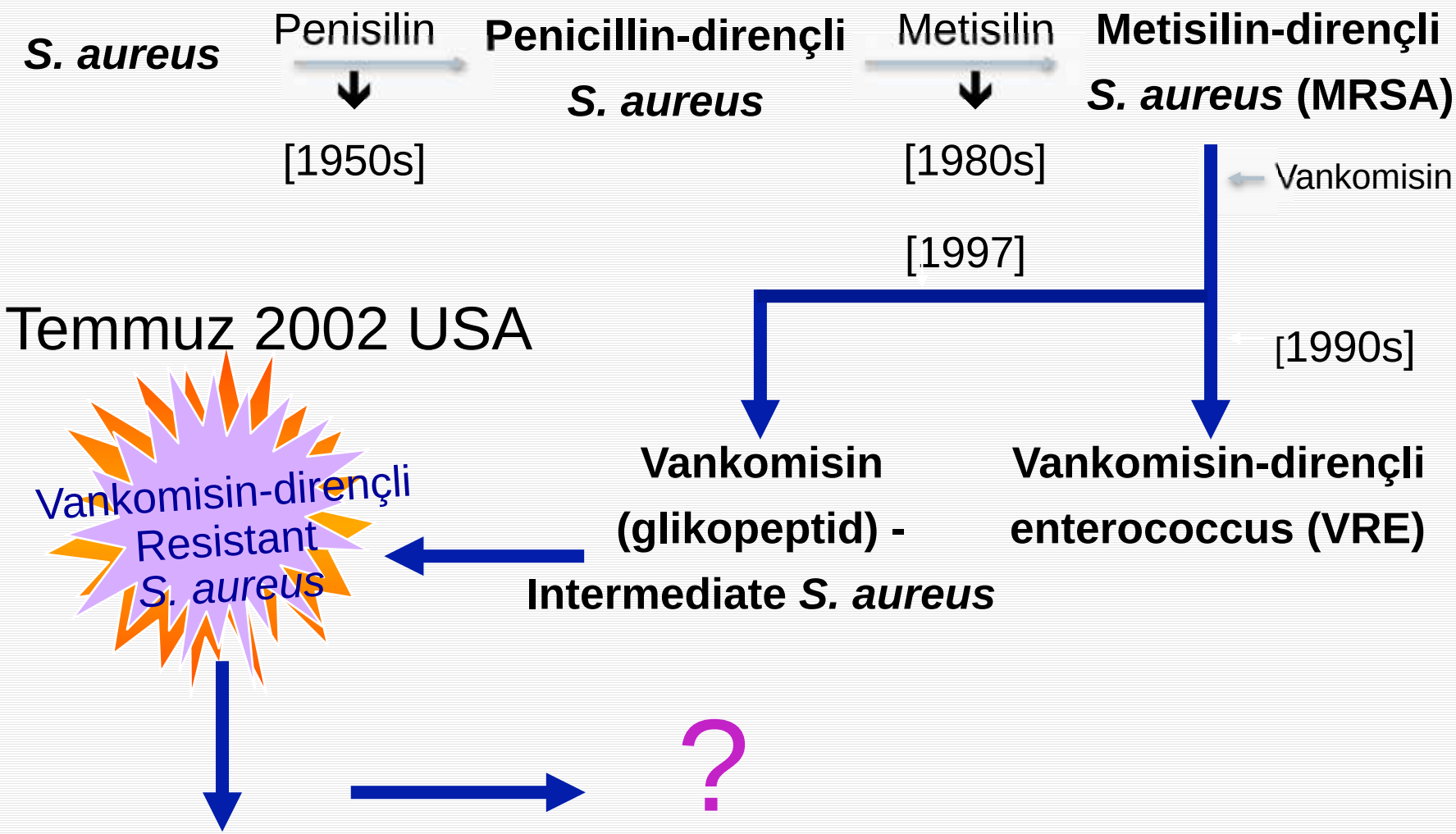
İç Hastalıkları A.D.

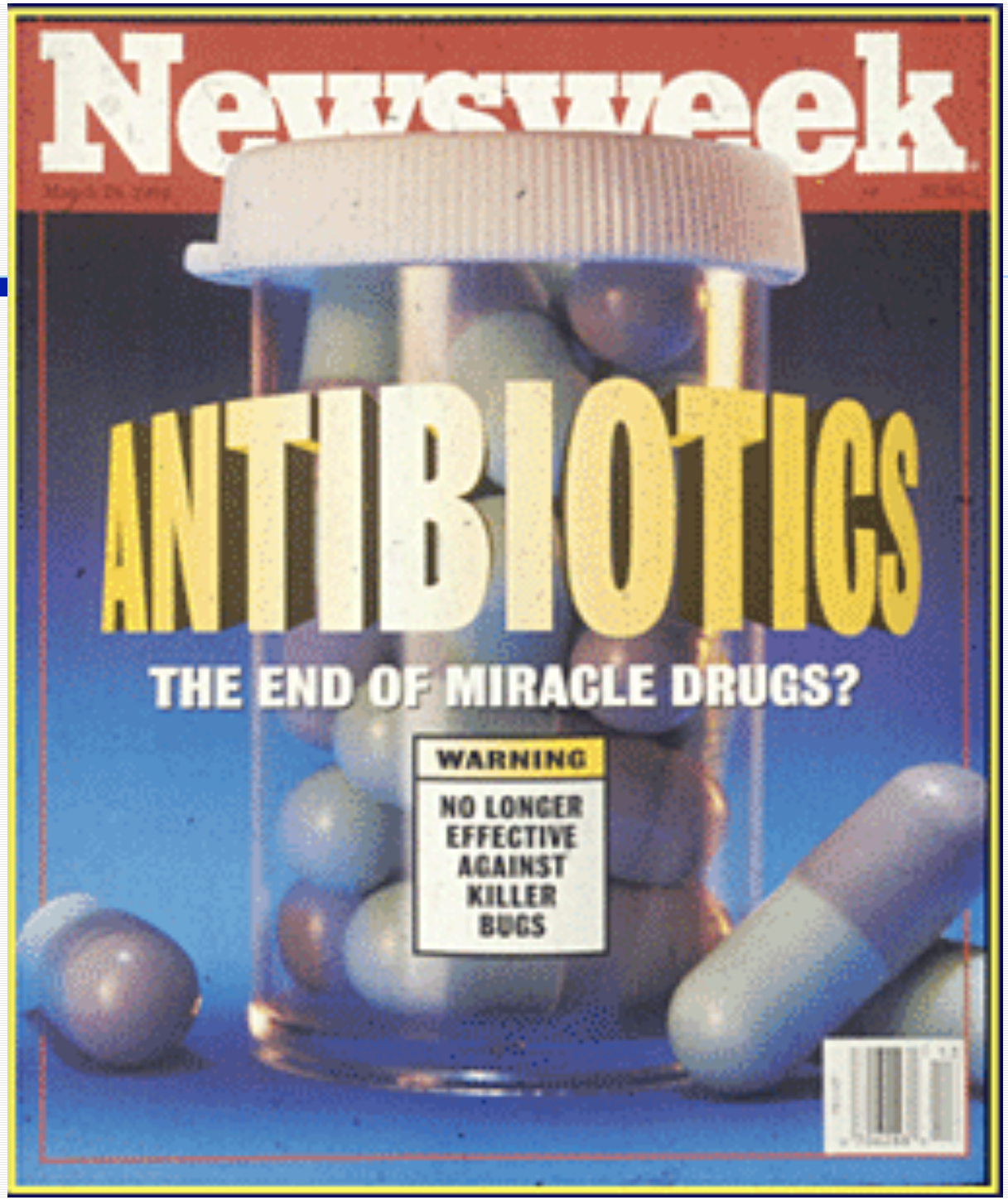
İnfeksiyon Hastalıkları Ünitesi

Antibiyotik Direnci

- ✓ Antibiyotik direncinde artış
- ✓ İlaç endüstrisin de yeni ilaç arayışında artış

Antibiyotik Direncinin Gelişimi




Newsweek
ANTIBIOTICS
THE END OF MIRACLE DRUGS?
WARNING
NO LONGER EFFECTIVE AGAINST KILLER BUGS

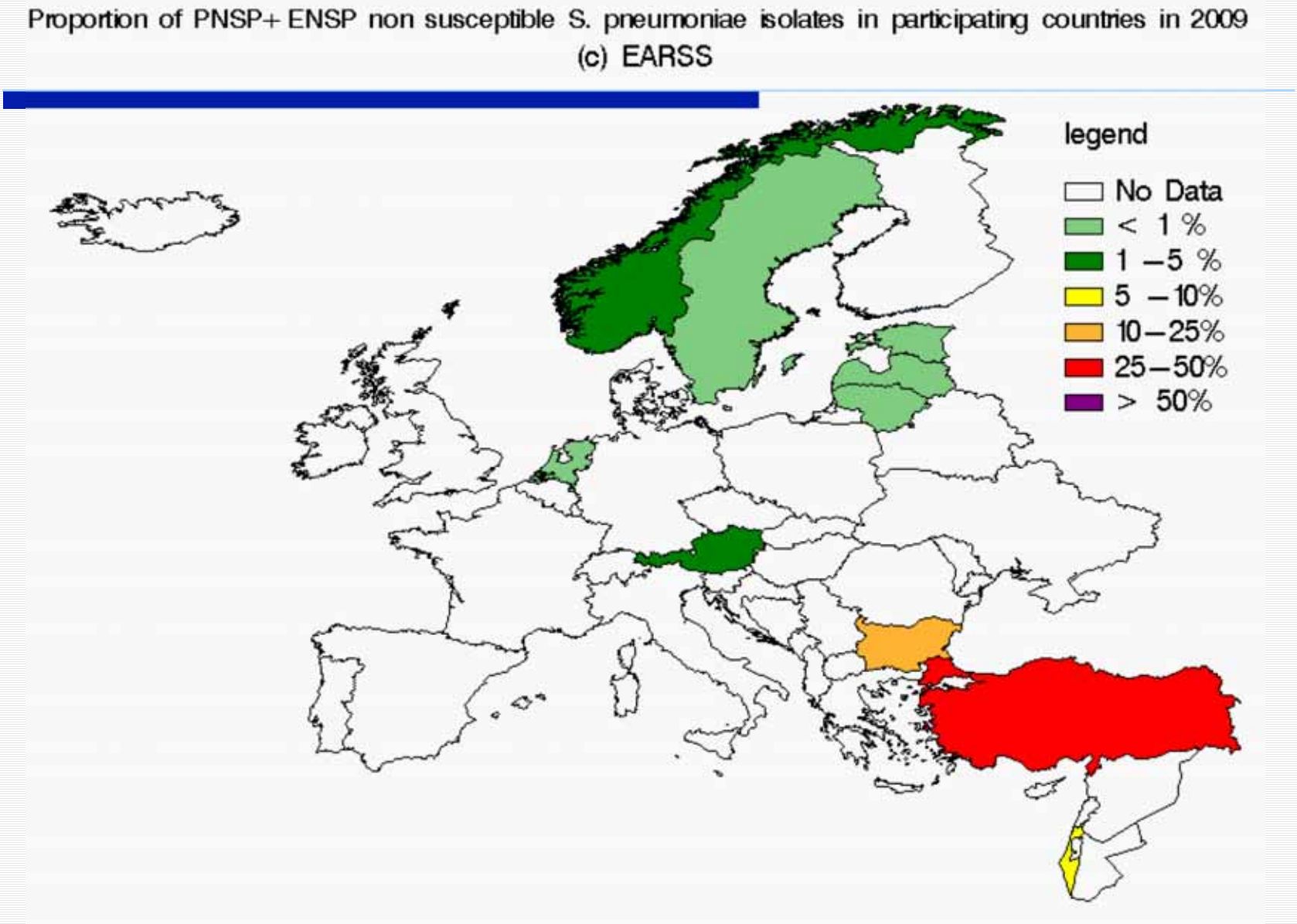
Antibiyotik Direnci

- Penisilin dirençli *S.pneumoniae*
- Metisilin dirençli *S.aureus*
- Vankomisin dirençli *S.aureus*
- Vankomisin dirençli enterokok

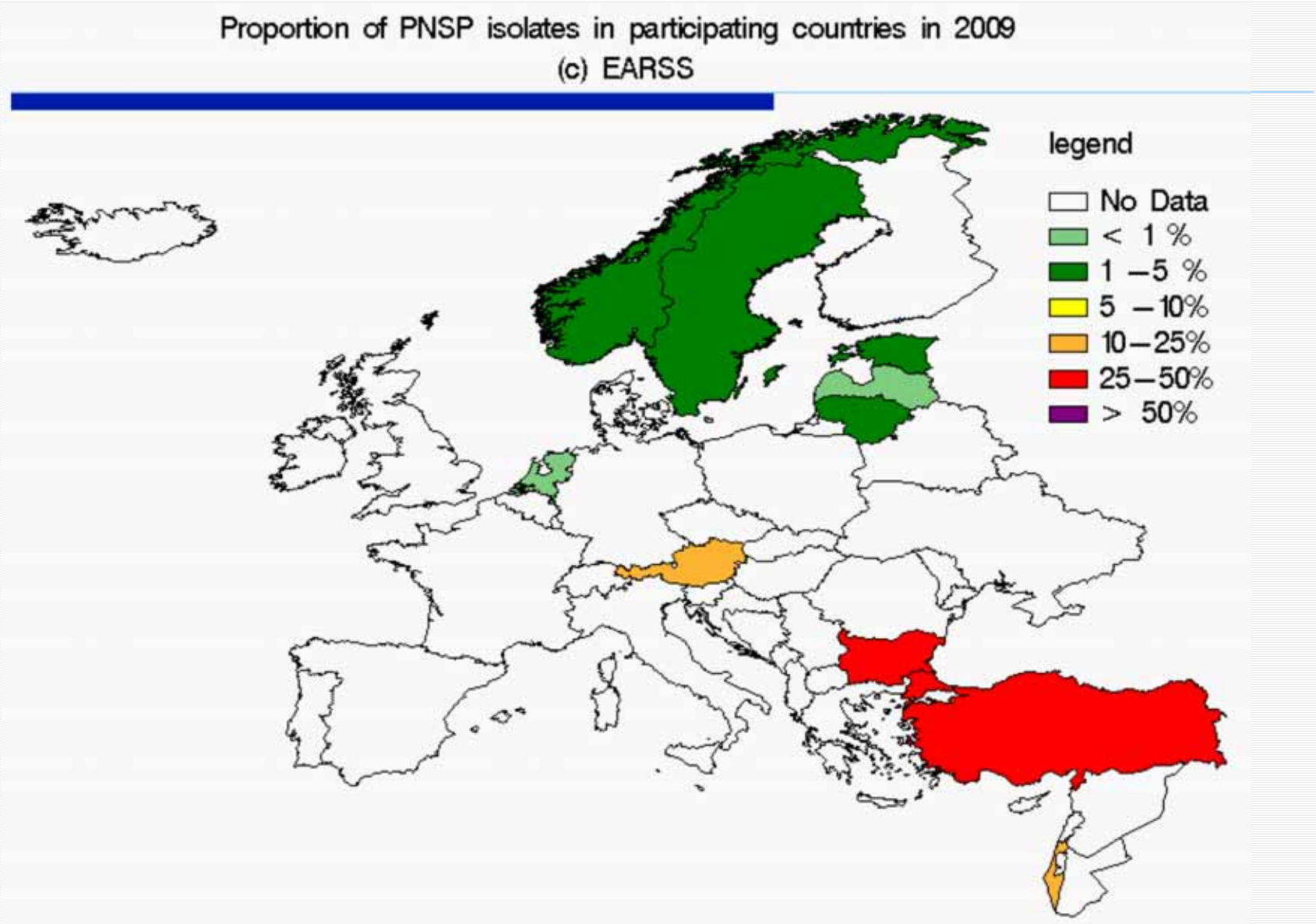
Direnç-Morbidite-Maliyet

- *S.pneumoniae* (Pnömoni)
  - PDSP HKS: 26.8 gün Maliyet $ 213
  - PHSP HKS: 11.5 gün Maliyet $ 736
- *S.aureus* (bakteremi)
  - MRSA HKS: 12 gün Maliyet: $ 27.083
  - MSSA HKS: 4 gün Maliyet: $ 9.661
- *E.faecalis/E.faecium* (mortalite)
  - VRE %53 VSE %21

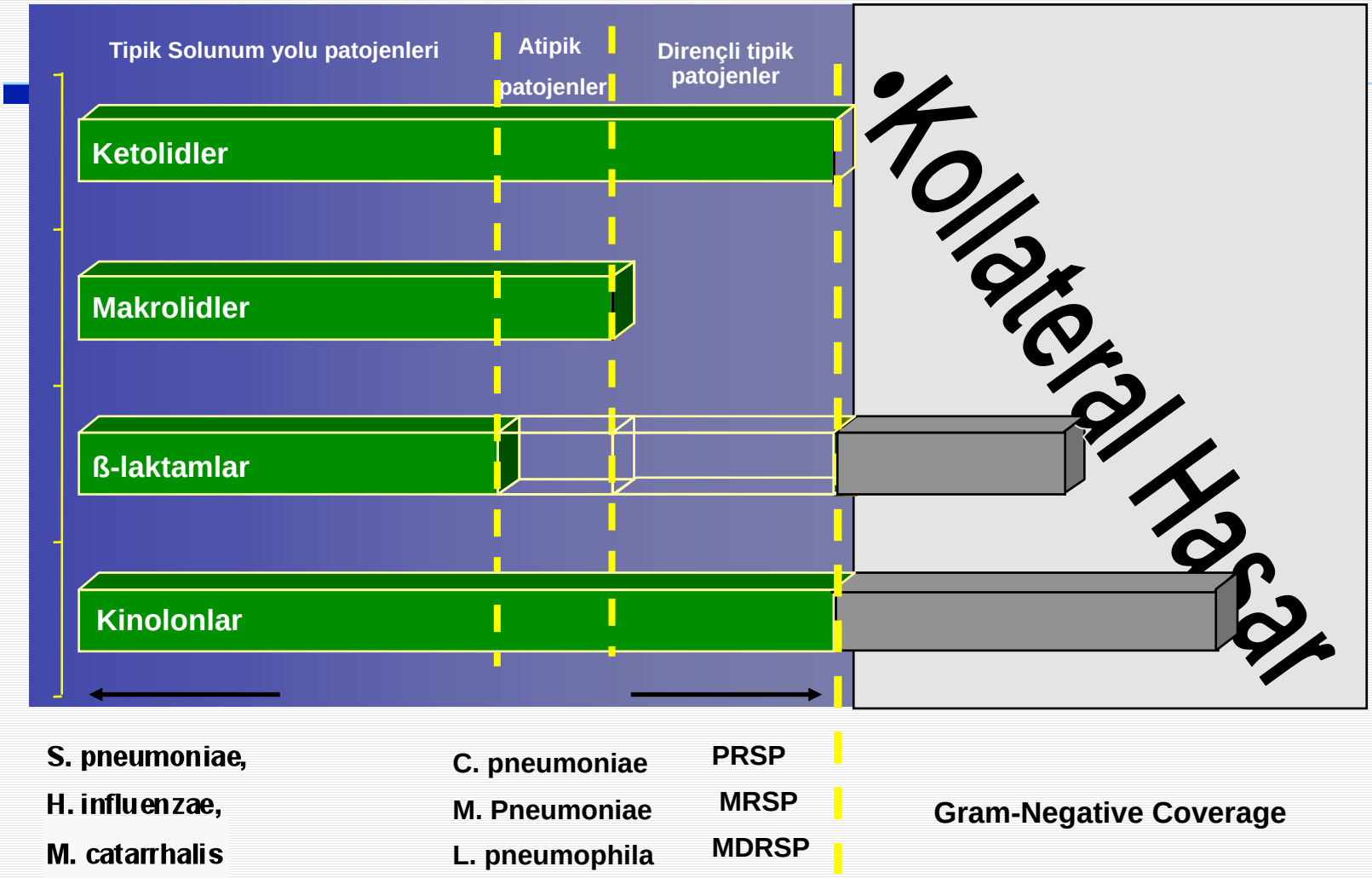
S.Pneumoniae PNSP + ENSP 2009



S.pneumoniae PNSP 2009

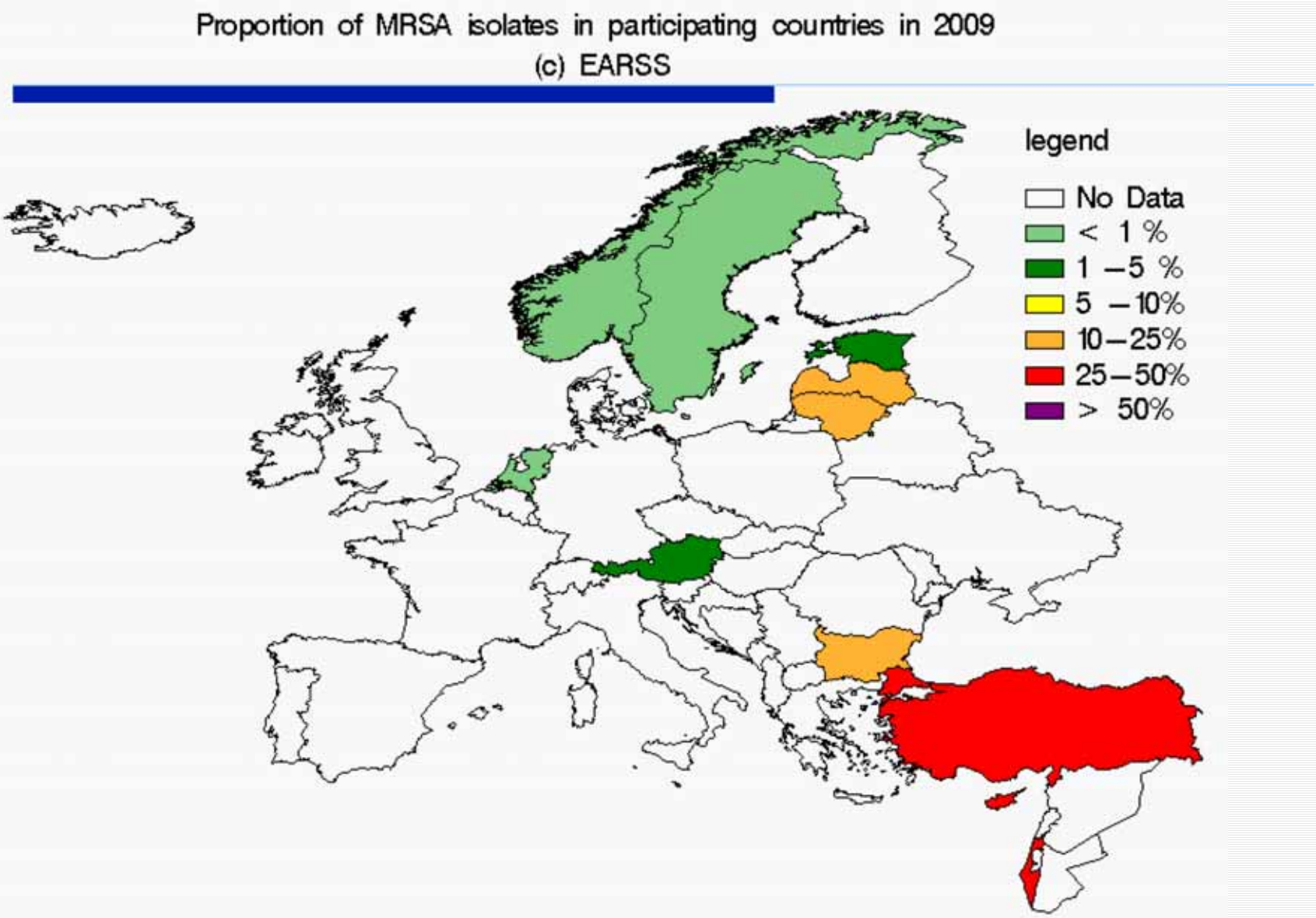


Aktivite Spektrumu

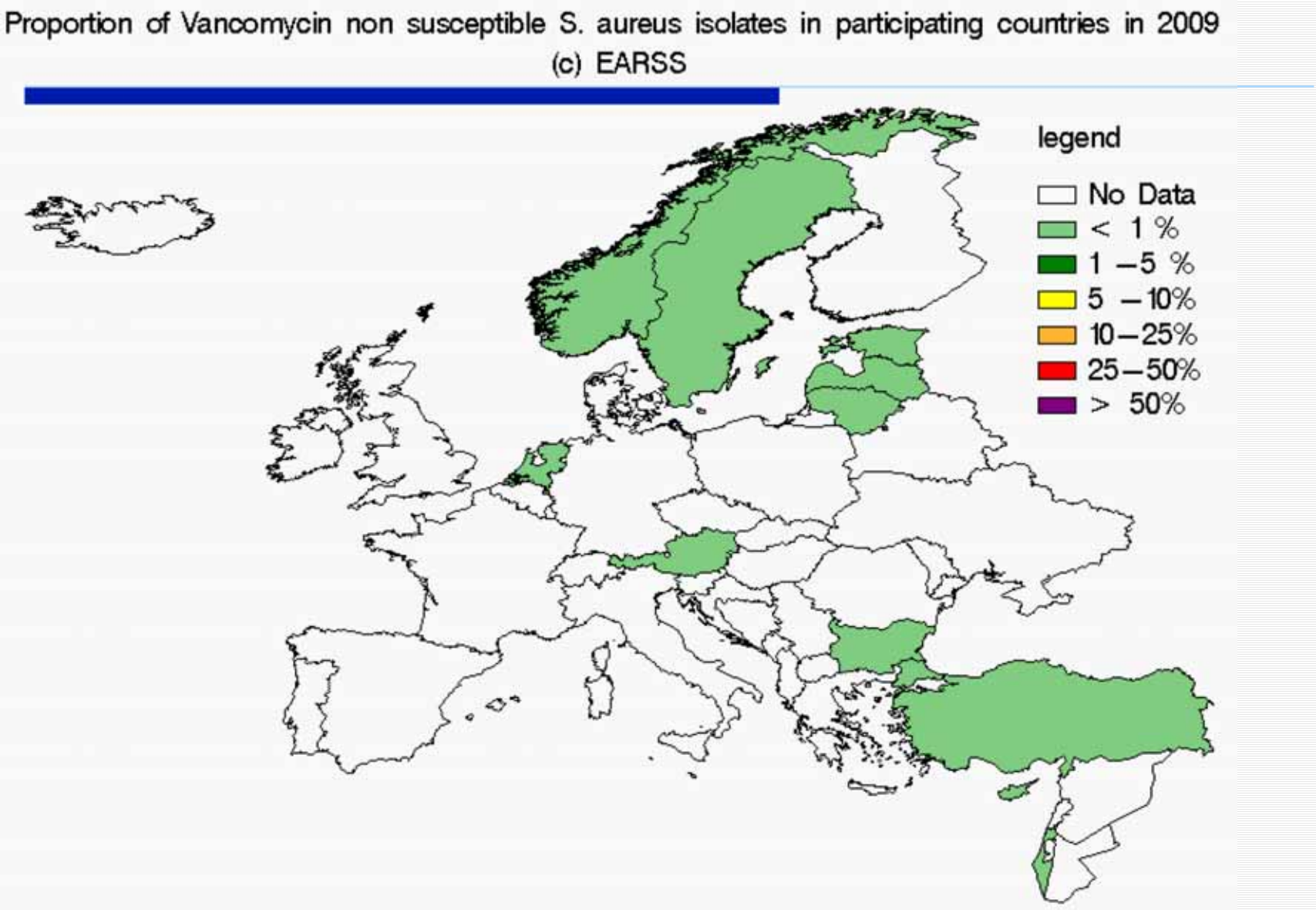


Odenholt I, Lowdin E, Cars O. *Antimicrob Agents Chemother.* 2001;45:23-29; Lonks JR, et al. *Clin Infect Dis.* 2002;35:556-564; Gleason PP. *Pharmacotherapy.* 2002;22:2s-11s; Neuhauser MM, et al. *JAMA.* 2003;289:885-888.

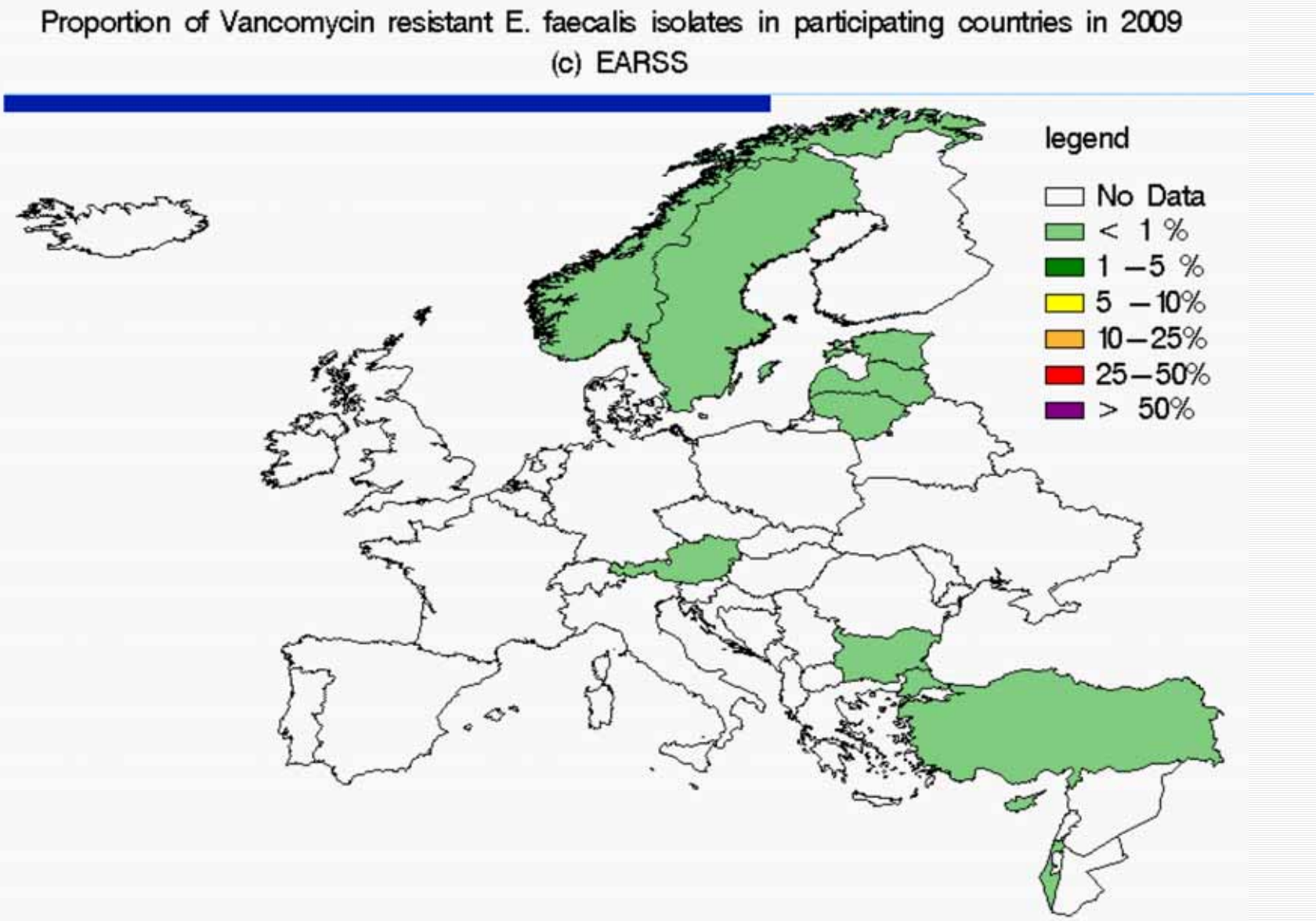
MRSA – Turkey 2009



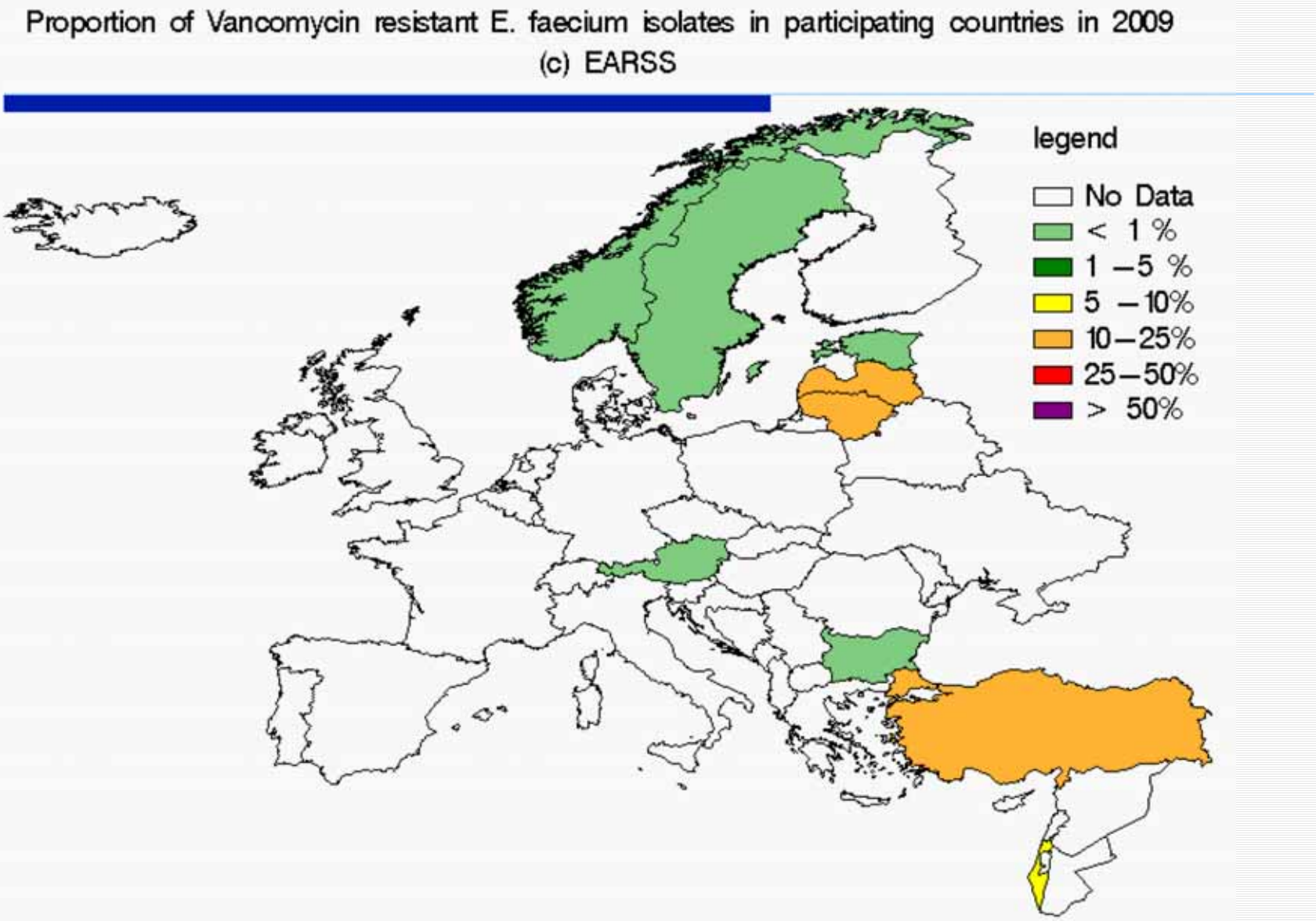
VanR S.aureus – Turkey 2009



E.feacalis VanR 2009



E.faecium Van R 2009



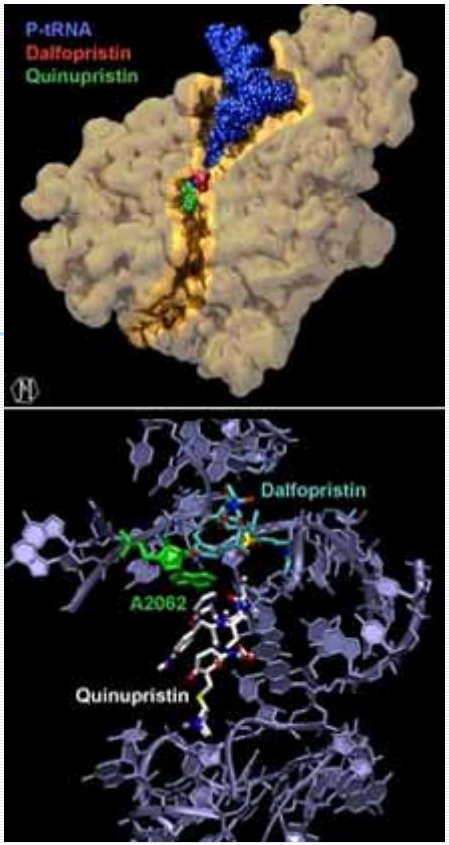
Multidrug-Resistant Bacterial Organisms Causing Major Clinical Problems.*

Organism and Antibiotic Resistance	Common Mechanism of Resistance	Recent, Resurrected, and Future Antimicrobial Agents with Potential Clinical Use
Hospital-associated MRSA†		
Vancomycin (both VISA and VRSA)	Thickening of cell wall (not fully elucidated); change in the last amino acid of peptidoglycan precursors	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Daptomycin	Associated with changes in cell wall and cell membrane (not fully elucidated)	Linezolid, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Linezolid	Mutations in the 23S ribosomal RNA genes; rarely, acquisition of a methyltransferase gene (*cfr*)	Daptomycin, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Vancomycin-resistant *Enterococcus faecium*‡		
Ampicillin (common)	Mutation and overexpression of *pbp5*	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline
High-level resistance to aminoglycosides	Acquisition of aminoglycoside-modifying enzymes; ribosomal mutations (streptomycin)	No alternative for a reliable bactericidal effect alone or in combination
Linezolid	Mutations in the 23S ribosomal RNA genes	Quinupristin–dalfopristin, daptomycin, tigecycline
Daptomycin	Unknown	Linezolid, quinupristin–dalfopristin, tigecycline
Quinupristin–dalfopristin	Enzymes that inactivate quinupristin–dalfopristin, target modification	Daptomycin, linezolid, tigecycline

Gram Pozitiflere Karşı Yeni İlaçlar

- Quinupristin/Dalfopristin
- Linezolid
- Daptomisin
- Glycyclines ; Tigecycline
- Televancin
- Dalbavancin
- Oritavancin
- Ceftobiprole
- Ceftaroline
- Ranbezolide
- Iclaprim
- *S. aureus* vaccine

Quinupristin/Dalfopristin



- Synercid®
- Semi-sentetik streptograminlerin sabit (30:70) karışımı
- 50S ribozom ünitesinde değişik yerlere bağlanarak protein sentezinin inhibisyonu

Quinupristin/Dalfopristin

- *E.faecium' a bakteriostatik, E.faecalis'e etkisiz*
- MRSA dahil *S.aureus* in vitro hassas
- FDA onayı:
  - MSSA veya *S.pyogenes'e bağlı komplike cilt ve yumuşak doku inf.*
  - VRE ile ilişkili bakteremi
- *E.faecium* direnci AVRUPA % 10 and ABD % 0.6 (SENTRY antimicrobial surveillance program)

Quinupristin/Dalfopristin

- Pnömoni ve infektif endokarditte daha az etkin, cilt ve yumuşak doku infeksiyonlarında yeterli
  - Maclayton DO. Ann Pharmacother 2007; 41: 235-44
  - Nichols RL, et al. J Antimicrob Chemother 1999; 44: 263-73

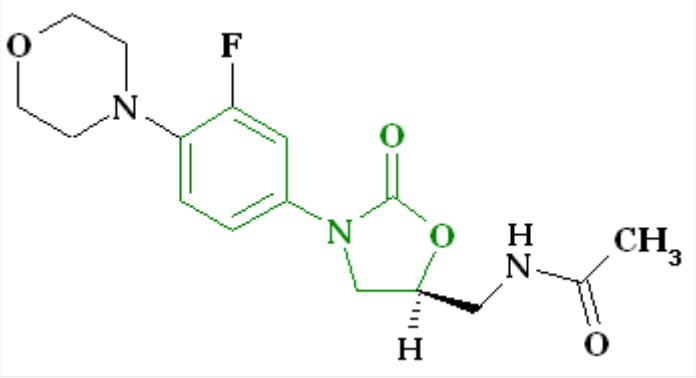
SF ile derin intravenöz uygulama

Quinupristin/Dalfopristin

- Venöz intolerans
- Artralji/myalji sendromu
- Hiperbilirubinemi and Karaciğer toksisitesi
- p450 3A4 isoenzim inhibitörü
  - *İlaç etkileşimi (Siklosporin), indirek QT uzaması*

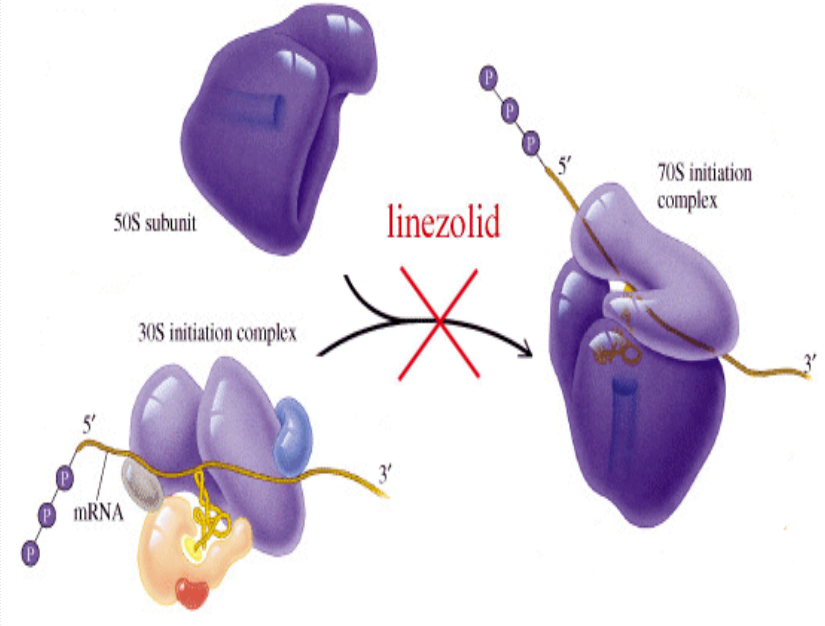
Linezolid

- Zyvox®
- Oxazolidinon grubu



Linezolid

- 50S ribozom ünitesine 30S ünitesine bağlanmasına yakın alanda bağlanır ve 70S kompleksinin oluşmasını engeller



Linezolid

- Gram pozitif bakterilerin çoğuna etkili
  - MSSA, MRSA, *S.pneumoniae, S.pyogenes*
  - *Enterococcus faecium*
- FDA onayı 2000
  - Cilt ve yumuşak doku infeksiyonları
  - Osteomyeliti olmayan diyabetik ayak infeksiyonları
  - Toplumda kazanılmış ve nozokomiyal pnömoni
  - VRE

Linezolid

- Yüksek biyoyararlanım
- İntravenöz veya oral
- Günde iki kez 600 mg
- Uzun süreli tedavi alacaklarda alternatif

Linezolid

- Cilt, yumuşak doku infeksiyonları ve pnömonide vankomisinden etkin
  - Wilson SE. Surg infec 2001; 21: 25-35
  - Hau T. Eur J Clin Microbiol infec Dis 2002; 21: 491-8
  - Wunderink RG, et al. Chest 2003; 124: 1789-97
- *Pnömonide vankomisine tek alternatif*
  - Maclayton DO. Ann Pharmacother 2007; 41: 235-44
- Endokarditte tartışmalı
  - Ruiz et al. Clin infec Dis 2002; 35: 1018-20

Linezolid

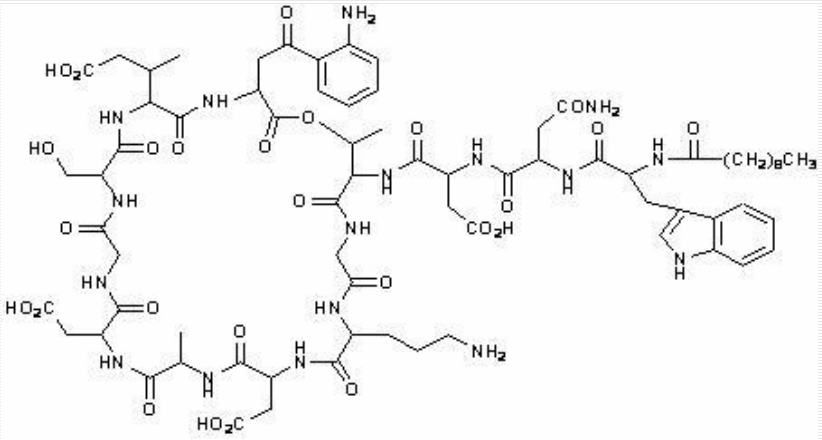
- Diyare, bulantı, başağrısı
- Serotonin sendromu
  - Antidepressants (SSRi)
- Kemik iliği supresyonu (anemi, lökopeni, trombositopeni, pansitopeni)
  - İki haftadan uzun tedavi, atta yatan myelosüpresyon
  - Myelosupresif ilaçlarla eş zamanlı tedavi
  - Kronik infeksiyon, antibiyotik kullanımı

Linezolid

- Pseudomembranöz enterokolit
- Laktik asidoz
- Optik nöropati
- FDA Uyarısı (3.16.2007):
  - Linezolid vs. vancomycin, oxacillin or dicloxacillin intravascular kateter ilişkili infekisyonlar
  - Gram-negatif infeksiyonu olanlarda yüksek mortalite

Daptomisin

- Cubicin®
- Siklik lipopeptidlerin ilk temsilcisi
- FDA onayı 2003
  - Komplike cilt ve yumuşak doku infeksiyonları

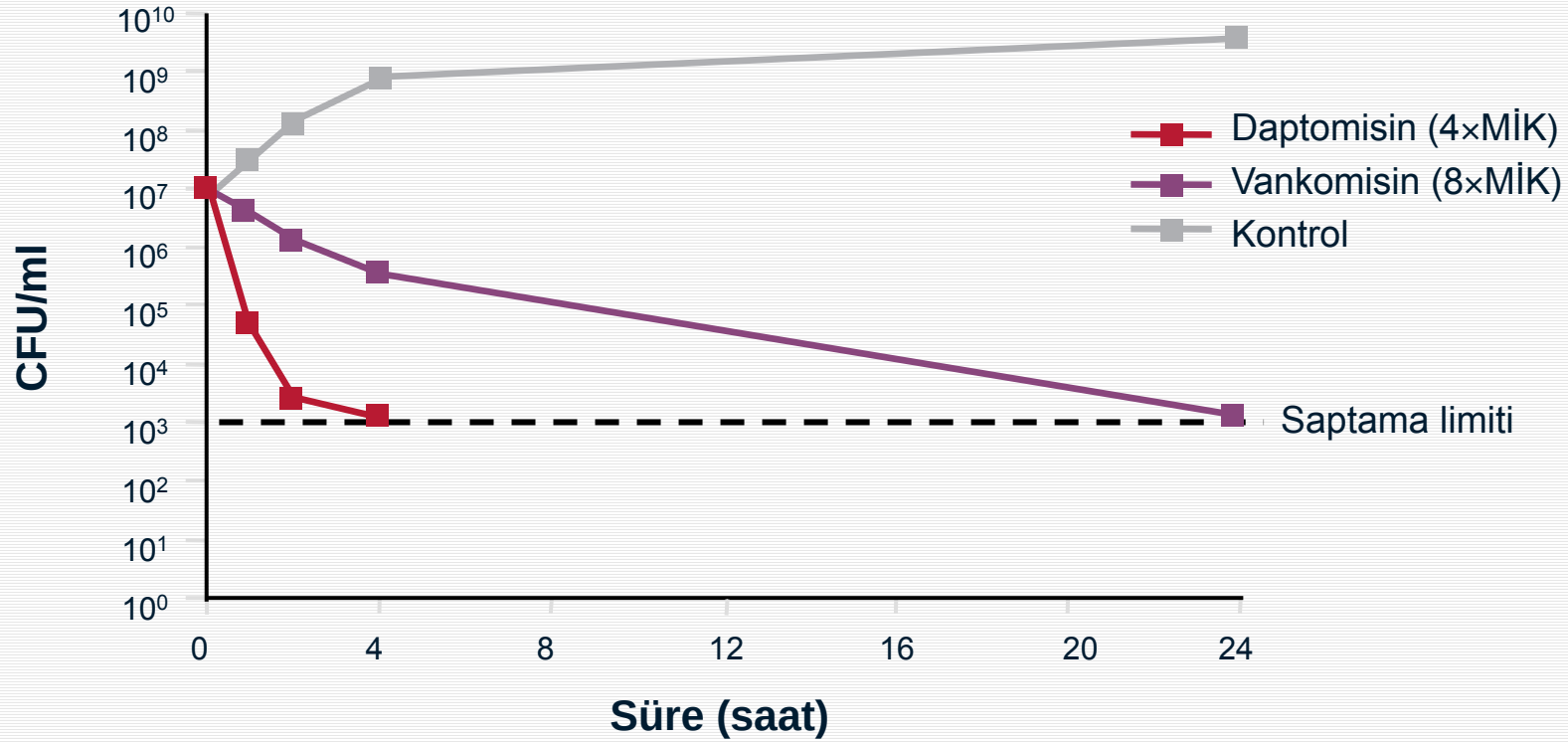


Daptomisin

- Bacterisidal aktivitesi pek çok ajandan yüksek
  - *Cha R, et al. Antimicrob Agents Chemother 2003; 47: 1598-603*
- Kemik, eklem, cilt ve yumuşak doku infeksiyonlarında etkin
- Sağ kalp endokarditinde etkin
  - *Fowler VG Jr, et al. N Eng J Med 2006; 17: 653-65*

Sürfaktan nedeniyle pnömonide etkisiz

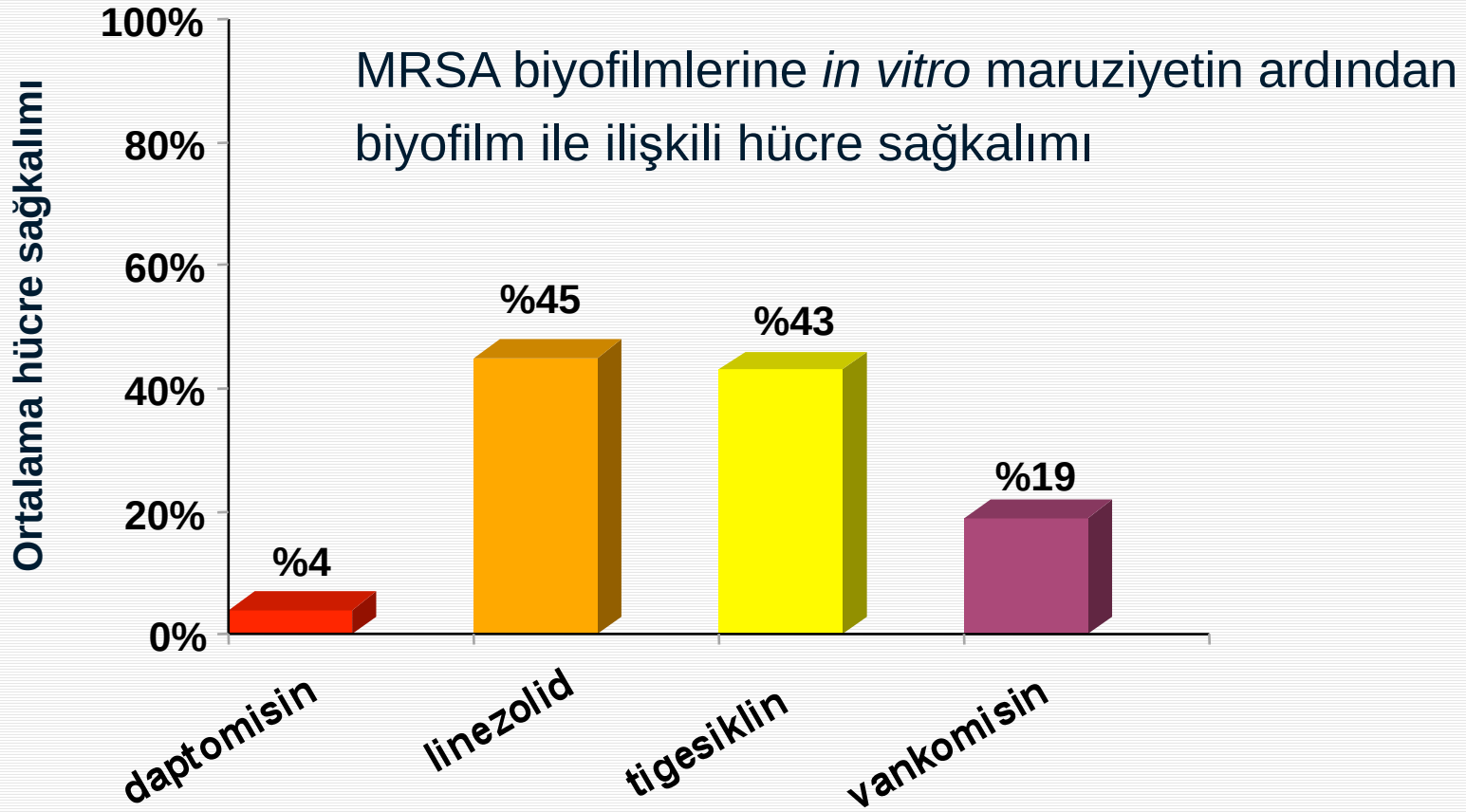
Daptomisinin *in vitro* olarak vankomisine karşı hızlı bakterisidal etkinliği



Daptomisin MİK=0.5 µg/ml, vankomisin MİK=1.0 µg/ml

Mortin LI *et al*. Poster presented at the 104th American Society of Microbiology General Meeting; May 23–27, 2004; New Orleans, LA. Poster O–022

Daptomisinin biyofilm içinde etkinliği

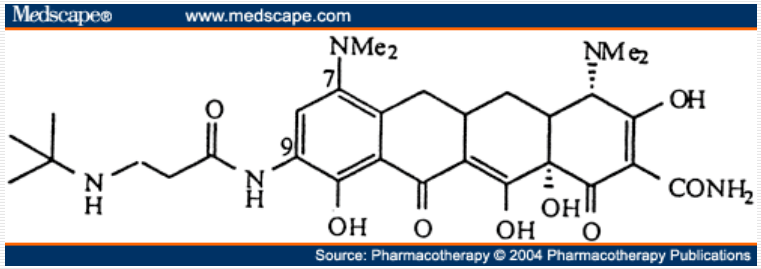


1. Smith et al, International Journal of Antimicrobial Agents 33 (2009) 374–378

Daptomisin

- Günde tek dozda etkili
- Yan etki profili düşük
  - Rabdomiyoliz ve nöropati??

Tigesiklin



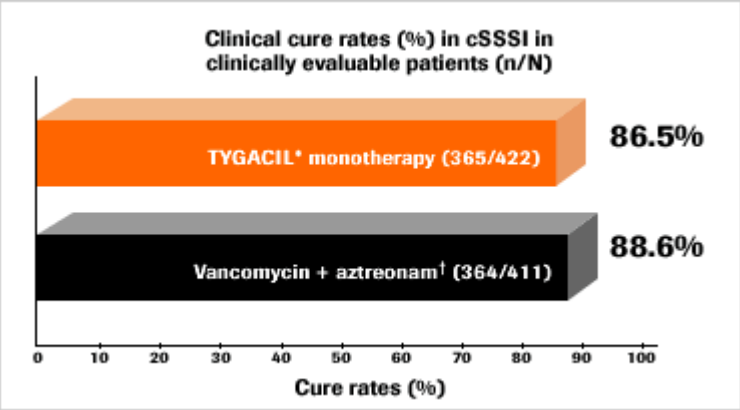
- Tygacil®
- Tetrasiklin derivesi
- 30S ünitesine bağlanıp, protein translokasyonunu önleyip peptid formasyonunu bozar

Tigesiklin

- Gram-pozitif mikroorganizmalar:
  - *Staphylococcus aureus*, *Enterococcus* spp., *Streptococcus pneumonia*, group A streptococci, group B streptococci and viridans streptococci.
- Gram-negatif mikroorganizmalar:
  - *Escherichia coli*, *Klebsiella pneumonia*, *Klebsiella oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia* spp., *Shigella* spp., *Salmonella* spp., *Citrobacter* spp., *Enterobacter* spp., *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *Acinetobacter spp., Burkholderia cepacia*, *Haemophilus influenza*, *Moraxella* spp., *Neisseria gonorrhea* and *Eikenella corrodens*.

Tigesiklin

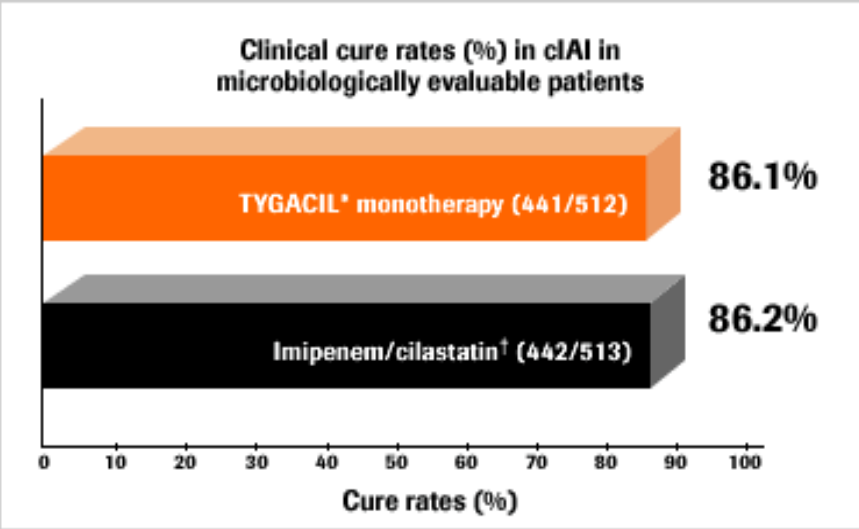
- Faz 3 randomize, çift kör çalışmalar (komplike deri ve yumuşak doku inf.: Tigesiklin ve diğer grup için iyileştirme oranlar 82.9% vs. 82.3% respectively. *(Sacchidanand S, et al. Int J ilfec Dis 2005; 9: 251-61*



- **833 hasta (422 tigesiklin 411 vankomisin ve aztreonam) Klinik yanıt benzer 86.5% (95% Ci, 82.9%-89.6%) and 88.6% (95% Ci, 85.1%-91.5%)** (*Ellis-Grosse EJ, et al. Clin infec Dis 2005: 41(Supp 5) S341-53)*

Tigesiklin

- Phase 3 çift kör çalışma
- 1642 komplike intraabdominal infeksiyonu olan erişkin



- **Klinik iyileşme oranları 86.1% (tigesiklin), 86.2% (imipenem/cilastatin) (95% CI -4.5% to 4.4%; p<0 .0001 for noninferiority). [*Babinchak T, et al Clin infec Dis 2005; 41 (Supp 5): 354-67]***

Tigecyline

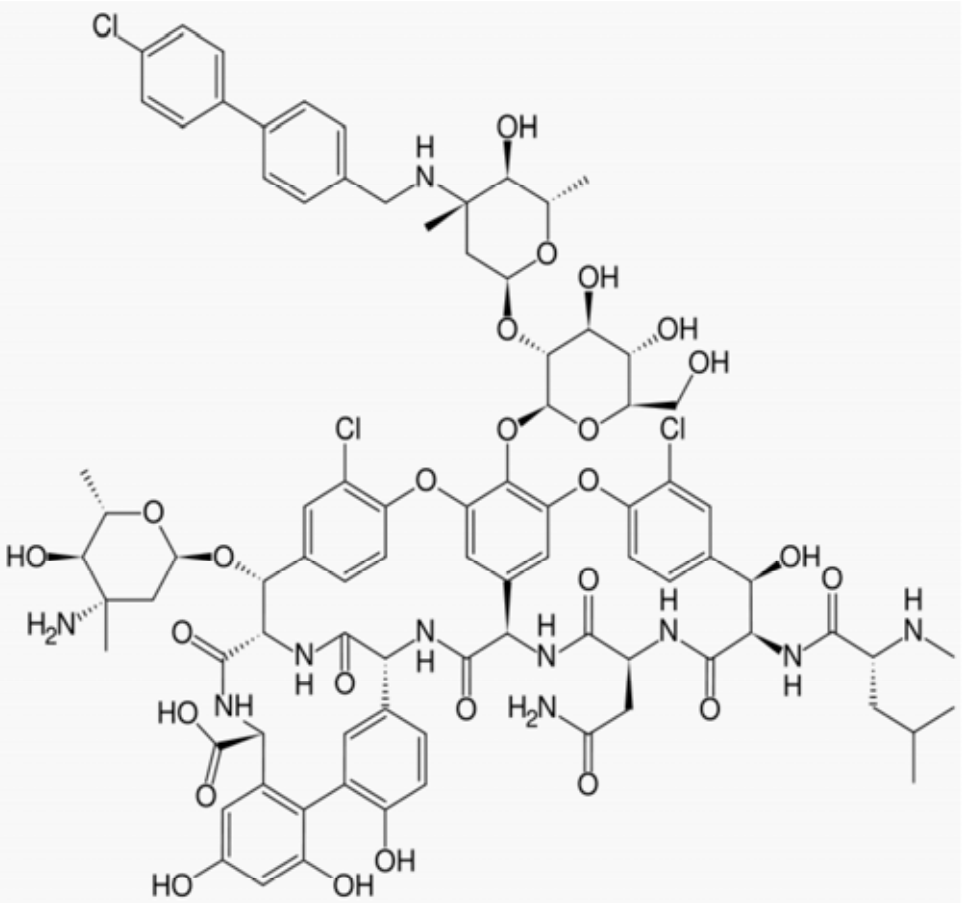
- Düşük yan etki profili
  - Bulantı kusma
  - İlaç etkileşimi yok

Yeni antibiyotikler gerekli mi???

	Avantajlar	Dezavantajlar
Linezolid	• Oral and IV • Bioyaralanım - 100% • Akciğer infeksiyonlarında vankomisinden üztün olabilir	• Statik • MIC breakpointe yakın • Nadir ama ciddi toksisite Kemik iliği süpresyonu, optik nevrit, laktik asidoz, nöropati
Daptomisin	• Endokardit çalışması • Aminoglikozidlerle sinerji • 12/26,000 direnç • 6 mg/kg doz • Resiztan suşlar	• SSS geçişi yok • Akciğer infeksiyonlarında yetersiz •Sadece IV • MIC creep • Myopati (CPK takibi)
Tigesiklin	• Geniş spektrum (*Pseudomonas aeruginosa dahil değil*)	• Statik • Sadece IV • GI intolerans (genellikle 48 saatte düzelen)

Oritavansin

- Glikopeptid
- (LY333328), vankomisinden 4-epi-vankosamin şekerinin eklenmesi ve vankosaminin yerini 4-epi-vankosaminin almasıyla farklılık gösterir.
- Streptokoklara karşı artmış intrinsik aktivite
- VRSA ve vanA enterekoklara etkin



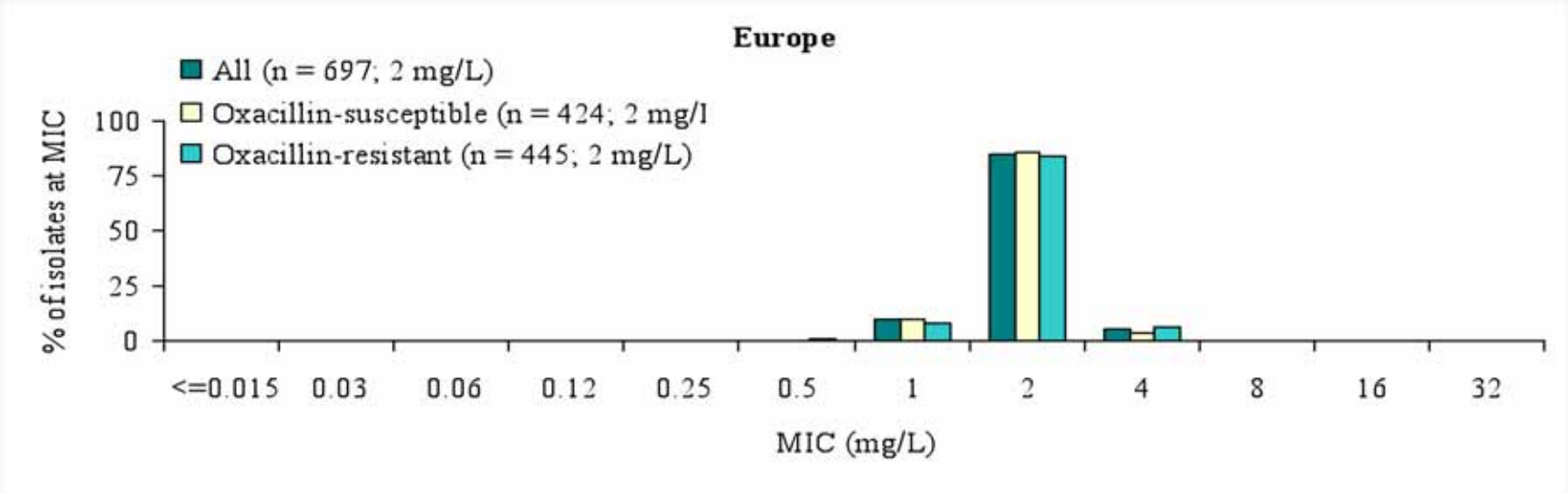
Oritavansin

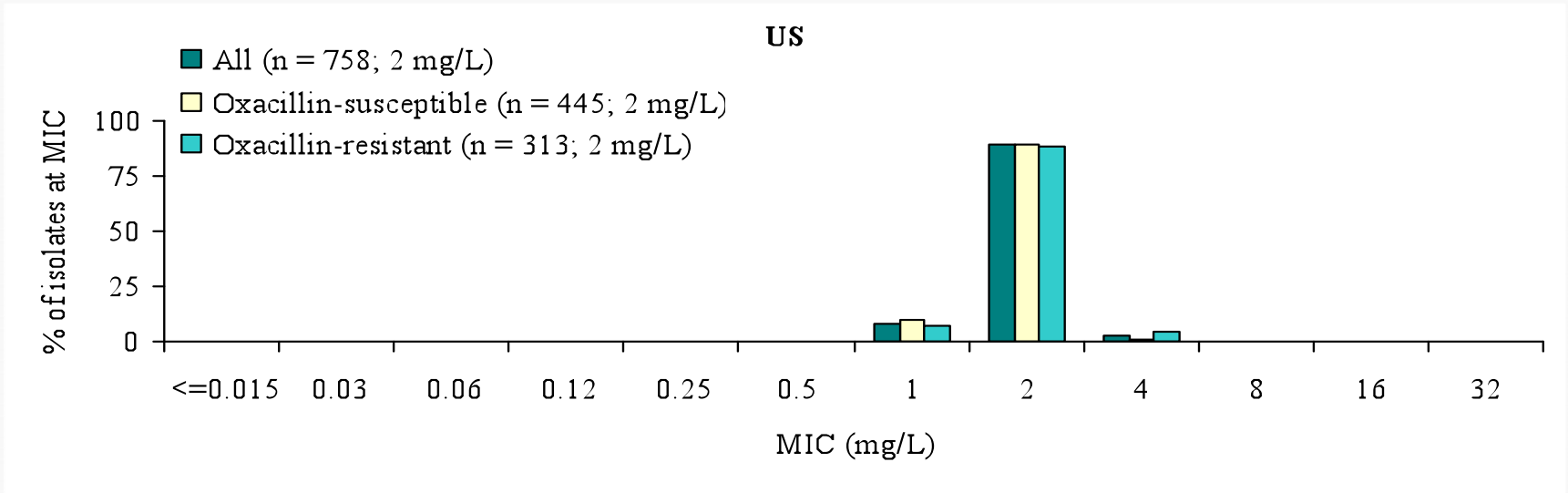
- Dimerize olur, büyümekte olan peptidoglikan zincirin iki köküne bağlanır.
- Lipofilik yan zincir hidrofobik interaksiyon aracılığıyla membrana en uygun pozisyonda yapışmaya yardım eder.
- Hücre duvarı sentezinin trans-glikolizasyon basamağını inhibe ettiğine dair kanıtlar mevcuttur.

Oritavansin

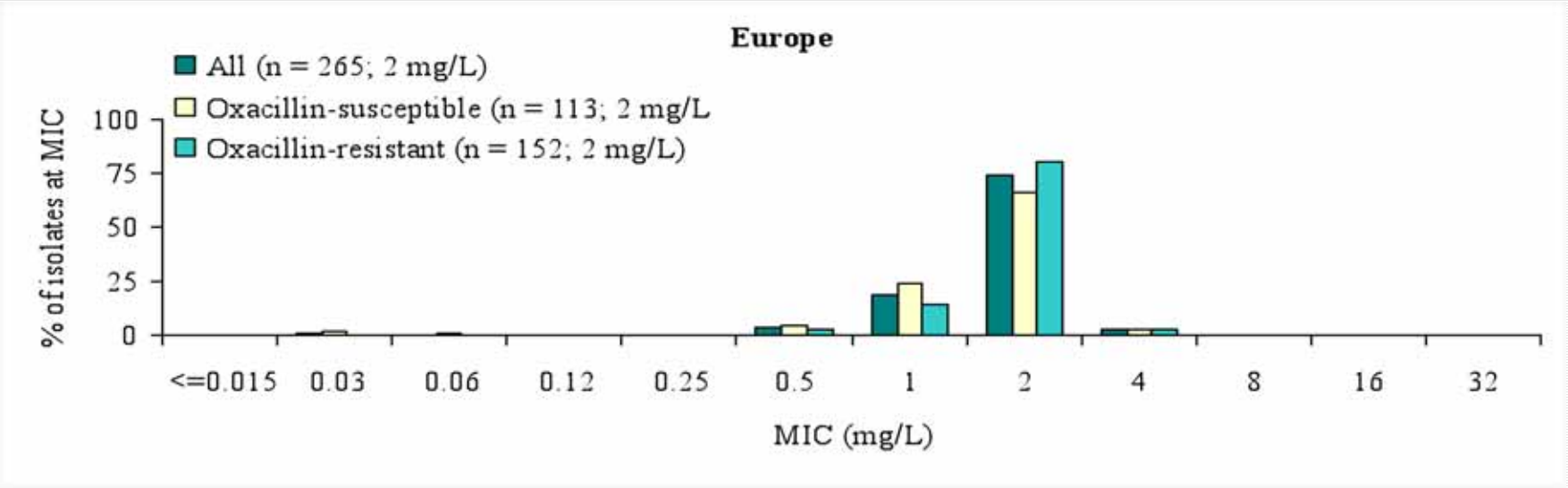
- Streptokoklar ve stafilokoklar *Peptostreptoccus türleri*, *Propionibacterium acnes*, *Clostridium perfringes* and *Corynobacterium jeikeium*.
- *vanA-, vanB-and vanC-* aracılı vankomisin direncinden, pnömokok ve viridans streptokoktaki orta ve yüksek penisilin direncinden, *Staphylococcus aureus'un* metisilin direncinden etkilenmez.

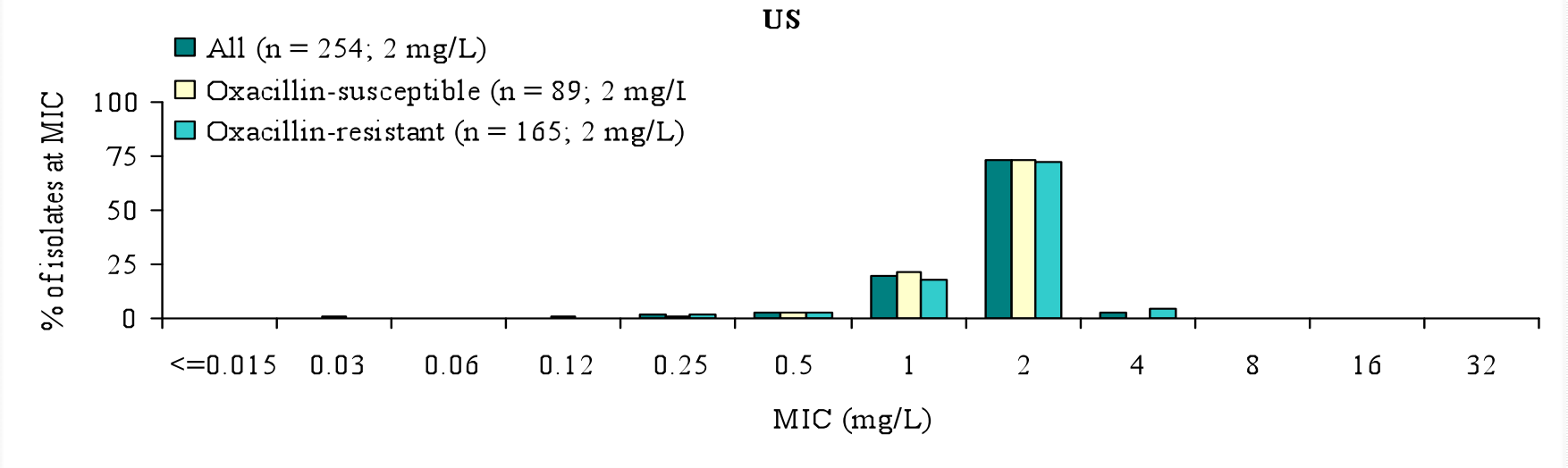
Activity of Oritavancin – *S. aureus*



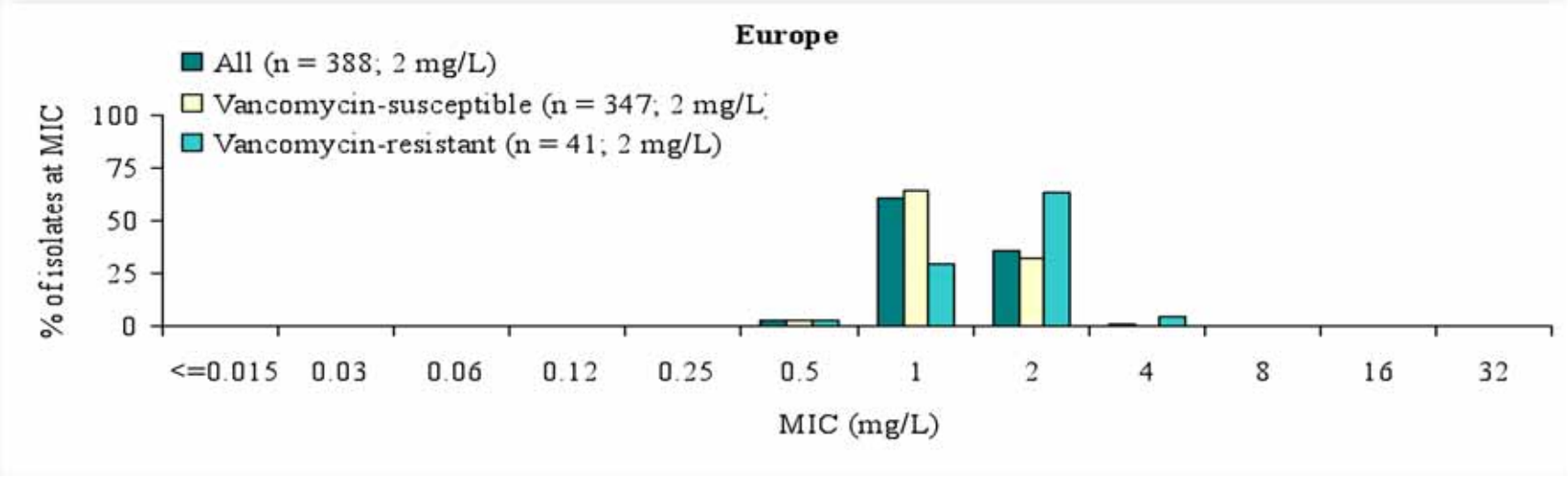


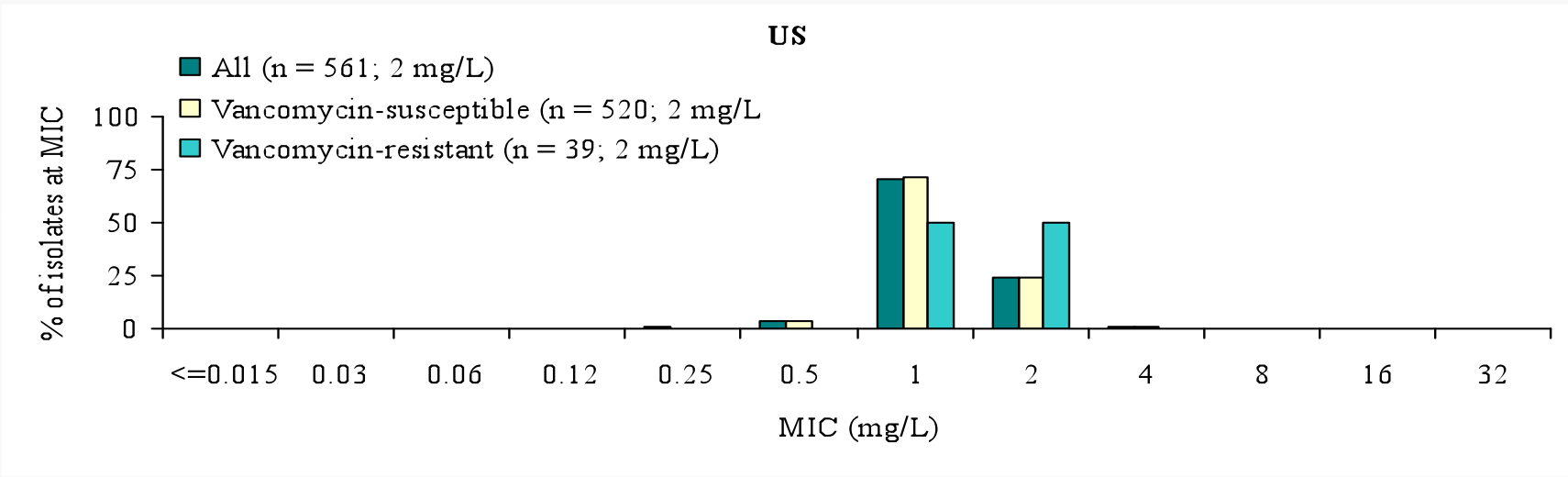
Activity of Oritavancin – Coagulase-Negative Staphylococci



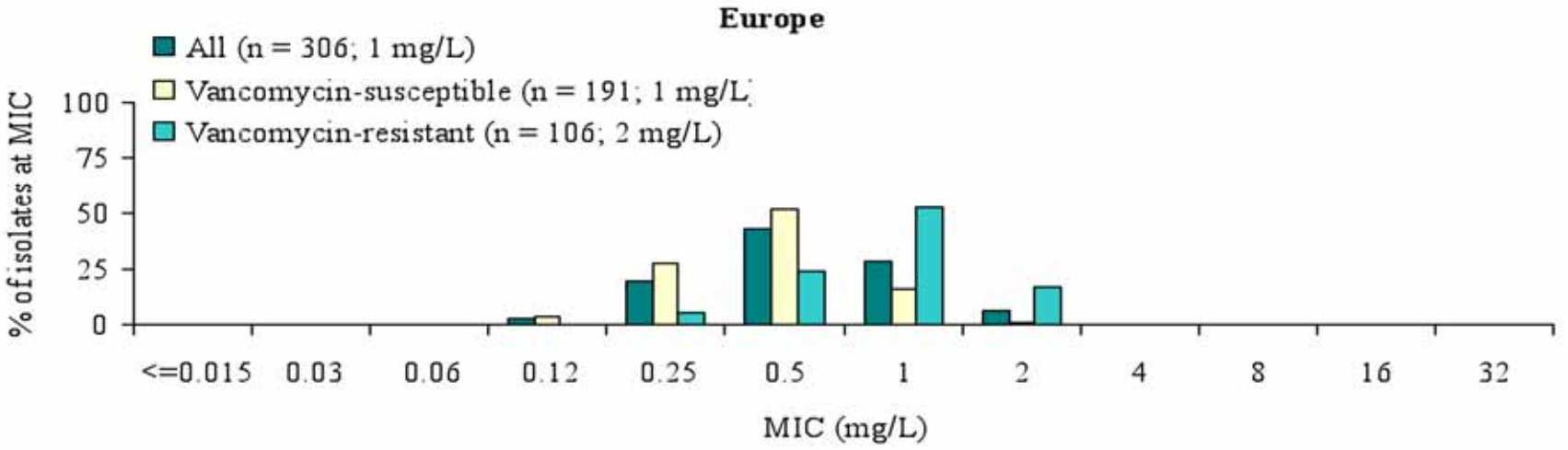


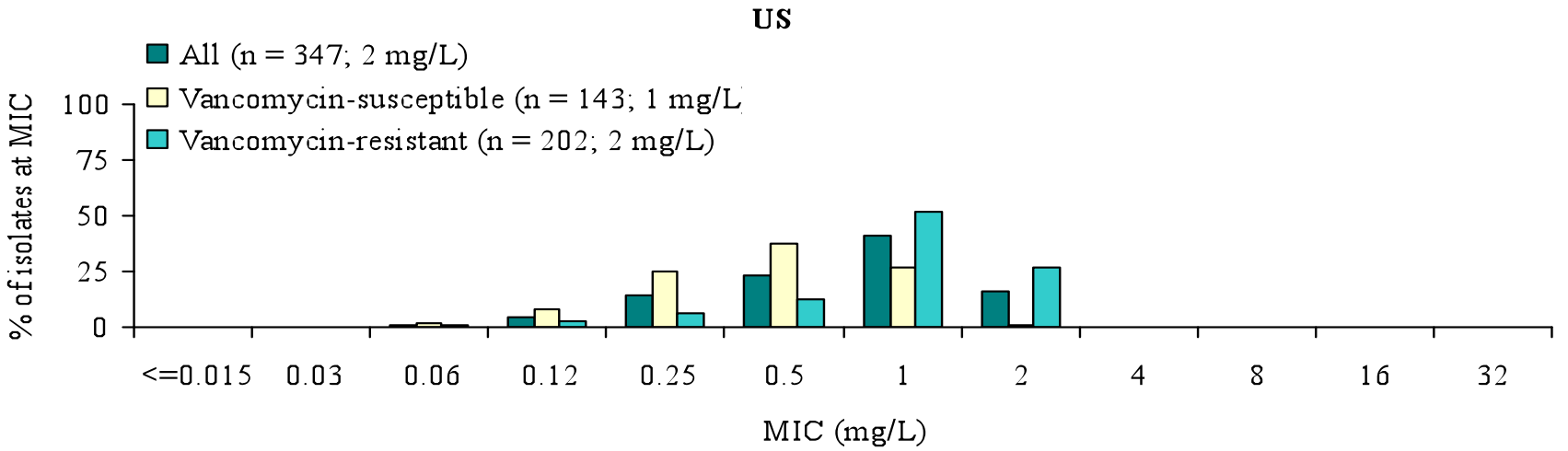
Activity of Oritavancin – *E. faecalis*



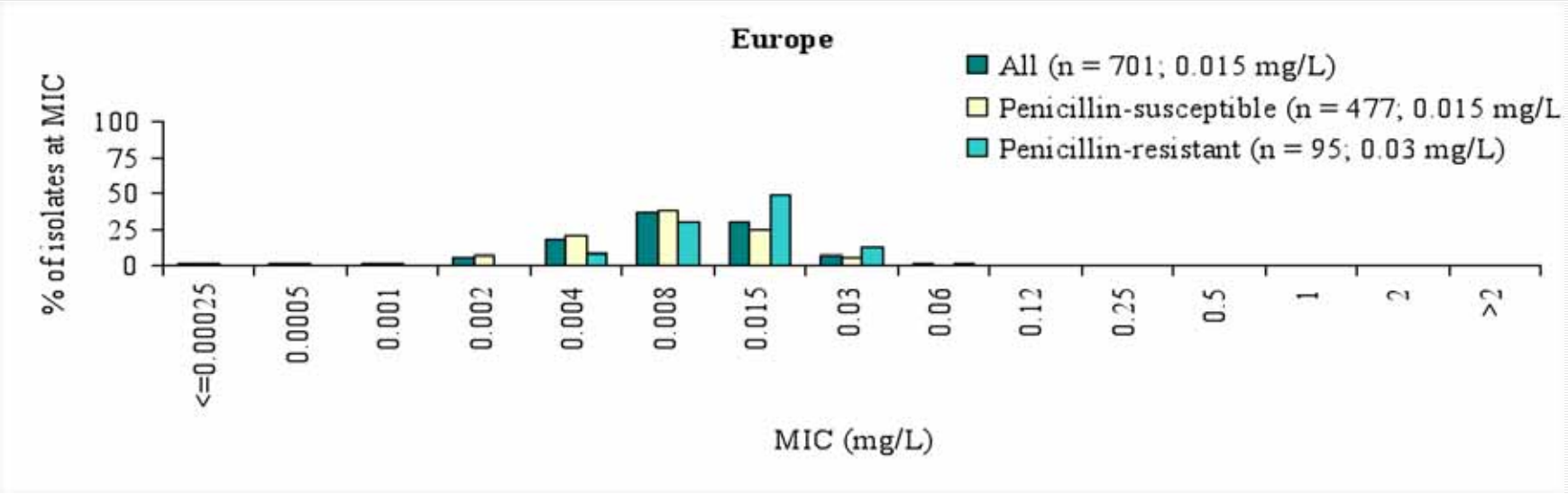


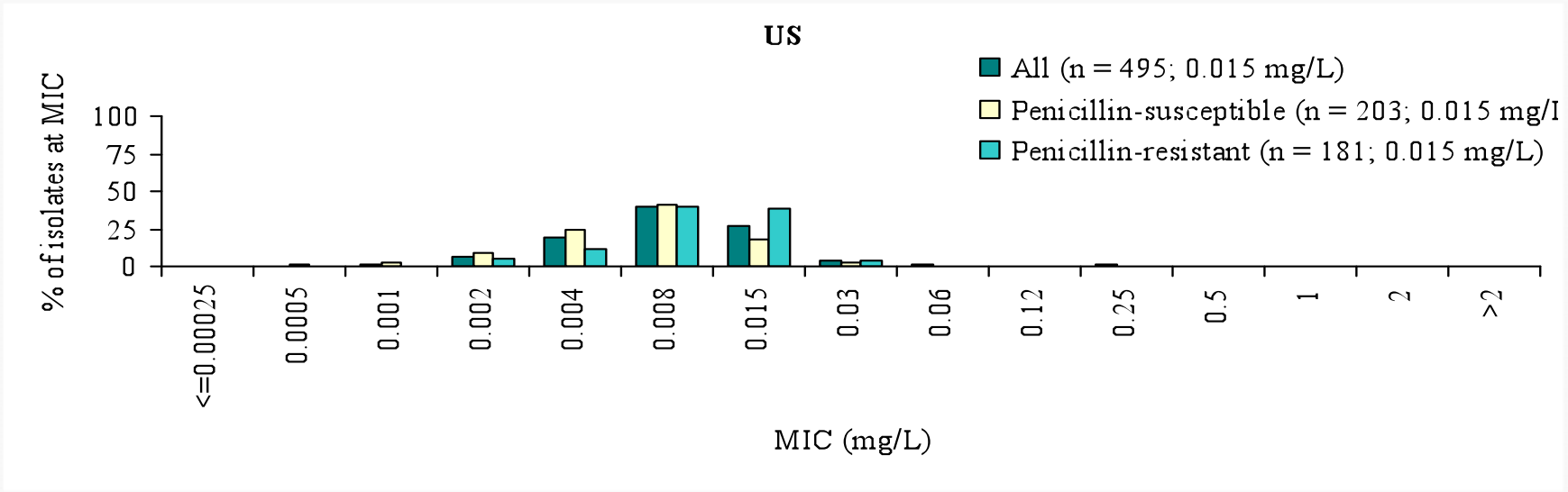
Activity of Oritavancin – *E. faecium*





Activity of Oritavancin – *S. pneumoniae*





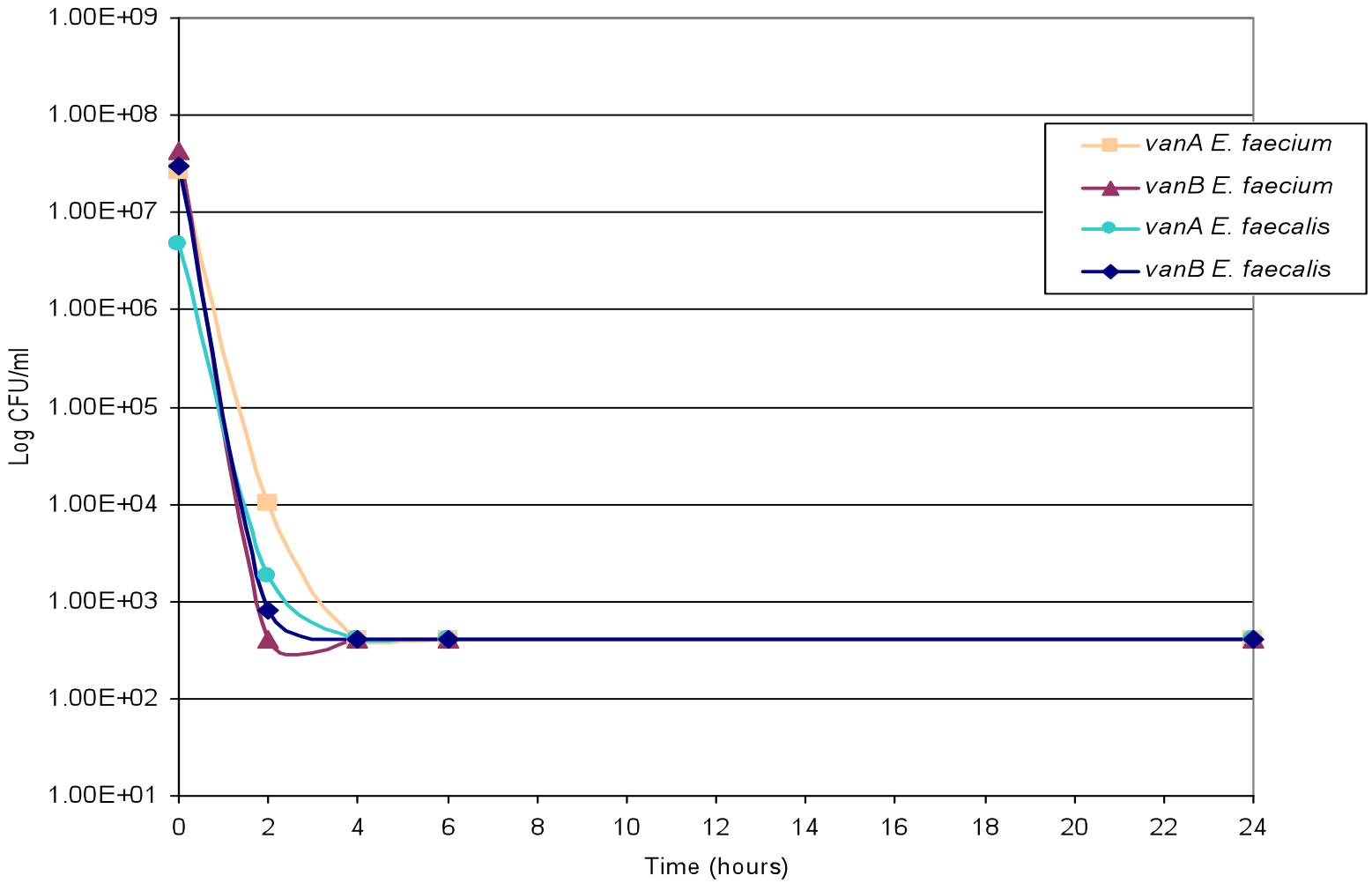
Activity (MICs) against Resistant Phenotypes

- hVISA/VISA (n = 19*): 2-4 mg/L
- CA-MRSA (n = 4): 2 mg/L
- VI-CNS (n = 9): 2-4 mg/L
- VanA *E. faecium* (n = 261): 0.06-2 mg/L
- VanB *E. faecium* (n = 39): 0.12-2 mg/L
- VanA *E. faecalis* (n = 50): 0.5-4 mg/L
- VanB *E. faecalis* (n = 29): 0.06-2 mg/L

*Includes Mu50

Timekill Kinetics – Enterococci

(Free peak/total trough concentration of 8 mg/L)



Oritavansin

- Hayvan modellerinde etkilidir
  - Ratlarda santral venöz kateter ilişkili infeksiyon modeli (vankomisin dirençli *Enterococcus faecalis*)
  - Tavşan endokardit modeli (MRSA and vankomisin hassas ve dirençli *E.faecalis*)
  - Nötropenik fare modeli (*S.aureus* American Type culture Collection 13709)
  - Tavşan menenji modeli (penisilin-duy. *S. Pneumonia*

Oritavansin

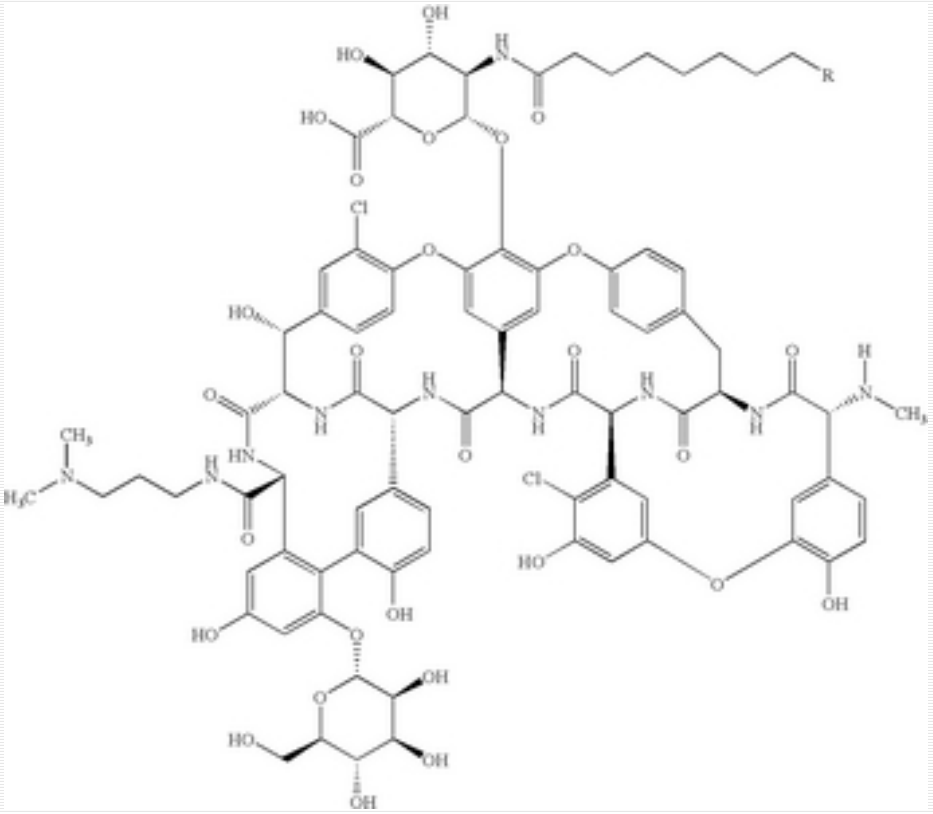
- Komplike cilt ve yumuşak doku infeksiyonlarında faz 2 çalışması vankomisin ve sefaleksinle karşılaştırma *(Mercier RC, et al. Expert Rev Anti-infec Ther 2005; 3: 325-32)*
- Yarı ömrü uzun
- Organizma içinde lizozomlarda birikme

Oritavansin

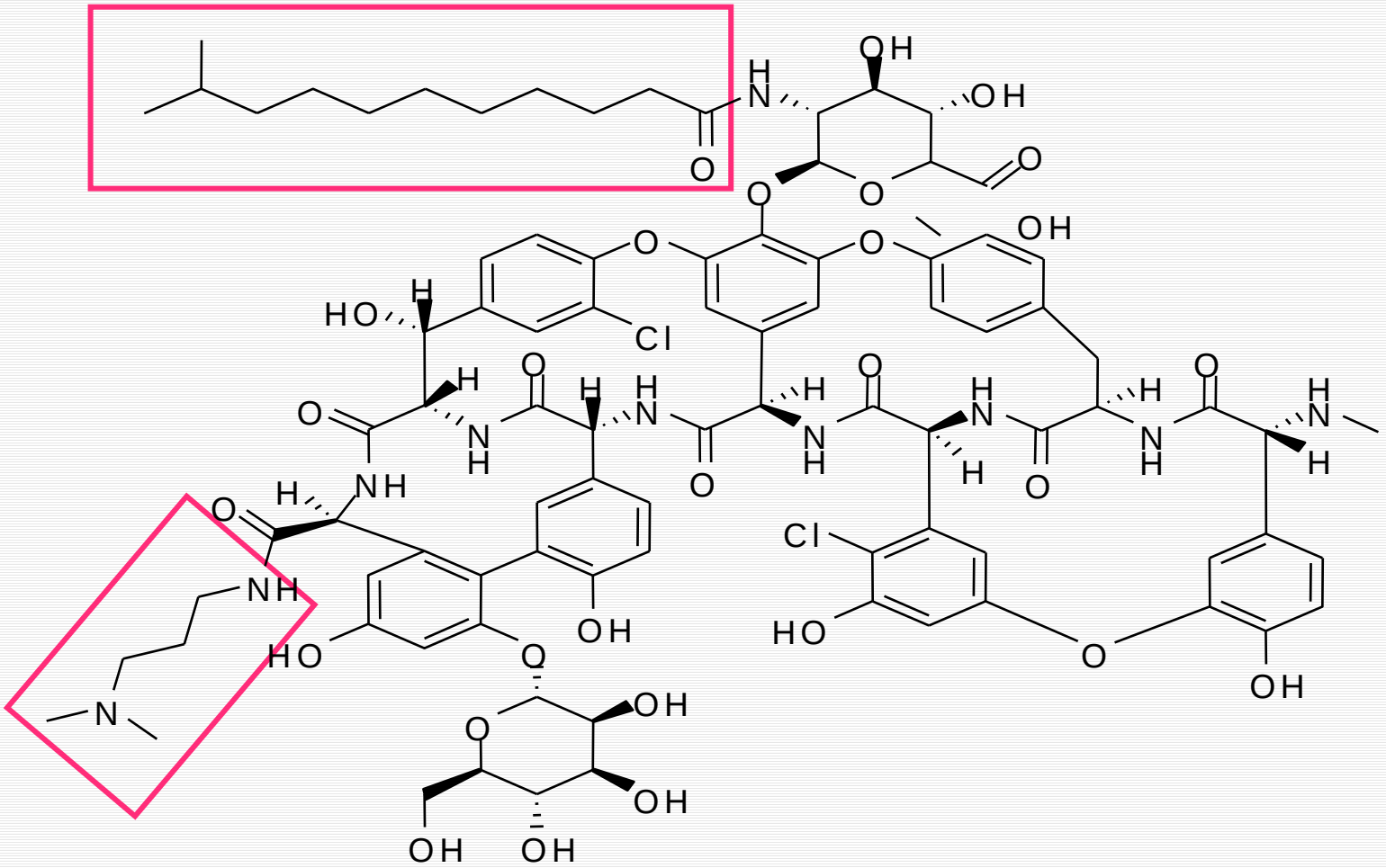
- Oritavancin has not yet been approved by the FDA. In general, oritavancin has been well-tolerated in clinical trials. The most commonly observed side effects in this clinical trial were headache, nausea, vomiting, constipation, and dizziness, which occurred at similar rates in the two treatment arms.

Dalbavancin

- Dalbavansin teikoplanin benzeri glikopeptid; A40926'ın modifikasyonu ile elde edilir
- Enterokok ve stafilokoklar dahil olmak üzere gram pozitif mikroorganizmalara karşı etkin



Dalbavancin; kimyasal yapı



Dalbavansin

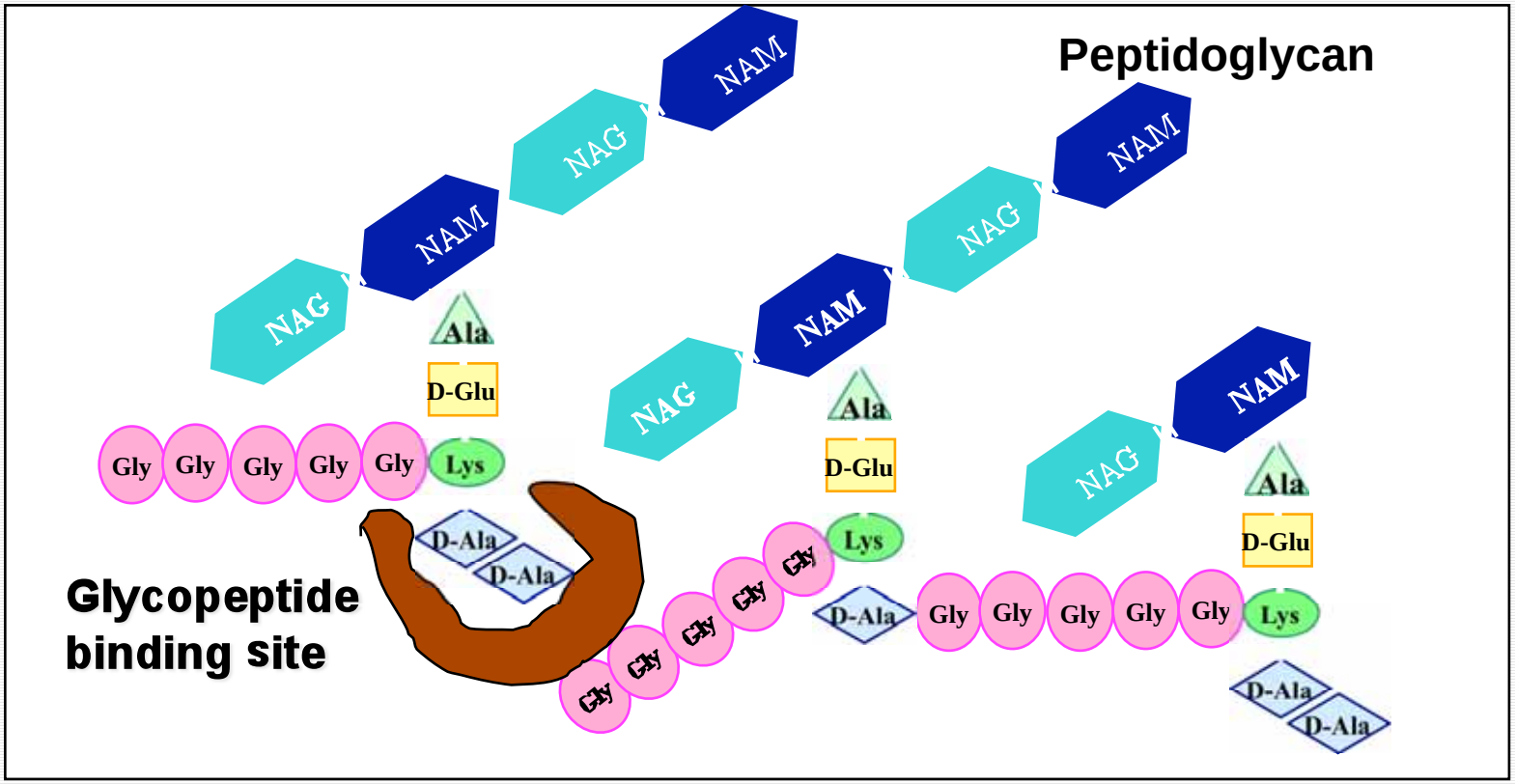
- Çok uzun yarı-ömür (9-12 gün)
- Haftalık doz avantajı (haftalık süper teikoplanin)
- In vitro ve in vivo diğer ajanlardan daha etkili
- Artmış MBC/MIC oranı

Dalbavancin
Mechanism of Action

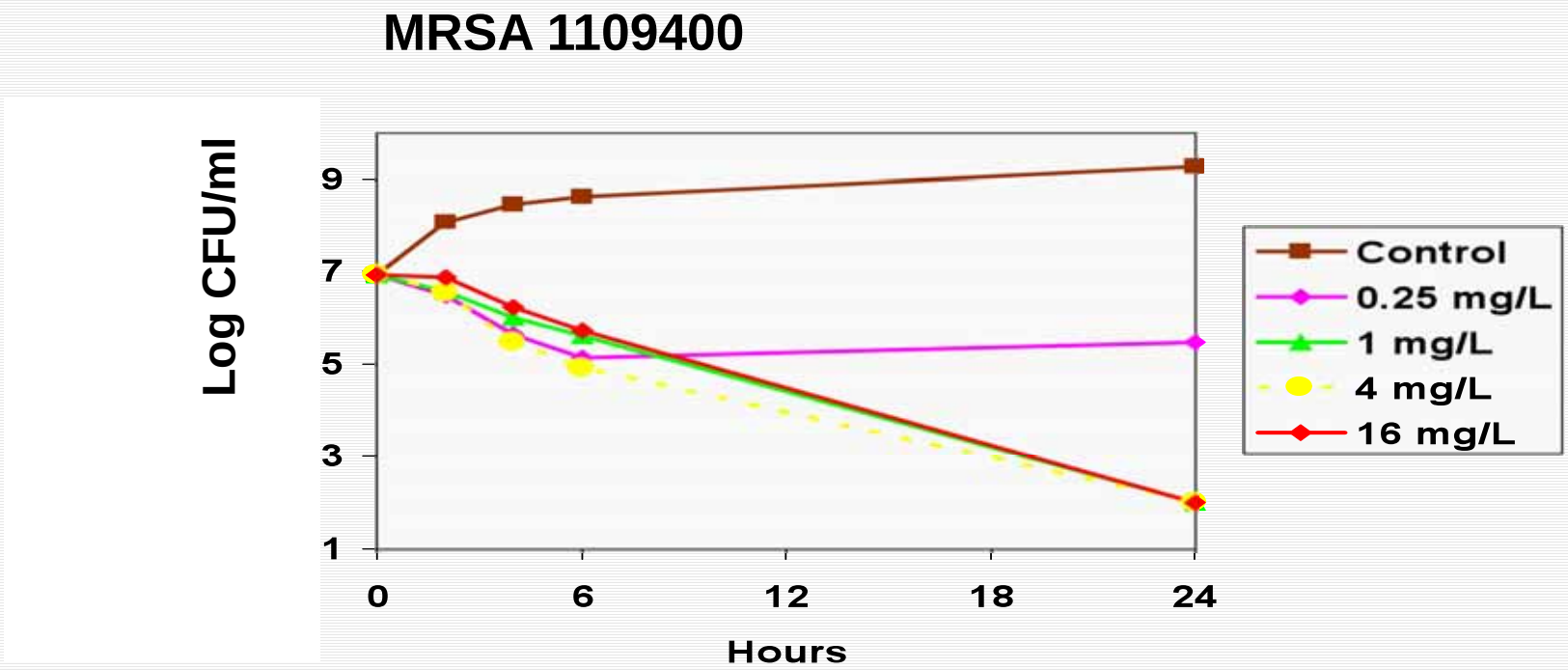
- Interferes with bacterial cell wall synthesis by binding to D-ala-D-ala and D-ala-D-ser
- Bactericidal
- No evidence of multiple mechanisms at relevant concentrations

Mechanism of Action of Dalbavancin

Blocks Bacterial Cell Wall Synthesis
By Binding to D-ala-D-ala



Bactericidal Activity of Dalbavancin



Goldstein AAC 2007;51:1150

Comparative Activity vs. Staphylococci

	MIC_{90} (mg/L)			
Organism	MSSA	MRSA	MS CoNS	MR CoNS
(N)	(2834)	(1119)	(353)	(1129)
Antibiotic				
Dalbavancin	0.06	0.06	0.06	0.12
Teicoplanin	1	4	4	4
Vancomycin	1	2	2	2

Jones. ICAAC 2004. Abstract E-2009.

Comparative Activity vs. Streptococci

Organism	S. pyogenes	other β-strep	viridans (Pen-NS)	pneumo (Pen-S)	pneumo (Pen-NS)
			MIC_{90} (mg/L)		
(N)	(173)	(216)	(49)	(604)	(286)
Antibiotic					
Dalbavancin	0.03	0.03	0.03	0.015	0.015
Vancomycin	0.5	1	0.5	0.5	0.5

Jones R. ICAAC 2004. Abstract F-2009

Comparative Activity vs. Vancomycin-Susceptible Enterococci

	MIC_{90} (mg/L)		
Organism	Van-S	Van-S	Other
	E. faecalis	*E. faecium*	*Enterococcus* spp.
(N)	(1324)	(189)	(76)
Dalbavancin	0.06	0.12	0.12
Vancomycin	2	2	>16

Data on File, Pfizer

Jones, R. ICAAC (2004) Poster E-2009

Comparative Activity vs. Vancomycin-Nonsusceptible Pathogens

	MIC Range (mg/L)		
	Dalbavancin	Vancomycin	Teicoplanin
VISA[1] (n=25)	0.06 - 1	8	4 - 32
VRSA[1,2] (n=2)	0.5, 16	>32	8, 32
Enterococci:[3]			
VanA (59)	0.03 - 32	>16	≥16
VanB (12)	0.015 - 0.25	>16	<2
VanC (6)	0.03 - 0.12	4-8	0.25 - 0.5

[1]Flamm, R. IDSA (2004) Poster 308

[2]Bozdogan, B. JAC (2003) 52:864

[3]Streit, J. DMID (2004) 48:137

Dalbavancin Pharmacokinetics

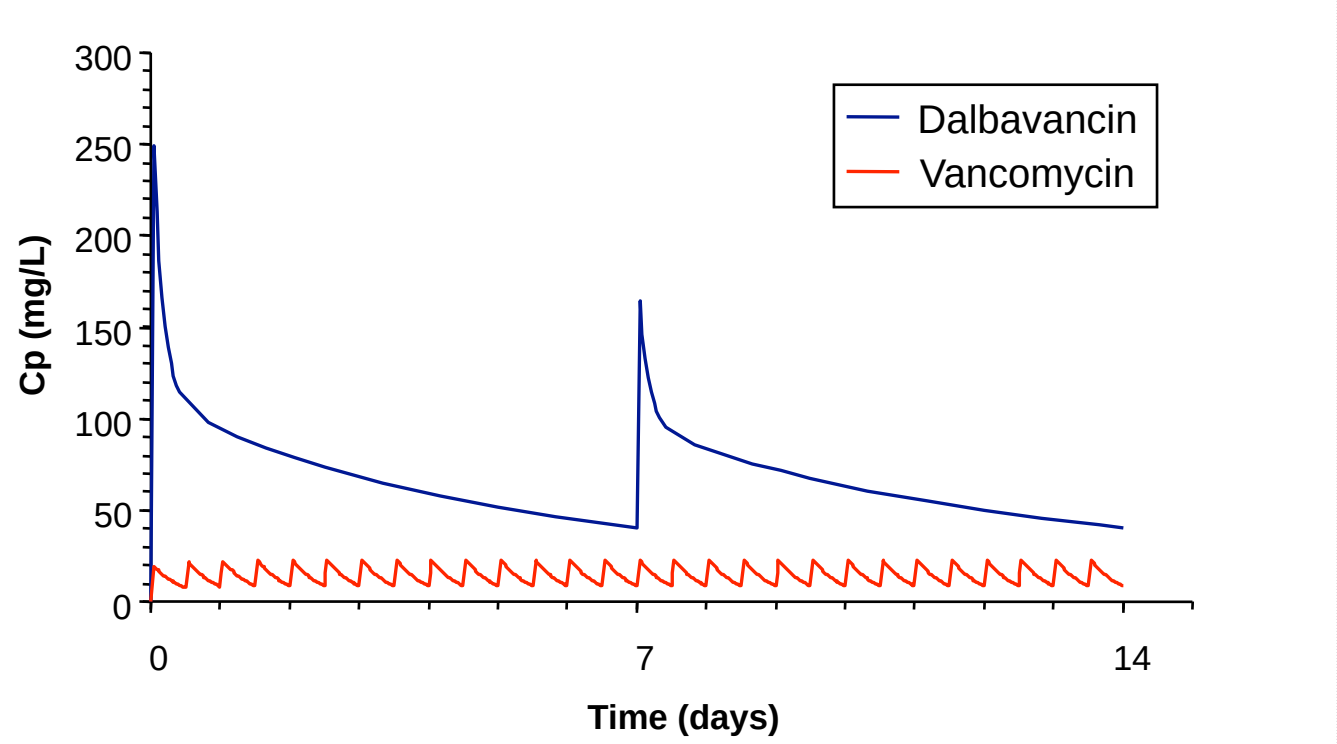
- Volume of distribution ~16 L
  - Good drug penetration into blister fluid
- Low potential for hepatic drug interactions
  - No metabolism by isolated human hepatocytes or microsomes
- Elimination by renal and nonrenal pathways

  ~40% of dose excreted unchanged in urine
- Predominant $t_{1/2}$ 5-7 days; supports once-weekly dosing

Dorr M JAC 2005;55 (suppl 2):ii25

Data on file, Pfizer

Dalbavancin and Vancomycin Plasma Concentrations



Dalbavancin (LD/MD): 1 g/0.5 g
Vancomycin (LD/MD): 1 g/0.75 g

Protein Binding

- Reversible plasma protein binding, ~93%
- Binding primarily to albumin
- Consistent across therapeutic range of concentrations

Data on file, Pfizer

Table 6

Summary of clinical trials with dalbavancin

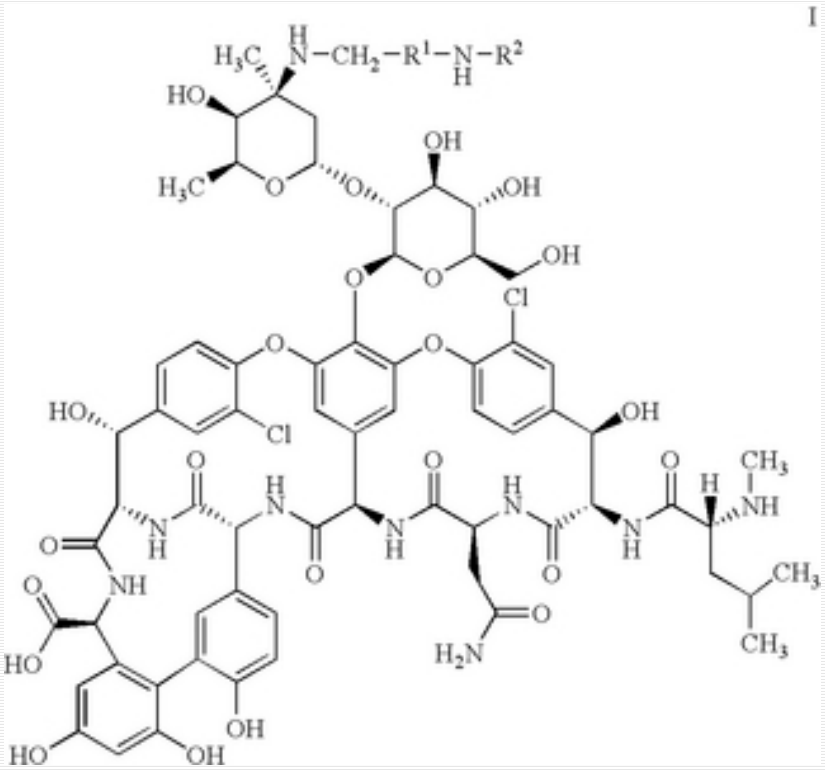
Reference	Patient population	Type of infection	Study regimens (# of patients)	Outcomes	Comments
Seltzer et al[31]	Adults with SSTI suspected or known to be caused by gram-positive bacteria.	SSTI that involved deep soft tissue and/or required significant surgical intervention, such as a major abscess, infected ulcer, major burn, or deep and extensive cellulites.	1,100 mg single IV dalbavancin (13) 1,000 mg/500 mg IV dalbavancin (17) Standard-of-care* (21)	Clinical response: 8/13 (62%) 16/17 (94%) 16/21 (76%)	Clinical response defined as cure or improvement of infection at follow-up visit. Response to single-dose dalbavancin measured at Day 24 and Day 34 for 2-dose dalbavancin, and 2 weeks after the last dose for comparator regimens.
Raad et al[34]	Adults with signs of bacteremia possibly or definitely associated with CR-BSI.	CR-BSI known or suspected to be cause by gram-positive pathogen.	1,000 mg/500 mg IV dalbavancin 1,000 mg vancomycin BID†	Clinical response: 20/23 (87%) 14/28 (50%)	Clinical response defined as cure or improvement of infection at follow-up visit such that no additional antibiotic treatment was warranted (21±3 d after treatment period).
Jauregui-Paredo et al[32]	Patients with cSSSIs.	cSSSI	1,000 mg / 500 mg IV dalbavancin 600 mg IV or IV/oral linezolid q 12 h for 14 d	Clinical success: 386/434 (88.9%)‡ 206/226 (91.2%)§ Micro success: 248/277 (89.5%)‡ 133/152 (87.5%)§	Primary end point defined as clinical response at test of cure in clinically evaluable patients. *S aureus* was the most common pathogen isolated; 56% were MRSA.
Goldstein et al[33]	Patients with SSSIs.	SSSI	Dalbavancin‖ Linezolid¶ Cefazolin¶ Vancomycin¶	Percent eradication at follow-up (all *S aureus*/MRSA) 88–93/90–91 89/89 91/– 83/82	Percent eradication determined in the microbiologically evaluable population. At baseline, 77% of gram-positive pathogens were *S aureus* and 38% were MRSA.

Tedavi İlişkili Yan Etkiler (≥2%)

Adverse Event	Percentage of Patients	
	Dalbavancin N=571	Linezolid N=283
Nausea	3.2	5.3
Diarrhea	2.5	5.7
Headache	1.9	1.8
↑LDH	1.9	1.8
↑GGT	1.9	1.4
Vomiting	1.9	1.1
Rash	1.8	1.8
Abnormal LFTs	1.6	1.1
Fungal vaginosis	0.9	1.8
Loose stools	0.4	2.1
Thrombocytopenia	0.2	2.5

Televansin

- Telavansin (TD-6424) vankomisinin semi-sentetik derivesi; desil-aminopropil derivesiyle vankosaminin alkillenmesi ile oluşur
- *S.pneumoniae ve S.aureus'a karşı artmış,* Van-A enterokok dahil tüm Gram-positif patojenlere karşı etkinlik



Televansin

- *in vitro* biofilm modellerinde etkinlik
- Hayvan modellerinde etkin
- Dokuya geçişi yüksek
- Post-antibiyotik etkisi
- QTc uzaması ile ilgili sorunlar

Televansin

Televancin is a rapidly bactericidal lipoglycopeptide analog of vancomycin. The mechanism of action is by inhibition of peptidoglycan chain formation through blockage of both the transpeptidation and transglycosylation steps; and by a direct effect on the bacterial membrane dissipating membrane potential and effecting changes in cellular permeability.

Barrett JF. Recent developments in glycopeptide antibacterials. Curr Opin Investig Drugs 2005; 6:781-90.

Televansin

The *in vitro* activity of telavancin demonstrates enhanced activity against MRSA, penicillin-resistant *S. pneumoniae,* GISA and Van A type enterococci. Telavancin achieves a higher volume of distribution into tissues and a prolongation of half-life [77]. A high level of protein binding (93%) occurs in human plasma and repetitive dosing does not lead to accumulation. The half-life is 7-9 hours at doses above 5 mg/kg [78]. Telavancin exhibit time-dependent killing [79].

Shaw JP, Seroogy J, Kaniga K, Higgins DL, Kitt M, Barriere S. Pharmacokinetics, serum inhibitory and bactericidal activity, and safety of telavancin in healthy subjects. Antimicrob Agents Chemother 2005; 49:195-201.

Televansin

Telavancin and its comparators of vancomycin or beta-lactam agent have been compared in a phase 2 trial for skin and skin-structure infections. Clinical cure rates were similar at 92% in for telavancin vs. 96% for comparator agents. Microbiologic rates of cure were noted to be 93% in the telavancin group and 95% among the comparator group[80]. For complicated skin and soft tissue infections, clinical cure rates were at 96% for telavancin and 90% for comparator agents. Microbiologic eradication was better with telavancin (92%) vs. comparator agents (78%, p = 0.07)

Stryjewski ME, Chu VH, O'Riordan WD, et al. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. Antimicrob Agents Chemother 2006; 50:862-7.

Televancin

Theravance, Inc (San Francisco, CA), has announced results from its ATLAS 1 and ATLAS 2 studies assessing the safety and efficacy of televancin, a rapidly acting bactericidal injectable antibiotic with multiple mechanisms of action, in the treatment of complicated skin and skin structure infections caused by Gram-positive bacteria. The 2 large, multicenter, multinational, double-blind, randomized, phase 3 clinical studies enrolled and treated 1867 patients, 719 of whom were infected with MRSA. In the combined data from both studies in patients with MRSA, clinical cure rates, microbiologic eradication rates, and overall therapeutic response favored televancin over vancomycin. The most common adverse events reported in patients receiving televancin were taste disturbance, nausea, and vomiting. Less than 1% of these events were considered severe.

▲ **Information: http://www.theravance.com**

Televancin

Telavancin is currently under assessment in phase 3 trials of hospital-acquired pneumonia. Adverse events associated with telavancin among patients included vomiting, paresthesias and dyspnea. Laboratory abnormalities included microalbuminemia and decreased platelets [81].

Stryjewski ME, Chu VH, O'Riordan WD, et al. Telavancin versus standard therapy for treatment of complicated skin and skin structure infections caused by gram-positive bacteria: FAST 2 study. Antimicrob Agents Chemother 2006; 50:862-7.

Televancin

- Efficacy of telavancin for treatment of surgical site infections, Wilson ve ark. *Critical Care* 2008, 12 (Suppl 2): P28doi: 10.1186/cc6249
- Vankomisin kadar etkili

Televancin

- In October the FDA issued a so-called approvable letter for televancin, suggesting it needed a re-analysis of clinical data and the resolution of manufacturing issues at a third-party manufacturer that was not specifically related to televancin.
- The FDA said it continues to review televancin's application but didn't give a timetable for completion of the review.

Oritavancin

- Glikopeptide
  - Vankomisinin yarı-sentetik türevi
- Geniş gram (+) kapsamı,

  MRSA dahil
- S.aureus karşı bakterisidal etki, MRSA dahil
- Faz 3 aşamasında
  - Vankomisine-dirençli enterokok suşlari dahil olmak üzere, cSSSI etkili, kan dolaşımı infeksiyonlarındaki kullanımı araştırılıyor
- Uzun yarı ömrü
- Günde tek doz intravenöz kullanımı

Dalbavancin

- 2. kuşak lipoglikopeptid
  - Teikoplanin türevi
- Etki mekanızması: hücre duvarı sentezini inhibe eder: bakterisidal
- Gram (+) bakterilere karşı çok etkili, MRSA dahil
- Uzun $t_{1/2}$ (8.5 gün) – Hafta tek doz
- Atılımı renal (%40) ve non-renal yollar ile
- Yan etkisi – en çok GİS
- Potansiyel klinik endikasyonları
  - SSSI (Faz 2 çalışmalarda vankomisine üstün)
  - CRBSI

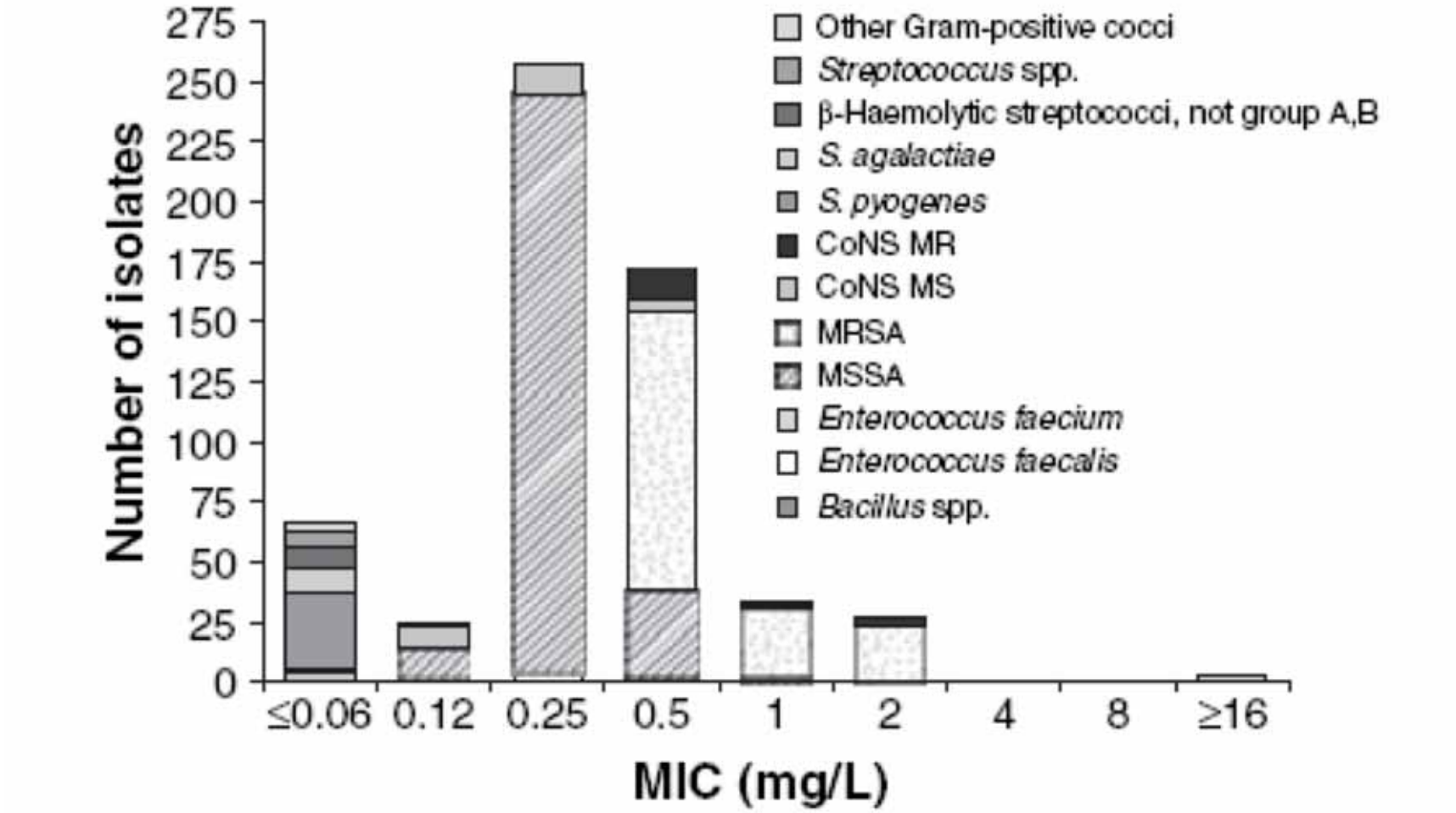
Telavancin

- Lipoglikopeptid
  - Vankomisinin yarı-sentetik türevi
- MRSA dahil, Gram (+) organismalara karşı hızlı bakterisidal aktivite
  - Multipl etki mekanizmaları
    - Hücre duvarı sentezini inhibe eder
    - Bakterinin membran fonksiyonları üzerinde direkt etki
- $T_{½}$: 6,9-9,1 saat, günde tek doz
- Faz 3 çalışmaları devam etmektedir (HAP, CSSI)

Ceftobiprole

- A novel broad-spectrum β-lactamase-stable parenteral cephalosporin with strong affinity for the penicilin-binding proteins PBP2a abd PBP2x responsible for resistance in staphylococci and pneumococci
- *in vivo*, good activity for ceftobiprole against *Gram-positive and Gram-negative bacteria*.
- Several animal models; mouse sepsis, abscess and pneumonia models, rat endocarditis and tissue cage models and a rabbit endocarditis model

Ceftobiprole



G.J Noel, *Clin Microbiol Infect* 2007; **13** (suppl 2): 25–29

Ceftobiprole

- Hayvan modelleri
  - Fare abse, sepsis ve pnömoni
  - Rat ve tavşan endokardit
- Nosokomiyal infeksiyonlarda monoterapi imkanı

Diğer Ajanlar

- Ceftaroline
- Ranbezolid
- İclaprim

Ceftaroline

- Ceftaroline is another broad-spectrum cephalosporin with activity against MRSA.
- Like ceftobiprole, ceftaroline inhibits bacterial cell wall synthesis and has enhanced binding affinity for PBP-2a resulting in anti-MRSA activity.
- Ceftaroline possesses potent bactericidal activity against many staphylococci, including both MSSA and MRSA.
- Ceftaroline retains activity against *S. aureus* with heterointermediate resistance to vancomycin (hVISA) and VISA.
- Ceftaroline is active against *S. pneumoniae,* including penicillin-intermediate and -resistant strains.

Ceftaroline

- Ceftaroline demonstrated similar clinical cure rates to vancomycin ± aztreonam in a phase II study for the treatment of cSSSIs.[39] Phase III studies for the treatment of community-acquired pneumonia and cSSSIs are currently under way.
- Pharmacokinetic studies in animals demonstrate ceftaroline achieves good lung penetration, and pending results from ongoing clinical trials will impact whether ceftaroline has a role as monotherapy in serious CAP or HCAP infections where MRSA is a potential etiologic organism.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2003, p. 1148–1150 Vol. 47, No. 3
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.3.1148–1150.2003

Antipneumococcal and Antistaphylococcal Activities of Ranbezolid (RBX 7644), a New Oxazolidinone, Compared to Those of Other Agents

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Department of Pathology, Hershey Medical Center, Hershey, Pennsylvania 17033[1]; Ranbaxy Research Laboratories, New Delhi, India[2]; and Department of Pathology, Case Western Reserve University, Cleveland, Ohio 44106[3]

Received 4 October 2002/Returned for modification 2 December 2002/Accepted 18 December 2002

For 260 pneumococcal and 266 staphylococcal strains, ranbezolid MICs ranged from ≤0.06 to 4 μg/ml. The MICs for pneumococci were similar irrespective of the strains' β-lactam, macrolide, or quinolone susceptibilities, and ranbezolid MICs for coagulase-negative staphylococci were lower than those for *Staphylococcus aureus*. Ranbezolid was bacteriostatic against pneumococci. Ranbezolid MICs were similar to or lower than those of linezolid. Vancomycin and quinupristin-dalfopristin were also very active.

Ranbezolide

TABLE 3. Summary of MICs (micrograms per milliliter) for *S. aureus* strains

Drug	Methicillin-resistant *S. aureus* (n = 68)			Methicillin-susceptible *S. aureus* (n = 65)		
	MIC range	MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}
Ranbezolid	0.25–4	2	4	0.5–4	2	2
Linezolid	0.5–4	2	4	1–4	2	4
Vancomycin	0.5–2	1	1	0.5–2	1	1
Teicoplanin	0.125–16	0.5	1	0.125–4	0.5	1
Quinupristin-dalfopristin	0.125–1	0.5	1	≤0.06–1	0.5	0.5

Ranbezolide

TABLE 4. Summary of MICs (micrograms per milliliter) for coagulase-negative staphylococci

Drug	Coagulase-negative, methicillin-resistant staphylococci (n = 69)			Coagulase-negative, methicillin-susceptible staphylococci (n = 64)		
	MIC range	MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}
Ranbezolid	≤0.06–4	0.25	1	≤0.06–1	0.125	0.5
Linezolid	1–4	2	4	0.5–4	1	2
Vancomycin	0.125–4	2	2	0.125–2	1	2
Teicoplanin	≤0.06–>16	4	16	0.06–8	1	4
Quinupristin-dalfopristin	0.125–2	0.25	0.5	≤0.06–1	0.25	0.5

İclaprim

Iclaprim is a diaminopyrimidine that inhibits the enzyme dihydrofolate reductase. Data on iclaprim are limited. However, it has activity against MRSA, and preliminary results from a phase 3 trial in patients with complicated SSTIs showed noninferiority of iclaprim to linezolid at the test of cure [44]. In this study, ~25% of the infections were due to MRSA.

44. Arpida. Intravenous iclaprim. Available at: http://www.arpida.ch/index.php?MenuID=13&UserID=1&ContentID=65. Accessed 2 February 2007.

Gülhane Mikrobiyoloji Günleri

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Antimikrobik Kemoterapi
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