İnfektif endokarditin antibiyotik tedavisinde antimikrobiyal direnç bir sorun mu?

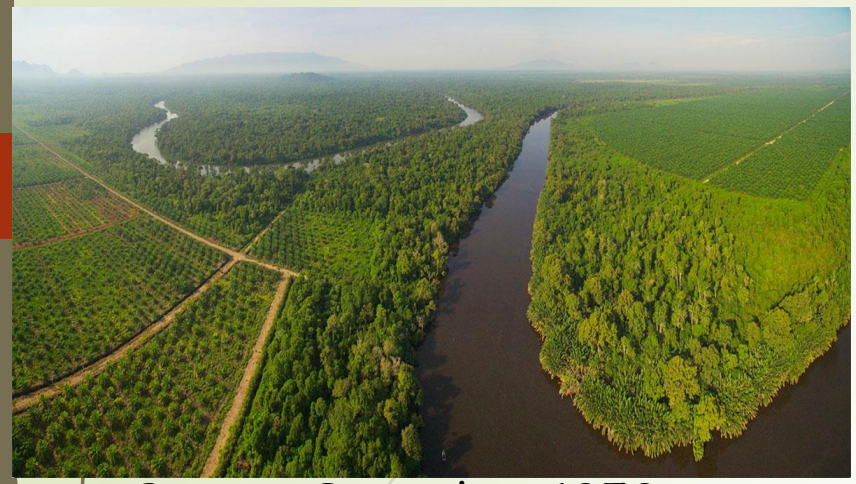
VANKOMİSİN

Dr. Süda TEKİN
Koç Üniversitesi Hastanesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Bölümü

KLİMİK

Sunum İçeriği

- Vankomisin ve direncinin saptanması
- Dirençte epidemiyoloji
- Stafilokok vankomisin MIC önemi
- Enterokoklarda vankomisin MIC önemi
- Vankomisin ve varsa seçenekleri



Borneo Ormanları-1950

Vankomisin

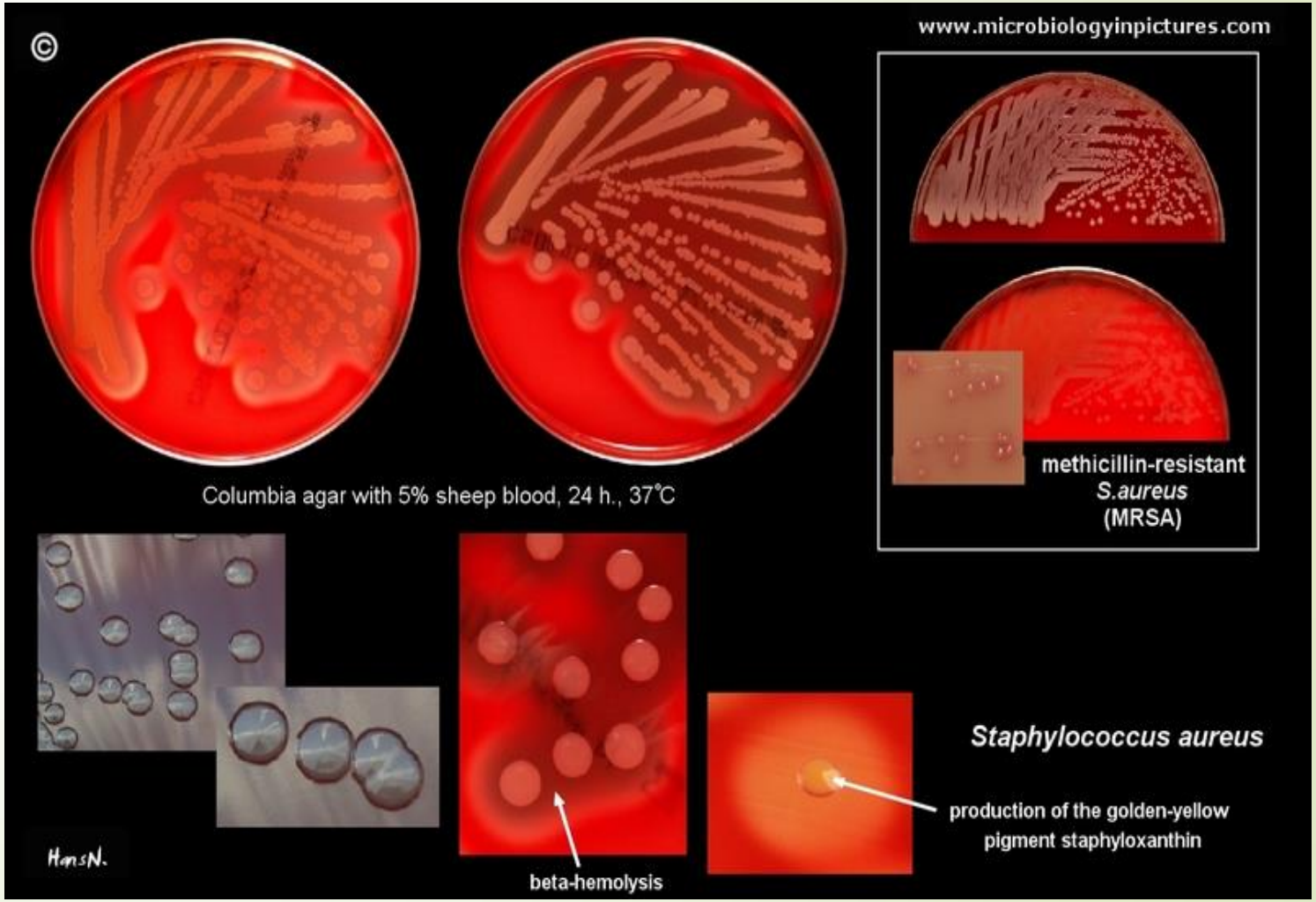
Edmund Carl Kornfeld

- *Amycolatopsis orientalis'in* (*Streptomyces orientalis*'in *Nocardia orientalis*) ürettiği bir madde
- 1953 yılında keşfedilen ilk glikopeptid
- **Vanquish (yenmek, alt etmek)**
- 1980'den sonra yoğun kullanım
  - Patent hakkı bittiği için, diğer antimikrobiyallere yapılan **yoğun pazarlama çalışmaları yapılmadı**
  - Gerçek bir klinik gereksinimle yerini kendisi buldu

Moellering RC. CID 2006; 42: S3-4

Stafilokoklar

Ne kadar sorun?



CLSI

CLINICAL AND LABORATORY STANDARDS INSTITUTE

- 1969 NCCLS
- 2001 CLSI

EUCAST- Avrupa Antibiyotik Duyarlılık Komitesi

- 1997'de oluşturuldu, bugünkü halini 2002'de aldı.

S.aureus'ta Vankomisin Duyarlılığının Belirlenmesi

- Disk difüzyon veya otomatize yöntemler azalmış duyarlılığı belirlemede yetersiz
- MIC belirlenmeli
  - BMD
    - Referans yöntem
  - E test
    - MIC değeri 0.5-1.5 kat dilüsyon daha yüksek
    - E test yöntemiyle belirlenmiş MIC değeri, tedavi başarısızlığını göstermede BMD'den daha iyi
    - Daha güvenilir ve pratik

Holmes NE. J Clin Microbiol 2012, 50(8):2548-52

Stafilokoklarda Vankomisin Direncinin Belirlenmesi

Tür	Vankomisin diski zon çapı		Vankomisin MIC değerleri µg/ml		
	Duyarlı	Dirençli	Duyarlı	Orta duyarlı	Dirençli
S.aureus					
CLSI-2015	ÖNERİLMEZ		≤2	4-8	≥16
EUCAST-2017	ÖNERİLMEZ		≤2		>2
Koagülaz- negatif stafilokok					
CLSI-2015	ÖNERİLMEZ		≤4	8-16	≥32
EUCAST-2017	ÖNERİLMEZ		≤4		>4

Staphylococcus spp.

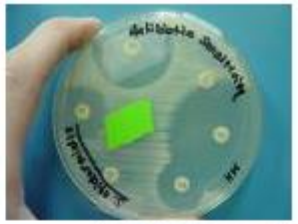
Glycopeptides and lipoglycopeptides[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
	S ≤	R >		S ≥	R <	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Dalbavancin[2]	0.125[3,4]	0.125[3]		Note[A]	Note[A]	1. Glycopeptide MICs are method dependent and should be determined by broth microdilution (reference ISO 20776). *S. aureus* with vancomycin MIC values of 2 mg/L are on the border of the wild type distribution and there may be an impaired clinical response. The resistant breakpoint has been reduced to 2 mg/L to avoid reporting "GISA" isolates intermediate as serious infections with "GISA" isolates are not treatable with increased doses of vancomycin or teicoplanin. 2. Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory. 3. MICs must be determined in the presence of polysorbate-80 (0.002% in the medium for broth dilution methods; agar dilution methods have not been validated). Follow the manufacturer's instructions for commercial systems. 4. *S. aureus* isolates susceptible to vancomycin can be reported susceptible to dalbavancin and oritavancin. 5. MRSA isolates susceptible to vancomycin can be reported susceptible to telavancin. A. Disk diffusion is unreliable and cannot distinguish between wild type isolates and those with non-*vanA*-mediated glycopeptide resistance.
Oritavancin, *S. aureus*[2]	0.125[3,4]	0.125[3]		Note[A]	Note[A]	
Teicoplanin, *S. aureus*[2]	2	2		Note[A]	Note[A]	
Teicoplanin, Coagulase-negative staphylococci[2]	4	4		Note[A]	Note[A]	
Telavancin, MRSA[2]	0.125[3,5]	0.125[3]		Note[A]	Note[A]	
Vancomycin, *S. aureus*[2]	2	2		Note[A]	Note[A]	
Vancomycin, Coagulase-negative staphylococci[2]	4	4		Note[A]	Note[A]	

Staphylococcus spp.

EUCAST Clinical Breakpoint Tables v. 7.1, valid from 2017-03-10

Oxazolidinones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
	S ≤	R >		S ≥	R <	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Linezolid	4	4	10	21[A]	21[A]	1. Isolates susceptible to linezolid can be reported susceptible to tedizolid. A. Examine zone edges with transmitted light (plate held up to light). B. Isolates susceptible to linezolid can be reported susceptible to tedizolid. For isolates resistant to linezolid, perform an MIC test.
Tedizolid	0.5[1]	0.5		Note[B]	Note[B]	







Stafilokoklarda direnç fenotipinden genotipe

Stafilokoklarda glikopeptidlere azalmış duyarlılık

- İlk kez 1997'de Japonya'da, daha sonra Avrupa ve ABD'de vankomisine duyarlılığı azalmış (MİK 8 µg/ml) *S. aureus* suşları ⟶ VISA/GISA
- 2002 ABD VRSA suşları

- Vankomisin disk testinde *vanA* geni taşıyan VRS
- İnhibisyon zonu gözlenmeyen izolatların tür düz
  doğrulanması gerekir.

S.aureus'ta vankomisin duyarlılığının belirlenmesine ilişkin notlar;

Disk diffüzyon yöntemi ile

- **VRSA** (MİK ≥ 16 µg/mL) saptanabilir ancak
- **VISA** (MİK 4-8µg/mL) veya **hVISA** (heteroVISA) saptanamaz

Vankomisine Direnç

- VRSA: Yok denilebilir
  - 2002'den beri 13 adet bildirildi
- VISA
  - ABD ve Avrupa'da %0.3'ün altında
- hVISA
  - Vankomisin MIC değeri orta duyarlılık aralığında bulunan alt popülasyon içeren, ancak tüm popülasyonunun MIC değeri duyarlı aralığında bulunan *S.aureus* suşu
  - Vankomisinle klinik başarısızlıktaki rolü?? Bildirimler var.
- MIC "creep"

Vardakas KZ. Mayo Clin Proc 2012;87: 349-63

Moise PA. Lancet Infect Dis 2009; 9: 617-24

Tablo 25 . Antimikrobiyal Direnç Oranları* ve Dağılımları.2015.

Antimikrobiyal Direnç Hızları				
ANTİMİKROBİYAL DİRENÇLİ PATOJEN	Birim sayısı	Etken sayısı (toplam)	Dirençli etken sayısı	Ağırlıklı genel ortalama
TÜRKİYE GENELİ				
VRE				
MRSA				
MRKNS				
SAĞLIK BAKANLIĞI DEVLET HASTANELERİ				
VRE				
MRSA	139(14)	566	269	47.53
MRKNS	115(15)	548	364	66.42
ÜNİVERSİTE HASTANELERİ				
VRE	105(51)	1458	240	16.46
MRSA	36(31)	948	353	37.24
MRKNS	63(36)	1476	1089	73.78
ÖZEL HASTANELERİ				
VRE	74(3)	217	44	20.28
MRSA	141(12)	604	185	30.63
MRKNS	81(19)	536	215	40.11

UHESA Özet Raporu, 2015

Denef Berzeg

Alıcı: bana

Süda Hanım, merhaba,

Siyami Ersek Hastanesinde hem *E.faecalis*, hem *S.aureus*'ta daptomisin direnci gördük, ancak vankomisin direnci görmedik

Iyi çalışmalar dilerim.

KÜH;

- 2015 => 16 MR*S. aureus* (1 suş MİK=2, 1 suş MİK= 4)
- 2016 => MRSA: 17 (4'ünde MİK= 2 , 1 MİK=4)
- 2017 => ilk 9 ay MRSA: 43 (1 MİK= 2, 1 MİK= 4)

- 2015 => VRE: 5
- 2016 => 29
- 2017 ilk 9 ay=> 30
- **VRE endokardit yok.**

Sit *et al. BMC Infectious Diseases* (2017) 17:274
DOI 10.1186/s12879-017-2384-y

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infection and the molecular characteristics of MRSA bacteraemia over a two-year period in a tertiary teaching hospital in Malaysia

Pik San Sit[1], Cindy Shuan Ju Teh[1], Nuryana Idris[1], I-Ching Sam[1], Sharifah Faridah Syed Omar[2], Helmi Sulaiman[2], Kwai Lin Thong[3], Adeeba Kamarulzaman[2] and Sasheela Ponnampalavanar[2*]

2011-2012 arası
209 MRSA suşu
Hepsi Vankomisin duyarlı

Table 3 Comparison between SCC*mec* types with the patient's demographic, clinical diagnosis and molecular characteristics of MRSA strains isolated from blood

	SCC*mec* III	SCC*mec* IV	SCC*mec* V	Untypeable	Total
	N = 60 (%)	*N* = 27 (%)	*N* = 2 (%)	*N* = 2 (%)	*N* = 91 (%)
Vancomycin MIC					
< 1.5 μg/mL	22 (36.7)	25 (92.6)	1 (50)	1 (50)	49 (53.8)
≥ 1.5 μg/mL	38 (63.3)	2 (7.4)	1 (50)	1 (50)	42 (46.2)

Influence of Vancomycin Minimum Inhibitory Concentration on the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Clinical Infectious Diseases 2008; 46:193–200

Alex Soriano,[1] Francesc Marco,[2] José A. Martínez,[1] Elena Pisos,[1] Manel Almela,[2] Veselka P. Dimova,[2] Dolores Alamo,[2] Mar Ortega,[1] Josefina Lopez,[1] and Josep Mensa[1]

Departments of [1]Infectious Diseases and [2]Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain

Toplam 414 MRSA bakteriyemi epizotu

- Vankomisin MIC of 1 mg/mL (38)
- Vankomisin MIC of 1.5 mg/mL (90)
- Vankomisin MIC of 2 mg/mL (40)
- Uygun olmayan AB tedavisi (246)

Influence of Vancomycin Minimum Inhibitory Concentration on the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Clinical Infectious Diseases 2008; 46:193-200

Table 3. Factors independently associated with shock in a logistic regression model of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Factor	OR (95% CI)	*P*
MIC		
1 μg/mL	1	
1.5 μg/mL	0.59 (0.33–1.05)	.07
2 μg/mL	0.33 (0.15–0.75)	.012
Female sex	1.81 (1.07–3.05)	.025
Liver cirrhosis	2.09 (1.06–4.11)	.03
Source of bacteremia		
Low risk	1	
Intermediate risk	1.25 (0.66–2.36)	.48
High risk	2.40 (1.28–4.49)	.008
Receipt of mechanical ventilation	3.19 (1.53–6.66)	.002

Table 4. Factors associated with mortality in a univariate analysis of patients with episodes of methicillin-resistant *Staphylococcus aureus* bacteremia.

Variable	Survival (*n* = 298)	Death (*n* = 116)	OR (95% CI)
MIC			
1 μg/mL	79 (26.51)	30 (25.86)	1
1.5 μg/mL	153 (51.34)	60 (51.72)	1.03 (0.6–1.7)
2 μg/mL	66 (22.14)	26 (22.41)	1.04 (0.6–1.9)

Case Report

DOI: 10.7860/JCDR/2016/21709.9085

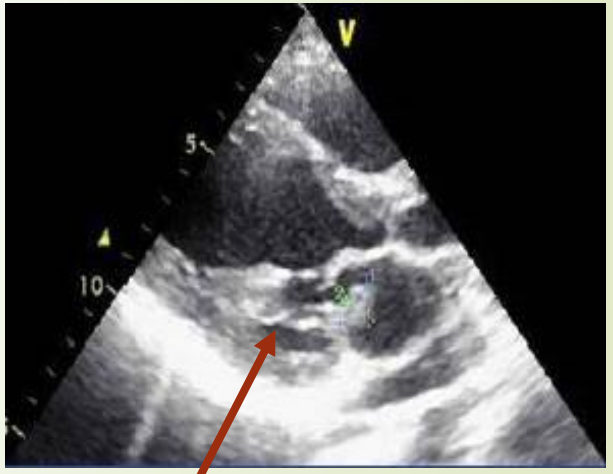
An Unusual Occurrence of Methicillin Resistant Staphylococcal Endocarditis with Vancomycin Creep Phenomenon – A Therapeutic Challenge

Internal Medicine Section

J Clin Diag Res. 2016;10: OD12-OD14

S SNEHA[1], SHANTHAN VENISHETTY[2], SHUBHA SESHADRI[3], M SUDHAKAR RAO[4], CHIRANJAY MUKHOPADHYAY[5]

- 41 yaşında sağlıklı erkek
- Kırık sonrası KBY
- Kan kültürü MRSA => Vankomisine duyarlı
- Vankomisin 2x 30 mg/kg 14 gün veriliyor



Vejetasyon

- Tekrarlayan kan kültürlerinde MRSA
- Tedavinin 5., 10. ve 14. günlerinde
- Vankomisin MIC; 0.5 → 2.0.

Tedavi daptomisin

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

- Vankomisin dozu ve seviyelerin izlemi
  - 2-3x15–20 mg/kg (her bir doz 2 gr'ı aşmamalı)
  - Yükleme dozu 25–30 mg/kg
  - Ciddi infeksiyonlarda vadi seviyesinin 15–20 µg/ml olması sağlanmalı
  - Vankomisin >AUC/MIC 400
  - Vadi seviyesinin izlemi
    - Dördüncü dozdan önce bakılmalı (haftada bir/günlük)
    - 5 günden uzun süreli kullanacaklar
    - Nefrotoksisite riski yüksek hastalar
    - Böbrek fonksiyonları bozuk olanlar

Rybak M. Am J Health-Syst Pharma. 2009;66:82-98.

Antimicrob Agents Chemother. 2014, 58(1):102

β-Lactams Enhance Vancomycin Activity against Methicillin-Resistant *Staphylococcus aureus* Bacteremia Compared to Vancomycin Alone

Thomas J. Dilworth,[a] Omar Ibrahim,[a] Pamela Hall,[b] Jora Sliwinski,[a] Carla Walraven,[c] Renée-Claude Mercier[a]

- MRSA eradikasyonunda **hVISA** durumunda kombinasyaon tedavi etkinliği
- ✓ Kan kültüründe MRSA, VAN MIC≤2mg/l

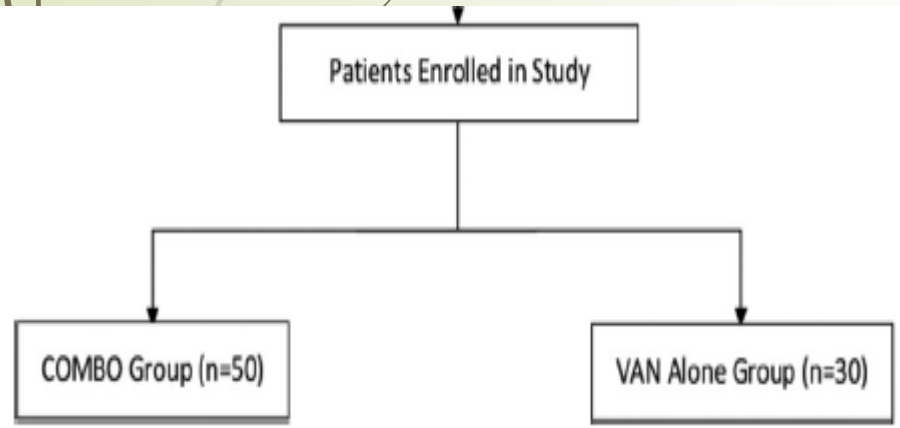


TABLE 3 Microbiological eradication in patients with MRSA bacteremia

Patient group	Eradication frequency by treatment group[a]		
	Combo	VAN alone	*P* value
All patients	48/50 (96.0)	24/30 (80.0)	0.021
Patients with IE	11/11 (100.0)	9/11 (81.8)	0.200

	Value for the group		
	Combo (n = 50)	VAN alone (n = 30)	*P* value[b]
Origin of bacteremia (no. of patients [%])			
Endocarditis	11 (22.0)	11 (36.7)	0.159
Osteomyelitis	11 (22.0)	4 (13.3)	0.327
Skin and soft tissue infection	5 (10.0)	1 (3.3)	0.402[f]
Other[i]	20 (40.0)	13 (43.3)	0.770
More than one source	3 (6.0)	1 (3.3)	>0.999[f]

AAC Journals.ASM.org

Antimicrob Agents Chemother. 2014, 58(1):102

β-Lactams Enhance Vancomycin Activity against Methicillin-Resistant *Staphylococcus aureus* Bacteremia Compared to Vancomycin Alone

Thomas J. Dilworth,[a] Omar Ibrahim,[a] Pamela Hall,[b] Jora Sliwinski,[a] Carla Walraven,[c] Renée-Claude Mercier[a]

TABLE 5 Multivariable analysis of the association between potential predictor variables and microbiological eradication in patients with MRSA bacteremia

Variable	Value for the variable[a]		
	AOR	95% CI	*P* value
Treatment group (Combo vs VAN alone)	11.24	1.72–144.34	0.010
Vancomycin serum level (mg/liter)[b]	0.93	0.86–0.98	0.006
Hemodialysis	0.042	0.01–0.25	≤0.001

Clinical Infectious Diseases

MAJOR ARTICLE

CID. 2016;62:173–80

Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Pilot Multicenter Randomized Controlled Trial

- MRSA bakteriyemisi →**kombine vankomisin+iv flukloksasilin** 4x2 g & **vankomisin** 2x1.5 g
- Sonlanım=> **Eradikasyon**

Susceptibility and Characteristics	Standard Therapy (n = 28)[a]	Combination Therapy (n = 31)
Antibiotic susceptibility		
Vancomycin MIC, median (IQR), μg/mL	0.75 (0.63–1.0)	0.75 (0.50–1.0)
Vancomycin MIC ≥1.5 μg/mL, No. (%)	4 (14)	2 (6)
Oxacillin MIC, median (IQR), μg/mL	256 (96–256)	256 (128–256)
Endocarditis	0 (0)	1 (3)

Clinical Infectious Diseases
MAJOR ARTICLE
CID. 2016;62:173–80

Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Pilot Multicenter Randomized Controlled Trial

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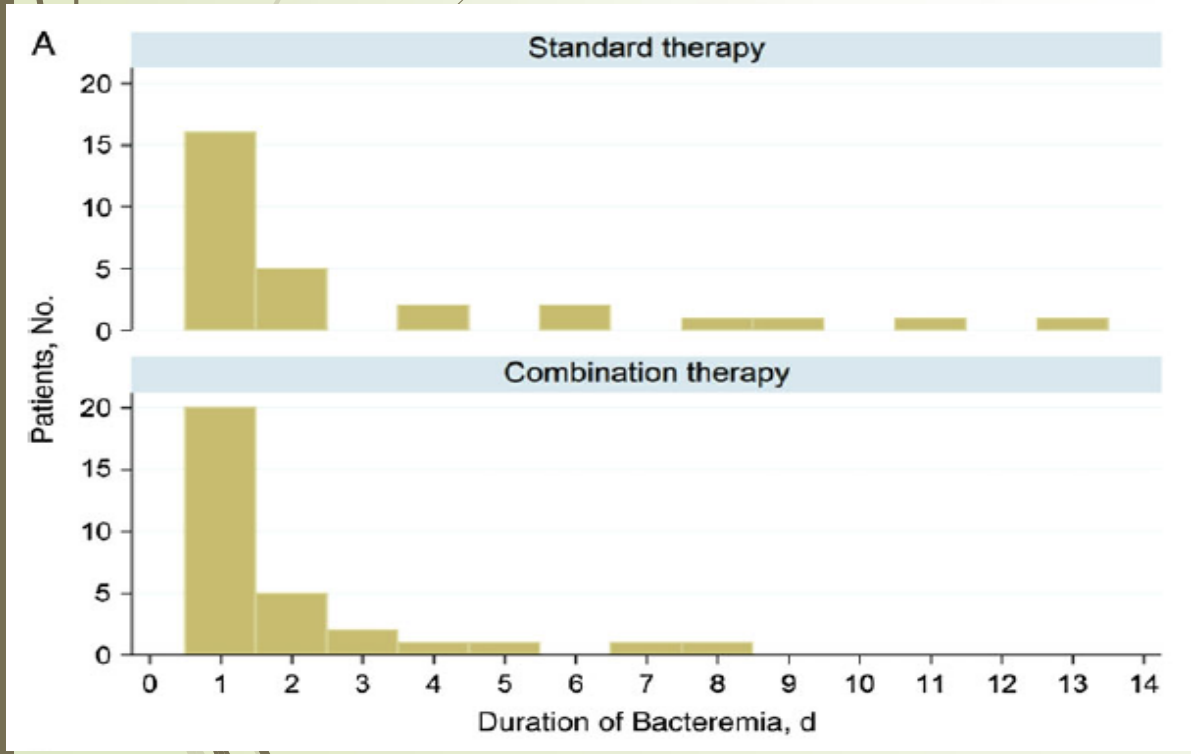
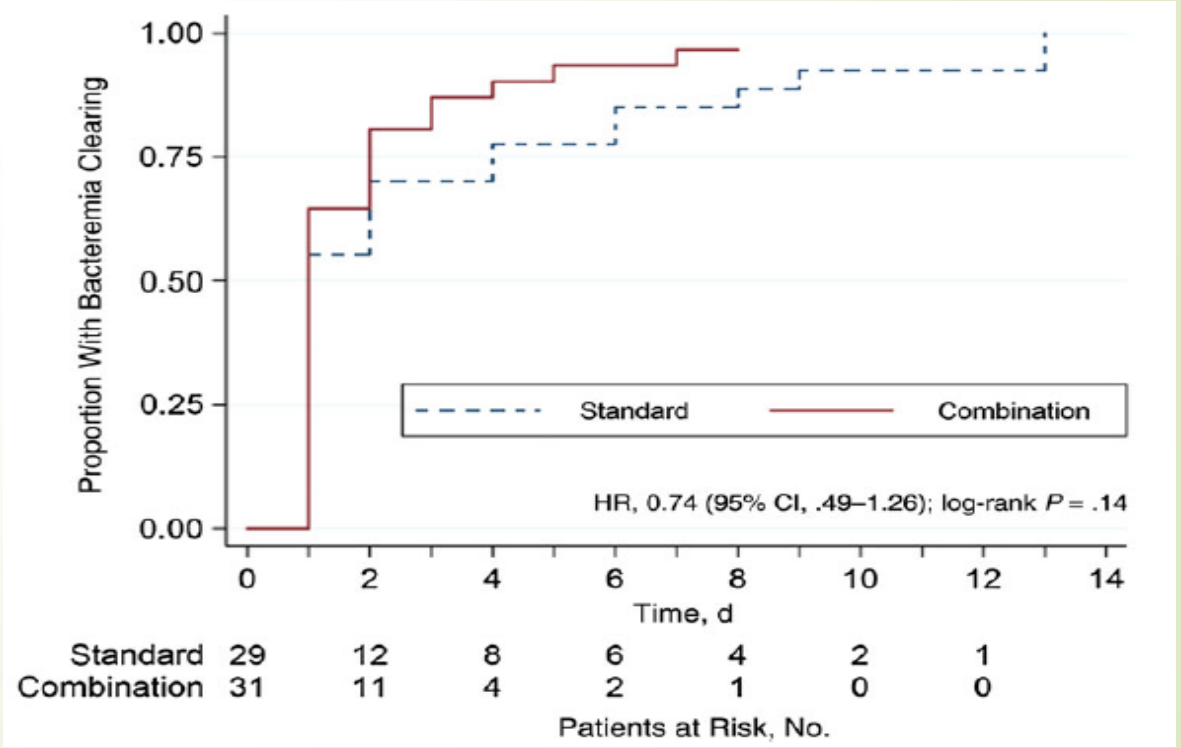
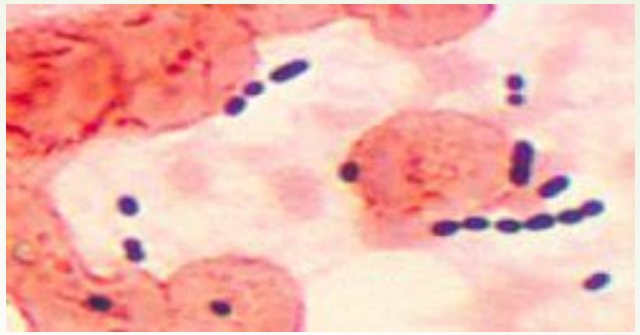
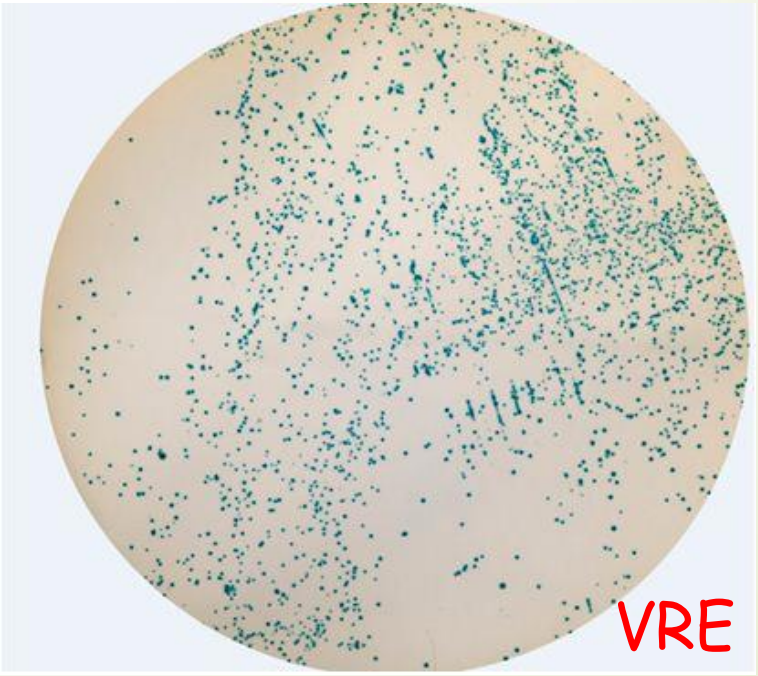




Enterokoklar





Enterococcus spp.

In endocarditis, refer to national or international endocarditis guidelines for breakpoints for *Enterococcus* spp.

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar
Inoculum: McFarland 0.5
Incubation: Air, 35±1°C, 18±2h (for glycopeptides 24h)
Reading: Read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light (except for vancomycin, see below).
Quality control: *Enterococcus faecalis* ATCC 29212

Penicillins[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Benzylpenicillin	-	-		-	-
Ampicillin	4	8	2	10	8
Ampicillin-sulbactam[2]	4[3]	8[3]		Note[A]	Note[A]
Amoxicillin[2]	4	8		Note[A]	Note[A]

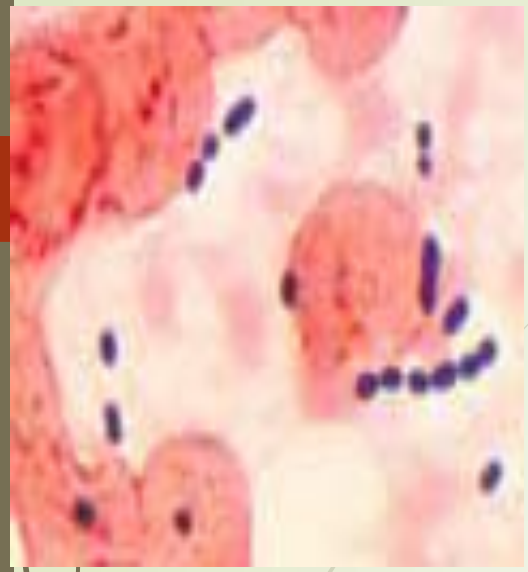
Notes
Numbered notes relate to general comments and/or MIC breakpoints.
Lettered notes relate to the disk diffusion method.

1. *E. faecium* resistant to penicillins can be considered resistant to all other beta-lactam agents including carbapenems.
2/A. Susceptibility to ampicillin, amoxicillin and piperacillin with and without beta-lactamase inhibitor can be inferred from ampicillin.
3. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
4. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.

Glycopeptides and lipoglycopeptides	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Dalbavancin	IE	IE		IE	IE
Oritavancin	IE	IE		IE	IE
Teicoplanin	2	2	30	16	16
Telavancin	IE	IE		IE	IE
Vancomycin	4	4	5	12[A]	12[A]

Notes
Numbered notes relate to general comments and/or MIC breakpoints.
Lettered notes relate to the disk diffusion method.

A. Vancomycin susceptible enterococci exhibit sharp zone edges and do not exhibit colonies in the inhibition zone. Examine zone edges with transmitted light (plate held up to light). If the zone edge is fuzzy, colonies grow within the zone or if you are uncertain, then perform confirmatory testing with PCR or report resistant (**see pictures below**) even if the zone diameter is ≥ 12 mm. Isolates must not be reported susceptible before 24 h incubation.



Enterokoklarda glikopeptid direnç fenotipleri

Fenotip	Vanko MİK	Teiko MİK	Ekspresyon	Kodlandığı yer	Konjugasyonla geçiş	Bulunduğu tür
VanA	64->1024	16-512	**İndüklenebilir**	Plazmid Transpozon	+	*E.faecalis, E.faecium, E.durans, E.gallinarum*
VanB	4-1000	0.5-1	**İndüklenebilir**	Çoğunlukla kromozom	+	*E.faecium, E.faecalis*
VanC	2-32	≤0.5	Yapısal	Kromozom	-	*E.gallinarum, E.flavescens,* ***E.casseliflavus***
VanD	64	4	Yapısal	Kromozom	-	*E.faecium* (çok nadir)
VanE	16	0.5	**İndüklenebilir**	Kromozom	-	*E.faecalis* (nadir)

Table 1 Characteristics of glycopeptide resistance phenotypes in *Enterococcus*

Resistance	Acquired								Intrinsic
	High		Variable	Moderate	Low				Low
Phenotype	VanA	VanM	VanB	VanD	VanE	VanG	VanL	VanN	VanC
Vancomycin MIC (mg/L)	64–1,000	>256	4–1,000	64–128	8–32	≤16	8	16	2–32
Teicoplanin MIC (mg/L)	16–512	96	0.5–1	4–64	0.5	Sensitive	≤0.5	≤0.5	0.5–1
Modification	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser
Location	Plasmid or chromosome	Plasmid or chromosome	Plasmid or chromosome	Plasmid or chromosome	Chromosome	Chromosome	Chromosome	Plasmid	Chromosome
Transferrable	Yes	Yes	Yes	No	No	Yes	No	Yes	No
Expression	Inducible	Inducible	Inducible	Constitutive or inducible	Inducible	Inducible	Inducible	Constitutive	Constitutive or inducible
Main Species	*E. faecalis*, *E. faecium*	*E. faecium*	*E. faecalis*, *E. faecium*	*E. faecalis*, *E. faecium*	*E. faecalis*	*E. faecalis*	*E. faecalis*	*E. faecium*	*E. gallinarum*, *E. casseliflavus*

Notes: Data from Boyd et al,[38] Lebreton et al,[39] McKessar et al,[40] and Xu et al.[41] Adapted from Courvalin P. Vancomycin resistance in Gram-positive cocci. *Clin Infect Dis.* 2006;42(Suppl 1):S25–S34, by permission of Oxford University Press.[37]

Abbreviations: MIC, minimum inhibitory concentration; D-Ala-D-Lac, D-alanine-D-lactate; D-Ala-D-Ser, D-alanine-D-serine.

Infection and Drug Resistance

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REVIEW

Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management

This article was published in the following Dove Press journal:
Infection and Drug Resistance
24 July 2015
Number of times this article has been viewed

Tristan O'Driscoll[1]
Christopher W Crank[2]

Abstract: Since its discovery in England and France in 1986, vancomycin-resistant *Enterococcus* has increasingly become a major nosocomial pathogen worldwide. Enterococci

Table 2 Surveillance of vancomycin-resistant enterococci around the world

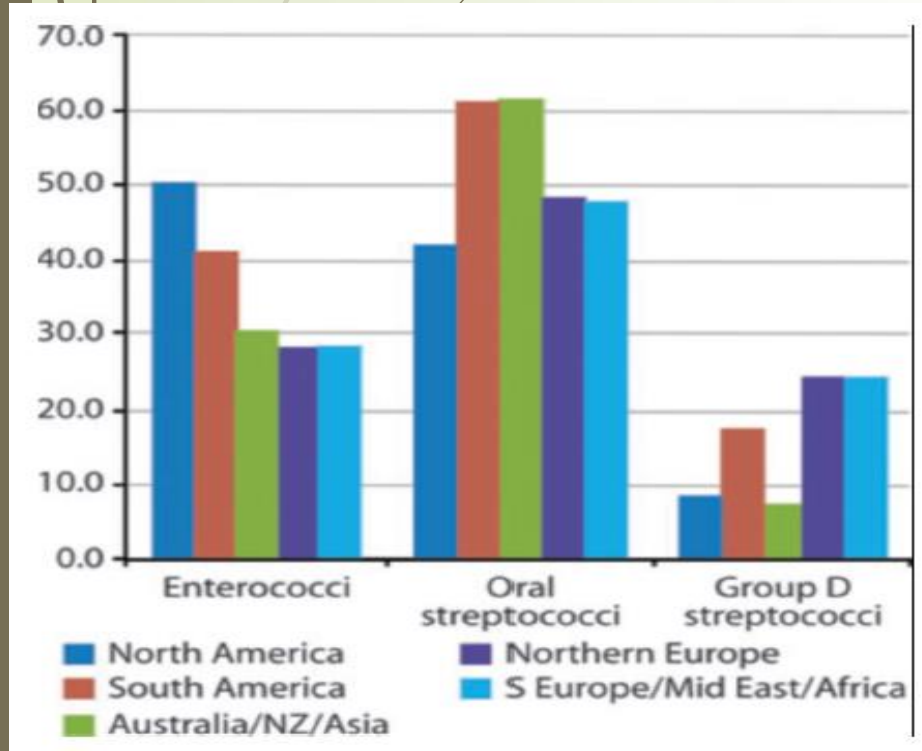
Species	Percent of *Enterococcus* isolates resistant to vancomycin by region (no of isolates)					
	Europe[8] 2013	US[11] 2009–2010	Worldwide[115] 2007–2012	Canada[50] 2007–2011	Asia-Pacific[118] 2007–2008	Latin America[118] 2007–2008
E. faecium	8.8 (729)	79.4 (2,572)	–	22.4 (60)	14.1 (270)	48.1 (54)
E. faecalis	1.0 (126)	8.5 (444)	10.3 (27)	0.1 (1)	0.01 (440)	3.1 (195)
All enterococci	4.0 (855)	35.5 (3,016)	–	6.0 (61)	11.9 (710)	12.9 (249)

Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study

Clin Microbiol Infect 2013; 19: 1140–7.

C. Chirouze[1,2], E. Athan[3], F. Alla[4], V. H. Chu[5], G. Ralph Corey[5], C. Selton-Suty[6], M.-L. Erpelding[4], J. M. Miro[7], L. Olaison[8], B. Hoen[1,2] and on behalf of the International Collaboration on Endocarditis Study Group*

- 2000-2006 arası, 28 ülke, 64 merkez
- 4794 İE hastası



- Enterokoklarda **vankomisin direnci** => 12 suş, 8'i kuzey ABD→%10 (8/79)

- *E. faecium* (3/16) > *E. faecalis* (7/364, **p 0.01**)
- **Hem Ampisilin** direnci *E. faecium* (9/16) > *E. faecalis* (8/404, **p <0.0001**)
- **Hem Vankomisin** direnci *E. faecium* (3/16) > *E. faecalis* (7/364, **p 0.01**).

Prolonged Use of Oritavancin for Vancomycin-Resistant *Enterococcus faecium* Prosthetic Valve Endocarditis

Brief Report OFID, 2015

Jennifer A. Johnson,[1] Eoin R. Feeney,[3] David W. Kubiak,[2] and G. Ralph Corey[4]

73 yaşında erkek

- ✓ Biyoprotez aort kapak, renal arter stenozu, KBY, L5-S1 metal
- ✓ Kan kültürü; *Enterococcus faecium*, Van R, Dapt S

Table 1. Susceptibility Testing of *Enterococcus faecium* Isolates

Antibiotic	Initial Presentation	First Recurrence (5 mo Later)	Second Recurrence (8 mo Later)
Ampicillin	KBD 6 mm (R)	KBD 6 mm (R) MIC > 256 µg/mL (R)	KBD 6 mm (R) MIC 256 µg/mL (R)
Vancomycin	KBD 6 [illegible]	KBD 6 mm (R)	KBD 6 mm (R)
Gentamicin	KB[illegible] (Syn)	KBD 26 mm (Syn)	KBD 28 mm (Syn)
Streptomycin	[illegible]mm (Syn)	KBD 22 mm (Syn)	KBD 26 mm (Syn)
Tetracycline	[illegible] 6 mm (R)	KBD 6 mm (R)	KBD 6 mm (R)
Doxycycline	–	KBD 12 mm	–
Telavancin	–	Initial: MIC > 32 µg/mL Repeat: MIC 0.19 µg/mL	Initial: MIC 32 µg/mL
Linezolid	KBD 30 mm (S)	KBD 31 mm (S)	KBD 35 mm (R) MIC 0.75 µg/mL (S)
Daptomycin	MIC 4 µg/mL (S)	Initial: MIC 4 µg/mL (S) Repeat: MIC 6 µg/mL (R)	Initial: MIC 4 µg/mL (S)
Quinupristin/dalfopristin	–	MIC 1.5 µg/mL (I)	–
Tigecycline	MIC 0.25 µg/mL	Initial: MIC 0.19 µg/mL Repeat: MIC 0.25 µg/mL	MIC 0.094 µg/mL
Oritavancin	–	MIC 0.5 µg/mL	MIC 0.5 µg/mL

Daptomisin

Abbreviations: KBD, Kirby Bauer disk diffusion test; MIC, minimal inhibitory concentration; R, resistant; S, sensitive; Syn, synergy likely.

Prolonged Use of Oritavancin for Vancomycin-Resistant *Enterococcus faecium* Prosthetic Valve Endocarditis

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Gentamicin	KBD 26 mm (Syn)	KBD 26 mm (Syn)	KBD 28 mm (Syn)
Streptomycin	KBD 21 mm (Syn)	KBD 22 mm (Syn)	KBD 26 mm (Syn)
Tetracycline	KBD 6 mm (R)	KBD 6 mm (R)	KBD 6 mm (R)
Doxycycline	–	KBD 12 m	–
Telavancin	–	Initial: µg/mL R 0.19 µg/mL	Initial: MIC 32 µg/mL
Linezolid	KBD 30 mm (S)	mm (S)	KBD 35 mm (R) MIC 0.75 µg/mL (S)
Daptomycin	MIC 4 µg/mL (S)	Initial: MIC 4 µg/mL (S) Repeat: MIC 6 µg/mL (R)	Initial: MIC 4 µg/mL (S)
Quinupristin/dalfopristin	–	MIC 1.5 µg/mL (I)	–
Tigecycline	MIC 0.25 µg/mL	Initial: MIC 0.19 µg/mL Repeat: MIC 0.25 µg/mL	MIC 0.094 µg/mL
Oritavancin	–	MIC 0.5 µg/mL	MIC 0.5 µg/mL

Linezolid+ tigesiklin

Abbreviations: KBD, Kirby Bauer disk diffusion test; MIC, minimal inhibitory concentration; R, resistant; S, sensitive; Syn, synergy likely.

Prolonged Use of Oritavancin for Vancomycin-Resistant *Enterococcus faecium* Prosthetic Valve Endocarditis

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Doxycycline	–	KBD 12 mm	
Telavancin	–	Initial: MIC > 32 µg/mL Repeat: MIC 0.19 µg/mL	
Linezolid	KBD 30 mm (S)	KBD 31 mm (S)	
Daptomycin	MIC 4 µg/mL (S)	Initial: MIC 4 µg/mL (S) Repeat: MIC 6 µg/mL (R)	
Quinupristin/dalfopristin	–	MIC 1.5 µg/mL (I)	
Tigecycline	MIC 0.25 µg/mL	Initial: MIC 0.19 µg/mL Repeat: MIC 0.25 µg/mL	
Oritavancin	–	MIC 0.5 µg/mL	

Abbreviations: KBD, Kirby Bauer disk diffusion test; MIC, minimal inhibitory concentration; R, resistant; S, sensitive; Syn, synergy likely.

L5-S1 metal çıkarılıyor
Ciddi KI süpresyonu
Oritavansin -7 hafta

Case Report

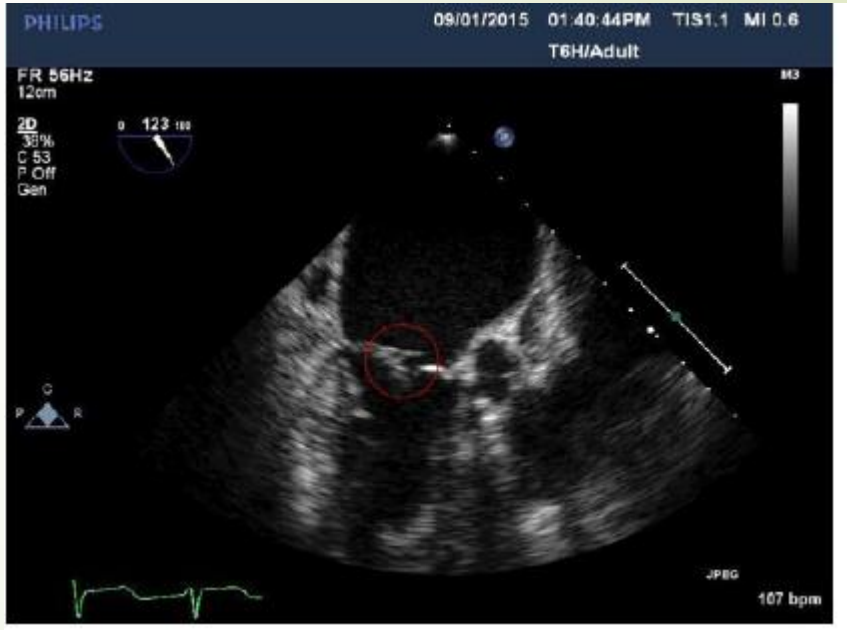
Daptomycin-Vancomycin–Resistant *Enterococcus faecium* Native Valve Endocarditis: Successfully Treated With Off-Label Quinupristin-Dalfopristin

Journal of Investigative Medicine High Impact Case Reports
July-September 2016: 1–3

DOI: 10.1177/2324709616665408
hic.sagepub.com
SAGE

- ✓ 87 yaşında kadın
- ✓ KBY, HT, AF ve tekrarlayan İYİ
- ✓ Ateş, İdrar kültürü =>VRE

linezolid



- ❖ Kan kültürü; *Enterococcus faecium* =>
  linezolid (OD) MIC 4
  vankomisin MIC >32
  daptomisin MIC 6

Cerrahi ve Q-D başarılı tedavi

Le Infezioni in Medicina, n. 3, 190-193, 2016

Antimicrobial susceptibility against penicillin, ampicillin and vancomycin of viridans group Streptococcus in oral microbiota of patients at risk of infective endocarditis

Serap Süzük[1], Banu Kaşkatepe[2], Mustafa Çetin[3]

- Şubat-Haziran 2015
- Ankara NEAH Kardiyoloji
- İE riski olan erişkin protez veya romatizmal kapak hastaları
- Alınmayanlar: son 15 gündür antibiyotik kullananlar
- Toplam 49 hastadan oral swab örnekleri alınmış

Antimicrobial susceptibility against penicillin, ampicillin and vancomycin of viridans group Streptococcus in oral microbiota of patients at risk of infective endocarditis

Serap Süzük[1], Banu Kaşkatepe[2], Mustafa Çetin[3]

Table 1 - Number and antibiotic susceptibility rates of VGS.

Group name	No. (%)	Penicillin		Ampicillin	
		Not susceptible* No. (%)	Susceptible No. (%)	Not susceptible* No. (%)	Susceptible No. (%)
S. *mitis* Group	16 (32.65%)	8 (50.00)		4 (25.00)	12 (75.00)
S. *anginosus* Group	16 (32.65%)	9 (56.25)	7 (43.75)	11 (68.75)	5 (31,25)
S. *sanguinis* Group	8 (16.33%)	6 (75.00)	2 (25.00)	6 (75.00)	2 (25.00)
S. *mutans* Group	6 (12.24%)	4 (66.67)	2 (33.33)	3 (50.00)	3 (50.00)
S. *salivarius* Group	3 (6.12%)	3 (100.00)	0 (0)	3 (100.00)	0 (0)

*resistant and reduced susceptibility.

Vankomisin direnci saptanmamış.

Published in final edited form as:
Curr Infect Dis Rep. 2012 August ; 14(4): 339–349. doi:10.1007/s11908-012-0270-8.

Enterococcal Endocarditis: Can We Win the War?

- ✓ Enterokoklar İE etkenleri arasında 3. sırada
- ✓ Mortalite yüksek **%16-28.9**

- VRE İE Hastalarda;
  - ❖ Mortalite *E. faecium* > *E. faecalis* (p=0.002)
  - ❖ Bakteriyemi süresi *E. faecium* > *E. faecalis* (p=0.002)

➢ VRE İE için yüksek riskler;
- ✓ Organ nakli (karaciğer önemli)
- ✓ Hemodiyaliz hastaları
- ✓ Santral venöz kateter varlığı

Forrest GN. J Infect. 2011; 63(6):420–8.

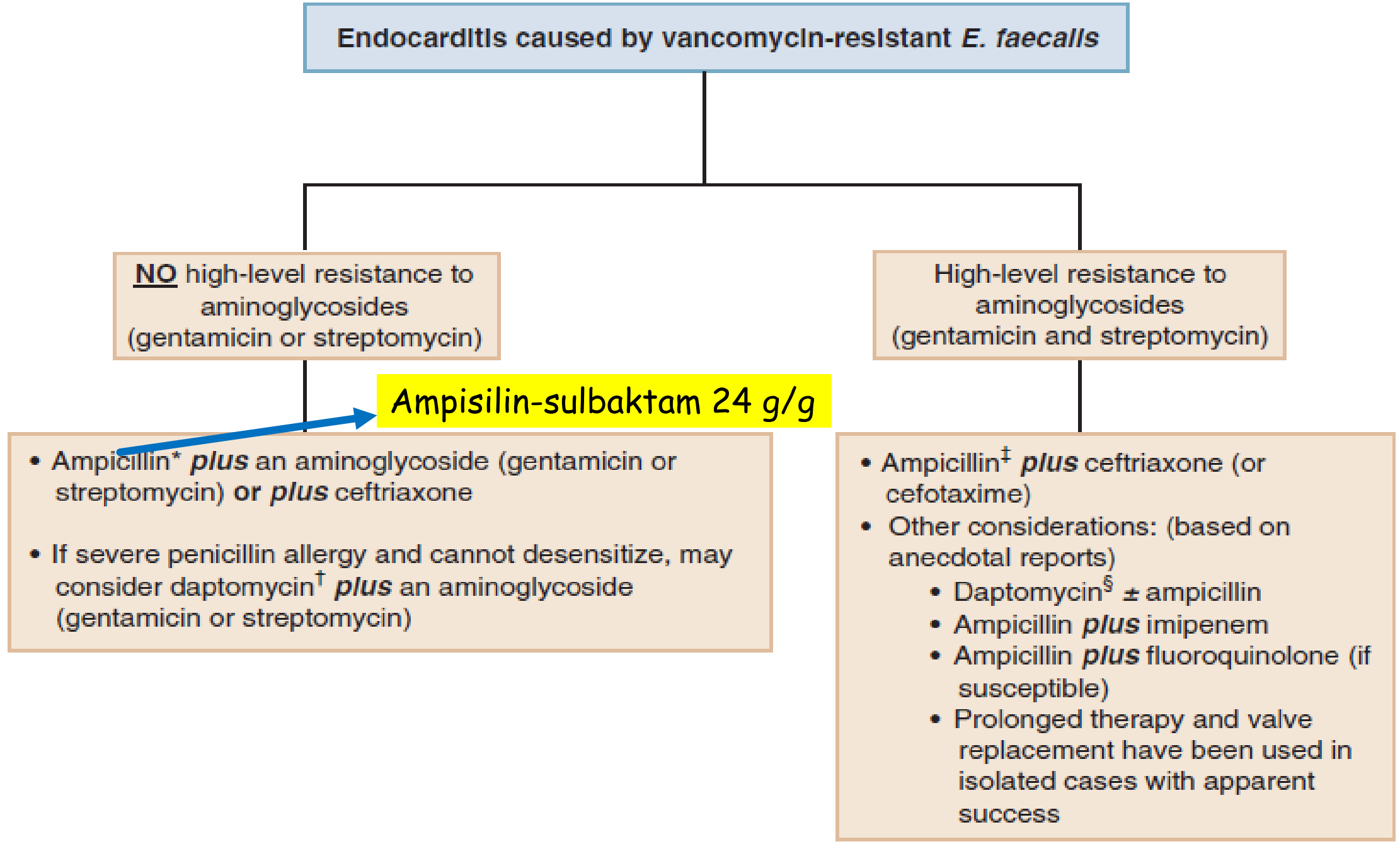
Endocarditis Caused by Resistant Enterococcus: An Overview

Katherine Reyes · Marcus Zervos

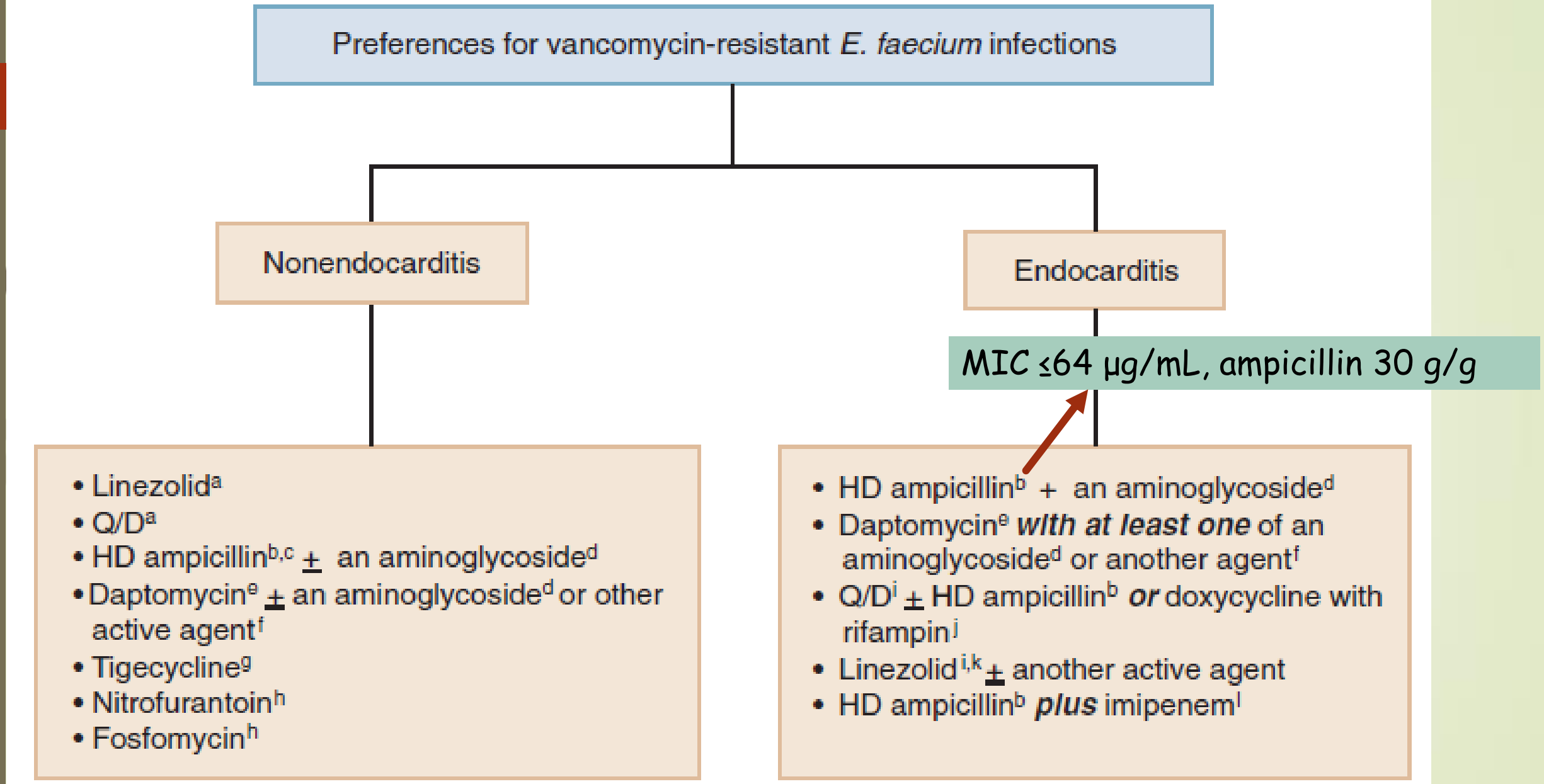
Table 2 Antimicrobial therapy for enterococcal endocarditis, mostly *E. faecium*

Enterococcus	Antibiotic	Dose	Comments
VRE, usually *E. faecium*	Quinupristin/ dalfopristin	7.5 mg/kg IV q8 h	Cases reports used in combination with ampicillin
			Needs a central line
			No activity against VRE *faecalis*
VRE, usually *E. faecium*	Linezolid	600 mg IV or PO	Bacteriostatic
		q12 h	Likely to be used in combination therapy and not as first-line agent
VRE, usually *E. faecium*	Daptomycin	6 mg/kg/d	Reports of resistance developing while on therapy
		Higher dose may be needed	Doses up to 12 mg/kg/d have been used
VRE, usually *E. faecium*	Daptomycin	6 mg/kg/d	Reports of resistance developing while on therapy
	plus	Higher dose may be needed	Doses up to 12 mg/kg/d have been used
	AMP		AMP has been shown to enhance daptomycin killing of AMP-R and VRE strains
VRE, usually *E. faecium*	Tigecycline	100 mg IV first dose, then 50 mg IV q12 h	Bacteriostatic
			Cases reports used in combination with daptomycin

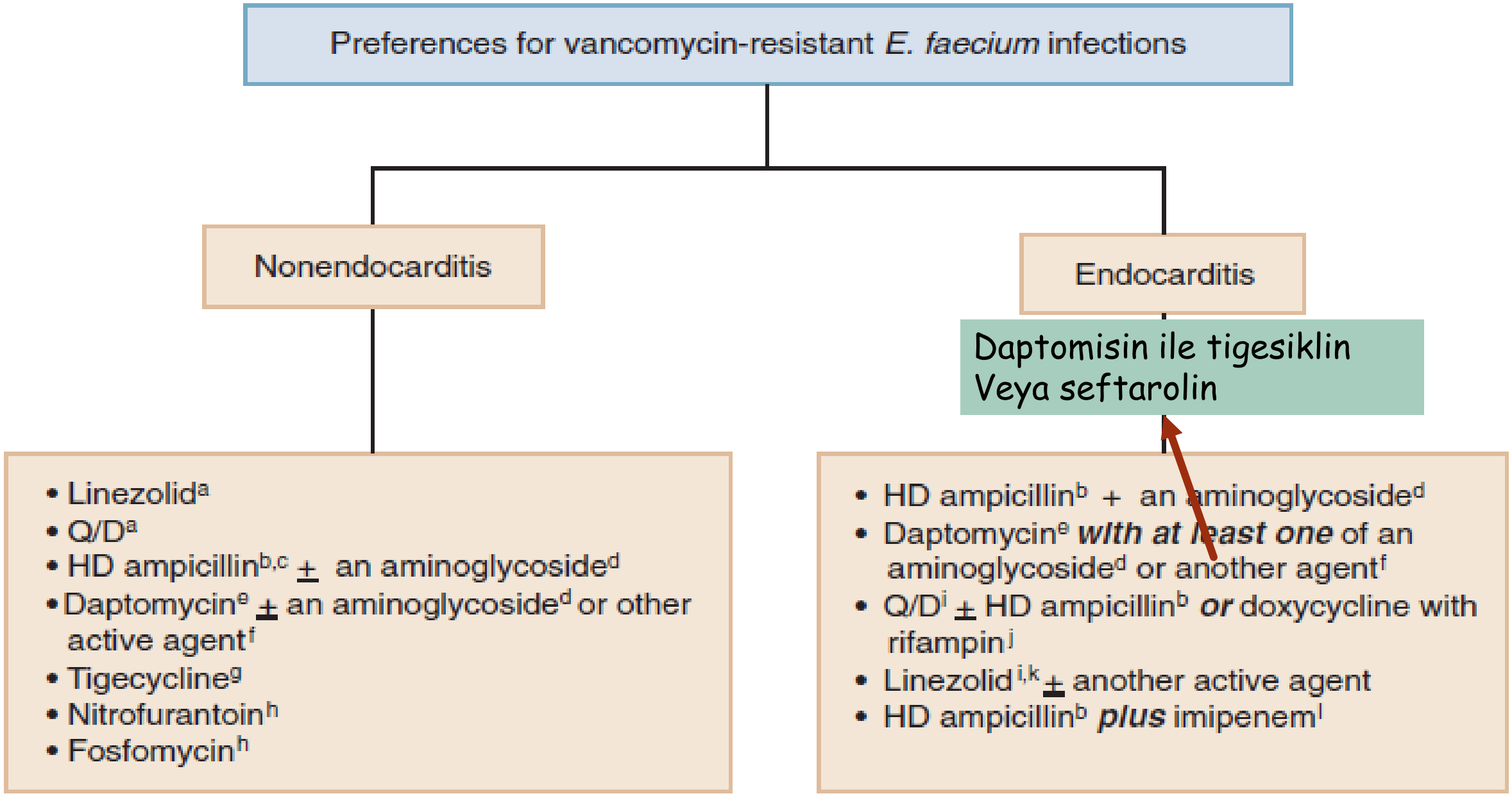
Note. PCN, penicillin; S, susceptible; R, resistant; AMG, aminoglycoside; AMP, ampicillin; IV, intravenous; VRE, vancomycin-resistant enterococcus



Mandell 2015 modified from Clin Microbiol Infect. *2010;16: 555-62.*



Mandell 2015 modified from Clin Microbiol Infect. *2010;16: 555-62.*



Mandell 2015 modified from Clin Microbiol Infect. *2010;16: 555-62.*

Infection and Drug Resistance

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REVIEW

Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management

This article was published in the following Dove Press journal:
Infection and Drug Resistance
24 July 2015
Number of times this article has been viewed

Infection and Drug Resistance 2015:8 217-230

and France in 1986, vancomycin-resistant
nosocomial pathogen worldwide. Enterococci

AHA/IDSA => linezolid EE tedavisinde kullanılabilecek ajan "uzman görüşü"

E. faecium dirençli; β-laktamlar, glikopeptidler ve AGA

Circulation. 2015;111: e394-e434

carditis

Daptomycin Q/D	• Consider 8–12 mg/kg/day • Only active against *E. faecium*
Daptomycin combination	• Combine with either HD ampicillin, ceftaroline, ceftobiprole, or tigecycline
Linezolid	

Sonuç olarak;

- Hayatı tehdit eden infeksiyon varlığında stafilokok ve enterokoklarda vankomisin direnci MIC ile belirlenmeli
- *S.aureus* için hVİSA (MIC "creep") sorun olabilir.
- Enterokoklarda; VRE İE için yüksek riskler belirlenmeli
- Ülkemiz için ciddi sorun olmasa da hastalar ve üremeler yakından izlenmelidir

Sağlık ellerimizde....