Daptomisin Direnci

Dr. Zeynep Memiş

Olgu

37 y erkek

Tip 1 DM

Hipertansiyon

Kronik böbrek yetmezliği (Son 5 aydır hemodiyaliz)

Koroner arter hastalığı (geçirilmiş MI)

Kronik Hepatit B infeksiyonu

Diyabetik retinopati

Periferik arter hastalığı

Olgu

9 Aralık 2014 Göztepe E.A.H İnfeksiyon Servisi

Bir aydır aralıklı ateş, iki doz vankomisin kullanımı

Kateter infeksiyonu ön tanısı ile yatış (10 gün)

daptomisin 6mg/kg (1x500/48 saat) 7 gün

seftazidim 2 gr/gün 10 gün

Yatış HK`de *K.pneumoniae*

EKO: kateter ucunda hareketli trombüs (1.7x1 cm)

Kateter değişimi, kontrol EKO normal, kateter kültüründe üreme yok

Kontrol HK`lerde üreme yok (3 set)

Olgu

8 Ocak 2015 Göztepe E.A.H İnfeksiyon Servisi

2 gündür ateş, yeni açılan juguler ven kateterinde kızarıklık, akıntı

Kateter giriş yeri infeksiyonu ön tanısı ile 2. yatış

seftazidim 2gr/gün 7 gün

daptomisin 6 mg/kg 15 gün

İlk EKO`da vegetasyonu yok

8-16-19-22 Ocak kan kültürlerinde MRSA üremesi

12 ve 14 Ocak kan kültürlerinde üreme yok

İkinci EKO´da sağ atriumda 3.4 x 2.2 cm vejetasyon

Olgu

23 Ocak 2015 Dr. Siyami Ersek E.A.H

daptomisin 500 mg/ 48 saat devam

4 Şubat: kitle eksizyonu postop kardiyak tamponad gelişimi

23 Ocak kan kültüründe MRSA (daptomisin dirençli)

teikoplanin 400mg/ 72 saat tedavi

Vejetasyon kültüründe MRSA

5 kez revizyon ve eksplorasyon op.

Mediastinit tablosu

Postop 44. gün eksitus

Olgu
Kan Kültürleri

Mikroorganizma	Test edilme zamanı	Vankomisin MIK	Daptomisin MIK
Kl.pneumoniae	8 gün vankomisin 7 gün daptomisin	-	-
MRSA (1)	Daptomisin 1. günü	1 (duyarlı)	0.50 (duyarlı)
MRSA (2)	Daptomisin 8. günü	2 (orta duyarlı)	-
MRSA (3)	Daptomisin 11. günü	2 (orta duyarlı)	-
MRSA (4)	Daptomisin 14. günü	2 (orta duyarlı)	-
MRSA (5)	Daptomisin 15. günü	E test: 1	2 (dirençli)

TABLE 1

Daptomycin MIC breakpoints established by the CLSI, FDA, and EUCAST

Organism	MIC breakpoint (μg/ml) established by[a]:					
	CLSI		FDA		EUCAST	
	S	R	S	R	S	R
Staphylococcus	≤1		≤1		≤1	>1
Enterococcus	≤4		≤4[b]			
Beta-hemolytic *Streptococcus*	≤1		≤1		≤1	>1
Viridans group *Streptococcus*, excluding *S. pneumoniae*	≤1					
Corynebacterium	≤1					
Lactobacillus	≤4					

[a] S, susceptible; R, resistant; CLSI, Clinical and Laboratory Standards Institute; FDA, Food and Drug Administration; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

[b] Due to the lack of clinical data, the FDA clinical breakpoint is approved for vancomycin-susceptible *E. faecalis* alone.

Daptomisin Direnci

Stafikok direnci % 0.04

62 vaka

Stefani S.Insights and clinical perspectives of daptomycin resistance in Staphylococcus aureus: A review of the available evidence. International Journal of Antimicrobial Agents 46 (2015)

Ancak tedavi altında azalmış duyarlılık % 5

(hVISA için %15, VISA %38-85)

Enterokok direnci % 0.6

8 vaka

(Kelesidis t, Daptomycin Nonsusceptible Enterococci: An Emerging Challenge for Clinicians CID 2011:52)

Table 1
Clinical reports of daptomycin (DAP) resistance.

Reference/location	Case description (*n*)	Age (years) and co-morbidities	Previous treatment with glycopeptides	Dosage of DAP	Time until development of non-susceptibility after usage (days)	DAP MIC shift	Strain characteristics	Salvage treatment	Resistance mechanism
Rezai et al., USA [62]	Bacteraemia and osteomyelitis (2)		NA	6 mg/kg		NA	NA	NA	ND
Mangili et al., USA [63]	Septic thrombophlebitis (1)	54/cirrhosis	VAN	4 mg/kg initial and after 4 days 6 mg/kg	28	Susceptible by KB to 2 mg/L	MRSA	LNZ and then VAN + GEN Death	ND
Hayden et al., USA [64]	Osteomyelitis (2)	86/total knee replacement; 61/IHD	VAN	6 mg/kg	35; 42	0.25–4 mg/L; 0.5–4 mg/L	MRSA (27 strains in the two cases, unrelated by PFGE, hDAP by PAP; one strain hVISA)	NS; DAP	ND
Vikram et al., USA [65]	Bacteraemia, vertebral osteomyelitis (1)	52/DM, micronodular cirrhosis of the liver, pulmonary fibrosis	VAN	6 mg/kg	28	0.5–4 mg/L	MRSA (5 isolates). VAN MIC 2–4 mg/L	LNZ, Q/D, RIF. Death	ND
Hirschwerk et al., USA [66]	Bacteraemia (1)	92/permanent pacemaker	VAN	7 mg/kg	42	0.75–2 mg/L	MRSA (5 serial isolates). VAN MIC of 2 mg/L; all related isolates	NA. Death	ND
Marty et al., USA [67]	Bacteraemia and probable vertebral osteomyelitis, immunocompromised (1)	61/bone marrow transplant	LNZ first, after VAN and GEN	6 mg/kg	20	0.25–4 mg/L	MRSA (4), all equal by PFGE	LNZ and then VAN + RIF	ND; lower bactericidal activity by time-to-kill experiments
Skiest, USA [68]	Septic arthritis and bacteraemia (1)	64/DM, obesity, breast cancer in remission	VAN	Initial dose 8 mg/kg followed by 6 mg/kg	28 weeks over the course of 2 years	? to 4 mg/L	Initial MRSA infection; after amputation the patient developed an MRSA infection. Another MRSA	LNZ	ND
Tsukimori et al., Japan [69]	Aortic prosthesis infection (1)	45/aortic aneurysm	VAN	6 mg/kg/day	10	? to >1 mg/L	MRSA isolates	LNZ and CLI	ND
Mariani et al., USA [70]	Bacteraemia and prosthetic joint infection (1)	64/total hip replacement	VAN	1 g i.v. q12h	46	0.5–8 mg/L	MRSA. VAN MIC 4 mg/L	NA	ND

Table 1 (*Continued*)

Reference/location	Case description (*n*)	Age (years) and co-morbidities	Previous treatment with glycopeptides	Dosage of DAP	Time until development of non-susceptibility after usage (days)	DAP MIC shift	Strain characteristics	Salvage treatment	Resistance mechanism
Julian et al., USA [71]	Prosthetic aortic valve, bacteraemic pacemaker and endocardial abscess (1)		VAN (trough levels were low)	NR		1–4-8 mg/L	MRSA (29 isolates) all related by PFGE hVISA/VISA		MprF I420N mutation in three of six strains sequenced
Huang et al., Taiwan [72]	Bacteraemia and endocarditis (1)		VAN (25 mg/kg) and TEIC (300 mg every 3 days)	6 mg/kg	2	1–4 mg/L	MRSA (11 related isolates). VAN MIC 1–4 mg/L	LNZ	ND
Murthy et al., USA [73]	Endocarditis (1)	40/IVDA with chronic HCV	VAN	6 mg/kg	10	1–3–4 mg/L	MRSA (4 related isolates by PFGE). USA300, PVL-positive clone	VAN + GEN + RIF	MprF T345A mutation found
Bennett et al., USA [74]	Bacteraemia and suspected UTI (1)		LVX (500 mg daily). VAN 1 g OD or b.i.d. with monitoring of serum concentration	6 mg/kg	21	0.5–4 mg/L	MRSA (5 related isolates by PFGE); USA100 clone; VAN MIC 0.75–1.5 mg/L, all strains were tolerant	DAP (8 mg/kg) + GEN	ND
Sakoulas et al., USA [75]	Bacteraemia and mitral valve endocarditis (1)	NS	LVX; VAN + GEN	NA	15	0.125–2 mg/L	MSSA (4 isolates). VAN MIC 2 mg/L	NAF + GEN	ND
Kuo et al., Taiwan [76]	Heart transplantation and suspicious post-operative sternum osteomyelitis (1)		VAN (750 mg twice a week); long-term treatment OD TEIC (200 mg daily). LNZ 600 mg daily	250 mg daily	ca. 5 months	0.5–2 mg/L	MRSA (12 related strains); 8 of 12 VISA	Died	ND
Sharma et al., USA [77]	Bacteraemia and IE (4) and osteomyelitis (2)	NS/DM, valvular heart disease	VAN alone and in combination	NA	5–21	0.125–0.5–2–4 mg/L	MRSA. VAN MIC 1–2 mg/L	VAN, RIF, GEN, SXT. Death	ND
Tenover et al., USA [78]	Bacteraemia and endocarditis (1)	60/IHD, DM	VAN (1 g/12 h)	6 mg/kg q48h	10 weeks	NR	MRSA (4 related isolates). VAN MIC 2–8 mg/L	SXT + Q/D and LNZ	ND
Cunha and Pherez, USA [79]	Bacteraemia and mitral valve endocarditis (1)		VAN (1 g/12 h, followed by 500 mg q24h for 4 days)	6 mg/kg for 7 days after high-dose 12 mg/kg q48h	NS	0.5–2 mg/L	MRSA (2 strains). VAN MIC between 1 and 2 mg/L	DAP + RIF. Death	ND

Kuo et al., Taiwan [80]	Bacteraemia (1)		VAN (1 g/12 h); FLZ (400 g/day for 10 days) and then AmB 30 mg/day and later CAS 50 mg/day	350 mg/24 h	17 weeks	0.5–2 mg/L	MRSA (10 related strains by PFGE). VAN MIC 2–4 mg/L (already resistant to DAP before exposure to the drug)	Death	ND
Kirby et al., UK [81]	CVC-associated infections and endocarditis (1)	41/chronic renal failure requiring haemodialysis	VAN + RIF TEIC FA	6 mg/kg	14 months	0.25–4 mg/L	MRSA (6 related strains as determined by PFGE, clone MRSA-15). All strains were hVISA and after VISA (VAN MIC 1–4 mg/L and TEIC MIC 1–16 mg/L)	TMP + RIF	ND
Hsu et al., Singapore [82]	Bacteraemia (6)		VAN	NR	2 weeks	0.19–4 mg/L	MRSA (19 strains; 4 strains of ST5 MRSA II clone; 14 strains of ST239-MRSA III clone, all related by PFGE); hVISA develop during glycopeptide therapies	NR	ND
Lee et al., Taiwan [83]	Bacteraemia, septic arthritis, vertebral osteomyelitis (1)	59/lymphoma	TEIC	12 mg/kg/day	17	0.5–4 mg/L	MRSA. VAN MIC 2 mg/L. hVISA	LNZ and CEF	ND
Mammina et al., Italy [84]	Leg ulcer (1)	30/congenital arteriovenous malformation	GEN SXT TEIC + GEN	Topical	30	8 mg/kg	Multiple MRSA ST398 isolates, all belonging to the same PFGE profile. hVISA	Surgical therapy	ND
Boyle-Vavra et al., USA [85]	Recurrent bacteraemia (1)		VAN and TZP	6 mg/kg	21	<0.25–2 mg/L	MRSA (2 isolates; related by PFGE and identified as USA800; ST5, *agrII*, SCC*mec* IVa). VAN MIC 1–2 mg/L	VAN + LVX. Death	Point mutation in *mprF* gene (S337L)
Kelley et al., Australia [86]	In vitro study on hVISA and VISA MRSA isolates								

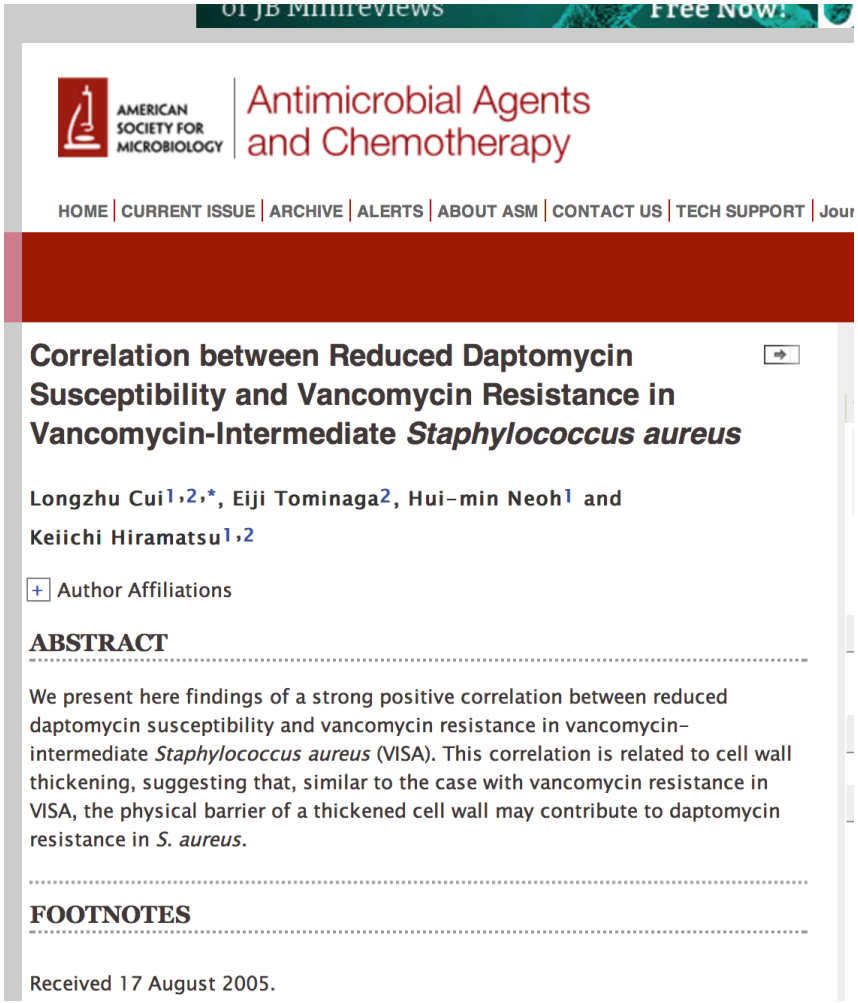
Table 1 (*Continued*)

Reference/location	Case description (*n*)	Age (years) and co-morbidities	Previous treatment with glycopeptides	Dosage of DAP	Time until development of non-susceptibility after usage (days)	DAP MIC shift	Strain characteristics	Salvage treatment	Resistance mechanism
van Hal et al., Australia [87]	Persistent bacteraemia secondary to vertebral osteomyelitis (1)	66/IHD, DM and COPD	VAN, LNZ, Q/D, TIG	No DAP	56	0.25–2 mg/L	MRSA (8 isolates, all related and identified as ST239-MRSA-III)	ND	ND
Chen et al., Taiwan [88]	Bacteraemia and ICD device-related endocarditis (1)	28/paroxysmal ventricular tachycardia	VAN, LNZ TEIC	6 mg/kg after 9 mg/kg and 12 mg/kg in combination with i.v. FOS 6 g/6 h	94	0.25–1 mg/L	MRSA (7 isolates, with the exception of the first and the last isolates, all were related by PFGE)	DAP high-dose plus FOS	ND
Kirby et al., UK [89]	Tricuspid valve endocarditis (1)	35/IVDA	TEIC and RIF	NR	7	0.19–4 mg/L	Group G streptococcus and MRSA (2) with TEIC MIC at 8 mg/L. CA-MRSA defined as PVL-positive and CIP-susceptible	CIP + LNZ	ND
Rose et al., USA [108]	Endocarditis (1)	NS/ESRD with haemodialysis, DM and obesity	DAP	6 mg/kg followed by 10 mg/kg	NR	0.75–2 mg/L	MRSA (*n* = 4, all related by *spa* typing t002 and ST5). VAN MIC of 4 mg/L. VISA	DAP high-dose + ceftaroline	Membrane integrity and fluidity
Sivakumar et al., Australia [90]	Prosthetic joint infection (1)	82/cardiac history and MRSA-positive at admission	VAN VAN + GEN TEIC for the hVISA	NR	42	MIC not reported but under TEIC the hVISA became DAP-resistant	Polymicrobial with MRSA (*n* = 3, the last was hVISA)	PRI + CIP	ND
Yu et al., Canada [91]	Endocarditis (1)	75/type II DM, obesity, hypertension, aortic valve replacement	VAN	6 mg/kg	37	1–>4 mg/L	MRSA (3 strains). VAN MIC 2–4 mg/L. hVISA to VISA	NR	ND
Levy et al., USA [92]	Left ventricular device infection (1)	40/alcoholic-related cardiomyopathy	VAN DOX	8 mg/kg, RIF and GEN	NS	0.25–1.5 and 8 mg/L	MRSA (6 strains all related by PFGE); all strains were hVISA; SCC*mec* II	LNZ and SXT	ND

Jongsma et al., USA [93]	Endocarditis and osteomyelitis (1)	50/DM and chronic active HCV; multiple MRSA infections treated with VAN	VAN and TZP	8 mg/kg, plus RIF	22	0.38–3 mg/L	MRSA (3 strains). VAN MIC 1–2 mg/L	Ceftaroline	ND
Velazquez et al., USA [94]	10 cases as follows: 4 SSTIs 2 native valve endocarditis 2 osteomyelitis 1 abdominal abscess 1 respiratory colonisation	8 of 10 had a significant medical history; 2 were healthy	7 of 10 received VAN or DAP previously; 2 never received DAP	NS	NS	2–4 mg/L	MRSA (8 strains; VAN MIC between 1.5 and 2 mg/L). MSSA (2 strains). All MRSA were typed and were USA600, USA300, USA100 and USA500. Almost unrelated	Different	ND
Dortet et al, France [95]	Right-sided IE (1)	55/COPD	AMC and LVX LNZ	7 mg/kg and after 16 mg/kg	68	0.25–2 mg/L	MRSA (3 isolates). VAN MIC 0.75–1.5 mg/L and RIF -resistant	VAN, GEN, LNZ	ND
Gasch et al., Spain [96]	Bacteraemia (7)	65–84/NS	VAN or DAP	8–10 mg/kg	NS	<0.5–2 mg/L	MRSA (7 unrelated isolates). VAN MIC 0.5–2 mg/L	NS	ND

MIC, minimum inhibitory concentration; NA, not available; ND, not determined; NS, not stated; VAN, vancomycin; KB, Kirby–Bauer test; MRSA, meticillin-resistant *Staphylococcus aureus*; LNZ, linezolid; GEN, gentamicin; IHD, ischaemic heart disease; PFGE, pulsed-field gel electrophoresis; hDAP, daptomycin-heteroresistant *S. aureus*; PAP, population analysis profile assay; hVISA, heterogeneous vancomycin-intermediate *S. aureus*; DM, diabetes mellitus; Q/D, quinupristin/dalfopristin; RIF, rifampicin; CLI, clindamycin; i.v., intravenous; q12h, every 12 h; NR, not reported; VISA, vancomycin-intermediate *S. aureus*; TEIC, teicoplanin; IVDA, intravenous drug abuse; HCV, hepatitis C virus; PVL, Panton–Valentine leukocidin; UTI, urinary tract infection; LVX, levofloxacin; OD, once daily; b.i.d., twice daily; MSSA, meticillin-susceptible *S. aureus*; NAF, nafcillin; IE, infective endocarditis; SXT, trimethoprim/sulfamethoxazole; q48 h, every 48 h; q24 h, every 24 h; FLZ, fluconazole; AmB, amphotericin B; CAS, caspofungin; CVC, central venous catheter; FA, fusidic acid; TMP, trimethoprim; CEF, cefpirome; TZP, piperacillin/tazobactam; SCC*mec*, staphylococcal cassette chromosome *mec*; COPD, chronic obstructive pulmonary disease; TIG, tigecycline; ICD, implantable cardioverter-defibrillator; FOS, fosfomycin; CA-MRSA, community-associated MRSA; CIP, ciprofloxacin; ESRD, end-stage renal disease; PRI, pristinamycin; DOX, doxycycline; SSTI, skin and soft-tissue infection; AMC, amoxicillin/clavulanic acid.

VISA-Daptomisin Direnci



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Correlation between Reduced Daptomycin Susceptibility and Vancomycin Resistance in Vancomycin-Intermediate *Staphylococcus aureus*

Longzhu Cui[1,2,*], Eiji Tominaga[2], Hui-min Neoh[1] and Keiichi Hiramatsu[1,2]

+ Author Affiliations

ABSTRACT

We present here findings of a strong positive correlation between reduced daptomycin susceptibility and vancomycin resistance in vancomycin-intermediate *Staphylococcus aureus* (VISA). This correlation is related to cell wall thickening, suggesting that, similar to the case with vancomycin resistance in VISA, the physical barrier of a thickened cell wall may contribute to daptomycin resistance in *S. aureus*.

FOOTNOTES

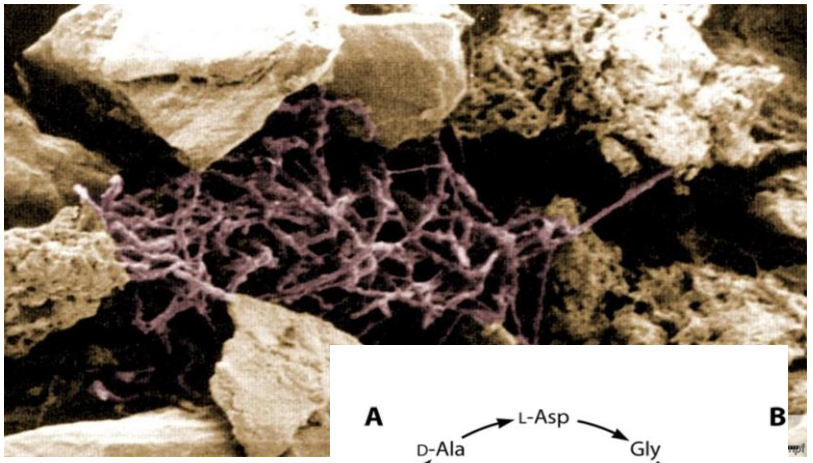
Received 17 August 2005.

VISA'da azalmış daptomisin duyarlılığı ile vankomisin direnci arasında güçlü bir pozitif korelasyon

Hücre duvarının kalınlaşması ile daptomisine duyarlılığın azalması

Dağdan Kliğine

"*Streptomyces roseosporus*" un fermantasyon ürünü



Lipopeptid sınıfın tek üyesi

13 üyeli a.asid, lipofilik kuyruk

2004 klinik kullanım

2009 ülkemizde ruhsat

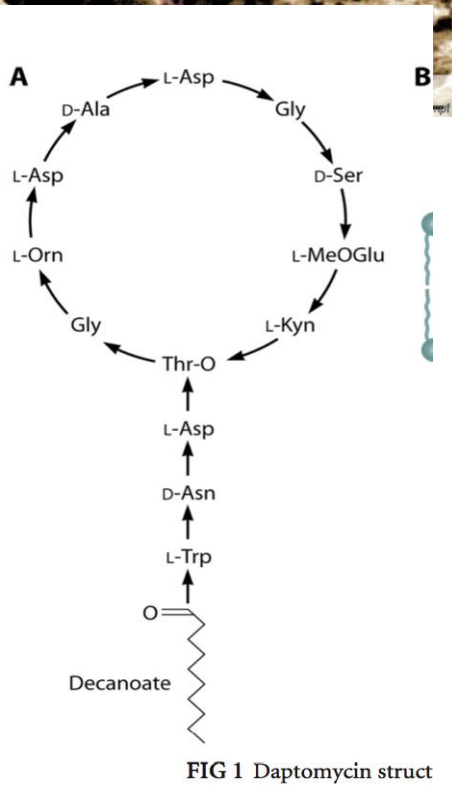


FIG 1 Daptomycin struct

Eissentein BI, Oleson FB, Baltz RH..Daptomycinfrom the mountain to the clinic wit essential help from Francis Tallly. CID 2010;10-15

Daptomisin

Aerop ve anaerop Gram-pozitif bakterilere karşı in vitro hızlı etkili (1-4 saat), bakterisidal, biyofilme etkin

- Stafilokoklar (**MRSA, VISA, VRSA** dahil),
- Enterokoklar (**VRE** *E. faecalis* ve *E. faecium*)
- Streptokoklar (**penisiline dirençli *Streptococcus pneumoniae)***
- *Lactobacillus, Pediococcus* ve *Leuconostoc*
- *Bacillus* ve *Corynebacterium*

Etki Mekanizması

Kalsiyum ile etkileşim

Gram-pozitif hücre membranına bağlanma

(lipoteikoik asit- fosfotidil griserol)

Sitoplazmik membranda oligomerizasyon ve transmembran kanal oluşumu

Hücre içi iyonların dışarı çıkması ve membran depolarizasyonu

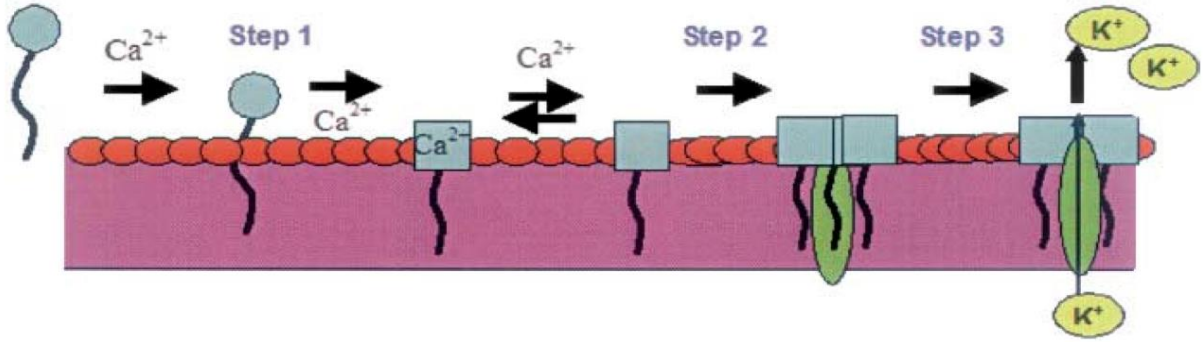


Figure 2. Daptomycin mechanism of action. Hypothetical steps: step 1, daptomycin binds to the cytoplasmic membrane in a calcium-dependent manner; step 2, daptomycin oligomerizes, disrupting the membrane; step 3, the release of intracellular ions and rapid cell death.

Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections
Journal of Antimicrobial Chemotherapy (2005) 55, 283–288

Klinik Kullanım

Komplike Yumuşak Doku İnfeksiyonları (4mg/kg)

*S.auerus´*a bağlı sağ kapak endokarditi (sol?)

S.auerus bakteriyemisi (6mg/kg)

Endokardit gibi derin yerleşimli ve yüksek inokülumlu infeksiyonlarda, tedavi sırasında direnç sorunu

Klinik Kullanım

Pnömoni önerilmez (Sağ kapak endokarditlerinde ortaya çıkabilen septik pulmoner embolilerin tedavisinde?)

MSS infeksiyonlarında önerilmez (BOS geçişi az)

Çocuklarda rutin önerilmez

Table 3 Treatment recommendations for MRSA bacteremia

Condition	IDSA [8]	ESCMID/ISC/ESC [59, 60, 62, 63]
Uncomplicated bacteremia	Vancomycin or daptomycin 6 mg/kg/dose IV once daily for 2 weeks	Vancomycin doses to trough plasma concentration of 15–20 mg/L or teicoplanin if nephrotoxicity is a concern (daptomycin if vancomycin is poorly tolerated) for 10–14 days Consider switching to linezolid PO in patients with a rapid response and negative cultures after catheter removal
Complicated bacteremia	Vancomycin or daptomycin 6 mg/kg/dose IV once daily for 4–6 weeks, depending on extent of infection	Vancomycin, but switch to daptomycin if there is poor response or use daptomycin first-line in patients with life-threatening infection, renal impairment, previous glycopeptide use, or vancomycin resistance or reduced susceptibility Treat for 4–6 weeks
Infective endocarditis, native valve	Vancomycin or daptomycin 6 mg/kg/dose IV once daily for 6 weeks	Vancomycin 30–60 mg/kg/day IV in 2–3 doses for 4–6 weeks Alternative therapies: daptomycin 10 mg/kg/day IV once daily for 4–6 weeks or TMP/SMX + clindamycin
Infective endocarditis, prosthetic valve	Vancomycin IV + rifampin 300 mg PO/IV for ≥6 weeks + gentamicin 1 mg/kg/dose IV q8h for 2 weeks	Vancomycin 30–60 mg/kg/day IV in 2–3 doses for ≥6 weeks + rifampin 900–1200 mg IV or orally in 2–3 doses for ≥6 weeks and gentamicin 3/mg/kg/day IV or IM in 1–2 doses for 2 weeks
Infective endocarditis, right-sided		Vancomycin 15 mg/kg q12h for 6 weeks or daptomycin ≥6 mg/kg/day for 4–6 weeks if patient has renal impairment, sustained bacteremia for >7 days, infection with a VISA strain Optional addition of short-term gentamicin to vancomycin Alternative option: vancomycin + rifampin
Infective endocarditis, left-sided		Vancomycin 15 mg/kg q12h for 4–6 weeks with early and careful attention to culture results Switch to high-dose daptomycin (10 mg/kg/day) if no response to vancomycin and isolate is susceptible Optional addition of short-term gentamicin to vancomycin Alternative option: vancomycin + rifampin
Persistent bacteremia, despite vancomycin treatment	If isolate is susceptible, high-dose daptomycin (10 mg/kg/day) + another agent[a] If isolate has reduced susceptibility to vancomycin and daptomycin, options for monotherapy or combination therapy are quinupristin/dalfopristin 7.5 mg/kg/dose IV q8h, linezolid 600 mg PO/IV bid, or telavancin 10 mg/kg/dose IV od	Daptomycin 10 mg/kg/day if isolates susceptible, possibly in combination with another agent (e.g., gentamicin, rifampicin, linezolid, a beta-lactam, or trimethoprim-sulfamethoxazole) Options for agents with reduced susceptibility to daptomycin or vancomycin, including quinupristin/dalfopristin, linezolid, or telavancin

Adapted from US and International guidelines and recommendations found in Garau et al. [60], Gould et al. 2011 [59], Gould et al. 2012 [62], Habib et al. [63], and Liu et al. [8]

[a]Options include gentamicin 1 mg/kg IV q8h, rifampin 600 mg PO/IV daily or 300–450 mg PO/IV bid, linezolid 600 mg PO/IV bid, trimethoprim-sulfamethoxazole 5 mg/kg IV bid, or a beta-lactam antibiotic

Abbreviations: *bid* twice daily, *ESC* European Society of Cardiology, *ESCMID* European Society of Clinical Microbiology and Infectious Diseases, *IDSA* Infectious Disease Society of America, *ISC* International Society of Chemotherapy, *IM* intramuscular, *IV* intravenous, *MRSA* methicillin-resistant *S. aureus*, *od* once daily, *PO* orally, *q8h/q12h* every 8/12 h, *TMP/SMX* trimethoprim/sulfamethoxazole, *VISA* vancomycin-intermediate *S. aureus*

Hassoun A. Incidence, prevalence, and management of MRSA bacteremia across patient populations—a review of recent developments in MRSA management and treatment2017. Critical care

Stafilokok Endokarditi

American Heart Association (AHA) 2015	European Society of Cardiology (ESC) 2015
Metisiline duyarlı stafilokok	**Metisiline duyarlı stafilokok**
Nafsilin – oksasisilin Sefazolin Alerji **daptomisin** alternatif	Oksasilin-kloksasilin-floksasin Sefazolin
Metisiline dirençli stafilokok	**Metisiline dirençli stafilokok**
Vankomisin **Daptomisin 8 mg kg**	Vankomisin **Daptomisin 10 mg/kg**

Enterokok Endokarditi

American Heart Association (AHA) 2015	European Society of Cardiology (ESC) 2015
Aminoglikozid , beta laktam ve vankomisin dirençli suşlarda	**Aminoglikozid , beta laktam ve vankomisin dirençli suşlarda**
Daptomisin 10 -12 mg/kg ve ampisilin veya seftrolin	**Daptomisin 10 mg kg ve ampisilin** Linezolid Kinoprustin dalfopuristin

Daptomisin Dozu

Endokardit için

MIK değeri bilinmiyorsa veya >0.25 mg/L

≥10 mg/kg

MIK değeri ≤0.25 mg/L ise 6–10 mg/kg

Yavuz S.S.İnfektif endokarditin tedavisinde daptomisin: Ne zaman kullanalım? *Turk Kardiyol Dern Ars 2017*

Stafilokoklarda Daptomisin Direnci

Hücre yüzeyi elektrik yükünün değişmesi ve elektrostatik geri püskürtme

I) Fenotipik olarak ***mprF*** (lizilfosfatidilgliserol sentetazı kodlar) **gen mutasyonu**

II) ***dlt'*** **operonun** aşırı üretimi (duvardaki lipoteikoik asit alanizasyonundan sorumlu)

Sonuç hücre dış yüzeyinde artmış pozitif yük

Miller W.R. Mechanism of Action and Resistance to Daptomycin in Staphylococcus aureus and Enterococci. Published by Cold Spring Harbor Laboratory Press.

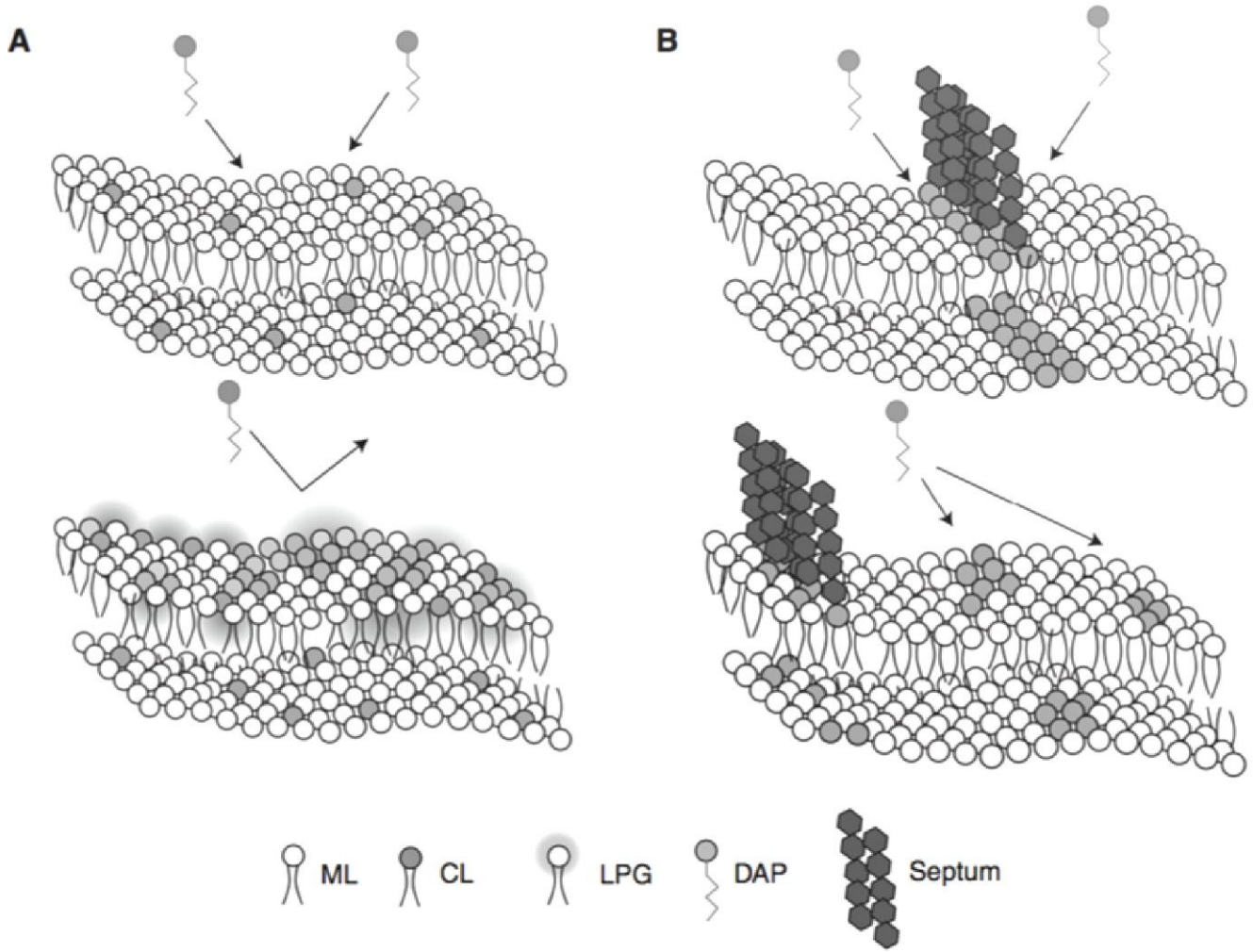


Figure 3. Strategies for resisting daptomycin membrane attack. (*A*) Repulsion: In *Staphylococcus aureus* and *Enterococcus faecium*, changes in cell-surface charge and membrane phospholipid content block daptomycin (DAP) membrane association and oligomerization. (*B*) Diversion: In *E. faecalis* sensitive to DAP cardiolipin (CL) clusters at the division septum. In resistant isolates, redistribution of CL microdomains "traps" DAP away from the septum. ML, membrane lipid; LPG, lysylphosphatidylglycerol.

Stafilokoklarda Daptomisin Direnci

Dlt operonun artmış ekspresyonu duvardaki teikoik asit içeriğinde artış ve **duvar kalınlaşması**

Membran fosfolipid kompozisyonun değiştirilmesi

Prostoglandin/kardiyololipin oranın

pgsA / cls2

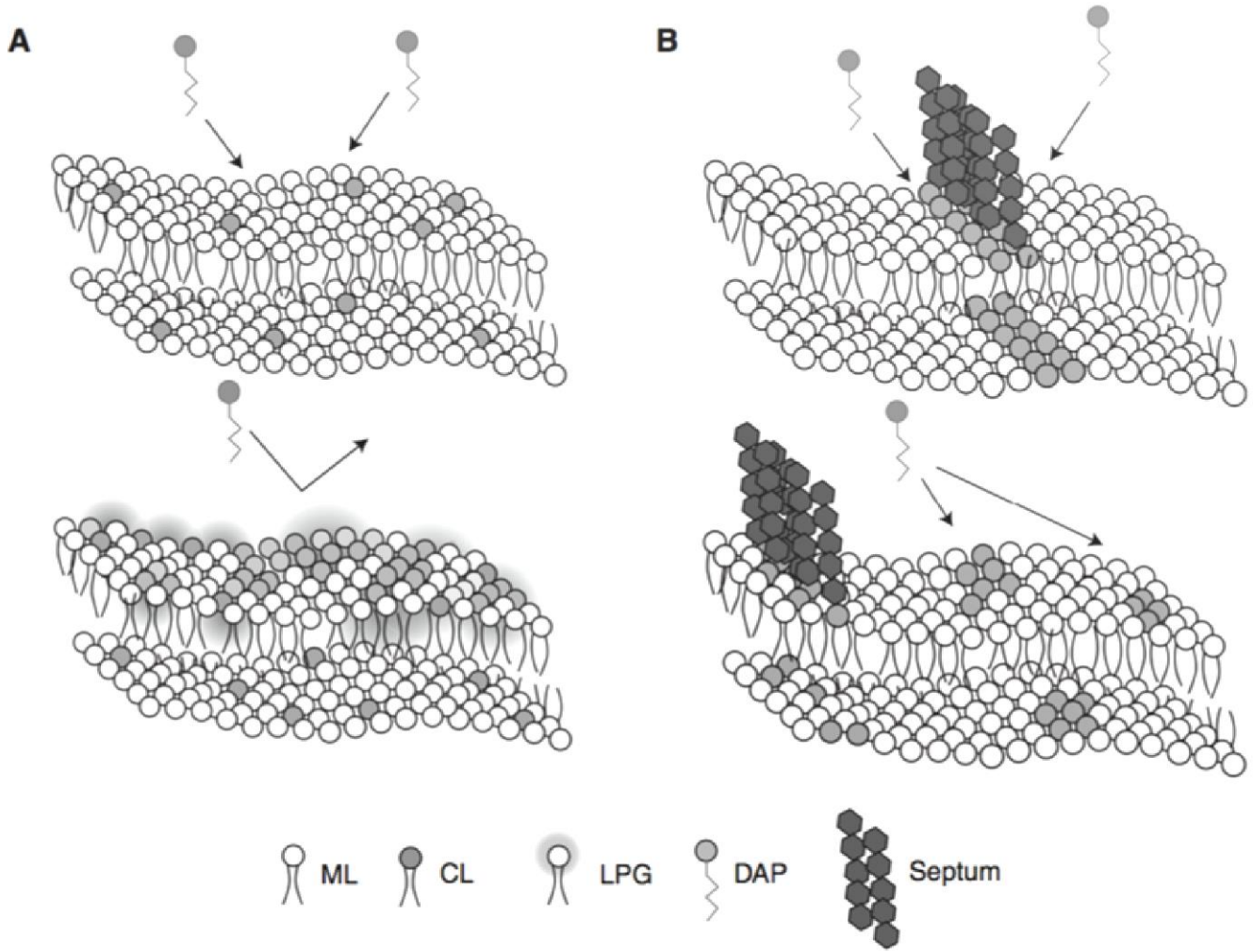
Sonuç membran **akışkanlığının değişmesi**

Miller W.R. Mechanism of Action and Resistance Daptomycin in Staphylococcus aureus and Enterococci. Published by Cold Spring Harbor Laboratory Press.2016

Enterokoklarda Daptomisin Direnci

Hücre yüzey yükünün değiştirilerek antibiyotiğin geri püskürtülmesi

E.fecalis **kardiyolipin (CL)** moleküllerinin mimari dağılımını değiştirerek antibiyotiği hedefinden saptırmak



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Daptomisin Direnci

Proposed mechanisms and genes associated with daptomycin resistance in *B. subtilis*, *S. aureus*, and enterococci.

Organism	Gene	Predicted Function	Proposed Mechanism of Resistance	Ref.
B. subtilis	*pgsA*	Phosphatidylglycerol synthase	Repulsion	24, 34
	liaFSR	Three-component regulatory system as part of the cell envelope stress response		24, 28, 34
S. aureus	*dltABCD*	Proteins that are involved in D-analylation of cell wall teichoic acids	Repulsion	63-68
	mprF	A bifunctional enzyme that catalyzes the lysinylation of phosphatidylglycerol and translocation of lysyl-phosphatidylglycerol from the inner to the outer leaflet of the cell membrane		46-62
	yycG	Two-component regulatory system of cell wall synthesis and homeostasis		57, 75, 76
	cls	Cardiolipin synthase		74, 77-80
	pgsA	Phosphatidylglycerol synthase		80
E. faecalis	*liaFSR*	Three-component regulatory system as part of the cell envelope stress response	Diversion	89, 91, 94
	cls	Cardiolipin synthase		89, 91, 97
	gdpD	Glycerophosphoryl diester phosphodiesterase		89, 91
E. faecium	*liaSR*	Histidine kinase and response regulator of three-component regulatory system	Repulsion	89, 98, 100, 105, 106, 126
	cls	Cardiolipin synthase		89, 101-105, 109
	yycFG	Two-component regulatory system of cell wall synthesis and homeostasis		101, 104, 109

Daptomisin Yüksek Doz Kullanımı

Table 3

Clinical outcome and safety in high-dose daptomycin studies

Authors	Patients	Daptomycin (dose, treatment duration)	Comparator (type, dose, treatment duration)	Efficacy results	Safety results
Katz et al[26]	N=100 patients with cSSTIs; aged ≥18 years	10 mg/kg/day, 4 days	Vancomycin 1 g every 12 hours, up to 14 days	Clinical success rate: 75.0% with daptomycin and 87.5% with comparator (95% CI for the difference: −27.9%, 2.9%)	Similar incidences of AEs: 56.3% with daptomycin group and 52.1% with vancomycin. AEs related to the study drug: 41.7% and 22.9%, respectively. Three patients had CPK elevations (>500 U/L)
Moise et al[38]	N=94 patients mainly with bacteremia, osteomyelitis, and endocarditis; aged ≥18 years	8–10 mg/kg/day, 15 days	None	Overall clinical success rate was 89%, with the lowest success rate seen in patients with endocarditis	29.8% of patients reported at least one AE or exhibited at least one abnormal laboratory result, and 6.4% of patients reported AEs as possibly related to daptomycin
Seaton et al[43]	N=1,097 patients mainly with osteomyelitis, foreign body/prosthetic infection, and endocarditis; aged ≥18 years	>6 mg/kg/day, 13–14 days	None	Overall clinical success rate was 81.9%	Daptomycin was well tolerated with no new or unexpected safety findings. Increased CPK was reported in 27 patients
Byren et al[58]	N=75 patients with osteomyelitis; aged ≥18 years	6 and 8 mg/kg/day, 42 days	Standard-of-care antibiotics (vancomycin, teicoplanin, or semisynthetic penicillin), 40 days	Clinical success rates were 58.3% for 6 mg/kg/day daptomycin, 60.9% for 8 mg/kg daptomycin, and 38.1% for the comparator	No differences in the incidence of serious AEs across groups. CPK elevation of >500 U/L with daptomycin occurred in four (6 mg/kg/day) and five patients (8 mg/kg/day), and with comparator in two patients
Carugati et al[59]	N=178 patients with left-sided infective endocarditis; aged ≥18 years	7.7–10 mg/kg/day, 39 days	Standard-of-care antibiotics (anti-staphylococcal penicillins, vancomycin, or ampicillin plus an aminoglycoside)	In-hospital mortality (primary outcome) was similar in both groups. Median time to clearance of methicillin-resistant *Staphylococcus aureus* bacteremia was 1.0 and 5.0 days ($P<0.01$) with daptomycin and standard-of-care antibiotics, respectively	Regimens with higher daptomycin doses were not associated with increased incidence of AEs
Casapao et al[60]	N=245 patients with enterococcal infections; aged ≥18 years	7.7–9.7 mg/kg/day, 10 days	None	Overall clinical success rate was 89%	No patients experienced AEs attributed to high- dose daptomycin therapy. Seven patients had CPK elevations, yet no high-dose daptomycin regimen was discontinued due to an elevated CPK

Abbreviations: AEs, adverse events; CI, confidence interval; CPK, creatine phosphokinase; cSSTIs, complicated skin and soft tissue infections.

Ruiz A:G.Daptomycin: an evidence-based review of its role in the treatment of Gram-positive infections Infect Drug Resist. 2016;

Beta-laktam ile Kombinasyon

Dış membran şarjını azaltır daptomisinin bağlanmasını arttırırlar

Seftrolin

Ampisilin

Nafsilin,

Sefazolin,

İmipenem, meropenem

Daptomisin Beta-laktam Sinerjisi (seesaw etkisi)

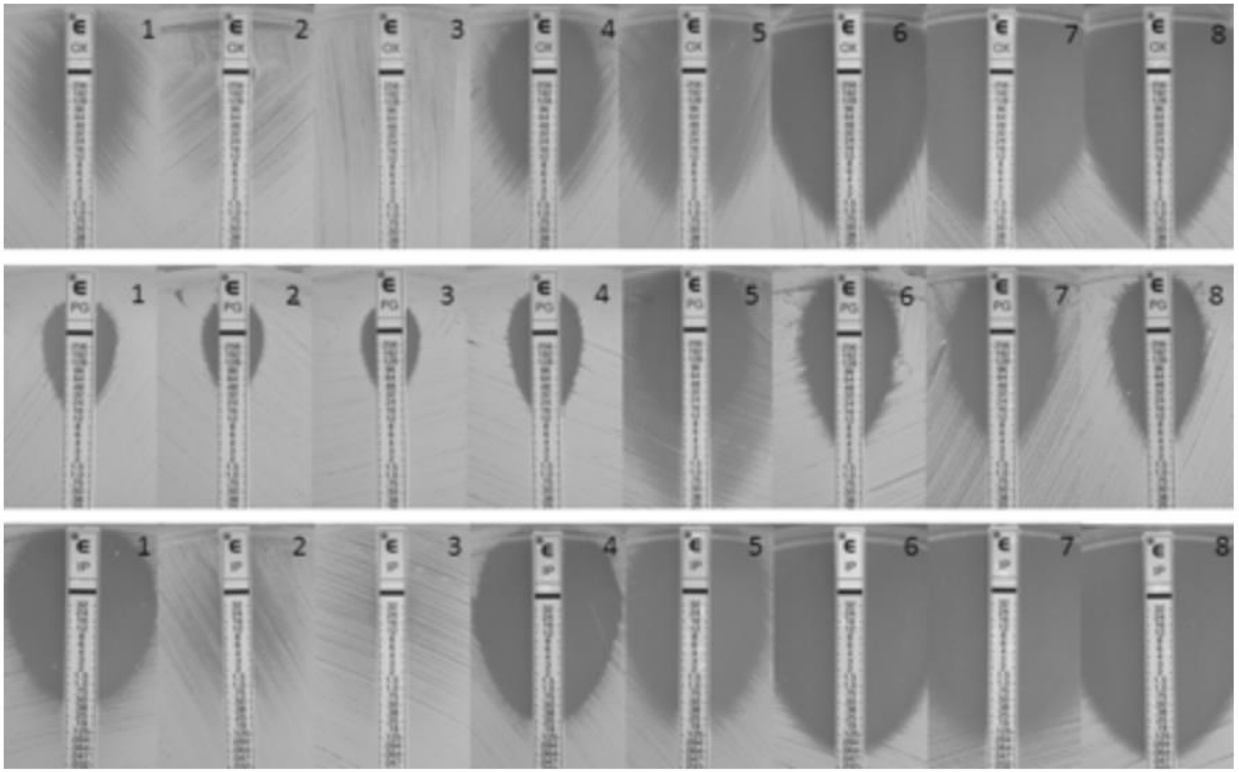

FIG. 1.

MICs of oxacillin (OX), penicillin (PG), and imipenem (IP) in eight consecutive *S. aureus* isolates recovered from blood cultures of a patient who was on daptomycin therapy. Isolates 1 to 5 were daptomycin susceptible, and isolates 6 to 8 were daptomycin nonsusceptible.

TMP-SMX Kombinasyonu

Yapay vegetasyonların kullandığı bir modelde daptomisine duyarlı suşlarda da duyarsız suçlarda etkin

Restrospektif bir derleme

- Daptomisine geçmeden önce vankomisin alan hastalar (%75) Tedavi değişikliği nedeni vankomisin MIK 2 olması (%60.7) Daptomisin 5 gün monoterapi ardından TMP-MXT eklendi.

Daptomisine duyarsız 6 hastada dolaşımdan temizlenme 6.5 gün

Daptomisine duyarlı olanlarda 2 gün olarak saptandı.

Özet

Komplike veya persistan MRSA bakteriyemisi veya doğal kapak endokarditinde

≥10mg /kg ve hücre duvarına aktif bir ajan (fosfomisin, nafsilin,klosasasilin, **sefazolin, ampisilin**) veya **TMP-SXT** ile kombinasyon

MRSA prostetik kapak yada koagülaz negatif stafilokok endokarditinde **rifampisin** ile kombine

Komplike enterekok bakteriyemisinde **ampisilin veya fosfomisin** ile kombine