SEICAV

Sociedad Española de Infecciones Cardiovasculares

Endocarditis por microorganismos multirresistentes

Dr. Enrique Navas Elorza

Bilbao, Septiembre, 2013

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Microorganismos a considerar

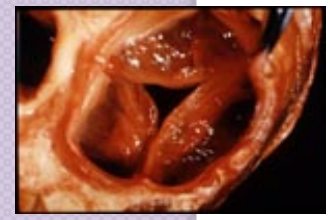
- ***S.aureus* R a meticilina**
- *Streptococcus viridans*
- *Enterococcus faecium VAN-R*
- Bacilos Gramnegativos

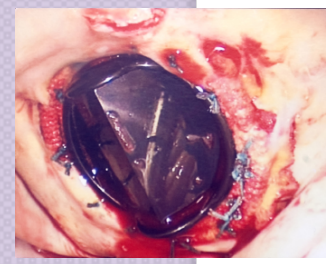
MRSA y Vancomicina

- **Vancomicina ha sido hasta muy recientemente el tratamiento de elección de las infecciones graves producidas por SAMR, y de los pacientes alérgicos a betalactámicos**
- El uso de Vancomicina en infecciones graves producidas por S.aureus OXA-S se asocia a mayor mortalidad y mayor probabilidad de recidiva comparado con el tratamiento con betalactámicos.
- **La aparición de cepas con sensibilidad disminuida a glicopéptidos, y su asociación en estudios observacionales con fracaso terapéutico a vancomicina han obligado a replantear el tratamiento de las infecciones sistémicas por SAMR.**

SAMR: Guidelines

AHA IDSA 2007	ESC 2009	IDSA 2011
VANCOMICINA 30 mg/kg/d bid 6 ss	**VANCOMICINA** 30 mg/kg/d bid 4-6 ss + **GENTAMICINA** 3 mg/kg/d bid/tid 3-5 días	**VANCOMICINA** 15-20 mg/kg/8-12 h 6 ss ó **DAPTOMICINA** 6-10 mg/kg/d 6 ss
VANCOMICINA 30 mg/kg/d bid + **RIFAMPICINA** 900 mg/d tid ≥ 6 ss + **GENTAMICINA** 3 mg/kg/d bid/tid 2 ss	**VANCOMICINA** 30 mg/kg/d bid + **RIFAMPICINA** 1200 mg/d bid ≥ 6 ss + **GENTAMICINA** 3 mg/kg/d bid/tid 2 ss	**VANCOMICINA** 15-20 mg/kg c 8-12h + **RIFAMPICINA** 900 mg/d tid ≥ 6 ss + **GENTAMICINA** 1 mg/kg/8h 2 ss





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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1990, p. 1227–1231 Vol. 34, No. 6
0066-4804/90/061227-05$02.00/0

Vancomycin for *Staphylococcus aureus* Endocarditis in Intravenous Drug Users

PETER M. SMALL AND HENRY F. CHAMBERS*

The Medical Service, San Francisco General Hospital, San Francisco, California 94110, and Department of Medicine, University of California, San Francisco, California 94143*

Received 17 October 1989/Accepted 4 April 1990

The clinical courses of 13 consecutive intravenous drug users with *Staphylococcus aureus* endocarditis treated principally with vancomycin were reviewed. Two patients, one with only right-sided endocarditis and the other with tricuspid and mitral valve endocarditis, had recurrences of positive blood cultures 2 days after completing a 4-week course of vancomycin. Two patients, both of whom eventually were cured, had modifications of therapy because of bacteremia persisting 7 and 16 days into therapy. One patient required an operation for recurrent fevers, and the resected vegetation showed evidence of active infection. Time-kill studies performed with nafcillin and vancomycin for 10 isolates of *S. aureus* showed that vancomycin was less rapidly bactericidal than nafcillin. Although vancomycin is used as an alternative to penicillinase-resistant penicillins for treatment of staphylococcal endocarditis, these findings raise the question of whether it is equivalent to these drugs in efficacy.

A A Ch, Junio 1990

TABLE 1. Clinical data for patients with unsatisfactory responses to vancomycin

Patient no.	Age (yr)	Sex[a]	Valve[b]	Vancomycin concn in serum (μg/ml)[c]	Vancomycin MIC/MBC (μg/ml)	Outcome
1	47	M	TV	T = 2.9	1/2	Relapse after 29 days of therapy
2	30	F	TV	P = 16.8	2/16	Relapse after 28 days of therapy
			MV	T = 7.4		
3	33	M	TV	P = 28.2	1/4	Bacteremia for 16 days
				T = 15.8		
4	26	F	TV	P = 43	1/	Bacteremia for 7 days
			MV	T = 15		
5	37	M	TV	P = 26	1/2	Gram-positive cocci on valve after 37 days of therapy
				T = 9.2		

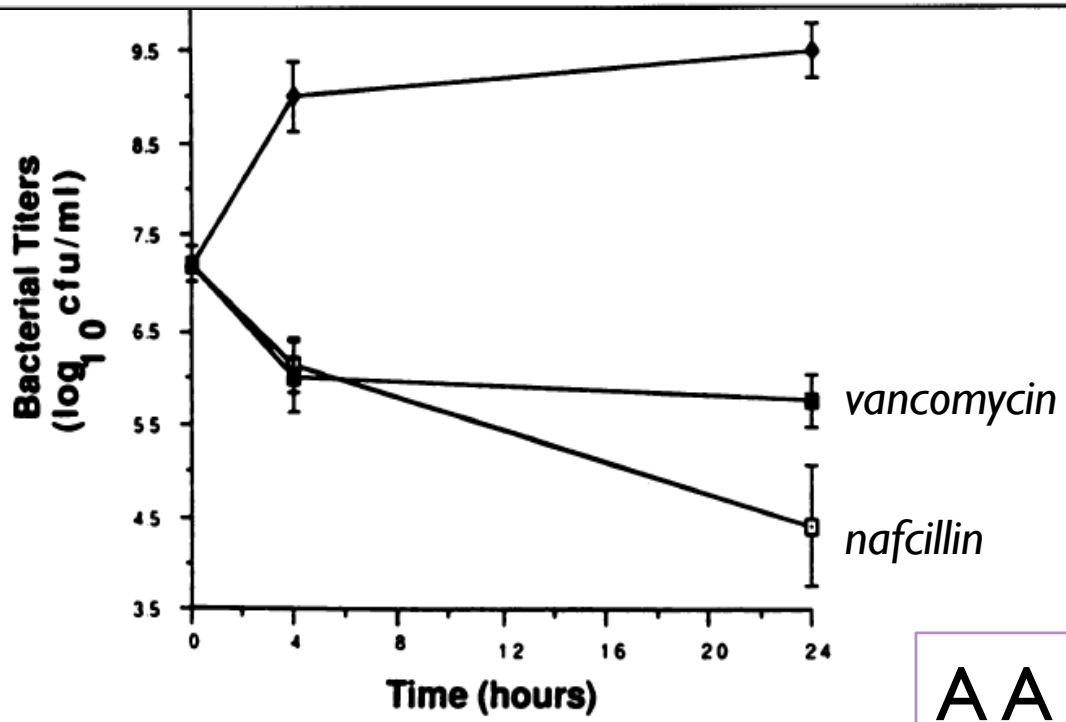

FIG. 1. Time-kill curves for nafcillin (□) and vancomycin (■) at a concentration of four times the MIC for 10 clinical isolates of *S. aureus*. ◆, Control.

A A Ch, Junio 1990

Antimicrobial Agents and Chemotherapy

Impact of Empirical-Therapy Selection on Outcomes of Intravenous Drug Users with Infective Endocarditis Caused by Methicillin-Susceptible *Staphylococcus aureus*

Thomas P. Lodise Jr., Peggy S. McKinnon, Donald P. Levine and Michael J. Rybak
Antimicrob. Agents Chemother. 2007, 51(10):3731. DOI: 10.1128/AAC.00101-07.

	Beta-lactámico n= 44	Vancomicina n=28	p
Edad (mediana)	42.6 (6.3)	40.7 (8.3)	0,5
HIV	11 (25.0)	3 (10.7)	0,1
Mortalidad			
- Global	5 (11.4)	11 (39.3)	0,005
- Izda/I+D	3 (27.3)	6 (66.7)	0,08
- Dcha	2 (6.1)	5 (26.3)	0,04

MRSA y Vancomicina

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Journal of Antimicrobial Chemotherapy (1997) **40**, 135–146

JAC

Correspondence

Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility

J Antimicrob Chemother 1997; **40:** 135–136

K. Hiramatsu[a]*, H. Hanaki[a], T. Ino[b], K. Yabuta[b], T. Oguri[c] and F. C. Tenover[d]

The MRSA strain (Mu50), which was isolated from the purulent discharge at the sternal incision site and from the debridement sample, had a vancomycin MIC of 8 mg/L by the broth microdilution method.[2] Vancomycin has the most reliable antimicrobial activity against MRSA. The emergence of resistance to vancomycin in *S. aureus* has been predicted[3,4] based on the high levels of resistance to vancomycin in enterococci and because transfer of the

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Infection with Vancomycin-Resistant *Staphylococcus aureus* Containing the *vanA* Resistance Gene

Soju Chang, M.D., M.P.H., Dawn M. Sievert, M.S., Jeffrey C. Hageman, M.H.S., Matthew L. Boulton, M.D., Fred C. Tenover, Ph.D., M.P.H., Frances Pouch Downes, Dr.P.H., Sandip Shah, M.S., James T. Rudrik, Ph.D., Guy R. Pupp, D.P.M., William J. Brown, Ph.D., Denise Cardo, M.D., and Scott K. Fridkin, M.D., for the Vancomycin-Resistant *Staphylococcus aureus* Investigative Team*

N Engl J Med 2003;348:1342-7

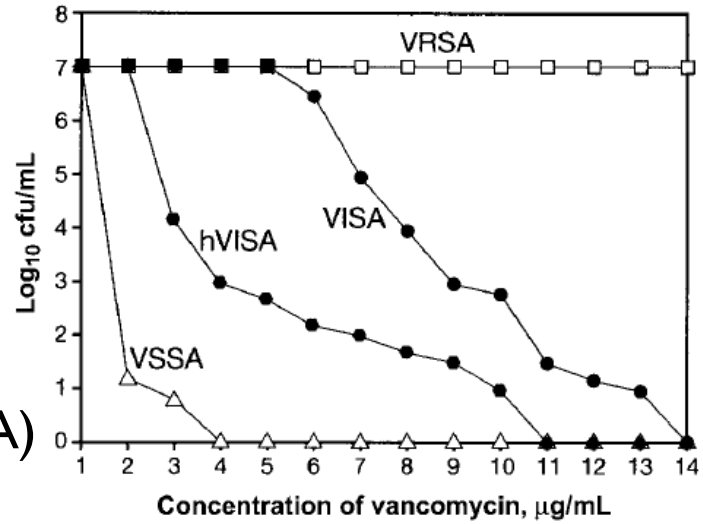
Sensibilidad a Vancomicina en MRSA

- Cepas **Tolerantes** a Vancomicina (MIC/MBC ratio >32, curvas de muerte).

- Cepas **VISA** y **hetero VISA** (Fenotipo identificable por técnicas PAP: population analysis profiles)

  - CMI: 1-4µg/ml en hVISA

  - CMI 4-8 µg/ml en VISA



- Cepas **Resistentes** a Vancomicina (VRSA)

  - CMI ≥16µg/ml

  - Contienen elementos genéticos de enterococo (Van A)

Microbiological Features of Vancomycin in the 21st Century: Minimum Inhibitory Concentration Creep, Bactericidal/Static Activity, and Applied Breakpoints to Predict Clinical Outcomes or Detect Resistant Strains

Clinical Infectious Diseases 2006; 42:S13–24

Table 5. Vancomycin minimum bactericidal concentration (MBC):MIC ratios for 213 strains of *Staphylococcus aureus*, including vancomycin-resistant *S. aureus* (VRSA), vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA (hVISA), and wild-type *(wt)* methicillin-resistant *S. aureus* (MRSA) isolates.

Strain	No. of isolates tested	No. of isolates, according to vancomycin MBC:MIC ratio						*% cepas tolerantes*
		1	2	4	8	≥16 + R[a]	≥32	
wt MRSA	105	42	21	11	15	7[b]	9[b]	15.2%
hVISA	88	8	5	6	4	64[c]	1[c]	73.9%
VISA	17	...	...	...	...	17[d]	...	100.0%
VRSA	3	...	...	...	...	3[e]	...	100.0%

Increased Vancomycin MICs for *Staphylococcus aureus* Clinical Isolates from a University Hospital during a 5-Year Period

Wang et al, J. Clin Microbiol, 2006

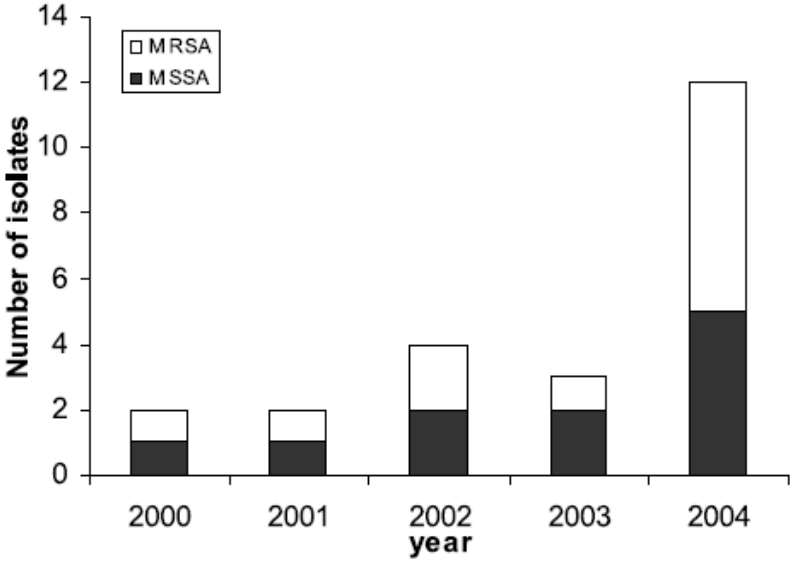


FIG. 1. Numbers of MRSA and MSSA isolates with vancomycin MICs of ≥2 μg/ml from 2000 to 2004.

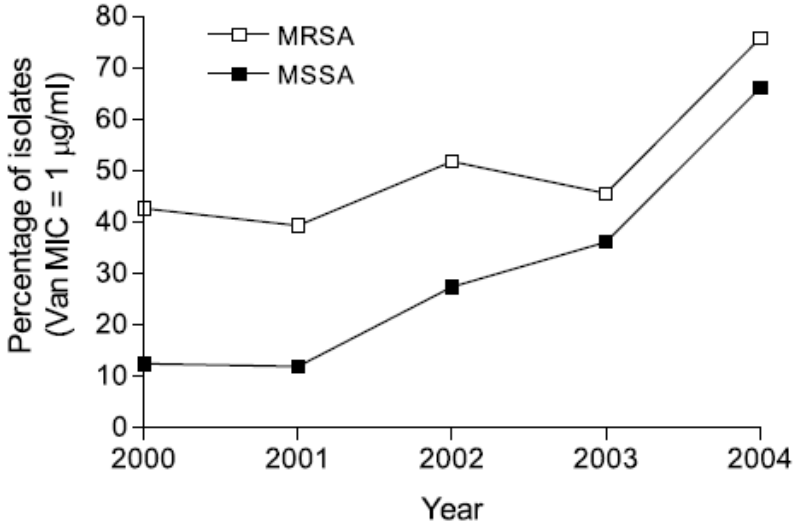


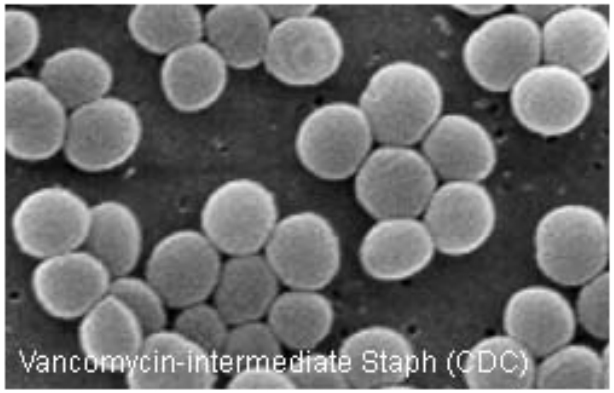
FIG. 2. Percentages of MRSA and MSSA isolates with a vancomycin (Van) MIC of 1 μg/ml from 2000 to 2004.

«MIC- CREEP»

Puntos de corte a Vancomicina en *S.aureus*

May 1, 2008

FDA Lowers Vancomycin Breakpoints for Staph Infections

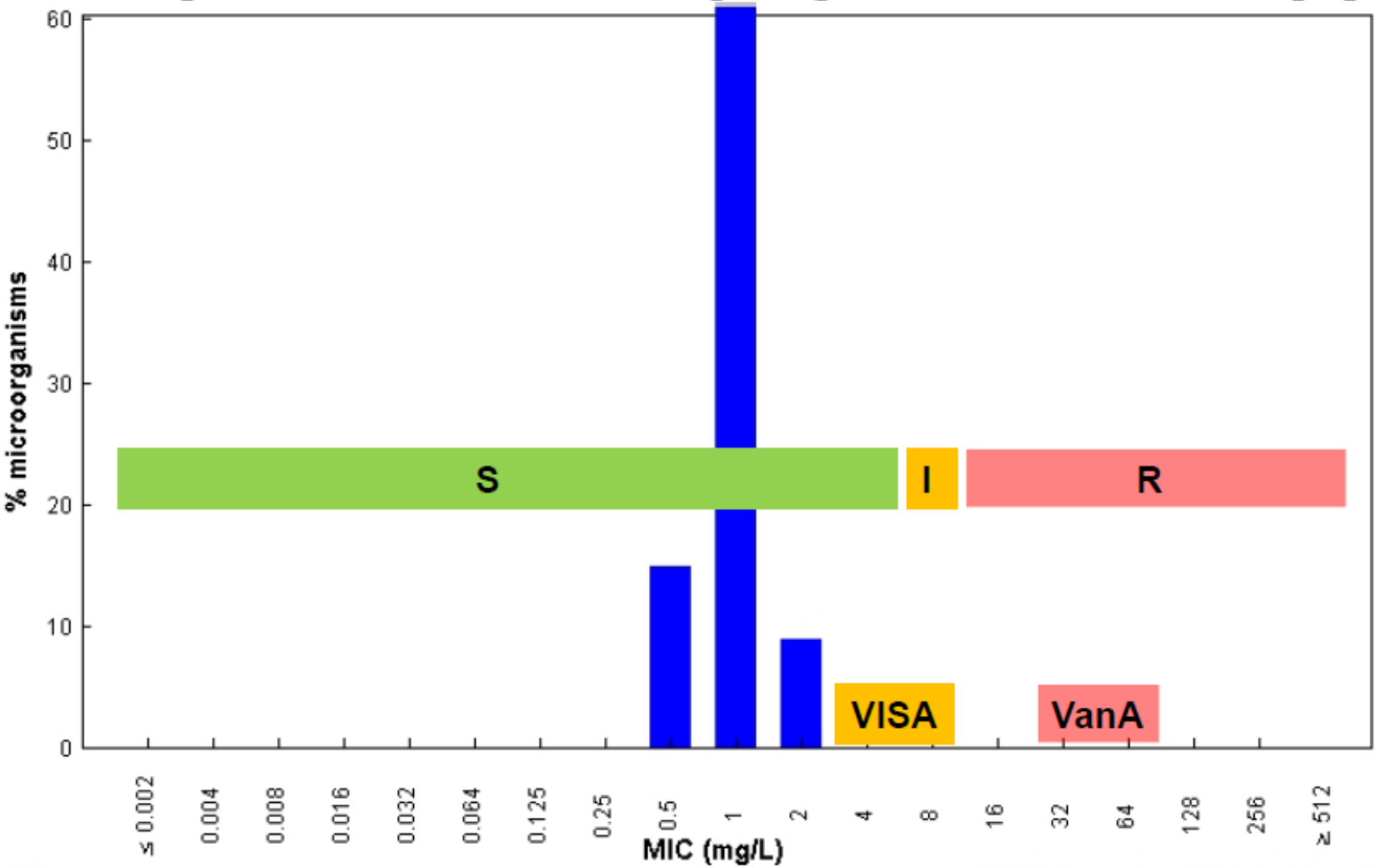

Vancomycin-intermediate Staph (CDC)

The Food and Drug Administration (FDA) has lowered the breakpoints for vancomycin in the treatment of *Staphylococcus aureus* to reflect growing rates of resistance, and in response to urging from IDSA and others.

According to a recently updated package insert for Baxter Healthcare Corporation's vancomycin injection in GALAXY plastic containers, the susceptibility test interpretive criteria for *S. aureus* have been changed as follows:

	Minimum Inhibitory Concentration (MIC) (µg/mL)		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Updated	≤2	4-8	≥16
Previous	≤4	8-16	≥32

Old EUCAST vancomycin breakpoints for *Staphylococcus* spp.



MIC
Epidemiological cut-off: WT ≤ 2 mg/L

87764 observations (33 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

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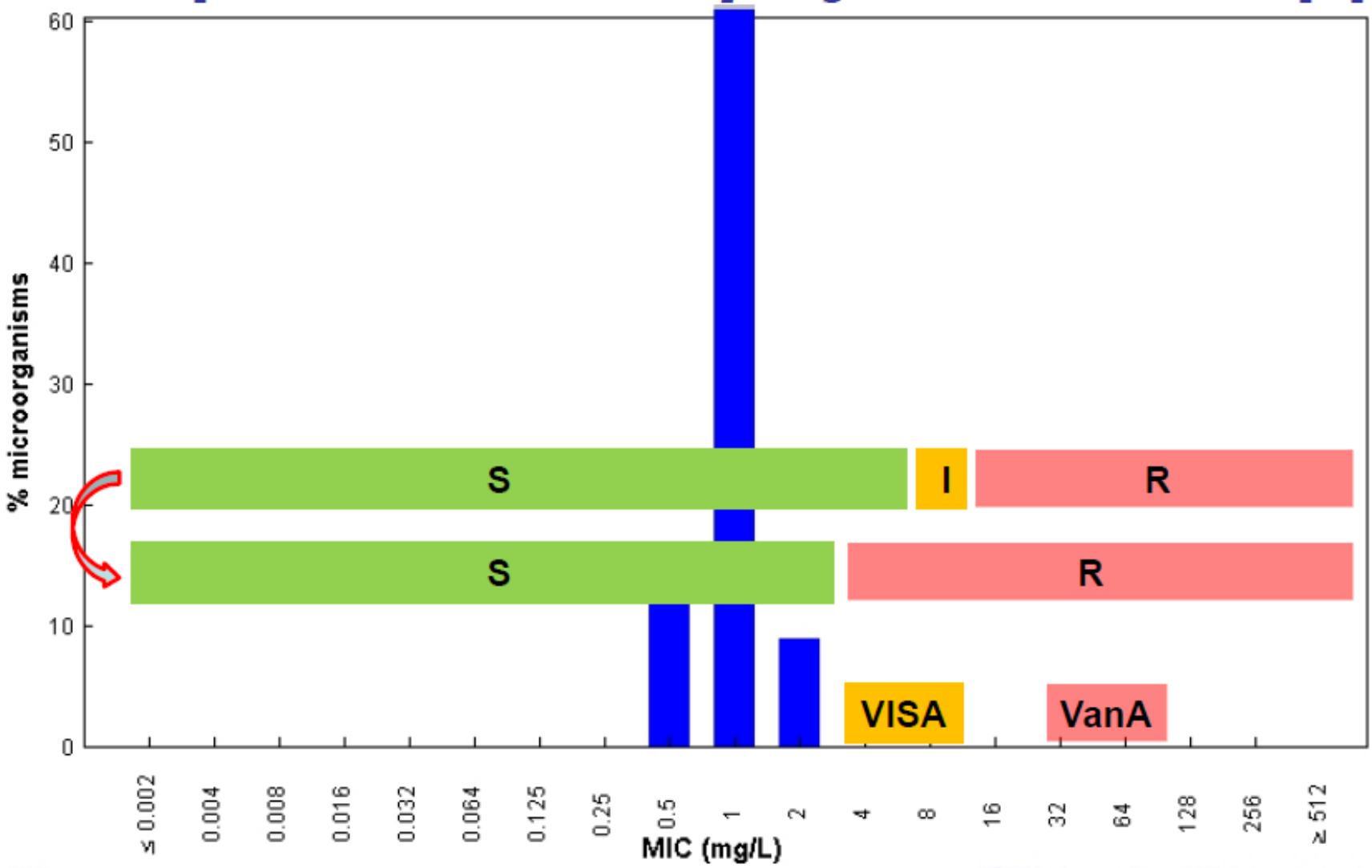

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Puntos de corte a Vancomicina en *S.aureus*

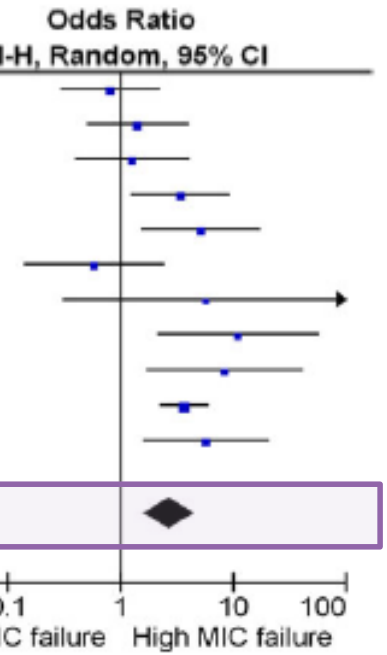
	S	I	R
CLSI	≤2µg/ml	2-8 µg/ml	>8µg/ml
EUCAST	≤2µg/ml	-	>2µg/ml

The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in Staphylococcus aureus Infections: A Systematic Review and Meta-analysis

Van Hal, *Clinical Infectious Diseases 2012;54(6):755–71*

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	14	37	12	28	10.9%	0.81 [0.30, 2.21]
Choi et al (15)	12	34	10	36	10.8%	1.42 [0.51, 3.91]
Ferry et al (17)	9	24	9	28	9.7%	1.27 [0.40, 3.98]
Hidayat et al (21)	20	51	7	44	11.0%	3.41 [1.27, 9.12]
Hsu et al (25)	17	45	4	38	9.3%	5.16 [1.56, 17.11]
Lalueza et al (32)	3	13	17	50	7.7%	0.58 [0.14, 2.40]
Lodise et al (36)	6	66	0	26	2.7%	5.69 [0.31, 104.78]
Moise et al (41)	11	14	5	20	6.5%	11.00 [2.16, 56.09]
Moise-Broder et al (42)	23	25	22	38	6.8%	8.36 [1.72, 40.68]
Takesue et al (53)	34	97	85	662	15.9%	3.66 [2.28, 5.89]
Yoon et al (58)	14	18	17	45	8.8%	5.76 [1.63, 20.41]
Total (95% CI)		**424**		**1015**	**100.0%**	**2.69 [1.60, 4.51]**
Total events	163		188			

Heterogeneity: Tau² = 0.38; Chi² = 22.59, df = 10 (P = 0.01); I² = 56%
Test for overall effect: Z = 3.75 (P = 0.0002)



Gráfica de Forest : **Fracaso terapéutico** según CMI a Vancomicina: CMI < 1.5 mcg/mL vs CMI ≥ 1.5 mcg/mL

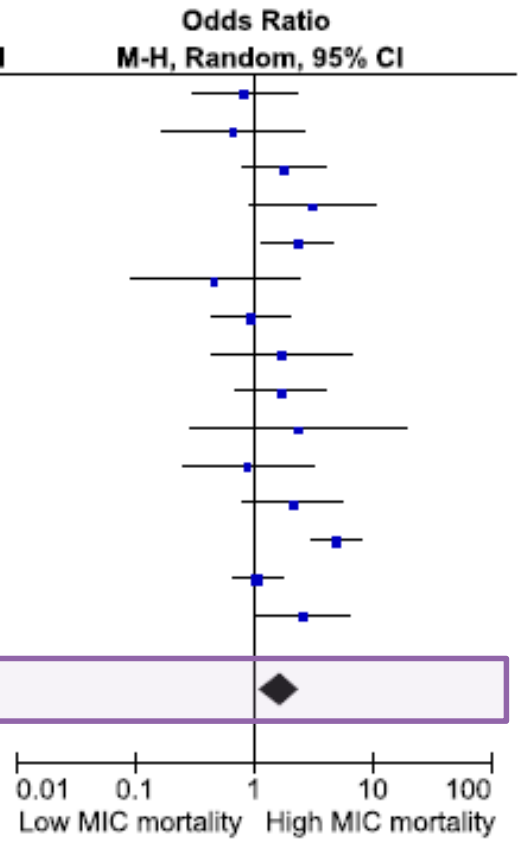
The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in Staphylococcus aureus Infections: A Systematic Review and Meta-analysis

Van Hal, Clinical Infectious Diseases 2012;54(6):755–71

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)	28	94	16	105	8.8%	2.36 [1.18, 4.71]
Lalueza et al (32)	2	13	14	50	3.6%	0.47 [0.09, 2.38]
Liao et al (34)	13	40	46	137	8.3%	0.95 [0.45, 2.02]
Lodise et al (36)	12	66	3	26	4.7%	1.70 [0.44, 6.61]
Musta et al (43)	60	206	7	36	7.4%	1.70 [0.71, 4.10]
Neuner et al (45)	39	186	1	10	2.5%	2.39 [0.29, 19.42]
Schweizer et al (50)	46	341	3	20	5.1%	0.88 [0.25, 3.13]
Soriano et al (52)	37	130	6	38	6.9%	2.12 [0.82, 5.49]
Takesue et al (53)	33	97	62	662	10.4%	4.99 [3.04, 8.18]
van Hal et al (54)	38	117	73	236	10.6%	1.07 [0.67, 1.73]
Wang et al (55)	13	26	27	97	7.3%	2.59 [1.07, 6.30]
Total (95% CI)		**1553**		**1568**	**100.0%**	**1.64 [1.14, 2.37]**
Total events	391		289			

Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%

Test for overall effect: Z = 2.65 (P = .008)



Gráfica de Forest : **Mortalidad** según CMI a Vancomicina:
CMI < 1.5 mcg/mL vs **CMI ≥ 1.5 mcg/mL**

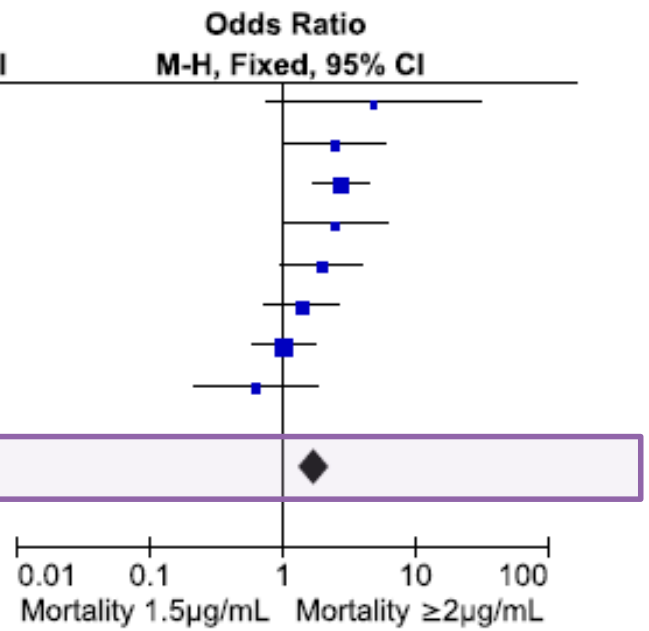
The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in Staphylococcus aureus Infections: A Systematic Review and Meta-analysis

Van Hal, *Clinical Infectious Diseases 2012;54(6):755–71*

Study or Subgroup	MIC≥2µg/mL Events	Total	MIC=1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bae et al (12)	4	6	9	31	1.1%	4.89 [0.76, 31.60]
Haque et al (19)	15	29	26	86	6.9%	2.47 [1.04, 5.85]
Holmes et al (23)	48	179	32	272	20.2%	2.75 [1.67, 4.51]
Musta et al (43)	10	21	50	185	5.8%	2.45 [0.98, 6.13]
Neuner et al (45)	21	76	18	110	11.6%	1.95 [0.96, 3.98]
Schweizer et al (50)	18	111	28	230	16.6%	1.40 [0.74, 2.65]
Soriano et al (52)	26	92	60	213	28.3%	1.00 [0.58, 1.73]
van Hal et al (54)	5	21	32	96	9.5%	0.63 [0.21, 1.86]
Total (95% CI)		**535**		**1223**	**100.0%**	**1.72 [1.34, 2.21]**
Total events	147		255			

Heterogeneity: Chi² = 13.50, df = 7 (P = .06); I² = 48%

Test for overall effect: Z = 4.29 (P < .0001)



Gráfica de Forest : **Mortalidad** según CMI a Vancomicina por Etest: CMI 1.5 mcg/mL vs **CMI ≥ 2 mcg/mL**

The Clinical Significance of Vancomycin Minimum Inhibitory Concentration in Staphylococcus aureus Infections: A Systematic Review and Meta-analysis

Van Hal, CID, 2012

On the basis of our findings, non-vancomycin anti-MRSA therapies should be considered for patients with MRSA BSI with high vancomycin MIC, especially for values ≥2.0 mcg/mL by Etest.

MRSA endocarditis y Vancomicina

- Inaceptable con CMI ≥ 2 mcg/ml

OPEN ACCESS Freely available online

PLoS one

Vancomycin Treatment of Infective Endocarditis Is Linked with Recently Acquired Obesity

Franck Thuny[1,2], Hervé Richet[1], Jean-Paul Casalta[3], Emmanouil Angelakis[1], Gilbert Habib[2], Didier Raoult[1,3]*

1 Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes, Université de la Méditerranée, Marseille, France, **2** Service de Cardiologie, Hôpital de la Timone, Marseille, France, **3** Pôle de Maladies Infectieuses, Hôpital de la Timone, Marseille, France

Abstract

Background: Gut microbiota play a major role in digestion and energy conversion of nutrients. Antibiotics, such as avoparcin (a vancomycin analogue), and probiotics, such as *Lactobacillus* species, have been used to increase weight in farm animals. We tested the effect of antibiotics given for infective endocarditis (IE) on weight gain (WG).

- ¿Vancomicina en endocarditis por SAMR con CMI 0,5-1 mcg/ml?

Staphylococcus aureus MR

Fármacos comercializados

Vancomicina
Daptomicina
Tigeciclina
Linezolid
Fosfomicina
Cotrimoxazol
Synercid
Ac. Fusídico

Combinaciones

Vanco-Genta-Rifa
Dapto-Cloxacilina
Dapto-Rifampicina
Fosfo-Imipenem
Dapto-Linezolid

En desarrollo

Telavancina
Dalvabancina
Oritavancina

Ceftarolina
Ceftobiprol

Iclaprim

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2006 VOL. 355 NO. 7

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

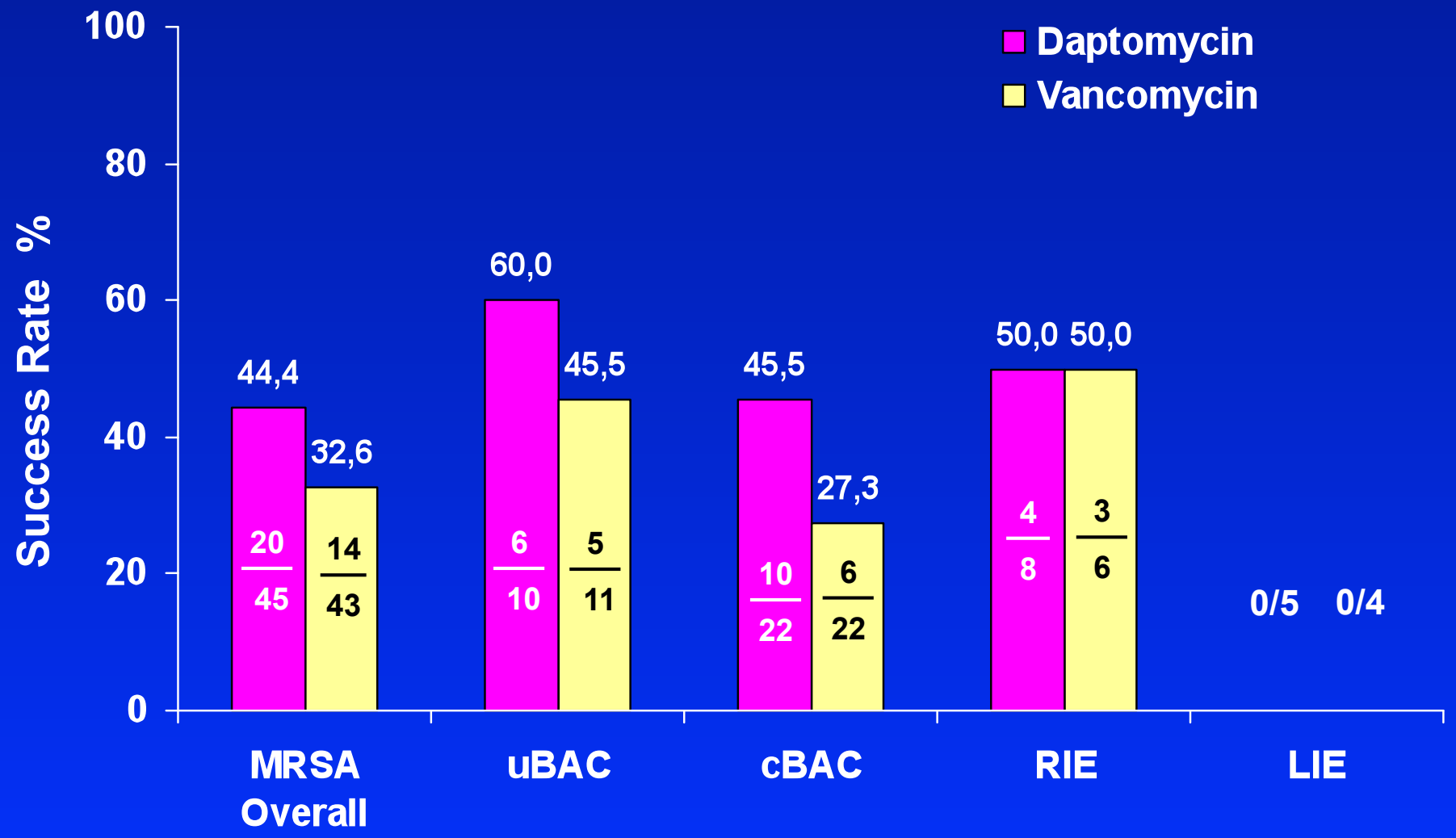
Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D.,

Table 1. Distribution of Successful Outcomes 42 Days after the End of Therapy.*

Successful Outcome	Daptomycin (N=120)	Standard Therapy (N=104)	Absolute Difference in Success Rates
	no. of patients/total no. (%)		*% (95% CI)*
Overall	53/120 (44.2)	42/104 (40.4)	3.8 (−9.2 to 16.7)
MRSA infection	20/45 (44.4)	14/43 (32.6)	11.9 (−8.3 to 32.1)
MSSA infection	33/74 (44.6)	28/60 (46.7)	−2.1 (−19.0 to 14.9)

* Patients received vancomycin for MRSA infections and either daptomycin or an antistaphylococcal penicillin for MSSA infections. CI denotes confidence interval.

MRSA - Success at TOC by Final Diagnosis (IEAC, ITT)



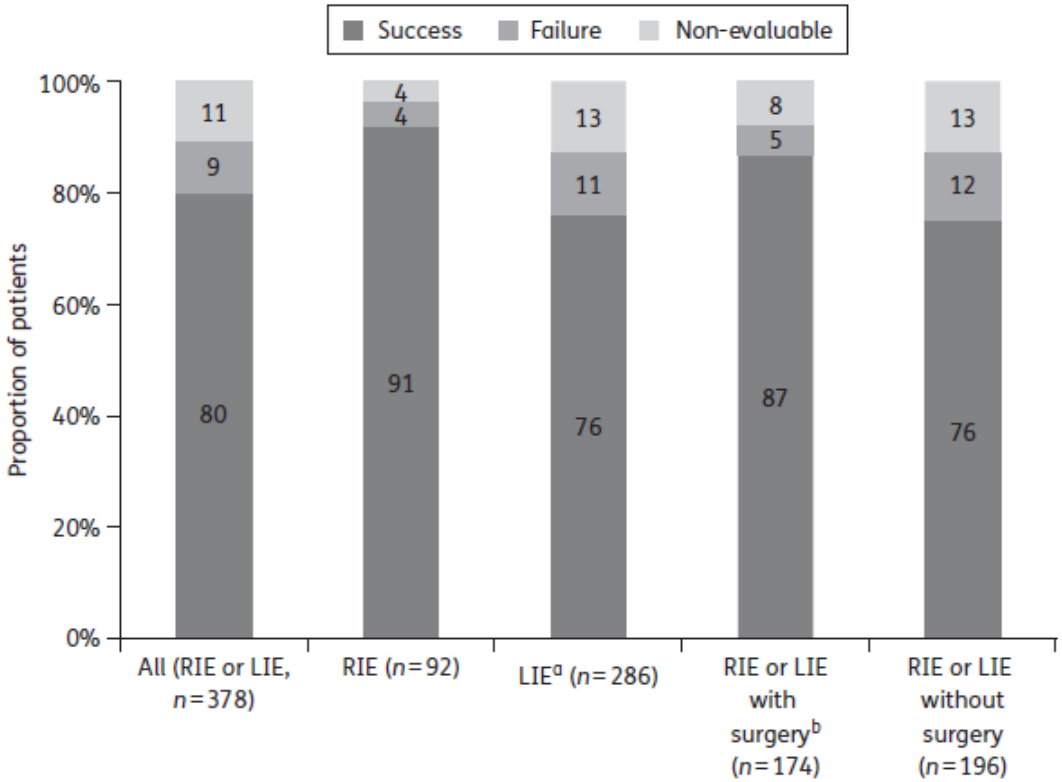
IEAC Reasons For Failure at TOC (ITT, > One Reason May Apply)

	Daptomycin N = 120	Comparator N = 115
Overall failure	67 (55.8%)	67 (58.3%)
Persisting or relapsing *S. aureus* infection	19 (15.8%)	11 (9.6%)
Clinical failure without persisting or relapsing *S. aureus* infection	4 (3.3%)	4 (3.5%)
Discontinued due to adverse event	8 (6.7%)	17 (14.8%)
Patient died	13 (10.8%)	13 (11.3%)
Non-study antibiotics	20 (16.7%)	16 (13.9%)
No blood culture drawn at TOC	9 (7.5%)	12 (10.4%)
Non-evaluable (e.g., withdrew consent, left AMA)	9 (7.5%)	14 (12.2%)

Daptomycin for the treatment of infective endocarditis: results from a European registry J Antimicrob Chemother 2013; 68: 936–942

Daptomycin for the treatment of infective endocarditis

JAC



S.aureus

Tasa de éxito:

- *Global:* 83%
- MRSA: 81%
- MSSA: 84%

(n=76)

59% (224): dosis 6 mg/kg

26% (98): dosis 6-12 mg/kg (mediana 8 mg/kg)

Daptomicina en endocarditis MRSA

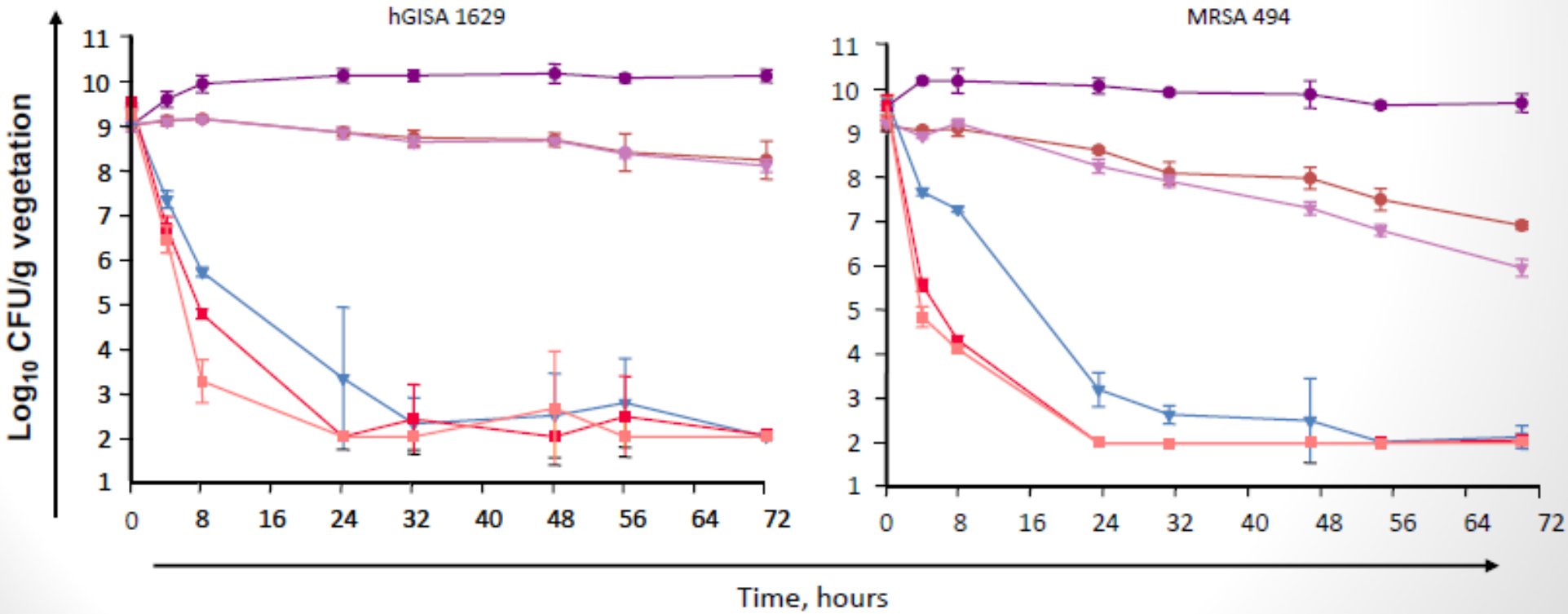
- Dosis recomendada:
  - 6 mg/kg: ficha técnica en bacteriemia-endocarditis
  - 10 mg/kg: propuesta en endocarditis por MRSA (8-12 mg/kg)

    Razón:
    - Act. bactericida concentración-dependiente
    - Modelos experimentales
    - Tolerabilidad en series observacionales
- Reducir dosis a c 48 h si ClCr < 30 ml/min

Evaluation of vancomycin and daptomycin for MRSA and hVISA

- Growth control
- Vancomycin
- High dose vancomycin
- Daptomycin 6 mg/kg
- Daptomycin 12 mg/kg
- Daptomycin 10 mg/kg

	MIC, µg/ml	
	hGISA 1629	MRSA 494
Vancomycin	0.5	1
Daptomycin	0.25	0.5



Leonard SN. & Rybak MJ. *J Antimicrob Chemother*. 2009; 63:155-160.

A multicentre evaluation of the effectiveness and safety of high-dose daptomycin for the treatment of infective endocarditis

Kullar et al, J Antimicrob Chemother, 2013

- 70 pacientes con endocarditis (54 MRSA) tratada con daptomicina ≥8 mg/kg/day:
  - Exito: 85.9%
  - Supervivencia (30d): 84.6%

Table 2. Patients with MRSA IE developing non-susceptibility to daptomycin

IE	DAP MIC (mg/L)	DAP MIC change	VAN MIC (mg/L)	VAN exposure (days)	Outcome
RIE	0.38→4	day 7 HD DAP	1.5→2	17	cleared on SXT
RIE	1→4	day 1 HD DAP	2→2	5	cleared on SXT
RIE	0.5→4	day 21 HD DAP	1→2	≤30 days prior to admission	organism persisted
LIE	1→4	day 8 HD DAP	2→2	2	cleared on HD DAP
RIE/LIE	0.5→4	day 11 HD DAP	hVISA 2→4	prior to admission VAN ×6 weeks	cleared on HD DAP
RIE/LIE	1→2	day 18 HD DAP	1.5→2	20	cleared on HD VAN

DAP, daptomycin; VAN, vancomycin; HD, high-dose; hVISA, heterogeneous vancomycin-intermediate *S. aureus*; SXT, trimethoprim/sulfamethoxazole.

Combinaciones con Daptomicina

OBJETIVO:

- Sinergia
- Prevenir el desarrollo de resistencia a daptomicina.

- Daptomicina-gentamicina
- Daptomicina-rifampicina
- Daptomicina-fosfomicina
- Daptomicina-betalactámico: efecto *«seesaw»*
- Daptomicina-cotrimoxazol

RIFAMPICINA

- Papel no bien definido como «adyuvante» en el tratamiento de las infecciones por Grampositivos:

  - Se admite su utilidad en las infecciones estafilocócicas de implantes ortopédicos (biofilm)

  - Efecto variable y contradictorio in vitro en diferentes combinaciones utilizadas (betalactámicos, quinolonas, glicopéptidos…)

  - Escasos estudios en humanos: sin que se aprecie antagonismo

  - Toxicidad e interacciones no despreciables

Rifampicina en endocarditis estafilocócica

- **Levine DP** et al (1991) Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis.

  Ann Intern Med 115:674–680

- **Van der Auwera P** et al(1985) Double-blind, placebo-controlled study of oxacillin combined with rifampin in the treatment of staphylococcal infections. *Antimicrob Agents Chemother 28:467–472*

- **Van der Auwera P** et al (1983) Clinical study of combination therapy with oxacillin and rifampin for staphylococcal infections.

  Rev Infect Dis 5 (Suppl 3):515– 522

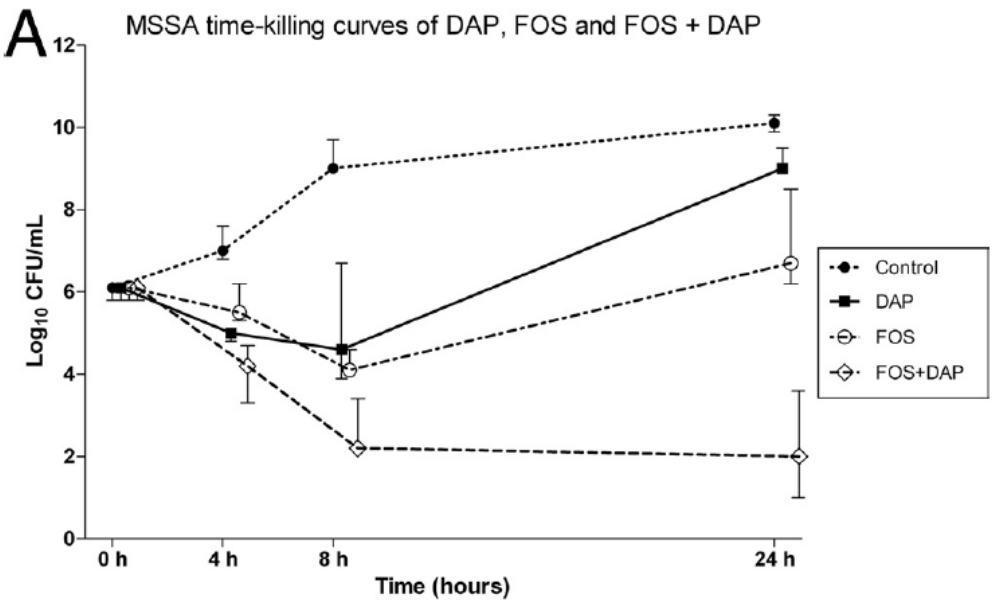
No demuestran impacto alguno en la respuesta ni mortalidad de los pacientes

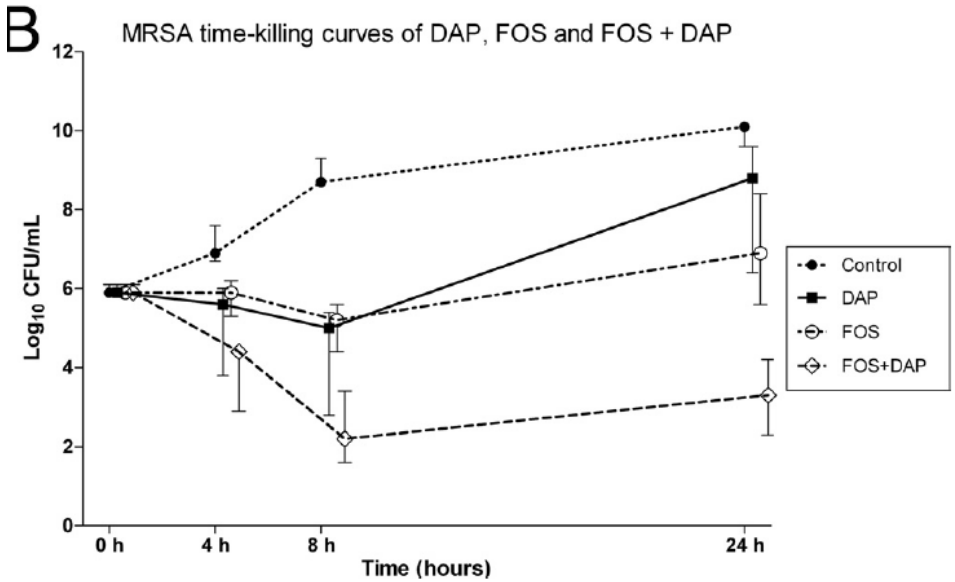
Relationship of In Vitro Synergy and Treatment Outcome with Daptomycin plus Rifampin in Patients with Invasive MRSA Infections Rose et al, Antimicrobial Agents and Chemotherapy 2013, 57 (7)

Subject no.	Age and sex	Comorbidity(ies)	Infection type	MICs (μg/ml)	DAP (mg/kg of body wt) + RIF (mg) therapy	Clinical outcome	Synergy analysis	
							Checkerboard[b]	Time-kill[c]
1	66, F	DM, HTN	Osteomyelitis	DAP, 0.13; RIF, 0.03	4 mg/kg DAP q24h for 135 days; 600 mg RIF p.o. QD for 175 days	Cure	S	S
2	59, M	CKD, HTN, obesity	Osteomyelitis	DAP, 0.13; RIF, 0.03	6 mg/kg DAP q48h for 84 days; 600 mg RIF p.o. QD for 23 days	Cure	S	S
3	47, M	HTN, SLE, obesity, MRSA colonization	Postoperative wound	DAP, 0.13; RIF, 0.06	6 mg/kg DAP q48h for 90 days; 300 mg RIF p.o. q24h for 14 days	Cure	S	Add
4	31, M	ICU stay, ESRD HD, MRSA colonization	Endovascular/HD line	DAP, 0.25; RIF, 0.06	8 mg/kg DAP q48h for 90 days; 600 mg RIF p.o. q24h for 85 days	Cure	S	S
5	30, M	DM	Osteomyelitis	DAP, 0.25; RIF, 0.03	4 mg/kg DAP q24h for 46 days; 300 mg RIF p.o. q12h for 43 days	Improvement	I	I
6	22, M	Obesity	Septic arthritis	DAP, 0.13; RIF, 0.03	4 mg/kg DAP q24h for 68 days; 600 mg RIF p.o. q24h for 15 days	Cure	S	S
7	42, M	DM, CKD with transplant	Osteomyelitis	DAP, 0.13; RIF, 0.06	4 mg/kg DAP q24h for 42 days; 600 mg RIF p.o. q24h for 6 days	Cure	S	S
8	53, F	HTN	Joint prosthesis	DAP, 0.25; RIF, 0.03	4 mg/kg DAP q24h for 68 days; 600 mg RIF p.o. q24h for 39 days	Failure	I	Ant
9	53, F	ESRD HD, DM, HTN, obesity	Osteomyelitis	DAP, 0.25; RIF, 0.06	6 mg/kg DAP q48h for 43 days; 600 mg RIF p.o. q24h for 39 days	Cure	S	S
10	76, M	ESRD HD, DM, COPD, HTN	Postoperative wound	DAP, 1; RIF, 8	6 mg/kg DAP q48h for 43 days; 300 mg RIF p.o. q24h for 43 days	Cure	S	I
11	50, M	ICU stay, obesity	Prosthetic valve endocarditis	DAP, 0.25; RIF, 0.06	6 mg/kg DAP q24h for 100 days; 600 mg RIF p.o. q24h for 115 days	Cure	S	I
12	47, F	ICU stay	Deep abscess	DAP, 0.25; RIF, 0.03	6 mg/kg DAP q24h for 13 days; 600 mg RIF p.o. q12h for 83 days	Failure	I	I

High-Dose Daptomycin plus Fosfomycin Is Safe and Effective in Treating Methicillin-Susceptible and Methicillin-Resistant Staphylococcus aureus Endocarditis

Miró et al, Antimicrob. Agents Chemother. 2012, 56(8):4511





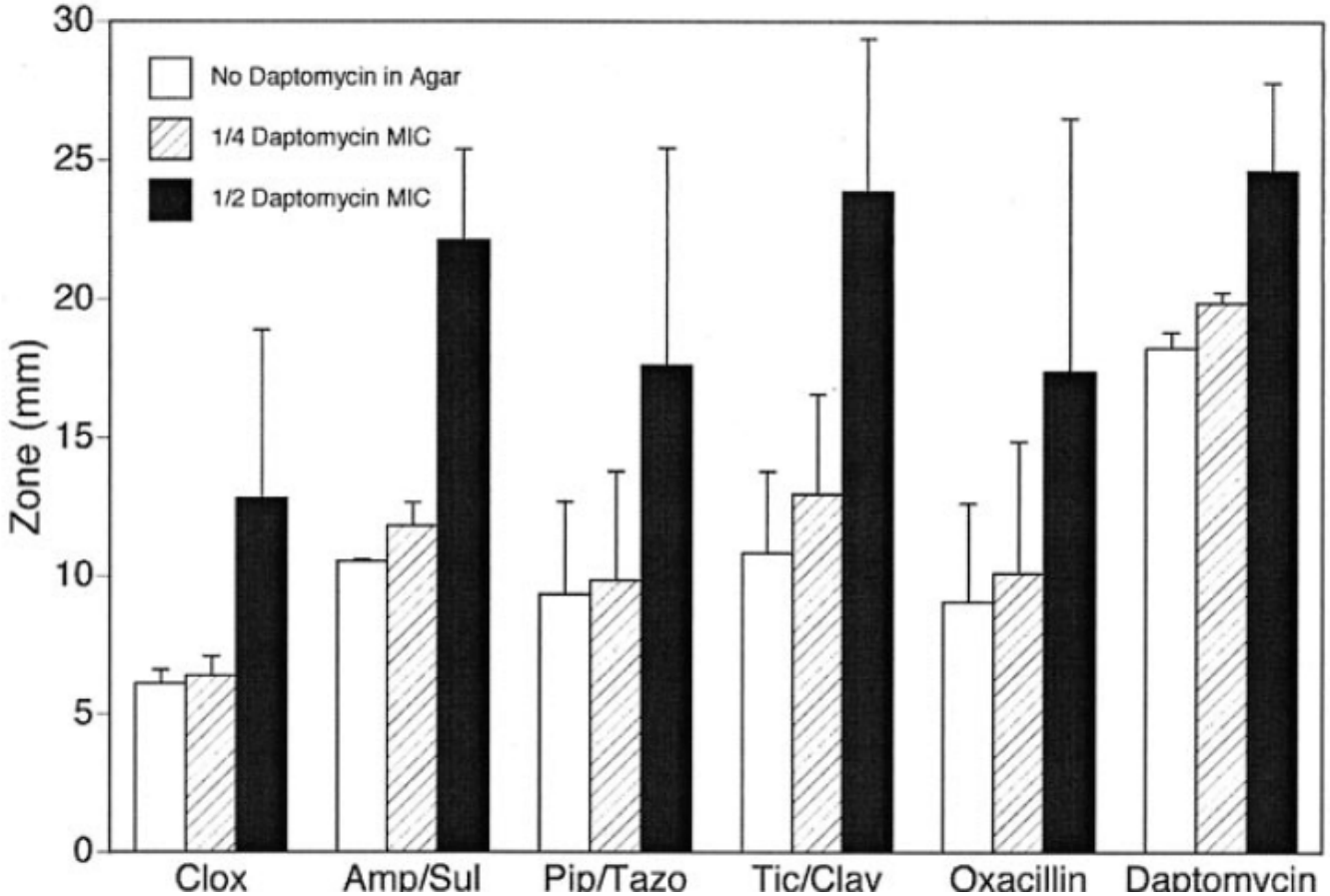
3 pacientes con endocarditis por *S.aureus* que fracasan con Daptomicina/vancomicina: (1 MSSA sobre prótesis, 2 MRSA):

- Daptomicina 10 mg/kg + Fosfomicina 2g c 6h
- Curación sin cirugía
- Demostración de sinergia y eficacia bactericida in vitro (curvas de muerte).

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2004, p. 2871–2875 Vol. 48, No. 8
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.8.2871–2875.2004

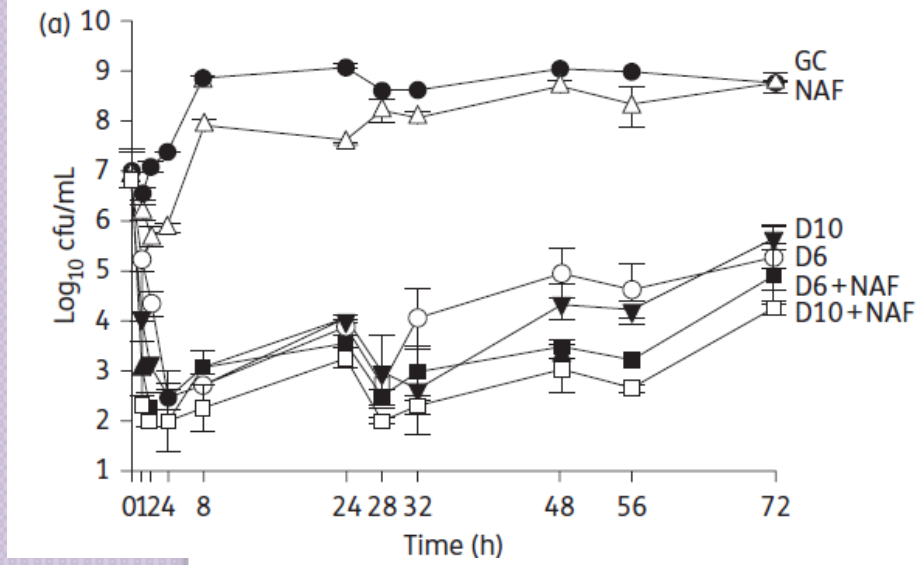
Synergy of Daptomycin with Oxacillin and Other β-Lactams against Methicillin-Resistant *Staphylococcus aureus*

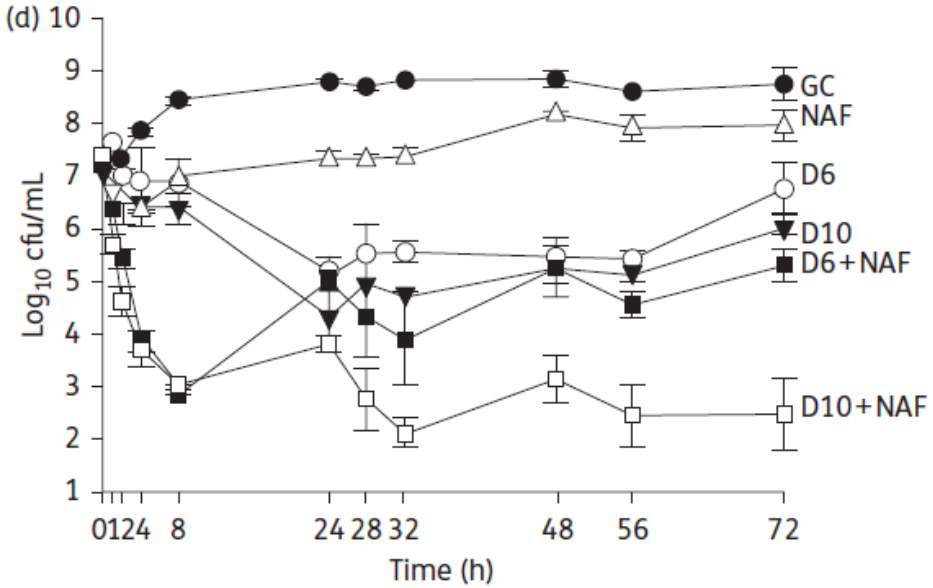
Kenneth H. Rand* and Herbert J. Houck



Evaluation of the combination of daptomycin and nafcillin against vancomycin-intermediate Staphylococcus aureus

J Antimicrob Chemother 2013; 68: 644–647





CMI: Dapto 0.5 mg/L Nafcillin 256 mg/L

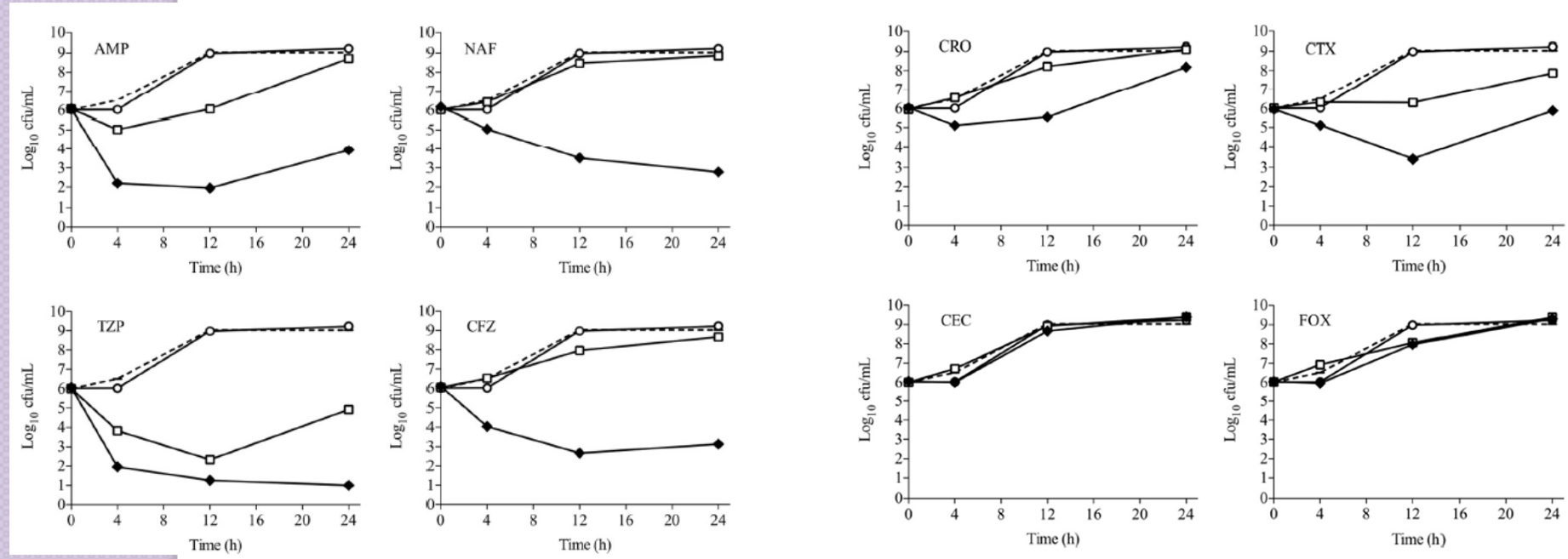
CMI: Dapto 2 mg/L Nafcillin 32 mg/L

Beta-Lactam Antibiotics Targeting PBP1 Selectively Enhance Daptomycin Activity against Methicillin-Resistant *Staphylococcus aureus*

Antimicrobial Agents and Chemotherapy 2013, 57 (10), 5005–12

Combinaciones de abcos con alta afinidad por PBP1

Combinaciones de abcos con baja afinidad por PBP1



β-lactams (BL) Targeting PBP1 Induce Cell Morphology Changes in Methicilin-Resistant *Staphylococcus aureus* to Selectively Enhance Daptomycin (DAP) Activity

A-021- ICAAC 2013

- Estudio de cepas de MRSA DAP-S/R:
  - PBP1 ampicillina, nafcilina, pip-tzb, cefazolina, cefepime, meropenem
  - PBP2 ceftriaxona, cefotaxima
  - PBP3 cefaclor
  - PBP4 (cefoxitin)

<u>Act. bactericida</u>

± 3-5 log

< 1 log

Efecto sobre la pared celular: engrosamiento, formación de septos e inducción de alteraciones morfológicas en la división celular

Ceftarolina: IDSA, 2012

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

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Salvage Therapy with Ceftaroline Combination for Persistent MRSA Bacteremia

[1]Eric Richards, MD; [2]Jerusha Taylor, PharmD, BCPS; and [3]Graeme Forrest, MBBS

[1] Division of Infectious Diseases, Oregon Health & Science University; [2] Pharmacy Services, Oregon Health & Science University; [3] Division of Infectious Diseases, Portland VAMC

ABSTRACT

Background:
Methicillin-resistant *Staphylococcus aureus* (MRSA) blood stream infections (BSI) are associated with significant morbidity and mortality. Clinical and microbiologic failure with agents such as Vancomycin (VAN) and Daptomycin (DAP) has become an increasing problem. There is little evidence to support the use of alternative agents alone or in combination with standard therapy. Ceftaroline fosamil (CEF) has in vitro activity against MRSA but has not been studied for clinical use in MRSA BSI or endocarditis.

Methods:
Retrospective chart review of all dispenses of CEF for bacteremia from 2010 to 2012 at Oregon Health & Science University (OHSU) and Portland VA Medical Center. Measured duration of bacteremia on monotherapy (MT) and combination therapy (CT), relapse rate, and adverse drug reaction (ADR).

Results:
All 6 patients experienced persistent bacteremia despite VAN and DAP treatment. Mean duration of MRSA bacteremia while on MT= 21.5days. Source control was achieved in all cases. VAN levels reached therapeutic goal of >15 mg/L within 48h in all cases and mean trough was 19.6 mg/L thereafter. DAP was dosed at 6-10mg/kg/day. All 6 patients then received combination CEF plus VAN or DAP. CEF was dosed equivalent to 600mg Q8h according to creatinine clearance. Mean duration of bacteremia after adding CEF= 3.5 days. Only 1 case experienced treatment relapse after CEF therapy. All experienced ADR, and three experienced ADR to CEF. Only case 4 died after progressing to ESRD and then declined hemodialysis.

Conclusion:
After failing MT for persistent MRSA BSI or endocarditis, addition of CEF to MT resulted in microbiologic success in all 6 cases and clinical cure in 5 of 6 cases.

CONTACT

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Phone: 503-494-7735

INTRODUCTION

- MRSA blood stream infections (BSI) are associated with significant morbidity and mortality (1)
- Persistent bacteremia and reduced-vancomycin susceptibility are predictors of worse outcomes (2, 3)
- Vancomycin (VAN) is considered standard therapy for MRSA BSI (4)
  - no antibiotic has been shown prospectively to be more effective than VAN for MRSA BSI
  - Daptomycin (DAP) has been shown to be non-inferior to VAN for MRSA BSI (5)
  - Ceftaroline (CEF), a new cephalosporin with activity against MRSA, has not been studied in comparison to VAN or DAP for BSI (6)
- Combination therapy has not been well studied in clinical settings

DEFINITIONS

- **Microbiologic Failure:** >7 days of bacteremia despite achieving source control and target VAN levels
- **Clinical Failure:** progression of signs/symptoms despite achieving source control and target VAN levels
- **Mono-Therapy (MT):** VAN (targeted to trough 15-20mg/L) or DAP (dosed 6 to 10 mg/kg/day)
- **Combination Therapy (CT):** VAN (targeted to trough 15-20mg/L) plus CEF 600mg IV Q8h or DAP 6-10 mg/kg/day plus CEF 600mg IV Q8h

METHODS

- Retrospective chart review of all dispenses of Ceftaroline for bacteremia from 2010 to 2012 at OHSU and Portland VAMC.
- MIC testing methods of clinical isolates:
  - VAN: Vitek2 broth microdilution then confirmed by Etest if ≥2
  - DAP: Disk diffusion then confirmed by Etest
  - CEF: Disk diffusion

RESULTS

	VAN MT	DAP MT	Total MT	CT
Mean duration of bacteremia (days)	15.1 (SD=15.5)	6.4 (SD=2.7)	21.5 (SD=16.7)	3.5 (SD=1.9)

- Mean VAN trough level at 48h = 19.6 mg/L. VAN trough >15 mg/L by 48h in all 6 cases
- Mean DAP dose = 8mg/kg/day; range of doses: 6 to 10mg/kg/day
- Reduced-VAN susceptibility (MIC=2) occurred in 4 of 6 cases, VISA (MIC=4) in 1 case
- VAN and DAP MICs increased while on MT in 4 cases, 2 of which reversed after changing to CT
- DAP non-susceptibility (MIC>1) occurred in 2 cases
- Relapse of bacteremia occurred in only 1 case after CT
- Mean duration of CT = 20.8 days
- ADR to CEF included neutropenia (2 cases), delirium (1case), AKI (1case)
- ADR to DAP included probable DAP-associated eosinophilic pneumonia (3 cases), elevated CPK (1 case)
- ADR to VAN included Rash (1 case)
- Only 1 patient died after CKD progressed to require IHD, patient and family declined IHD→ hospice

RESULTS

Case	Age Sex	Comorbid Conditions	APACHE II Score	Source of Infection	Metastatic Infection	Source Control	VAN MIC DAP MIC	Days of bacteremia on VAN MT	Days of bacteremia on DAP MT	Total days of bacteremia on MT	Reason for switch from MT to CT	Days of bacteremia on CT	Relapse of infection	Adverse drug reactions
1	59 M	DM, CKD, CHF, Gout, Obesity	12	Septic arthritis	none	Knee & ankle washout	VAN = 2 → 4 → 2 DAP = 1 → 4 → 2 Ceftaroline S	11	4 8mg/kg/day	15	Persistent bacteremia DAP MIC=4	3 DAR/CEF	No	DAP: Probable eosinophilic pneumonia → CEF alone CEF: AKI → Linezolid
2	69 M	CKD DM CAD	15	Laminectomy surgical site	Spinal osteomyelitis	Spinal debridement x3 (hardware retained)	VAN = 1 → 2 DAP = 0.25	4	8 10mg/kg/day	12	Persistent bacteremia VAN MIC = 2	1 DAR/CEF	No	DAP: Probable eosinophilic pneumonia
3	67 M	Lympho-proliferative Disorder	22	Central venous catheter	Pulmonary emboli Endophthalmitis Av endocarditis	Line removed Aortic valve replacement	VAN = 1 DAP = 0.5	13	7 8mg/kg/day	20	Persistent bacteremia Lung Abscess	5 DAR/CEF	No	DAP: Probable eosinophilic pneumonia → VAN alone
4	28	IVDU	11	IVDU	Meningitis Spinal osteomyelitis	Laminectomy	VAN = 1 DAP = N/A	5	2 8mg/kg/day	7	Persistent bacteremia Progression of CNS symptoms	4 DAR/CEF	No	CEF: Neutropenia DAP: elevated CK → VAN VAN: eosinophilia/rash → T/S
5	65 F	DM, Lung & Vulvar CA s/p chemo/XRT	17	PICC	Meningitis Aortic & mitral valve Spinal osteomyelitis	Av debridement MV repair MV replacement Vertebral corpectomy	VAN = 1 → 2 → 1 DAP = 0.25	46	8 8mg/kg/day	54	Persistent bacteremia VAN MIC=2	2 VAN/CEF	Endocarditis Osteomyelitis (off antibiotics)	DAP: elevated CPK → Linezolid
6	81 M	ESRD on HD DM CAD	16	Dialysis AV fistula	Spinal osteomyelitis	Fistula resection Spinal laminectomy	VAN = 1→ 2 DAP = 0.5 → 4	12	9 8mg/kg/day	21	Persistent bacteremia VAN MIC=2 DAP MIC=4	6 VAN/CEF	No	CEF: Delirium, neutropenia at wk 10 of CEF → Doxycycline

DISCUSSION

- This case series describes 6 deep-seated MRSA BSI with microbiologic failure using VAN, then DAP, followed by rapid clearance of bacteremia after adding of CEF.
- Use of MT in deep-seated infections with persistent bacteremia can be associated with development of VAN or DAP resistance as observed in this series(7,8,9)
- In our series, DAP susceptibility was restored in DAP non-susceptible MRSA isolate after addition of CEF to DAP, as has been demonstrated in the literature (10)
- Possible or probable DAP-associated eosinophilic pneumonia developed in 3 of our 6 cases, which is a much higher incidence than previous reports (11)
- Neutropenia was associated with CEF in 2 cases, delirium in 1 case, AKI in 1 case. All resolved after stopping CEF
- Rose et al showed that *in vitro*, DAP-CEF or DAP-Oxacillin combinations inhibit increases in DAP MIC over time when compared to DAP MT. Synergy with DAP-CEF in DAP-non-susceptible MRSA has been ascribed to changes in cell membrane charge and membrane fluidity. It is unclear if this mechanism confers synergy in DAP susceptible isolates as well (10,12)

CONCLUSIONS

- Failure of MT for persistent MRSA BSI was successfully salvaged in all 6 cases with CT, and only 1 relapse occurred
- Due to inherent confounders of a retrospective salvage study, we cannot conclude that CT is more effective than MT as the treatments were given in series and thus cumulative effect may have influenced the outcomes
- CT should be considered for salvage treatment of MRSA persistent BSI and may prevent or delay development of antibacterial resistance
- Because DAP plus CEF exhibits *in vitro* and *in vivo* synergistic bactericidal activity, greater than exhibited by other anti-staphylococcal beta-lactams, prospective studies are needed to investigate the role of initial CT in MRSA BSI.
- DAP plus CEF should be considered for treatment of DAP-non-susceptible MRSA BSI
- Prospective clinical studies are needed to further investigate the role of CEF monotherapy versus CT in MRSA BSI

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Figure 1: S.aureus from case 1 exhibiting heteroresistance. **Figure 2**: Colony 1 (left blood agar) having VAN MIC =2, and colony 2 (right blood agar) with VAN MIC=4.

6 casos → 2 con endocarditis; aclaramiento de la bacteriemia asociando Ceftarolina (4 +**daptomicina**; 2 +**vancomicina**)

The use of ceftaroline fosamil in methicillin-resistant Staphylococcus aureus endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. *J Infect Chemother (2013) 19:42–49*

Table 1 Case summaries

Patient Age (years)/ gender	Diagnoses	Positive cultures[a]	Antimicrobial MIC (mg/l)[b]	Ceftaroline dose and duration[a]	Prior and concurrent anti-MRSA Agents	Renal function (CrCl in ml/min)	Microbiological cure[c,d]	Clinical cure[e]	Adverse drug reactions
1 66/M	Endocarditis (probable)	Blood: days *1, 3*	Vancomycin# (2) Daptomycin# (0.75) Ceftaroline# (0.5)	600 mg IV every 12 h on days 5–20 600 mg every 8 h on days 20–47	Vancomycin IV days 1–5	CrCl = 71 mL/min	Yes (day 11)	No	*C. difficile* infection
2 53/M	Endocarditis (probable) Pulmonary septic emboli	Blood: days *1*, **2, 3, 4**	Vancomycin (1) Ceftaroline# (0.5)	600 mg IV every 12 h on days 2–55	Daptomycin IV 7 mg/kg/day days 1–2 Linezolid IV days 1–5 Gentamicin IV days 2–4	CrCl = 21–56 mL/min	Yes (day 5)	Yes	None
3 80/M	Endocarditis (probable) Infected pacemaker Septic hip	Blood: days *1, 4–7, 9, 15–18, 20*	Daptomycin# (≤2) Ceftaroline# (0.5) Vancomycin (2)	600 mg IV every 8 h on days 20–42	Vancomycin IV days 2–9, 52–66 Daptomycin 7 mg/kg daily on days 10–51 Gentamicin days 3–4, 9 Rifampin days 51–52	CrCl = 23–43 mL/min	Yes	Yes (day 22)	Fever, rash, and eosinophilia (day 41)
4 55/M	Endocarditis (possible) Pyomyositis of pectoral muscle at site of previous tunneled dialysis catheter	Blood: days *1–2*, **3–6**)	Vancomycin (0.5, 1, 2) Ceftaroline# (0.75)	200 mg IV every 12 h on days 3–9	Vancomycin IV days 1–3 Clindamycin IV days 2–3	End-stage renal disease on hemodialysis thrice weekly CrCl < 10 mL/min	Yes	Yes (day 7)	None
5 85/M	Endocarditis (probable) AICD pocket infection	Blood: days *1–2*, **3, 4, 5, 6, 7**	Vancomycin (2) Ceftaroline# (0.25)	400 mg IV every 12 h on days 3–6	Vancomycin IV days 1–3 Gentamicin IV days 1–6 Rifampin day 6	CrCl = 15–20 mL/min	No	No	None

Fosfomicina-Imipenem (ISCVID-2007)

Efficacy and safety of fosfomycin plus imipenem for the treatment of methicillin-resistant Staphylococcus aures (MRSA) native valve endocarditis or vascular-graft infections: preliminary results of a clinical trial

A. del Rio, A. Moreno, C. Peña[1], C. Cervera, D. Soy, C.A. Mestres, C. Suarez[1], J.C. Pare, F. Marco, J. Carratalá[1], J.M. Gatell, J.M. Miro and the Hospital Clinic Endocarditis Study Group
Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona;
[1] Hospital de Bellvitge-IDIBELL, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

7 pacientes con endocarditis / infección endovascular por MRSA que fracasan con vancomicina (HC + a partir del día +7):

- Fosfomicina 2 g c 6 h + Imipenem 1 g c 8 h ± Vancomicina
- Curación microbiológica en 6/7 (89%): HC día +30 (-)

↓

ENSAYO CLINICO FOSIMI

Lipo-glicopéptidos

- **Telavancina:**

  - No inferior a Vancomicina en INFPB y Neumonía, pero más nefrotóxica que vanco (OR 2.22; PlosOne, 2012)

- **Dalvabancina:**

  - Ensayo clínico abierto en bacteriemia asociada catéter (34 VAN 33 DAL); eficacia mayor que vancomicina; bien tolerada (Raad et al, CID, 2005)

- **Oritavancina:**

  - No ensayos clínicos en bacteriemia.

Linezolid therapy for infective endocarditis

Clin Microbiol Infect 2007; 13: 211–215

- 9 casos del HGUGM + 33 de la literatura
- Motivo de su utilización:
  - 60% Fracaso
  - 28% Intolerancia
  - 12% Tto secuencial
  - 1% Resistencia a tto. alternativo
- Etiología:
  - *Staphylococcus* 31 (74%)
  - *Enterococcus spp.* 10 (24%)
  - Otros: 2 (1%)
- Curación en 8/11 endocarditis por MRSA

Otros

- NUEVAS OXAZOLIDINONAS:
  Eperezolid
- ICLAPRIM
- PLEUROMUTILINAS

ESCARDIO guidelines, 2009

Streptococcus grupo viridans y S.bovis

- Sensibilidad a Penicilina:

S	I
< 0.125 mg/L	0.125 - 2 mg/L
Pen- G, 12–18 mU/d ó Amoxicilina 100-200 mg/kg/d ó Ceftriaxona, 2 g/d 4 ss	Pen- G 24 mU/d ó Amoxicilina 200 mg/kg/d 4 ss y Gentamicina 3 mg/kg/d 2 ss
Pen- G, Amoxicilina ó Ceftriaxona y Gentamicina 3 mg/kg/d ó Netilmicina 4-5 mg/kg/d qd 2 ss	
Vancomicina, 30 mg/kg/d 4ss	Vancomicina, 30 mg/kg/d 4ss y Gentamicina 3 mg/kg/d 2 ss

(CMI > 4 → Vancomicina)

Endocarditis Caused by Penicillin- Resistant Viridans Streptococci: 2 Cases and Controversies in Therapy

Clinical Infectious Diseases 2001; 33:577–9

Table 1. Outcomes of treatment of 8 cases of penicillin-resistant viridans streptococcal endocarditis.

Reference	Year	Isolate	Penicillin MIC, μg/mL	Treatment	Outcome
Karchmer et al. [5], Karchmer [6]	1979, 1981	Species not identified	0.7	Penicillin for 6 days, then cephalothin for 13 days, then vancomycin for 9 days	Cured
Parrillo et al. [4]	1979	*Streptococcus mitis*	2.7	Penicillin and gentamicin for 6 weeks	Cured
Parrillo et al. [4]	1979	*Streptococcus sanguis*	0.7	Penicillin and gentamicin for 7 weeks	Cured
Wilson and Geraci [7]	1985	Species not identified	1.0	Penicillin and streptomycin for 2 weeks	Cured
Levitz [1]	1999	*S. mitis*	>4	Vancomycin for 4 weeks	Cured
Lonks et al. [2]	1999	*S. mitis*	2 and 3	Multiple antibiotics and surgery	Cured
Current report	2001	*S. mitis*	1.5	Penicillin and gentamicin for 6 weeks	Cured
Current report	2001	*S. sanguis*	>4	Vancomycin and gentamicin for 16 days	Died

Infective Endocarditis Due to Penicillin-Resistant *viridans group* Streptococci

Clinical Infectious Diseases 2007; 44: 1585–92

- Clínica Mayo, 1967-2006:

  29 casos de endocarditis por *S.viridans* con CMI $\geq$ 0.12 mg/mL

- CMI: 0,5 → 9 (31%)
  1 → 16 (55%)
  2 → 2 (6.9%)
  4 → 2 (6.9%)
- La mayoría curan con las pautas clásicas de betalactámico-aminoglucósido ó vancomicina

Streptococcus grupo viridans y S.bovis

- Resistencia a penicilina:

- CMI: 0,5-2 mg/L: Peni(ampi/CRO) + *agl*

- CMI $\geq$ 4 mg/L*: fracasos con beta-lactámicos: VANCOMICINA

* Descrito especialmente en *Streptococcus mitis*

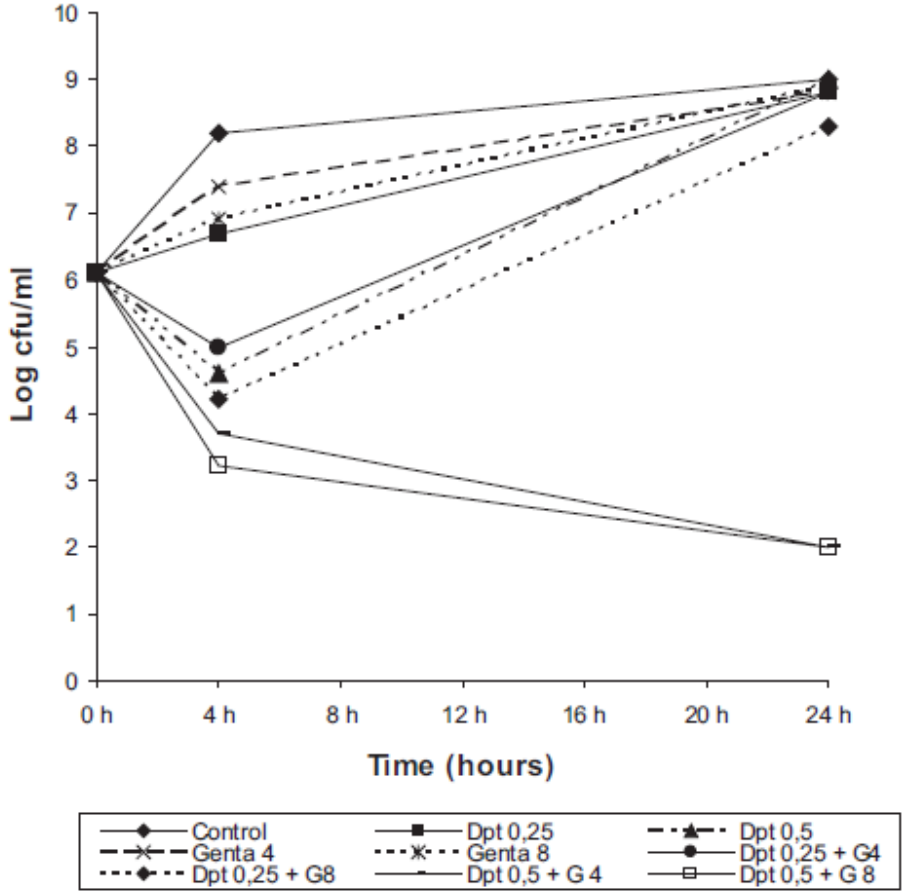
Early In Vitro and In Vivo Development of High-Level Daptomycin Resistance Is Common in Mitis Group Streptococci after Exposure to Daptomycin

Antimicrob. Agents Chemother. 2013, 57(5):2319

TABLE 3 Rates of selection of resistance and high-level resistance after exposure to daptomycin

Microorganism(s)	No. of strains	No. (%) screening positive[a]	No. (%) that were[b]: DNS (MIC, ≥2 mg/liter)	HLDR (MIC, ≥256 mg/liter)
Mitis group	92	74 (80)	61 (66)	25 (27)
S. mitis	51	35 (69)	30 (59)	14 (27)
S. oralis	19	18 (95)	14 (74)	9 (47)
S. sanguis	15	15 (100)	11 (73)	2 (13)
S. gordonii	4	4 (100)	4 (100)	0 (0)
S. parasanguis	3	2 (67)	2 (67)	0 (0)
Bovis group	54	2 (4)	0	0
Anginosus group	10	5 (50)	5 (50)	0
Mutans group	8	0	0	0
Salivarius group	4	0	0	0

[a] Screening was considered positive if the microorganism grew in the presence of 0.5 mg or 1 mg/liter daptomycin.
[b] DNS, daptomycin nonsusceptible; HLDR, high-level daptomycin resistance.



Incidence of High-Level Gentamicin Resistance (HLGR) among Viridans Group Streptococci (VGS) *ICAAC 2013, C2-545*

- Univ. de Texas: aislados de VCS de hemocultivos, años 2010-12
- 35 VGS:

  - *S. mitis* group (n=13)
  - *S. sanguinis* group (n=7)
  - *S. bovis* group (n=4)
  - *S. salivarius* group (n=3)
  - *S. mutans group (n=1)*
  - *Otros VGS (n=2)*

  Ningun caso con HLGR

- 34 aislados de *S.bovis* (1999-2011) :
  Un caso con HLR a *gentamicina*

Enterococo

- 8-32% de las bacteriemias

Registro ICE:

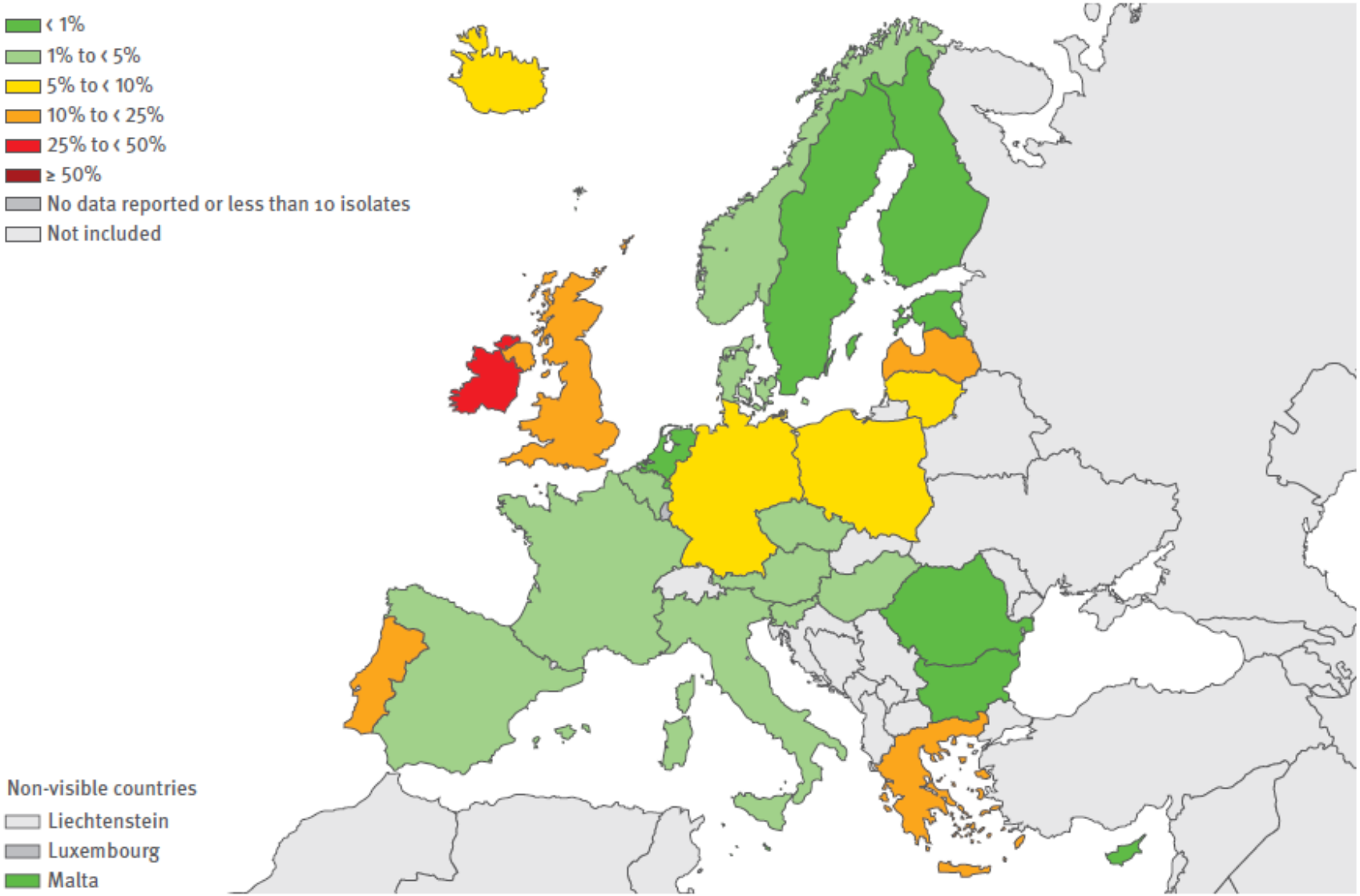
1285 pacientes con Endocarditis izquierda:

- 107 por enterococo (8,3%)

40 no identificación de especie

- *Enterococcus faecalis* 62/67 (94 %)
- *Enterococcus faecium* 4/67 (4,5 %)
- *Enterococcus durans* 1/67 (1,5 %)

Enterococcus faecium: percentage of invasive (blood and cerebrospinal fluid) isolates resistant to vancomycin, 2010

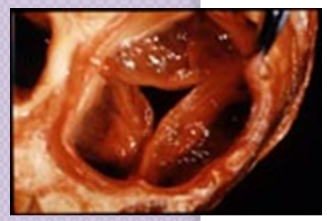


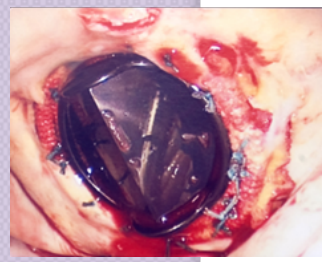
Source: EARS-Net. Only data from countries reporting more than 10 isolates are shown.

ECDC-2012

Enterococo: Guidelines

AHA IDSA 2007	ESC 2009
Ampicilina 12gd 4-6 ss ó **Pen-G** 18-30 mU/d 4-6ss y **Gentamicina** 3 mg/kg/d 4-6ss	**Ampicilina (Amoxicilina)** 200 mg/kg/d y **Gentamicina** 3 mg/kg/d bid/tid 4-6ss
Vancomicina, 30 mg/kg/d 6ss y **Gentamicina** 3 mg/kg/d 6ss	**Vancomicina,** 30 mg/kg/d 6ss y **Gentamicina** 3 mg/kg/d bid/tid 6ss





<u>HLR-AMINOGLUCOSIDO</u>
Ampicilina-Ceftriaxona

<u>AMPI-R:</u>
Vancomicina+Gentamicina

<u>VANCO-R</u>:
Linezolid

Synercid

Imipenem-Ampicilina

Ampicilina-Cefriaxona

Daptomicina: desarrollo de resistencia durante el tratamiento en enterococo

- *Kelesidis T* et al. Daptomycin nonsusceptible enterococci: an emerging challenge for clinicians. ***Clin Infect Dis 2011; 52: 228–34.***
- *Kelesidis T et al*. De novo daptomycin nonsusceptible enterococcal infections. ***Emerg Infect Dis 2012; 18: 674–6.***
- *Kelesidis T et al*. Case-control study comparing de novo and daptomycin-exposed daptomycin-nonsusceptible Enterococcus infections. ***Antimicrob Agents Chemother 2012; 56: 2150–2***
- *Kelesidis T et al*. Evolution of high-level daptomycin resistance in Enterococcus faecium during daptomycin therapy is associated with limited mutations in the bacterial genome. ***J Antimicrob Chemother 2013; 68: 1926–1939***

Defining Daptomycin (DAP) Mutant Prevention Exposures in Vancomycin Resistant Enterococcus (VRE) faecium and faecalis. *A-020, ICAAC 2013*

- Modelo PK/PD simulado de dosificación de daptomicina para la prevención de mutantes dapto-R en cepas de *E.faecalis* y *E.faecium* –VAN-R

- Se confirma la actividad dosis dependiente:
  - DAP 4-8 mg/kg no previene DAP-R
  - DAP 10-12 mg/kg SÍ

Sinergia Daptomicina-Ampicilina

- **Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci.**
  Rand et al, Journal of Antimicrobial Chemotherapy (2004) 53, 530–532

- **Ampicillin Enhances Daptomycin- and Cationic Host Defense Peptide- Mediated Killing of Ampicillin- and Vancomycin-Resistant Enterococcus faecium.**
  Sakoulas et al, Antimicrob. Agents Chemother. 2012, 56(2):838.

Enterococus faecium VAN-R

AMPI- CMI < 64
No HLR-Ag

- Ampi HD (hasta 30g)
+ Genta/Estrepto

AMPI- CMI < 64
HLR-Ag

- Dapto HD -Ampi HD
- Qp/Dp + Ampi-HD ó doxi-Rif
- Linezolid + 2º abco
- Ampi-Imipenem*

** Si CMI imipenem < 32*

AMPI- CMI > 64
No HLR-Ag

- Dapto HD
+ Genta/Estrepto
- Qp/Dp + 2º abco
- Linezolid + 2º abco

AMPI- CMI > 64
HLR-Ag

- Dapto HD + 2º abco
- Qp/Dp + 2º abco
- Linezolid + 2º abco

Non-HACEK Gram-Negative Bacillus Endocarditis

Ann Intern Med. 2007;147:829-835

- Cohorte ICE: Casos 2000-2005

  2761 casos de EI

  49 (1,8%) *Bacilos gramnegativos no-HACEK*

Table 3. Treatment and Outcome of Non-HACEK Gram-Negative Bacillus Endocarditis, according to the Infecting Organism*

Organism	Patients Infected, *n*	Antibiotic Treatment, *n/n* (%)	Surgical Treatment, *n/n* (%)	Complications, *n/n* (%)†	In-Hospital Mortality, *n/n* (%)
Escherichia coli	14	Monotherapy with β-lactam: 5/14 (36) Combination therapy: 9/14 (64)‡	4/14 (29)	11/14 (79)	3/14 (21)
Pseudomonas aeruginosa	11	Monotherapy with aminoglycoside: 3/11 (27) Combination therapy: 8/11 (73)§	6/11 (55)	8/11 (73)	4/11 (36)
Klebsiella species	5	Monotherapy: 4/5 (80)‖ Combination therapy: 1/5 (20)¶	2/5 (40)	2/5 (40)	2/5 (40)
Serratia species	4	Monotherapy: 0/4 (0) Combination therapy: 4/4 (100)**	4/4 (100)	3/4 (75)	0/4 (0)
Other	15	Monotherapy with β-lactam: 6/15 (40) Combination therapy: 8/15 (53)†† Missing: 1/15 (7)	9/15 (60)	10/15 (67)	3/15 (20)

HACEK Infective Endocarditis: Characteristics and Outcomes from a Large, Multi-National Cohort *PlosONE 2013; 8 (5), e63181*

HACEK organisms	Number (%)
***Haemophilus* spp.**	**31 (40)**
Haemophilus parainfluenzae	28 (36)
Haemophilus sp. other[a]	3 (4)
***Aggregatibacter* spp.**	**26 (34)**
Aggregatibacter actinomycetemcomitans	15 (20)
Aggregatibacter aphrophilus	5 (6)
Aggregatibacter paraphrophilus	5 (6)
Aggregatibacter segnis	1 (1)
***Cardiobacterium* spp.**	**11 (14)**
Cardiobacterium hominis	10 (13)
Cardiobacterium valvarum	1 (1)
Eikinella corrodens	**4 (5)**
***Kingella* spp.**	**4 (5)**
Kingella kingii.	2 (3)
Kingella denitrificans	1 (1)
Kingella sp.	1 (1)
HACEK (not otherwise specified)	**1** (1)
Total	**77**

- Cohorte ICE:
  años 2000-06
  5591 casos de EI
  77 (1,4%) HACEK

- Sensibilidad:
  24/25 PENI-S*
  48/49 AMPI-S
  50/50 Cftrx-S
  30/32 GEN-S

*Unica cepa R: *A.aphrophilus*

- *S.aureus* R a meticilina
  - Vancomicina: opción solo si CMI 0,5-1
  - Daptomicina HD: 10-12 mg/kg
  - Daptomicina-Fosfomicina
  - Dapto-Cloxacilina/Ceftarolina
  - Fosfomicina-Imipenem
- *Streptococcus viridans*
  - Vancomicina si CMI $\geq$ 4
  - Posibilidad de HLRA en *S.bovis*
- *Enterococcus faecium van-R*
  - No emplear Daptomicina en monoterapia
- Bacilos Gramnegativos:
  - HACEK: > 99% Cef-3G sensibles

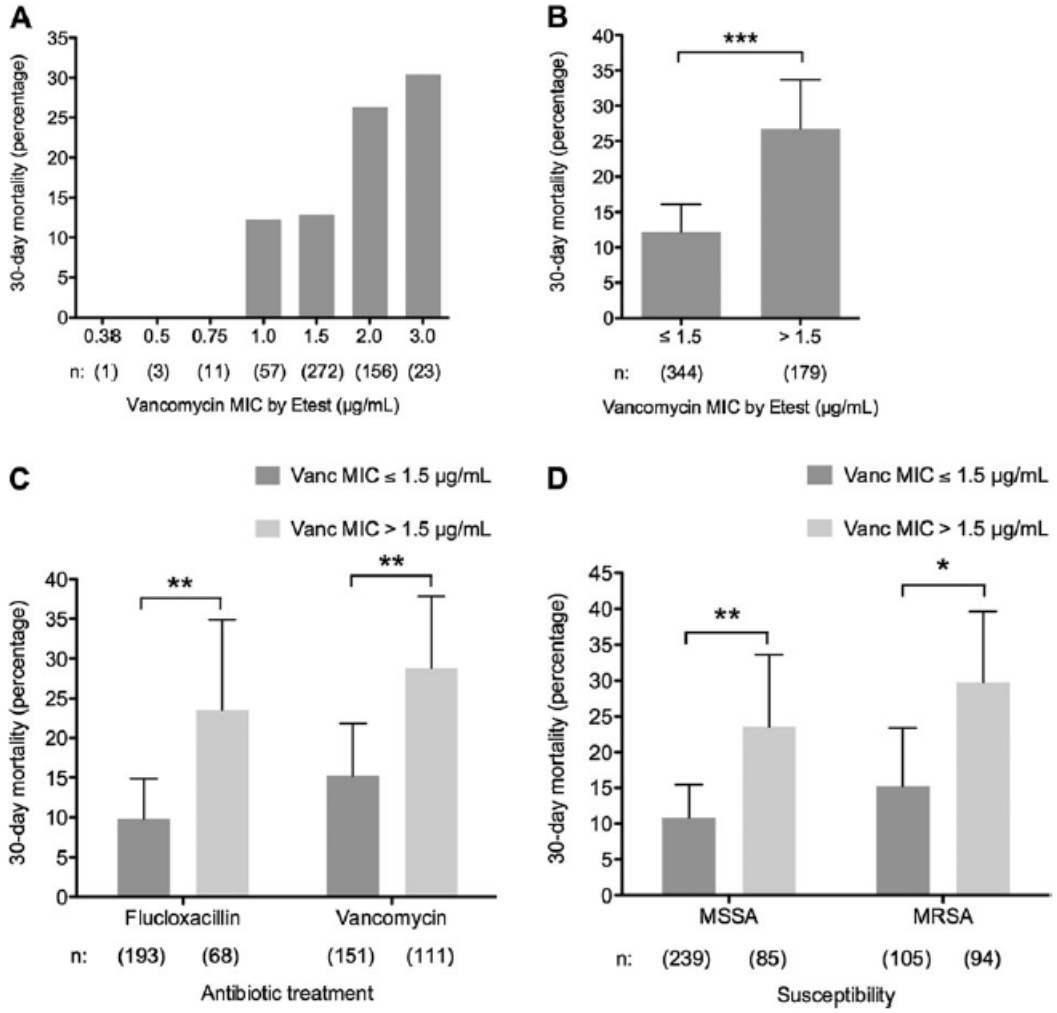
SEICAV

Sociedad Española de Infecciones Cardiovasculares

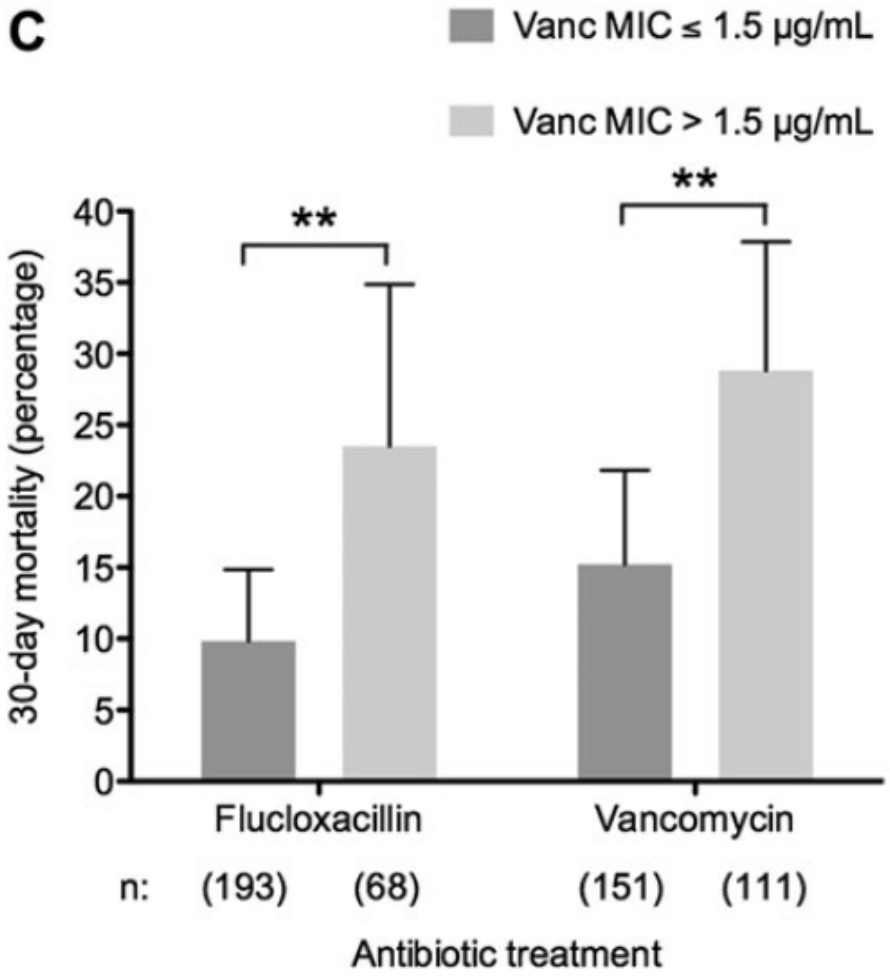
Muchas Gracias

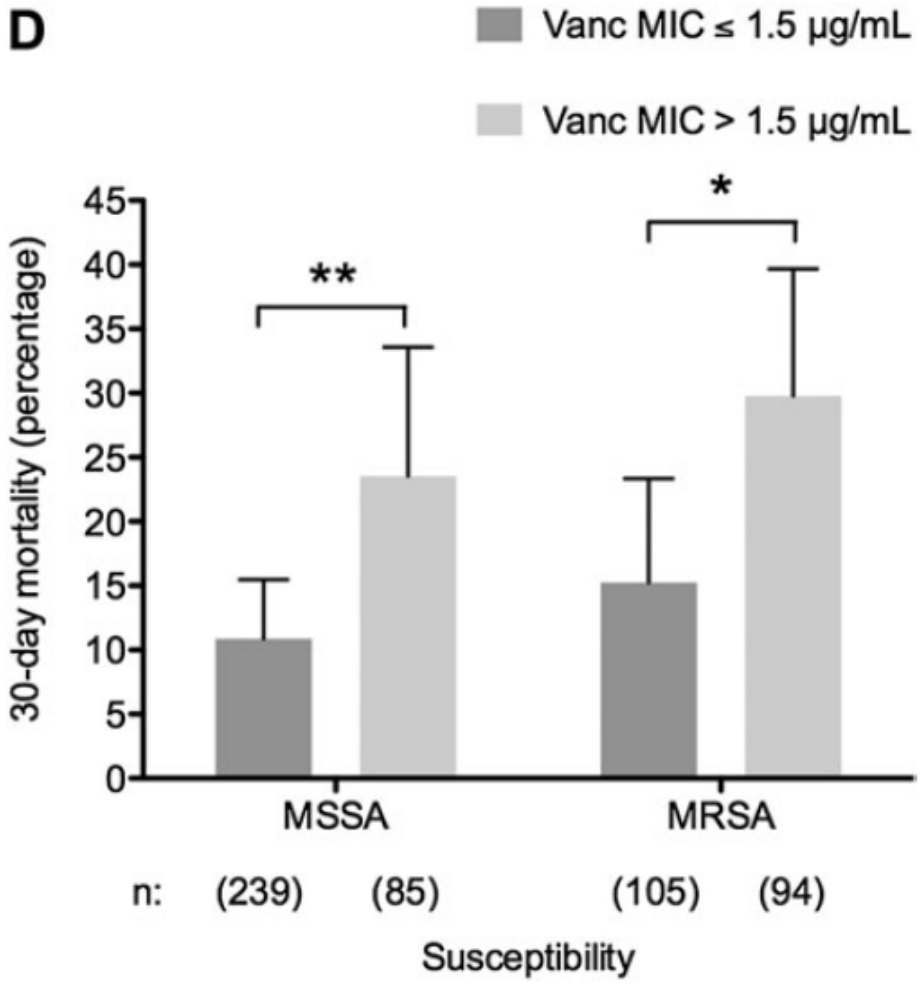
Antibiotic Choice May Not Explain Poorer Outcomes in Patients With Staphylococcus aureus Bacteremia and High Vancomycin Minimum Inhibitory Concentrations

Holmes et al, ***The Journal of Infectious Diseases 2011;204:340–47***



El aumento de CMI a Vancomicina se asocia a peor pronóstico también en bacteriemia por MSSA





Staphylococcus aureus Endocarditis: A Consequence of Medical Progress

JAMA, 2005

Variable†	No. (%) Methicillin-Susceptible *S aureus* (n = 283)	No. (%) Methicillin-Resistant *S aureus* (n = 141)	*P* Value	Multivariate Model Odds Ratio (95% CI)‡
Type of IE				
Prosthetic valve	54 (19.1)	23 (16.3)	.49	
Native valve	189 (66.8)	100 (70.9)	.39	
Other and unknown	40 (14.1)	18 (12.8)	.70	
Male sex	184 (65.0)	74 (52.5)	.01	
Age, medi				
Region				
United				
Brazil				
Austra				
Europe				
Hemodialy				
Diabetes r				
Chronic in				
Cancer				
Recent inv				
Presumed				
Presumed				
Health				
No				
No				
Comm				
Unkno				
Outcome				
Systemic embolization other than stroke	74 (26.2)	25 (17.7)	.07	
Surgery this episode	106 (37.5)	55 (39.0)	.76	
Persistent bacteremia	25 (8.8)	60 (42.6)	<.001	6.2 (2.9-13.2)
In-hospital death	66 (23.3)	42 (29.8)	.14	

	MSSA (283)	MRSA (141)	p
Prótesis	54 (19,1%)	23 (16,3%)	.49
Cirugía CV	106 (**37,5%**)	55 (**39%**)	.76
B.Brecha	25 (8.8%)	60 (42,6%)	< .001
Muerte	66 (23,3%)	42 (29,8%)	.14

Daptomicina + Ceftarolina IDSA, 2012

Case	Age Sex	Comorbid Conditions	APACHE II Score	Source of Infection	Metastatic Infection	Source Control
1	59 M	DM, CKD, CHF, Gout, Obesity	12	Septic arthritis	none	Knee & ankle washout
2	69 M	CKD DM CAD	15	Laminectomy surgical site	Spinal osteomyelitis	Spinal debridement x3 (hardware retained)
3	67 M	Lympho-proliferative Disorder	22	Central venous catheter	Pulmonary emboli Endophthalmitis AV endocarditis	Line removed Aortic valve replacement
4	28	IVDU	11	IVDU	Meningitis Spinal osteomyelitis	Laminectomy
5	65 F	DM, Lung & Vulvar CA s/p chemo/XRT	17	PICC	Meningitis Aortic & mitral valve Spinal osteomyelitis	AV debridement MV repair MV replacement Vertebral corpectomy
6	81 M	ESRD on HD DM CAD	16	Dialysis AV fistula	Spinal osteomyelitis	Fistula resection Spinal laminectomy

Daptomicina + Ceftarolina IDSA, 2012

VAN MIC DAP MIC	Days of bacteremia on VAN MT	Days of bacteremia on DAP MT	Total days of bacteremia on MT	Reason for switch from MT to CT	Days of bacteremia on CT	Relapse of infection
VAN = 2 → 4 → 2 DAP = 1 → 4 → 2 Ceftaroline S	11	4 8mg/kg/day	15	Persistent bacteremia DAP MIC=4	3 DAP/CEF	No
VAN = 1 → 2 DAP = 0.25	4	8 10mg/kg/day	12	Persistent bacteremia VAN MIC = 2	1 DAP/CEF	No
VAN = 1 DAP = 0.5	13	7 8mg/kg/day	20	Persistent bacteremia Lung Abscess	5 DAP/CEF	No
VAN = 1 DAP = N/A	5	2 6mg/kg/day	7	Persistent bacteremia Progression of CNS symptoms	4 DAP/CEF	No
VAN = 1 → 2 → 1 DAP = 0.25	46	8 8mg/kg/day	54	Persistent bacteremia VAN MIC=2	2 VAN/CEF	Endocarditis Osteomyelitis (off antibiotics)
VAN = 1→ 2 DAP = 0.5 → 4	12	9 8mg/kg/day	21	Persistent bacteremia VAN MIC=2 DAP MIC=4	6 VAN/CEF	No

Streptococcus viridans (alfa-hemolíticos)

- Grupo *S. mitis*
- Grupo *S. mutans*
- Grupo *S. salivarius*
- Grupo *S. bovis*
- Grupo *S. anginosus* (antes grupo *S. milleri*)

  Incluyen variantes con β-hemólisis que aglutinan con antígenos A,C,F y G
- «Estreptococos deficientes nutricionales»: Incluyen *Abiotrophia* sp and *Granulicatella* sp

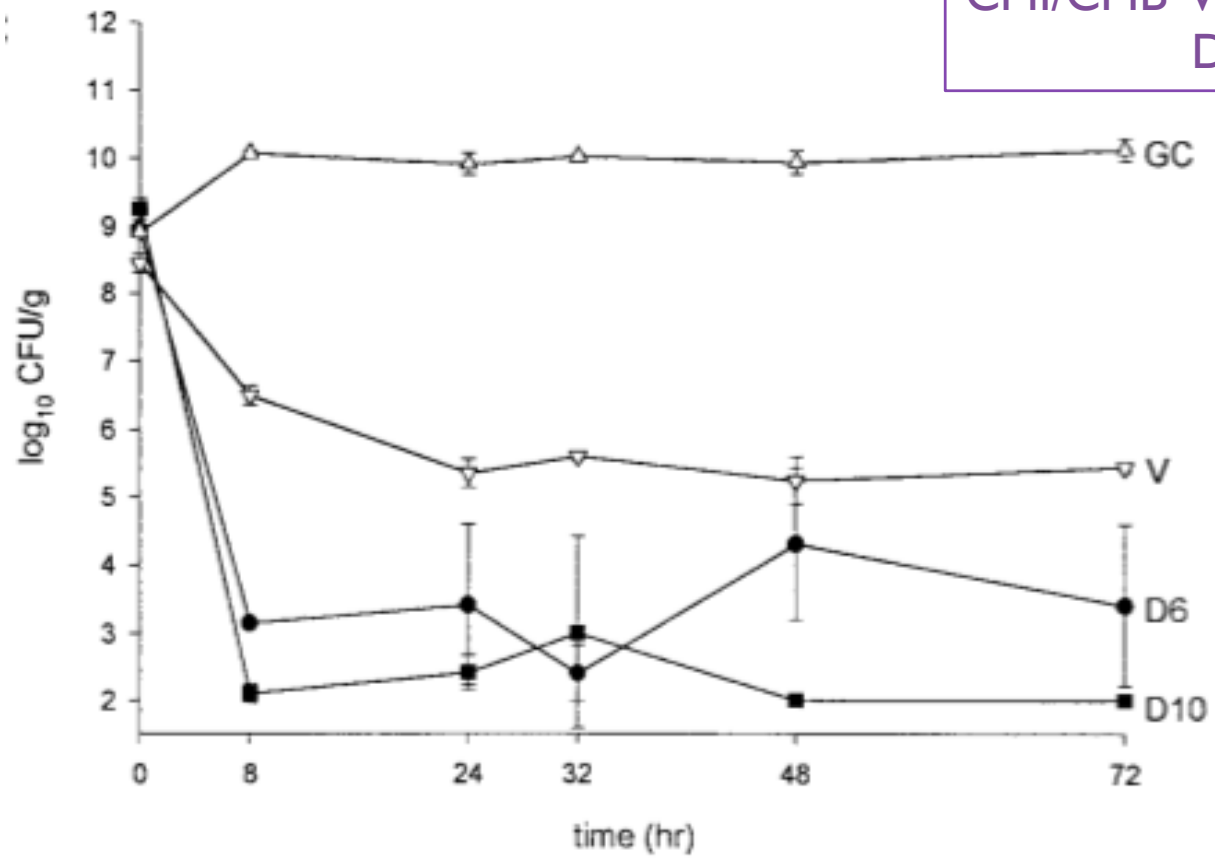
Bactericidal activities of two daptomycin regimens against clinical strains of glycopeptides intermediate-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus* isolates in an in vitro pharmacodynamic model and simulated endocardial vegetations.

Akins RL, Rybak MJ , *Antimicrob Agents Chemother*. 2001;45(2):454-459.

Cepa : MRSA-494

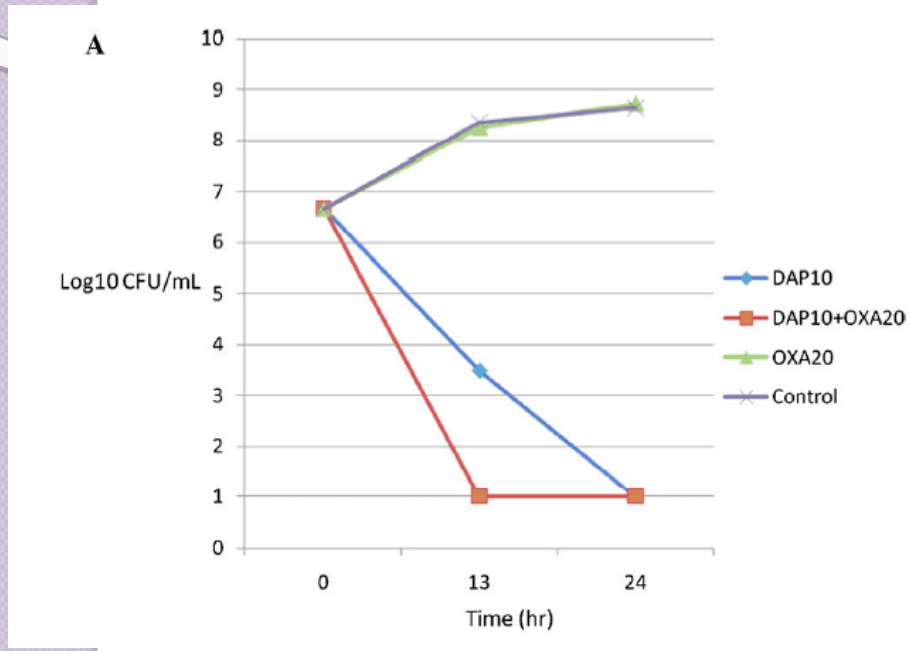
CMI/CMB Vanco 1/4

Dapto 0,5/1

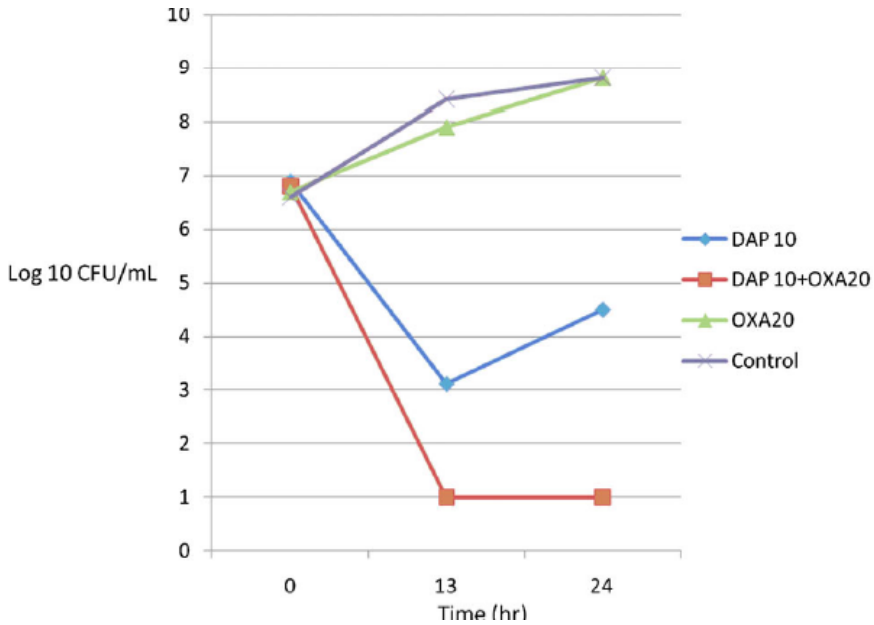


Use of Antistaphylococcal b-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to Methicillin-Resistant Staphylococcus aureus: Role of Enhanced Daptomycin Binding

Clinical Infectious Diseases 2011;53(2):158–163



MRSA

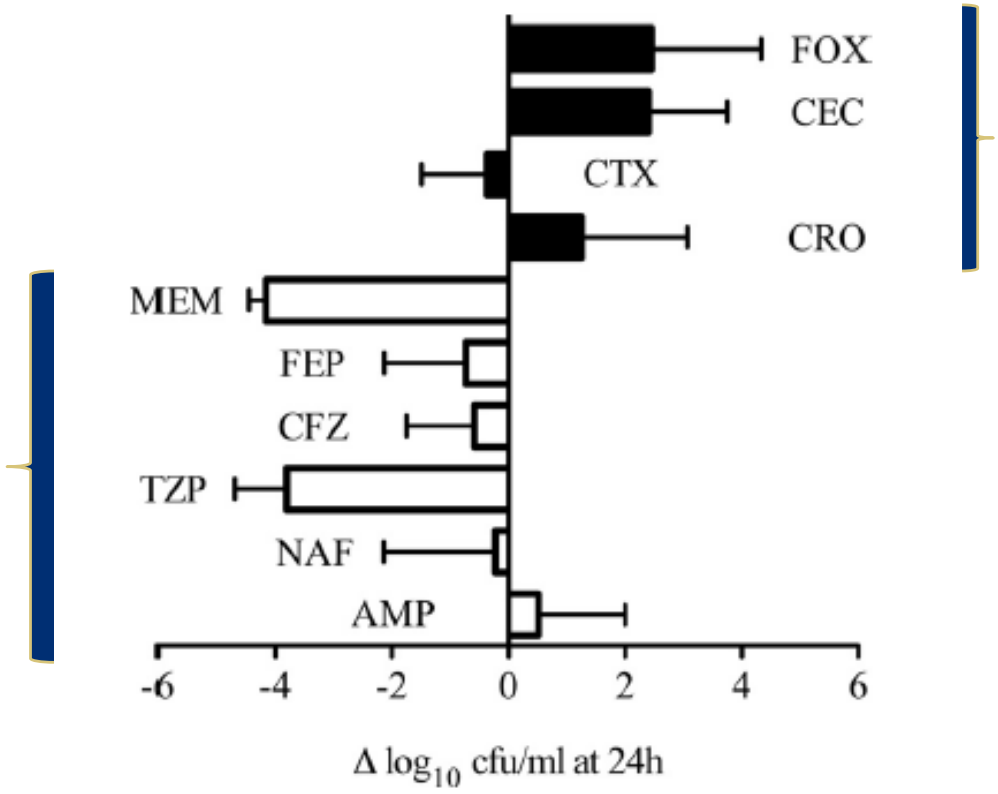


DAP-R-VISA

Beta-Lactam Antibiotics Targeting PBP1 Selectively Enhance Daptomycin Activity against Methicillin-Resistant *Staphylococcus aureus*

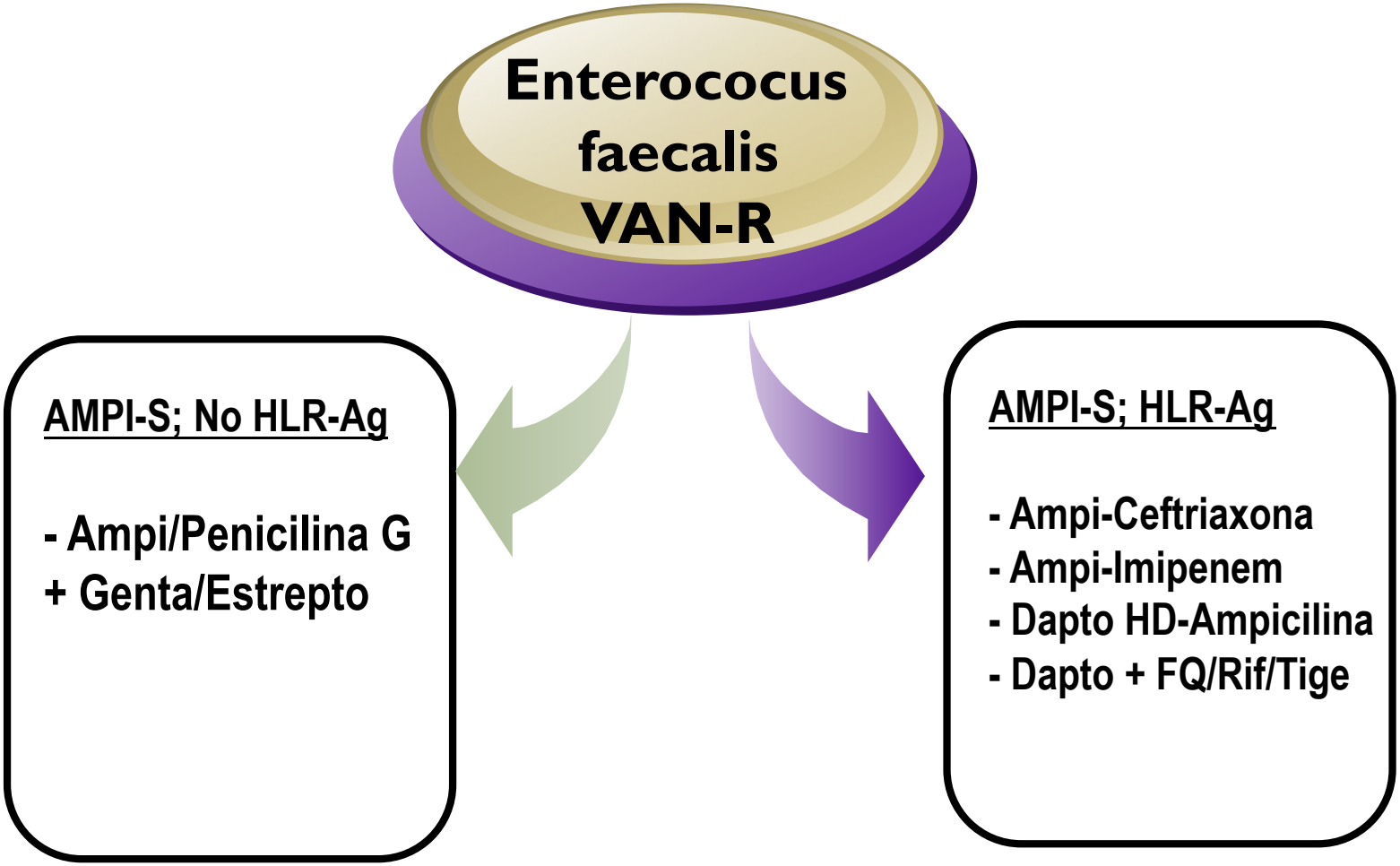
Antimicrobial Agents and Chemotherapy 2013, 57 (10), 5005–12

Actividad de Daptomicina en combinación con betalactámicos



NO Preferencia
Por PBP1

Preferencia
Por PBP1


Enterococus faecalis VAN-R
AMPI-S; No HLR-Ag
- Ampi/Penicilina G + Genta/Estrepto
AMPI-S; HLR-Ag
- Ampi-Ceftriaxona
- Ampi-Imipenem
- Dapto HD-Ampicilina
- Dapto + FQ/Rif/Tige

Antimicrobial Susceptibilities of Clinical Isolates of HACEK Organisms.
Antimicrobial Agents and Chemotherapy, 2013 57(4):1989–91

	Todos los aislados CMI 50/90 % S (n=70)	*Aggrega-tibacter actino-mycetem-comitans (n=2)*	*Aggrega-tibacter aphrophilus (n=11)*	*Haemo-philus para-influenzae n= 37*	*Cardio-bacterium hominis n=2*	*Eikenella corrodens n= 17*	*Kingella kingae n=1*
Ampi cilina	0,25/1 **95,8 %**	ND **50%**	0,5/0,5 **100%**	0,25/1 **97,3%**	ND **100%**	0,25-1 **100%**	≤0,12
Amoxi-Clav	2 **100%**	ND **100%**	2 **100%**	2 **100%**	ND **100%**	2 **100%**	≤2
Ceftriax ona	0,03/0.12 **100%**	ND **100%**	0,03/0,03 **100%**	0,03-0,5 **100%**	ND **100%**	0,03/0,12 **100%**	≤ 0,03
Levoflo xacino	003/0,12 **100%**	ND **100%**	≤0,03/0,06 **100%**	0,03-0,12 **100%**	ND **100%**	0,03/0,06 **100%**	≤ 0,03
Cotrimo xazol	0,06-0,25 **93,2%**	ND **100%**	≤0,06/0,25 **100%**	0,06/1 **86,2%**	ND **100%**	0,06/0,5 **100%**	≤ 0,06
Claritro-micina	4/16 **55,7%**	ND **100%**	0,12/>16 **54,5%**	16/>16 **32,4%**	ND **100%**	2/8 **100%**	0,25

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Teicoplanin Compared with Vancomycin for Treatment of Experimental Endocarditis Due to Methicillin-Resistant *Staphylococcus epidermidis*

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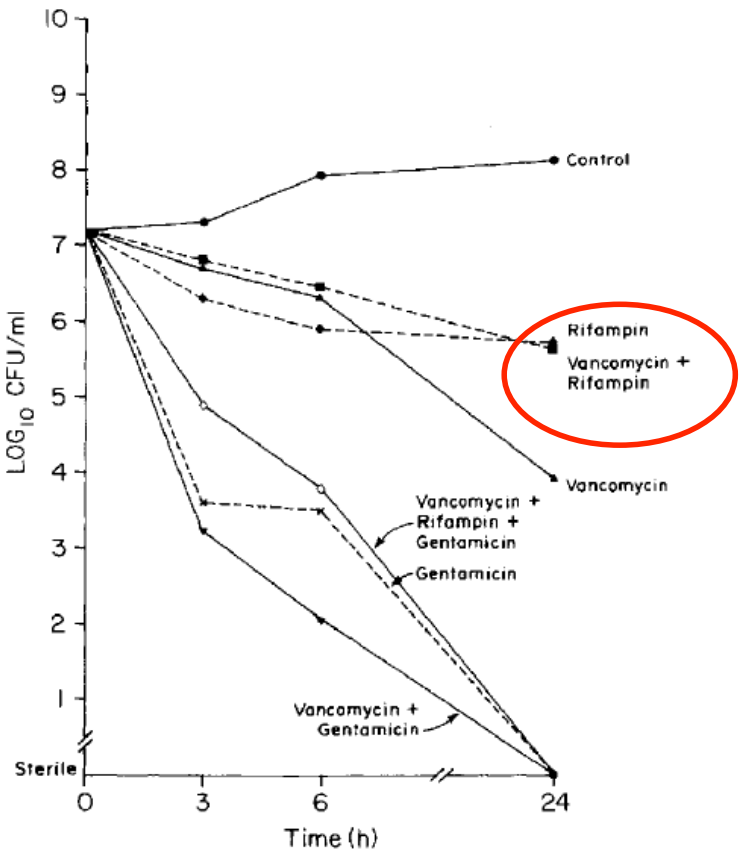

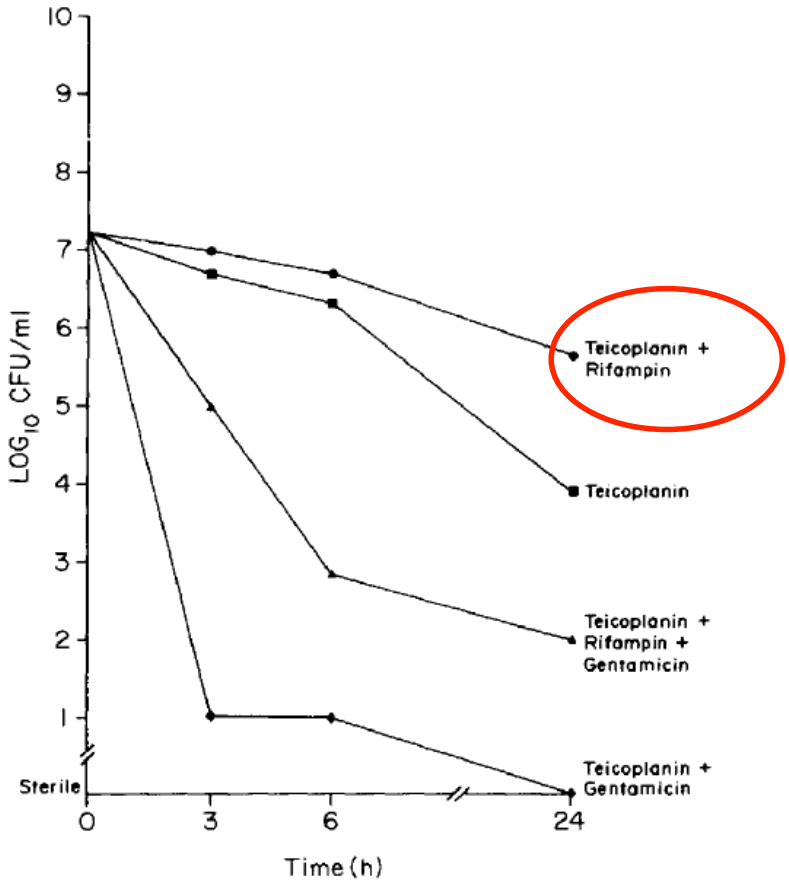

RESISTENCIA ADQUIRIDA a RIFAMPICINA

- **0/433 pacientes en tres estudios no aleatorizados con infecciones graves por S.aureus:**

- Schrenzel J et al: A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal infection. ***Clin Infect Dis 2004, 39:1285–1292***.

- Ruotsalainen E et al: Levofloxacin does not decrease mortality in Staphylococcus aureus bacteraemia when added to the standard treatment: a prospective and randomized clinical trial of 381patients. ***J Intern Med 2006, 259:179–190***.

- Khanlari B et al: A rifampicin-containing antibiotic treatment improves outcome of staphylococcal deep sternal wound infections. ***J Antimicrob Chemother 2010, 65:1799–1806.***

- **20-40% de pacientes en series cortas:**

- Riedel DJ et al: Addition of rifampin to standard therapy for treatment of native valve infective endocarditis caused by Staphylococcus aureus. ***Antimicrob Agents Chemother 2008, 52:2463–2467.***

- Lai CC et al: Emergence of rifampicin resistance during rifampicin-containing treatment in elderly patients with persistent methicillin-resistant Staphylococcus aureus bacteremia. ***J Am Geriatr Soc 2010, 58:1001–1003.***

- Ju O et al: Emergence and spread of rifampicinresistant, methicillin-resistant Staphylococcus aureus during vancomycinrifampicin combination therapy in an intensive care unit. ***Eur J Clin Microbiol Infect Dis 2006, 25:61–62.***