Stafilococco aureo ed Enterococco

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Napoli

Disclosure of potential conflicts of interest

Emanuele Durante Mangoni, MD PhD

- My Institution has received research funding for my group from **MSD**, **Pfizer**
- I have received personal fees or participated in advisory boards or have been in the speaker's bureau of **Pfizer, MSD, Angelini, Bio-Merieux, Abbvie, Sanofi-Aventis, Medtronic,** and **DiaSorin**.

S. aureus – prevalence of methicillin resistance

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9]

2011: 7 years old

Treatment options for MR Staphylococci

Site of infection	first line therapy	Alternatives	Future considerations	Other notes
Bacteremia/IE	Vancomycin	Daptomycin Teicoplanin Daptomycin + Ceftaroline (synergy)	Ceftaroline Ceftobiprole	Avoid: Clindamycin TMP-SMX Tigecycline
Mild SSTI with abscess <5 cm	Incision and drainage			
Moderate SSTI	TMP-SMX Clindamycin* Doxycycline/Minocycline Linezolid			* Limited due to increased resistance
Severe or complicated SSTI	Vancomycin	Daptomycin Linezolid Telavancin*	Ceftaroline Ceftobiprole Dalbavancin Oritavancin Tedizolid	* Only to be used when alternative treatments are not suitable due to safety concerns
Pneumonia	Vancomycin Linezolid	Telavancin*	Ceftobiprole	* Only to be used when alternative treatments are not suitable due to safety concerns Avoid: Daptomycin, Tigecycline
Bond and joint infections	Vancomycin	Daptomycin Vancomycin + Rifampin Linezolid Consider: TMP-SMX Clindamycin Fluroquinolone* Doxycycline/Minocycline	Tedizolid	*Not to be used as monotherapy

Is It Time to Replace Vancomycin in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections?

Sebastiaan J. van Hal[1,2] and Vance G. Fowler Jr[3,4]

Vancomycin weaknesses:

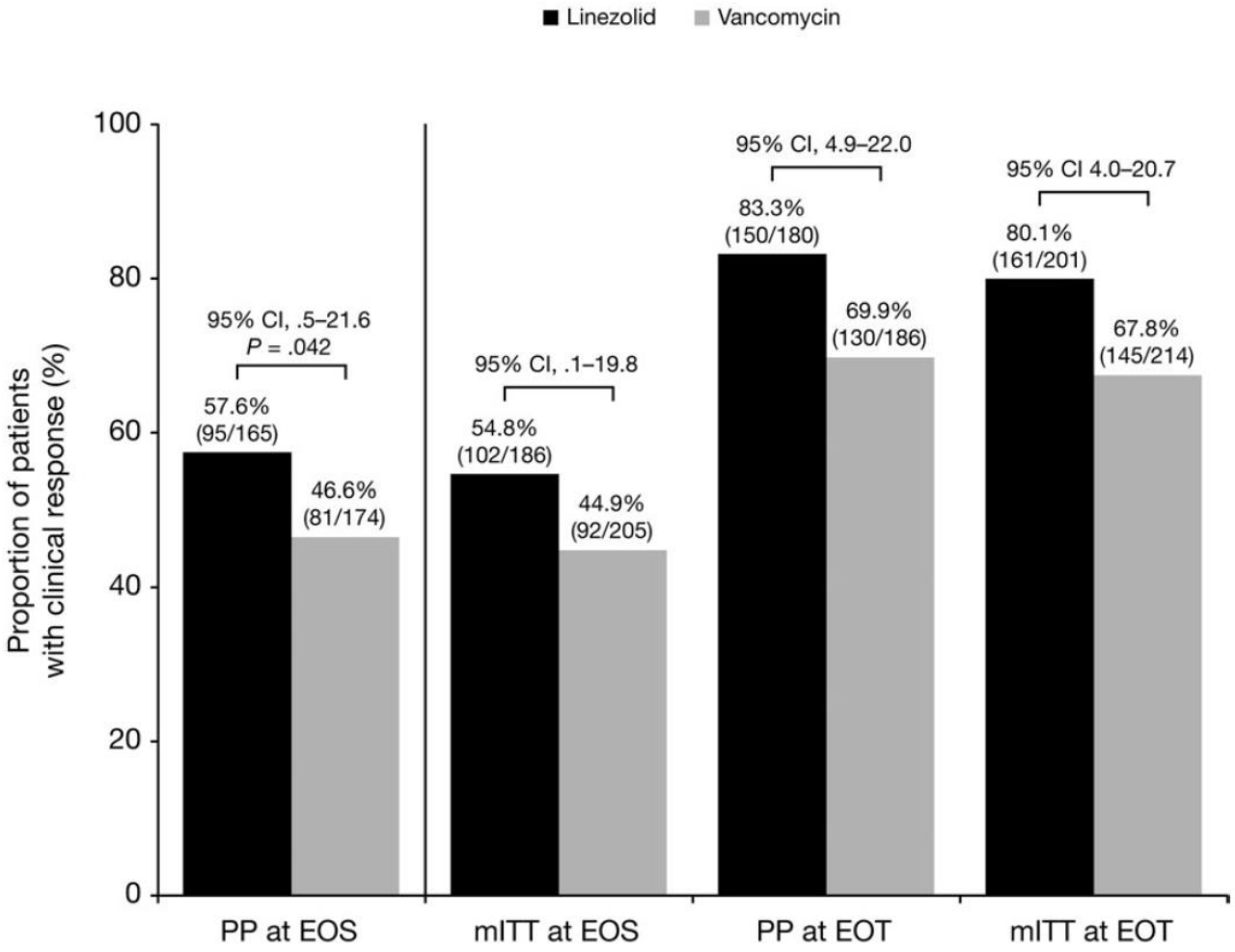
1) slow bacterial killing
2) poor tissue penetration (e.g. lung)
3) slow clearance of bacteraemia
4) high mortality

30-day mortality
24% for MRSA BSI *

* ANZCOSS dataset

How Vancomycin performs compared to other anti-MRSA Agents

MRSA Pneumonia: Zephyr Study Outcomes

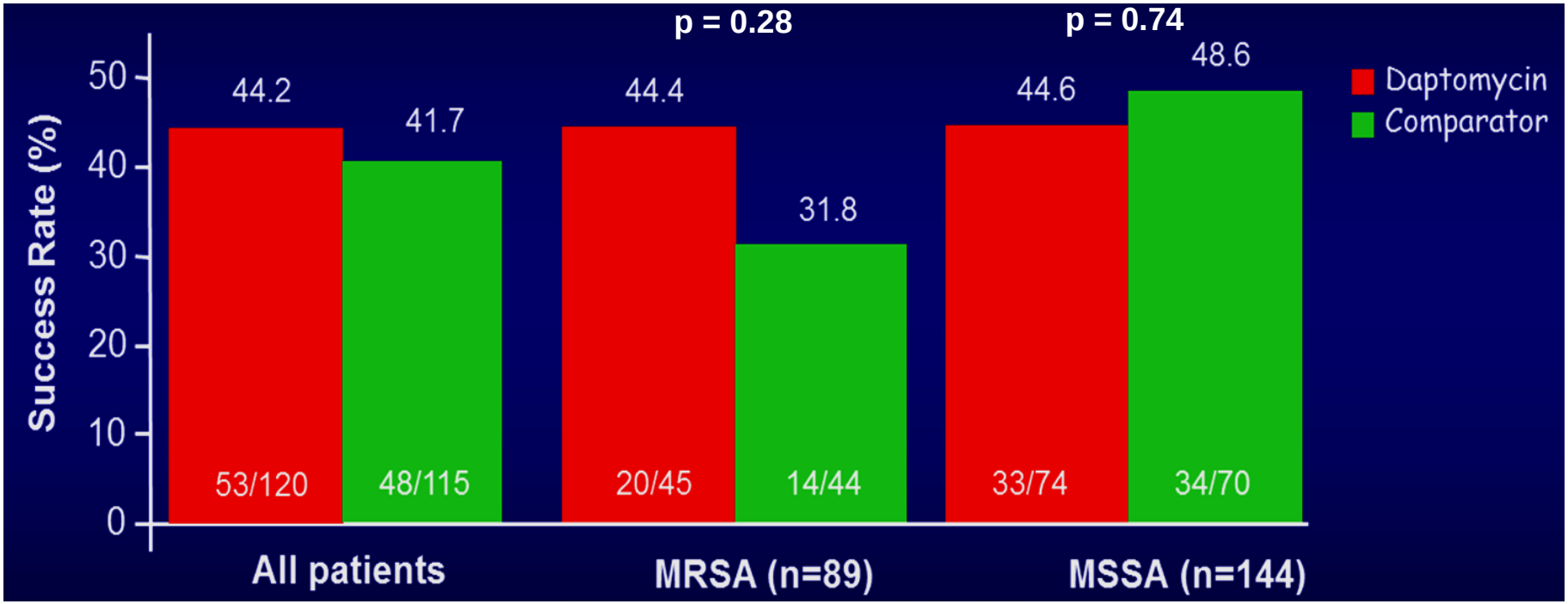


Nephrotoxicity:

Vancomycin	**18.2%**
Linezolid	**8.4%**

Clin Infect Dis 2012; 54:621–9.

Daptomycin has equal activity against BSI due to met-S AND met-R Staph. aureus



6 mg/kg/d

	DAPTO	COMPARATOR	
median time to clearance of bacteremia			
MRSA	**8**	**9**	**p = 0.25**
MSSA	**4**	**3**	**p = 0.28**

An open-label, pragmatic, randomized controlled clinical trial to evaluate the comparative effectiveness of daptomycin versus vancomycin for the treatment of complicated skin and skin structure infection

Teresa L. Kauf[1*], Peggy McKinnon[2], G. Ralph Corey[3], John Bedolla[4], Paul F. Riska[5], Matthew Sims[6],

Daptomycin ($n = 118$)	Vancomycin ($n = 106$)
4 mg/kg once daily	according to institutional protocol.

Table 2 Health economic outcomes

Outcome	Unadjusted (PAS)			Adjusted (MVAS)	
	Daptomycin ($n = 118$)	Vancomycin ($n = 106$)	*P* value	Rate ratio[b]	*P* value
IRLOS, hours, mean (SD)	91.5 (57.8)	93.2 (60.8)	0.823	1.002 (0.844–1.191)	0.979
Total LOS, hours, mean (SD)	98.5 (77.0)	101.2 (72.1)	0.785	1.018 (0.861–1.204)	0.833
Total inpatient cost, 2012 US$, mean (SD)[a]	9641 (6683)	9083 (5855)	0.509	0.940 (0.803–1.101)	0.442

Primary study outcome: Infection Related Length Of Stay

No difference between DAPTO and VANCO

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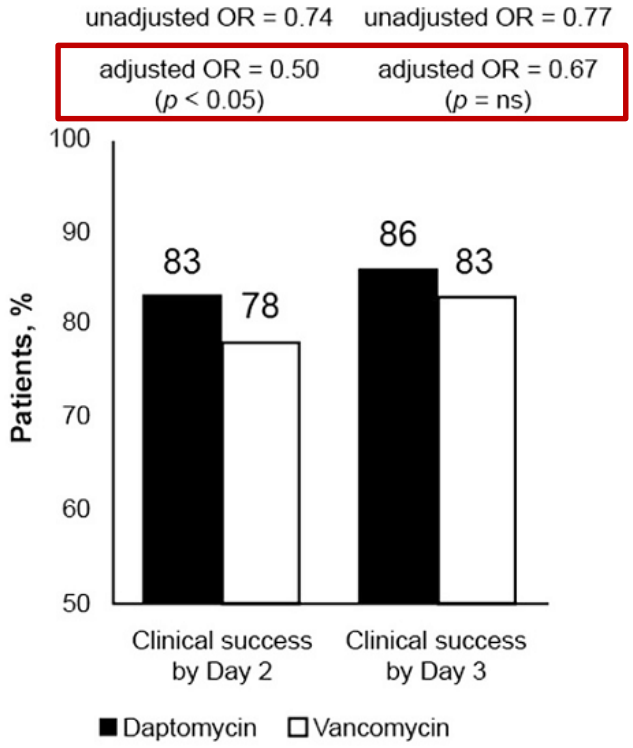
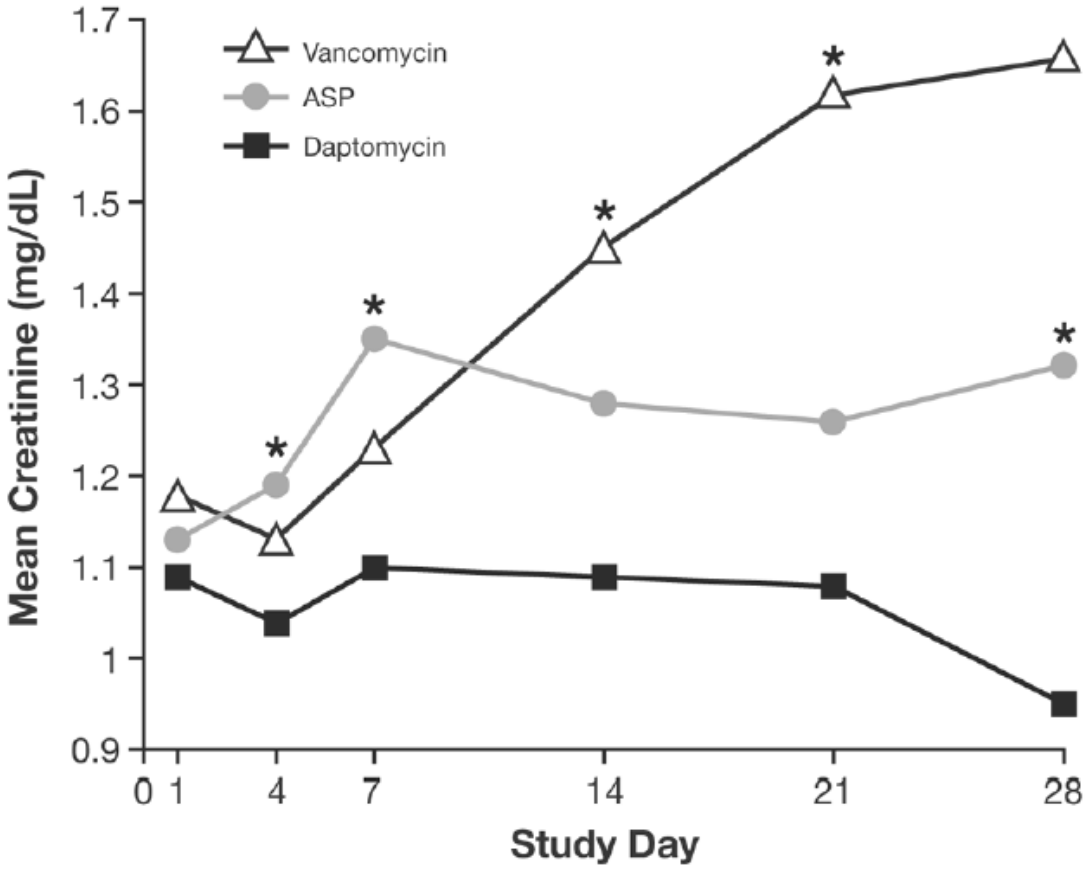


NEPHROTOXICITY OF VANCOMYCIN vs DAPTOMYCIN



Vancomycin is as much nephrotoxic as Gentamycin

Cosgrove SE et al. *Clin Infect Dis*. 2009;48:713-21

High-Dose Daptomycin for Cardiac Implantable Electronic Device–Related Infective Endocarditis

Emanuele Durante-Mangoni, Roberta Casillo, Mariano Bernardo, Cristina Caianiello, Irene Mattucci, Daniela Pinto, Federica Agrusta, Roberta Caprioli, Rosina Albisinni, Enrico Ragone, and Riccardo Utili

Department of Internal Medicine, University of Naples S.U.N., and Unit of Infectious and Transplant Medicine, A.O.R.N. "V. Monaldi," Naples, Italy

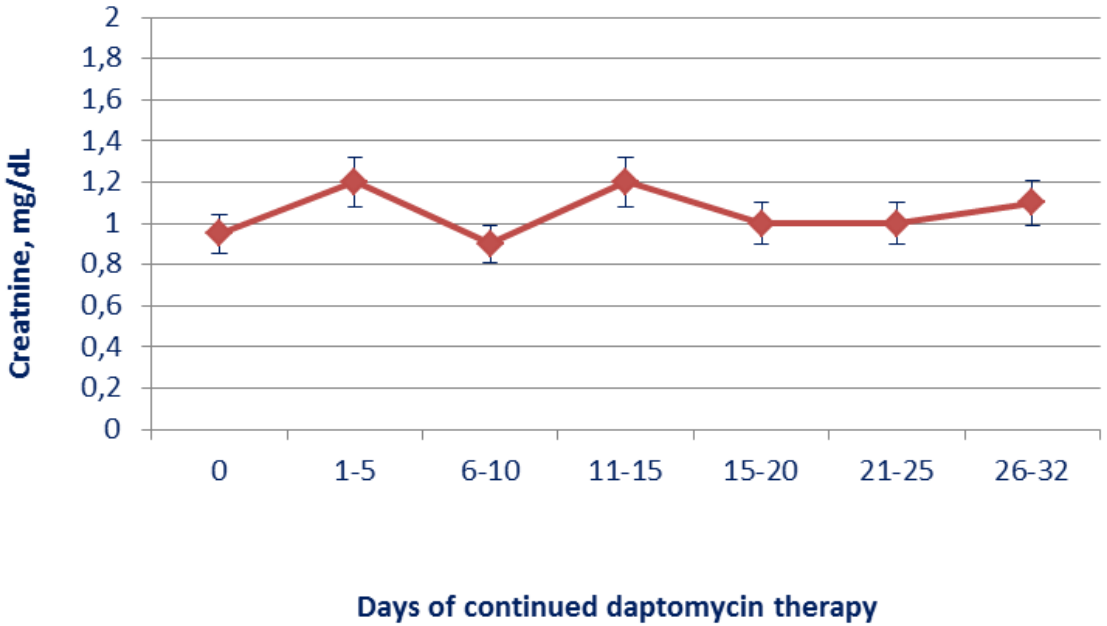
21 pts bacteremic at the time of Dapto start

19 (91%) cleared bacteremia after a median of 4 days [2-8]

Safety of treatment with high-dose daptomycin in 102 patients with infective endocarditis

Emanuele Durante-Mangoni [a,b,*], Roberto Andini [a], Antonio Parrella [a], Irene Mattucci [a],

Daptomycin does not impair renal function



Renal impairment	Incidence
RIFLE R	7.9%
RIFLE I	0.9%

Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant *Staphylococcus aureus*: randomised controlled trial

Mical Paul,[1,2] Jihad Bishara,[1,2] Dafna Yahav,[2,3] Elad Goldberg,[2,4] Ami Neuberger,[5,6] Nesrin Ghanem-Zoubi,[7] Yaakov Dickstein,[6,8] William Nseir,[9] Michael Dan,[2,10] Leonard Leibovici[2,3]

Table 2 | Study outcomes. Values are numbers (percentages) unless stated otherwise

	All		
Outcome	**Trimethoprim-sulfamethoxazole**	**Vancomycin**	**Effect estimate (95% CI)***
Treatment failure, day 7—ITT†	51/135 (38)	32/117 (27)	1.38 (0.96 to 1.99)

	Bacteraemia		
Outcome	**Trimethoprim-sulfamethoxazole**	**Vancomycin**	**Effect estimate (95% CI)***
Treatment failure, day 7—ITT†	23/41 (56)	20/50 (40)	1.40 (0.91 to 2.16)

Tailoring Vanco vs Alternative Agents for MRSA infections

from MIC values to clinical judgement

NO KIDNEY DISEASE
NO CHRONIC COMORBIDITIES
ABILITY TO MEASURE THROUGH LEVELS
NEED TO REDUCE COSTS

VANCOMYCIN
OPTIMISED DOSAGE

KIDNEY DISEASE
MEDICAL COMORBIDITIES
OUTPATIENT THERAPY IN STABLE CASES
WEALTHIER HOSPITAL ENVIRONMENT

ALTERNATIVE RX

Australian Therapeutic Guidelines: Antibiotic version 15,

loading dose of 20–35 mg/kg

15–20 mg/kg 12-hourly (q12h)

Table 1 Adjustment of starting maintenance vancomycin doses according to renal function (for a 70-kg adult)

Creatinine clearance (mL/min)	Starting maintenance dosage	Timing of trough (pre-dose) plasma concentration measurement
More than 90	1.5 g 12-hourly	Before the fourth dose
60 to 90	1 g 12-hourly	Before the fourth dose
20 to less than 60	1 g 24-hourly	Before the third dose
Less than 20	1 g 48-hourly	48 hours after the first dose
On haemodialysis [58]	25 mg/kg	Immediately prior to next haemodialysis session

Vancomycin-based combinations

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

Joshua S. Davis,[1,3,a] Archana Sud,[4,5] Matthew V. N. O'Sullivan,[5,7] James O. Robinson,[11,12] Patricia E. Ferguson,[5,8] Hong Foo,[9]

Table 3. Primary Outcome Measure

	Duration of Bacteremia, d[b]			
Population[a]	Standard Therapy	Combination Therapy	Ratio of Means (95% CI)	*P* Value
ITT population				
Mean (SD)	3.00 (3.35)	1.94 (1.79)	0.65 (0.41–1.02)	.06
Median (IQR)	1 (1–2)	1 (1–4)	. . .	. . .
Per-protocol population				
Mean (SD)	2.92 (3.37)	1.82 (1.59)	0.62 (0.38–1.01)	.055
Median (IQR)	1 (1–2)	1 (1–4)	. . .	. . .

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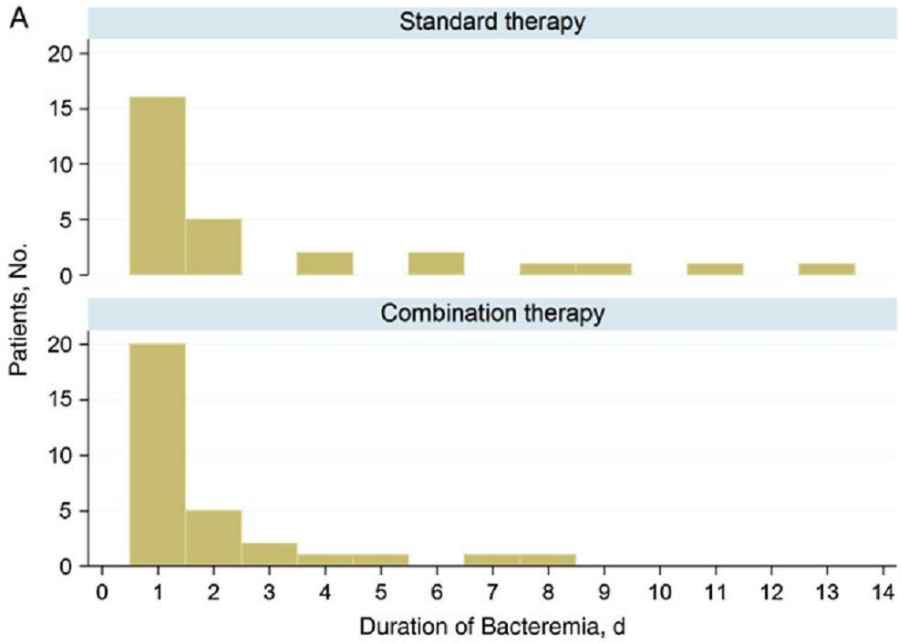
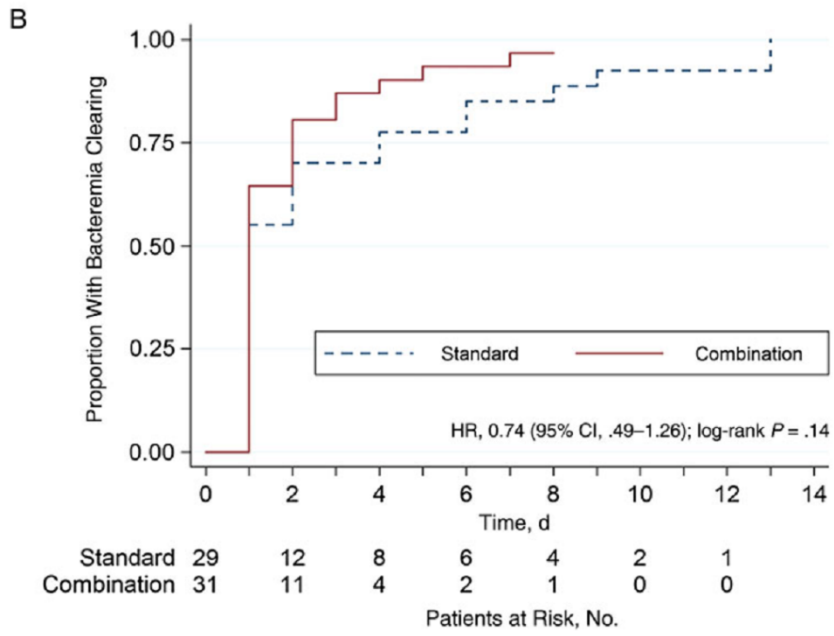




Combination therapy with an aminoglycoside for *Staphylococcus aureus* endocarditis and/or persistent bacteremia is associated with a decreased rate of recurrent bacteremia: a cohort study

T. L. Lemonovich[1] ✉, K. Haynes[2], E. Lautenbach[2,3,4,5] and V. K. Amorosa[3,6]

87 patients: 48 MRSA, 39 MSSA

	Aminoglycoside (n = 49)	No aminoglycoside (n = 38)	RR (95%C.I.)	p value
duration of bacteremia	5 days	5 days	Na	0.49
6-month all-cause mortality	51%	42.1%	1.17 (0.81–1.69)	0.41
complications of IE	71.4%	73.7%	0.95 (0.64–1.43)	0.82
recurrence within 6 months	**8.2%**	**23.7%**	**0.51 (0.22–1.17)**	**0.04**

Multivariable analysis of clinical variables associated with recurrent bacteremia

Variable	Unadjusted OR	Adjusted OR (95% CI)	*p* value
Aminoglycoside therapy	0.29	0.26 (0.07–0.98)	0.046
MRSA isolate	5.50	5.93 (1.19–29.47)	0.030

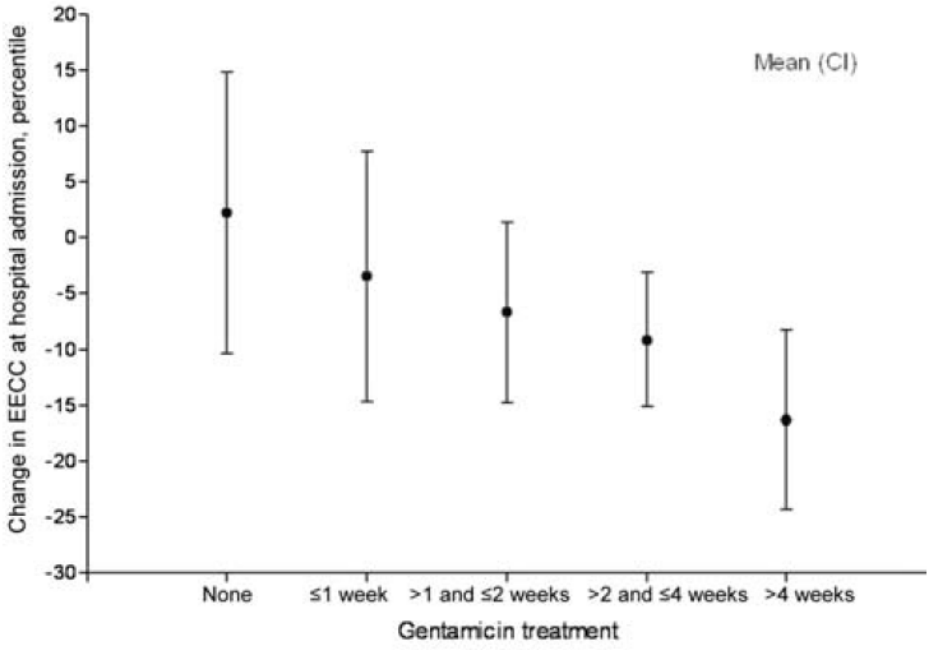
Initial Low-Dose Gentamicin for *Staphylococcus aureus* Bacteremia and Endocarditis Is Nephrotoxic

MS and MR S. aureus

Decrease	Received gentamicin, no. (%) of patients		P^b
	Yes[a] (n = 122)	No[a] (n = 100)	
Clinically significant decrease in CrCl	27 (22)	8 (8)	.005
Sustained 50% decrease in CrCl	7 (6)	0 (0)	.02
Sustained 25% decrease in CrCl	26 (21)	9 (9)	.02
Discontinuation of use of study medication because of renal events	4 (3)	1 (1)	.38

Severity of Gentamicin's Nephrotoxic Effect on Patients with Infective Endocarditis: A Prospective Observational Cohort Study of 373 Patients

Kristine Buchholtz,[1] Carsten T. Larsen,[1] Christian Hassager,[2] and Niels E. Bruun[1]



Università degli Studi della Campania *Luigi Vanvitelli*

Clinical Infectious Diseases 2009; 48:65–71

Ospedali dei Colli Monaldi · Cotugno · C.T.O.

Aminoglycosides for MRSA Infections: Use with caution or avoid

- Elderly
- Chronic kidney disease K/DIGO ≥3
- Endocarditis with heart failure
- Use of diuretics
- Iodinated contrast media for coronary angiography

Rifampin

- ✓ Penetration into biofilm and abscesses
- ✓ Kills organisms in stationary phase

- ✗ Rapid emergence of resistance during monotherapy and with high bacterial loads

Slow Response to Vancomycin or Vancomycin plus Rifampin in Methicillin-resistant *Staphylococcus aureus* Endocarditis

Donald P. Levine, MD; Barbara S. Fromm, MA; and B. Ramesh Reddy, MD

Prospective, randomized, controlled, open-label trial
22 patients: Vancomycin 1 g every 12 hours (mono -therapy)
20 patients: Vancomycin 1 g every 12 hours + rifampin 600 mg orally once daily (combo) for 28 days
MRSA infective endocarditis – All NVE

Outcomes

	Monotherapy	Combination therapy	p value
Cure rate	18 [82%]	18 [90%]	>0.20 (NS)
Duration of bacteremia	7 days	9 days	>0.05 (NS)

Vancomycin trough concentrations were 11.4 µg/mL and 10.4 µg/Ml (p=0.20)

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2008, p. 2463–2467 Vol. 52, No. 7
0066-4804/08/$08.00+0 doi:10.1128/AAC.00300-08

Addition of Rifampin to Standard Therapy for Treatment of Native Valve Infective Endocarditis Caused by *Staphylococcus aureus*▽

David J. Riedel,[1]* Elizabeth Weekes,[2]† and Graeme N. Forrest[3]

NVE
MRSA 79%

RIF add after median 3 days

	Rifampin N = 42	No Rifampin N = 42	P-Value
Duration of bacteremia	5.2 days	2.1 days	0.002
Emergence of Resistance	21%	0%	< 0.001
Increased LFTs	23%	2%	0.014
Drug Interactions	52%	0%	< 0.001
Survival	79%	95%	0.048

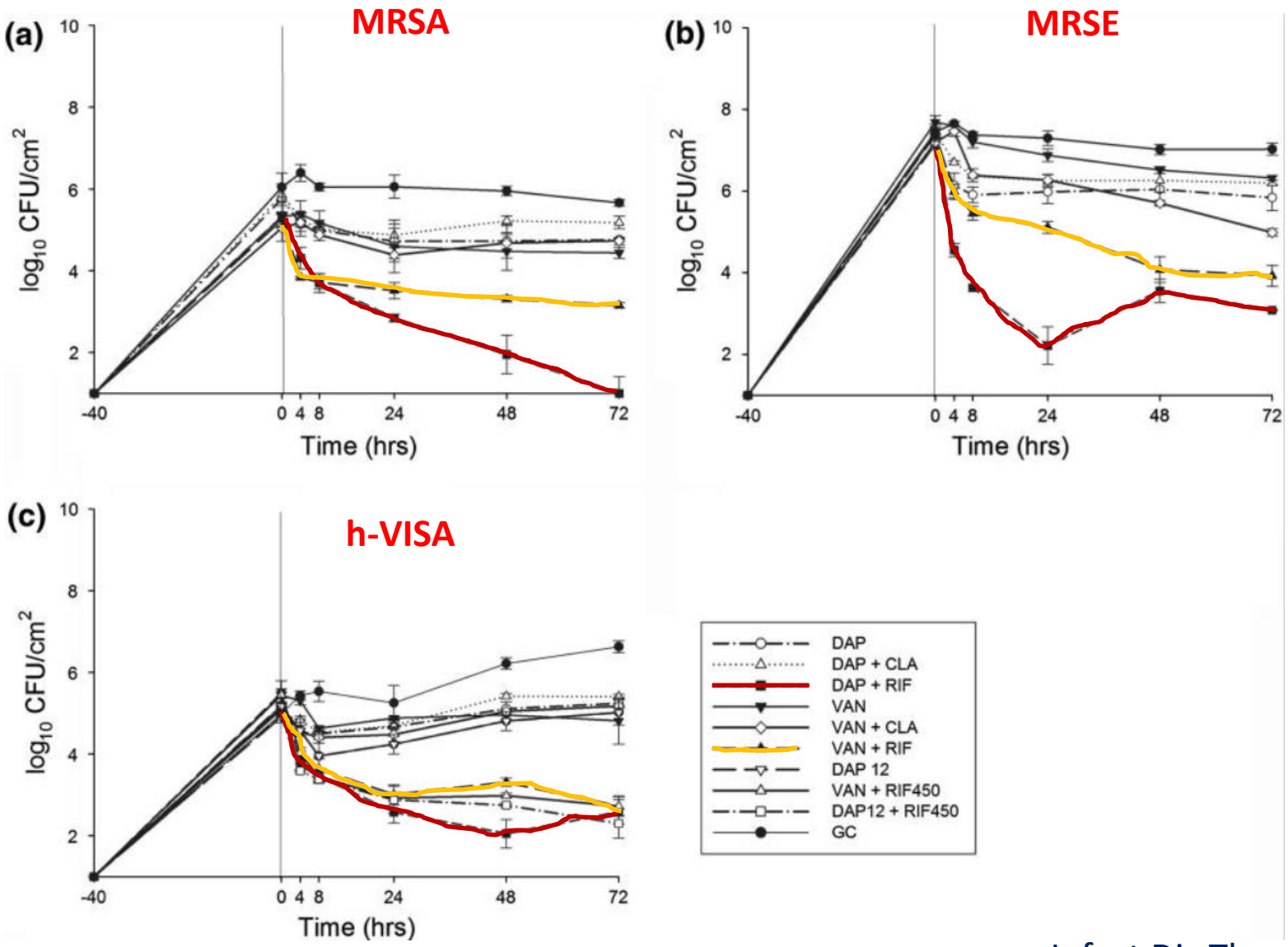
Infect Dis Ther (2015) 4:51–65
DOI 10.1007/s40121-014-0055-5

ORIGINAL RESEARCH

Evaluation of High-Dose Daptomycin Versus Vancomycin Alone or Combined with Clarithromycin or Rifampin Against *Staphylococcus aureus* and *S. epidermidis* in a Novel In Vitro PK/PD Model of Bacterial Biofilm

Ashley D. Hall Snyder · Celine Vidaillac · Warren Rose · John P. McRoberts · Michael J. Rybak

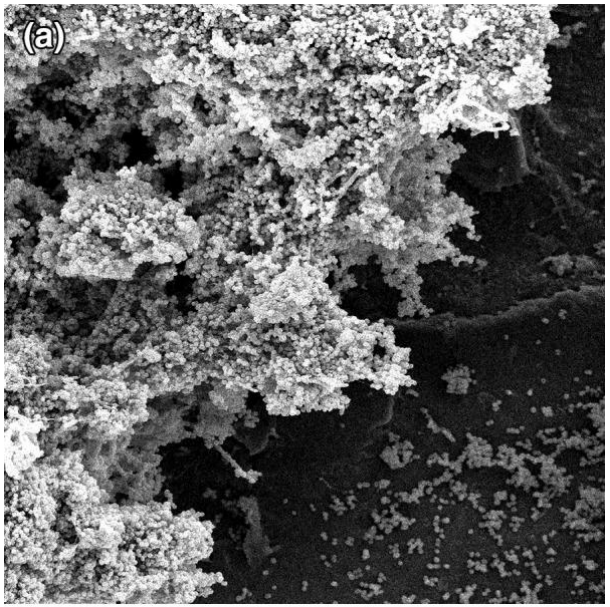
Rifa+Dapto/Vanco: best combination vs staph biofilm



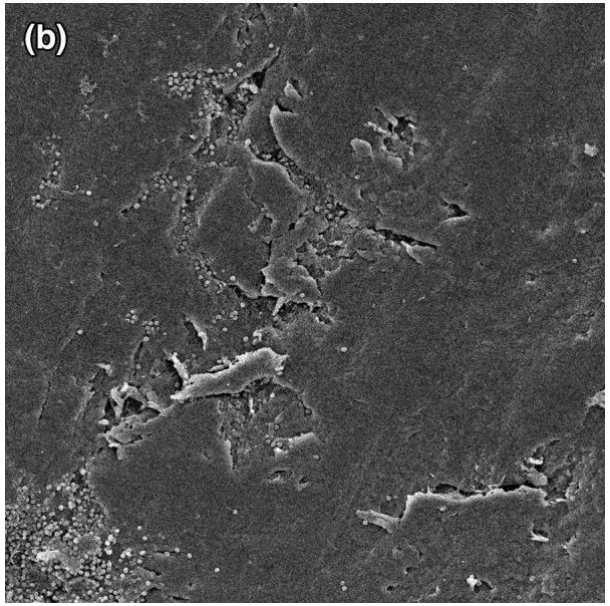
Infect Dis Ther (2015) 4:51–65

MRSE embedded in biofilm

SEM images are at 1000× magnification



a prior to antibiotic exposure



b after 72 h of DAP + RIF exposure

Rifampin use in MRSA Infections

- Biofilm-associated infection
- When prosthesis remains in place
- Not in acute, bacteremic cases
- Not in chronic liver disease patients, epilepsy, polypharmacy
- When drug-drug interactions are not an issue

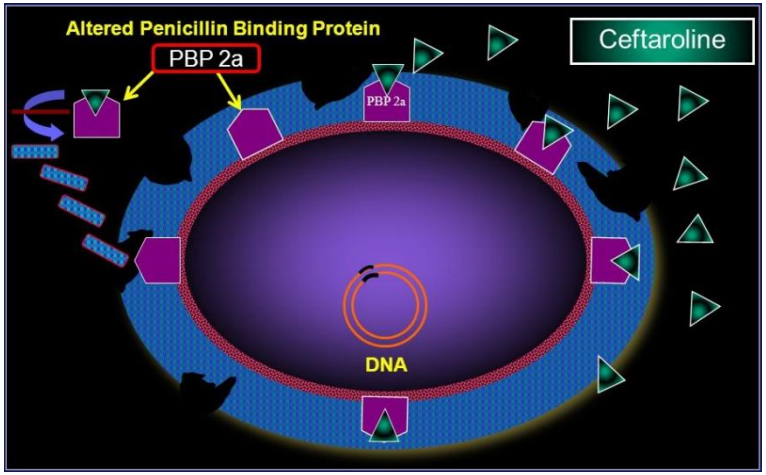
- Start rifampin after bacterial burden has decreased / blood cult. cleared

New / Innovative Options against MRSA

- **Ceftaroline - Ceftobiprole**
- **Dalbavancin**
- **Fosfomycin-based combinations**

Ceftaroline - Ceftobiprole

- 5th gen cephalosporins, excellent safety profile
- Bind to the altered transpeptidase PBP2a (mecA gene product)
- Allow to treat MRSA infections and rare penicillin-resistant pneumococci with a beta-lactam
- Bactericidal, PD T>MIC



Integrated Analysis of CANVAS 1 and 2: Phase 3, Multicenter, Randomized, Double-Blind Studies to Evaluate the Safety and Efficacy of Ceftaroline versus Vancomycin plus Aztreonam in Complicated Skin and Skin-Structure Infection

G. Ralph Corey,[1] Mark Wilcox,[4] George H. Talbot,[2,a] H. David Friedland,[2] Tanya Baculik,[2] Gary W. Witherell,[2] Ian Critchley,[2] Anita F. Das,[3] and Dirk Thye[2]

Table 4. Clinical Cure Rates by Analysis Population at the Test-of-Cure Visit

Population, type of infection	Cure rate, no. of patients cured/total no. of patients (%)		
	Ceftaroline	Vancomycin plus aztreonam	Difference,[a] % (95% CI)
Clinically evaluable	559/610 (91.6)	549/592 (92.7)	−1.1 (−4.2 to 2.0)
MITT	595/693 (85.9)	586/685 (85.5)	0.3 (−3.4 to 4.0)
Microbiologically evaluable	434/468 (92.7)	421/446 (94.4)	−1.7 (−4.9 to 1.6)
Gram positive only	348/371 (93.8)	330/350 (94.3)	−0.5 (−4.1 to 3.1)
Gram negative only	29/34 (85.3)	24/24 (100)	−15.6 (−31.6 to −1.2)
Mixed gram positive and negative	57/63 (90.5)	67/72 (93.1)	−2.6 (−13.4 to 7.2)
Polymicrobial infection	125/136 (91.9)	134/139 (96.4)	−4.2 (−10.5 to 1.5)

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Table 5. Clinical Cure Rates for Selected Baseline Isolates at the Test-of-Cure Visit

	Cure rate, no. of patients cured/total no. of patients (%)			
	Isolates identified in ME population		Isolates identified in mMITT population	
Organism	Ceftaroline	Vancomycin plus aztreonam	Ceftaroline	Vancomycin plus aztreonam
Staphylococcus aureus	352/378 (93.1)	336/356 (94.4)	377/425 (88.7)	356/409 (87.0)
MRSA	142/152 (93.4)	115/122 (94.3)	155/179 (86.6)	124/151 (82.1)
MSSA	212/228 (93.0)	225/238 (94.5)	221/245 (90.2)	233/258 (90.3)
Streptococcus pyogenes	56/56 (100)	56/58 (96.6)	56/63 (88.9)	57/62 (91.9)
Streptococcus agalactiae	21/22 (95.5)	18/18 (100)	25/27 (92.6)	19/21 (90.5)
Enterococcus faecalis	20/25 (80.0)	22/24 (91.7)	20/28 (71.4)	23/28 (82.1)
Escherichia coli	20/21 (95.2)	19/21 (90.5)	21/23 (91.3)	19/21 (90.5)
Pseudomonas aeruginosa	NA	NA	20/25 (80.0)	22/25 (88.0)
Proteus mirabilis	10/15 (66.7)	20/21 (95.2)	11/16 (68.8)	20/23 (87.0)
Klebsiella pneumoniae	17/18 (94.4)	13/14 (92.9)	17/18 (94.4)	14/19 (73.7)

Multicenter Observational Study of Ceftaroline Fosamil for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections

Evan J. Zasowski,[a] Trang D. Trinh,[a] Kimberly C. Claeys,[a,b] Anthony M. Casapao,[a,c] Noor Sabagha,[a] Abdalhamid M. Lagnf,[a] Kenneth P. Klinker,[d] Susan L. Davis,[a,e] Michael J. Rybak[a,f,g]

Efficacy was evaluated in 126 patients

MRSA BSI sources: lower respiratory tract (32.5%)
infective endocarditis (24.6%)

Clinical success was observed for 86 (68.3%) of the patients in the efficacy population, with 28 (22.2%) experiencing in-hospital mortality

Pts with cleared BSI on CEFT: 115 (91.3%)

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Safety was evaluated in 211 patients

median duration of ceftaroline therapy: 11 days (IQR, 5-15 days)

Adverse reactions were uncommon:

- *Clostridium difficile* infection — 6 patients (2.8%)
- Rash — 7 patients (3.3%)
- Neutropenia — 3 patients (1.4%)

Mean time from CEFT start to neutropenia: 16 days

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Treatment information	
No. (%) of patients with:	
Infectious diseases consult[f]	113 (93.4)
Source control pursued[g]	42 (34.7)
Prior directed therapy with vancomycin	107 (84.9)
Prior directed therapy with daptomycin	48 (38.1)
Ceftaroline dosing frequency	
Every 8 h	66 (52.4)
Every 12 h	54 (42.9)
Every 24 h	6 (4.8)
Ceftaroline dose	
600 mg	76 (60.3)
400 mg	19 (15.1)
300 mg	11 (8.7)
200 mg	20 (15.9)
Median ceftaroline inpatient duration (days) (IQR)	13 (5–21)
No. (%) of patients receiving combination therapy with:	
Daptomycin	28 (22.2)
Vancomycin	3 (2.4)
Gentamicin	3 (2.4)
Rifampin	5 (4.0)

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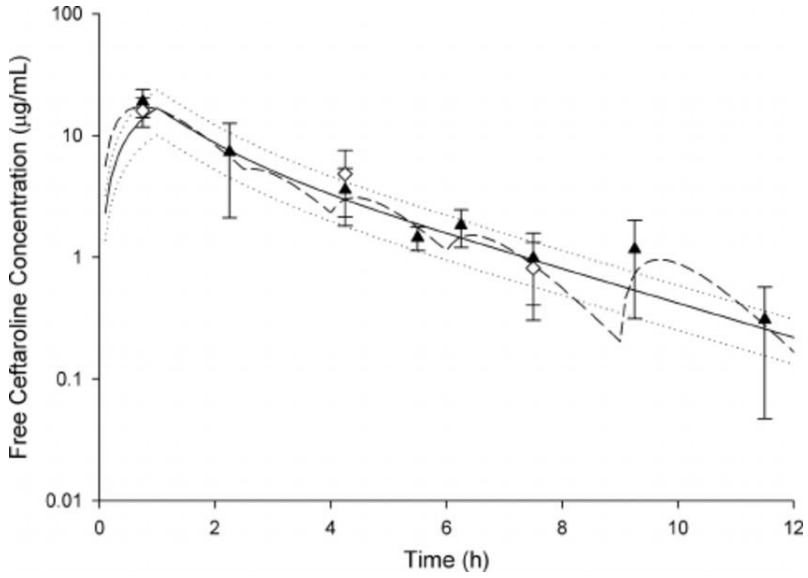
TABLE 2 Multivariable logistic regression analysis of factors independently associated with treatment failure with ceftaroline in the efficacy population[a]

Variable	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
APACHE II score	1.100 (1.037–1.166)	1.093 (1.044–1.145)
Malignancy	6.000 (1.111–32.405)	3.127 (1.009–9.686)
Lower respiratory tract source	2.632 (1.198–5.783)	
Bone/joint source	0.442 (0.153–1.274)	
Ceftaroline dose		
600 mg		
400 mg	3.856 (1.350–11.017)	
300 mg	2.892 (0.785–10.651)	
200 mg	2.314 (0.814–6.577)	

[a]$P = 0.574$ as determined by a Hosmer-Lemeshow goodness-of-fit test and a variance inflation factor of <3 for all variables included for model entry. CI, confidence interval.

Ceftaroline use & safety

- 600 mg q12h, normal renal function eGFR>50
- <50-30 mL/min: 400 mg q12h
- <30 mL/min: 300 mg q12h
- <15 ml/min or HD: 200 mg q12h (after HD)
- IV infusion over 60’



- CDI may occur; 10% develop a positive direct Coombs test

Ceftobiprole use & safety

- 500 mg q8h, normal renal function eGFR>50
- <50-30 mL/min: 500 mg q12h
- <30 mL/min: 250 mg q12h
- <15 ml/min or HD: 250 mg q24h (after HD)
- IV infusion over 120’

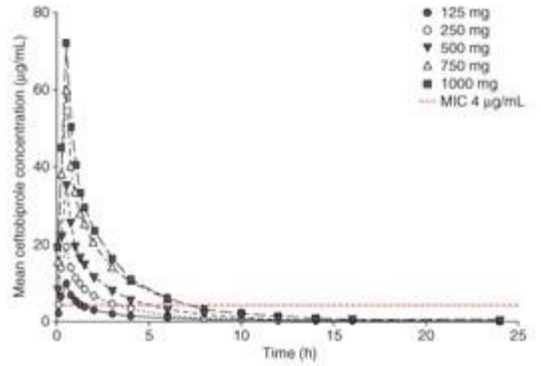
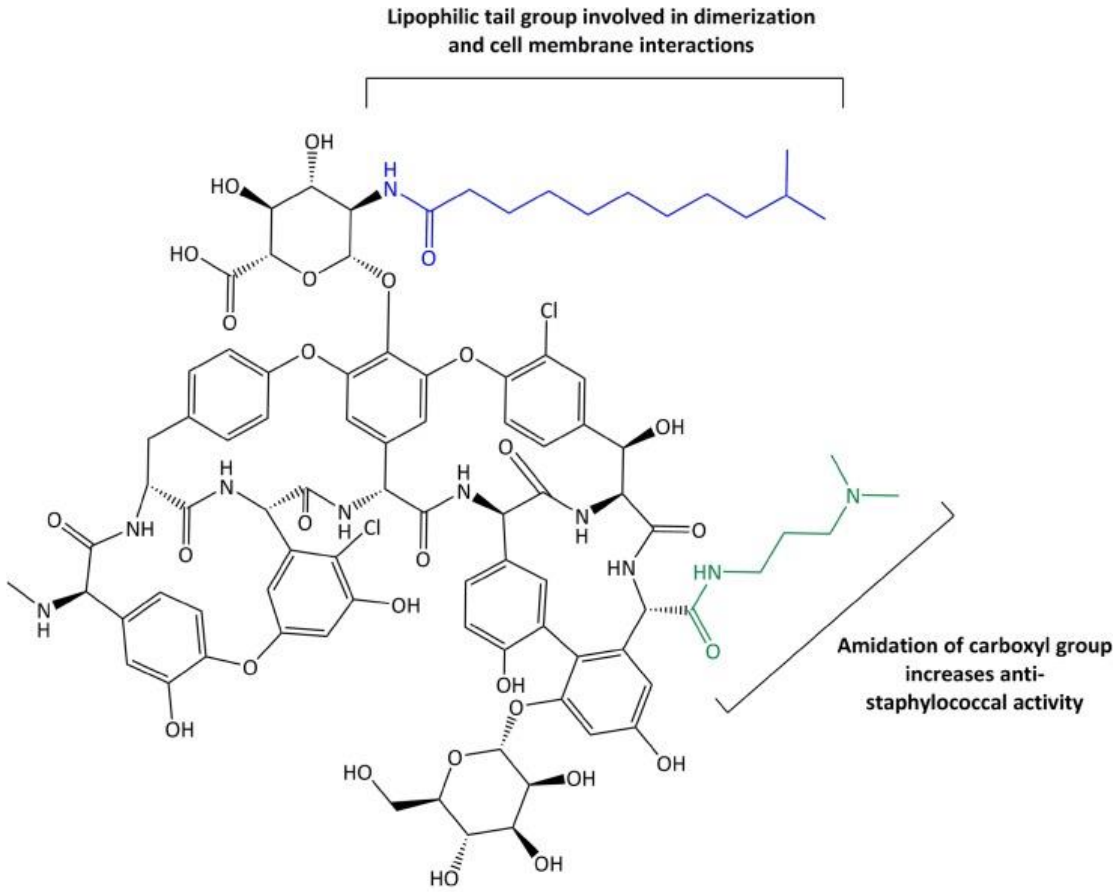


Fig. 2. Mean plasma ceftobiprole (BAL 9141) concentration-time profiles following single ascending intravenous 30-min infusions of ceftobiprole at 125, 250, 500, 750 or 1000 mg in healthy subjects (adapted from Schmitt-Hoffmann et al.,[2] with permission).

- CDI may occur; few patients may develop hypersensitivity reactions

Summary: Ceftaroline / Ceftobiprole

- Are an option for salvage treatment
- Rapidly clear bacteremia
- Well tolerated
- Standard dose may not be optimal for MRSA BSI / IE



Dalbavancin

Table 1 Dalbavancin MICs for several gram-positive organisms [15–18, 25–27]

	Number of isolates	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range	% Susc.
S. aureus [15–18, 25, 27]	64,843	0.06	0.06	≤0.008 to 0.5	99.7
MSSA [15–18, 25, 27]	37,222	0.06	0.06	≤0.008 to 0.5	99.7
MRSA [15–18, 25, 27]	27,261	0.06	0.06	≤0.008 to 0.5	99.6
hVISA [18]	10	0.25	0.5	0.12 to 0.5	20
VISA [18]	8	0.5	N/A	0.5 to 2	0
DNS SA [25]	37	0.06	0.12	≤0.03 to 0.5	91.9
LR SA [25]	19	0.06	0.12	≤0.03 to 0.5	100
CNS [15, 16, 27]	473	≤0.03	0.06	≤0.03 to 0.25	99.6
MS CNS [15, 16, 27]	281	≤0.03	0.06	≤0.03 to 1	N/A
MR CNS [15, 16, 27]	193	≤0.03	0.12	≤0.03 to 0.25	N/A

Table 1 Dalbavancin MICs for several gram-positive organisms [15–18, 25–27]

	Number of isolates	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range	% Susc.
β-hemo strep [15, 16, 26]	1242	≤0.03	≤0.03	≤0.03 to 0.25	98.6
Viridans strep [15, 16, 26]	786	≤0.03	≤0.03	≤0.03 to 0.25	99.7
S. anginosus [26]	190	≤0.03	≤0.03	≤0.03 to 0.06	100
S. milleri [26]	14	≤0.03	≤0.03	≤0.03 to 0.06	100
S. bovis [26]	47	≤0.03	0.06	≤0.03 to 0.12	100
S. dysgalactiae [26]	50	≤0.03	0.06	≤0.03 to 0.12	100
S. mitis [26]	305	≤0.03	0.06	≤0.03 to 0.25	99.7
S. mutans [26]	20	≤0.03	0.06	≤0.03 to 0.12	100
S. salivarius [26]	49	≤0.03	0.06	≤0.03 to 0.25	98
GAS [15, 16, 26]	506	≤0.03	≤0.03	≤0.03 to 0.12	100
GBS [15, 16, 26]	287	≤0.03	0.12	≤0.03 to 0.25	94.4
S. pneumoniae [27]	893	≤0.03	≤0.03	≤0.03 to 0.12	100
PSSp [27]	739	≤0.03	≤0.03	≤0.03 to 0.12	100
PISp [27]	120	≤0.03	≤0.03	≤0.03 to 0.12	100
PRSp [27]	34	≤0.03	≤0.03	≤0.03	100

Table 1 Dalbavancin MICs for several gram-positive organisms [15–18, 25–27]

	Number of isolates	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range	% Susc.
Enterococcus spp. [15, 16]	116	0.06	>4	≤0.03 to >4	56
VSE [15, 16]	63	≤0.03	0.12	≤0.03 to 0.25	96.8
VRE [15, 16]	53	>4	>4	≤0.03 to >4	7.5
VanA VRE [15, 16]	49	>4	>4	0.25 to >4	0
VanB VRE [15, 16]	4	≤0.03	0.12	≤0.03 to 0.12	100
E. faecalis [16]	25	0.06	>4	≤0.03 to >4	76
VSE *faecalis* [16]	19	≤0.03	0.06	≤0.03 to 0.06	100
VRE *faecalis* [16]	6	>4	>4	>4	0
E. faecium [16]	31	1	>4	≤0.03 to >4	41.9
VSE *faecium* [16]	11	0.06	0.12	≤0.03 to 0.12	100
VRE *faecium* [16]	20	>4	>4	≤0.03 to >4	10

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Sailaja Puttagunta, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (–4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	–1.5 (–7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	–0.1 (–4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	–1.0 (–5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (–3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (–2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	–1.5 (–4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	–1.4 (–4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	–0.7 (–3.0 to 1.5)

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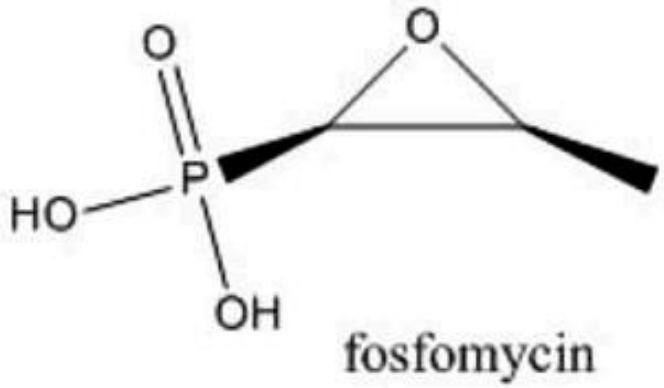
Table 4. Adverse Events.

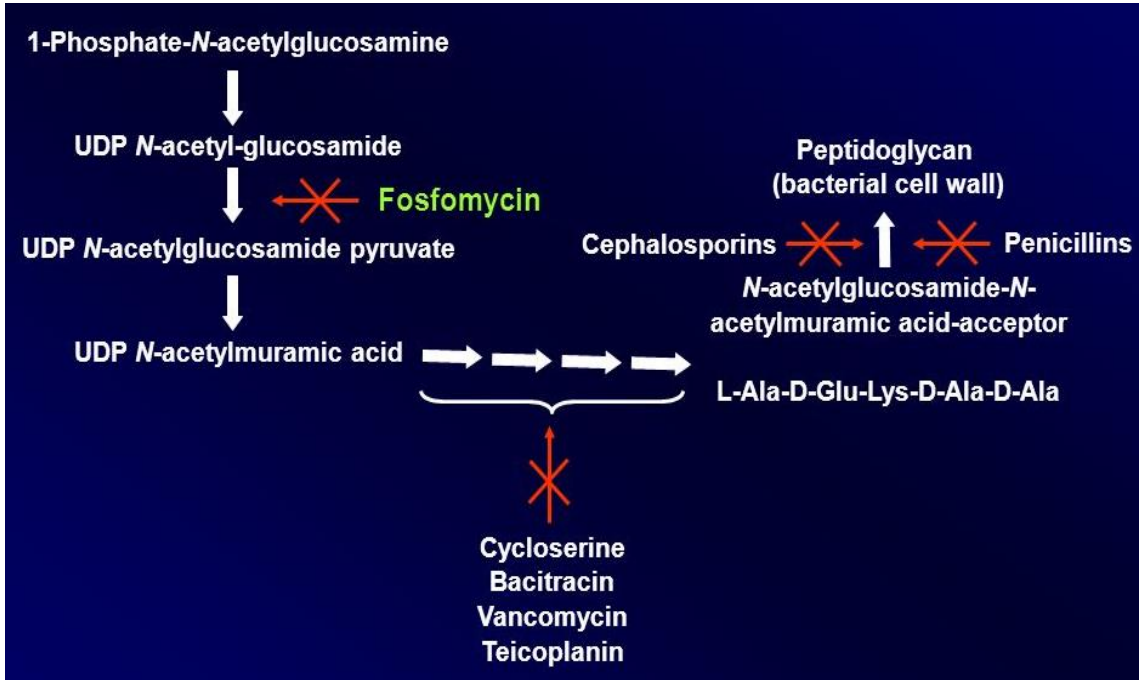
Variable	Dalbavancin (N=652)	Vancomycin–Linezolid (N=651)	P Value*
Any adverse event			
Any event — no. of patients (%)	214 (32.8)	247 (37.9)	0.05
Total no. of events	540	645	0.05
Treatment-related adverse event†			
Any event — no. of patients (%)	80 (12.3)	89 (13.7)	0.45
Total no. of events	139	183	0.02
Serious adverse event — no. of patients (%)			
Any event	17 (2.6)	26 (4.0)	0.16
Treatment-related event†	2 (0.3)	4 (0.6)	0.41
Death — no. (%)‡	1 (0.2)	7 (1.1)	0.03
Treatment-limiting adverse event — no. of patients (%)§	14 (2.1)	13 (2.0)	0.85
Most common treatment-related adverse event — no. of patients (%)¶			
Nausea	16 (2.5)	19 (2.9)	0.62
Diarrhea	5 (0.8)	16 (2.5)	0.02
Pruritus	4 (0.6)	15 (2.3)	0.01

Summary: Dalbavancin

- Is an option for parenteral outpatient rx
- Use upfront in ABSSSI not yet BSI
- Due to spectrum of activity and biofilm penetration, deserves consideration for cardiovascular prosthesis infections



fosfomycin



bactericidal with a broad spectrum including:

- Gram-positives (e.g. Enterococcus faecalis and Staph aureus)
- Gram-negatives (e.g. E. coli & Klebsiella)

Fosfomycin disodium IV PK

- High serum concentrations with 2 - 4 g every 6 h
- Adequate penetration into various tissues, including lung, central nervous system, and bone
- Rapid onset of resistance, always combine in serious infections

- Vials of 2, 4 and 8 g

Fosfomycin disodium: Safety

- It is a very well tolerated drug
- AE are mostly GI: nausea, vomiting and diarrhea
- Skin rashes
- AE occur in 5% of patients

- With a (recommended) daily dose of intravenous fosfomycin up to 8–16 g, the amount of sodium administered can range from 2.6 to 5.3 g per day (1 g of fosfomycin delivers 330 mg [14.4 mEq] of sodium).

Efficacy and Safety of Fosfomycin Plus Imipenem as Rescue Therapy for Complicated Bacteremia and Endocarditis Due to Methicillin-Resistant *Staphylococcus aureus*: A Multicenter Clinical Trial

Ana del Río,[1,a] Oriol Gasch,[2,3,a] Asunción Moreno,[1] Carmen Peña,[2] Jordi Cuquet,[4] Dolors Soy,[1] Carlos A. Mestres,[1] Cristina Suárez,[2] Juan C. Pare,[1] Fe Tubau,[2,5] Cristina Garcia de la Mària,[1] Francesc Marco,[1,6] Jordi Carratalà,[2] José M. Gatell,[1] Francisco Gudiol,[2] José M. Miró[1], and the FOSIMI Investigators[b]

synergism between these antibiotics against MRSA is associated with changes in the proportion of specific membrane penicillin-binding proteins (PBP) induced by fosfomycin, specifically PBP2a in the MRSA membrane, which can regress, leading strains to regain their susceptibility to beta-lactams

Efficacy and Safety of Fosfomycin Plus Imipenem as Rescue Therapy for Complicated Bacteremia and Endocarditis Due to Methicillin-Resistant *Staphylococcus aureus*: A Multicenter Clinical Trial

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Patients

Twelve of the 16 patients enrolled in the study were diagnosed with IE, 2 with vascular graft infection and 2 with complicated bacteremia. Their main clinical characteristics are summarized in Table 1. Median patient age was 67.5 years (range, 25–87); 13 patients (81%) had previous chronic comorbid conditions. Although the patients had received appropriate antibiotic therapy for a median of 9.5 days (range, 6–30), MRSA was still detected in the blood cultures of 14 patients. The other 2 patients were diagnosed with relapse, both 14 days after the end of appropriate antibiotic therapy. The median (interquartile range [IQR]) vancomycin trough level before switching either to a second drug or to fosfomycin plus imipenem was 18.1 μg/mL (range, 11.3–19.8).

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Treatment and Outcomes

As a whole, fosfomycin plus imipenem was administered for a median of 28 days (range, 4–75) as rescue therapy. In all cases, blood cultures were negative 72 hours after the first dose.

Efficacy and Safety of Fosfomycin Plus Imipenem as Rescue Therapy for Complicated Bacteremia and Endocarditis Due to Methicillin-Resistant *Staphylococcus aureus*: A Multicenter Clinical Trial

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Side effects attributable to the antibiotic combination were observed in 5 patients. Leucopenia and fungal bloodstream infection were diagnosed in 1 patient each, while 3 patients with liver cirrhosis had sodium overload that required more frequent paracentesis. One of these 3 patients died of hypernatremia, metabolic acidosis, and acute renal failure (episode 14). Antibiotics did not have to be withdrawn in any of the remaining 15 patients.

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

José M. Miró,[a] José M. Entenza,[b] Ana del Río,[a] Maria Velasco,[c] Ximena Castañeda,[a] Cristina Garcia de la Mària,[a] Marlyse Giddey,[b]

TABLE 2 *S. aureus* strains tested and MICs

Strain[a]	MIC (μg/ml)		
	Daptomycin	Fosfomycin	Vancomycin
MSSA 1112	0.5	8	1
MSSA P3	0.5	4	1
MSSA P4	0.5	8	1
MSSA P7	0.5	8	1
MSSA 4297	0.5	1	1
MSSA RN4220	0.5	4	0.5
MSSA 678	1	8	1
MRSA 277	0.25	4	2
MRSA P8	0.5	4	1
MRSA 2167	0.5	16	2
MRSA 4194	0.25	8	1
MRSA 726	0.25	16	0.5
GISA PC3	2	8	8
GISA ATCC 700788	0.5	16	8

3 patients with left-sided staphylococcal endocarditis (1 with MSSA prosthetic aortic valve endocarditis and 2 with MRSA native-valve endocarditis) were **successfully treated with high-dose intravenous daptomycin** (10 mg/kg/day) **plus fosfomycin** (2 g every 6 h) for 6 weeks.

Università degli Studi della Campania *Luigi Vanvitelli*

Antimicrobial Agents and Chemotherapy p. 4511–4515
August 2012 Volume 56 Number 8

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

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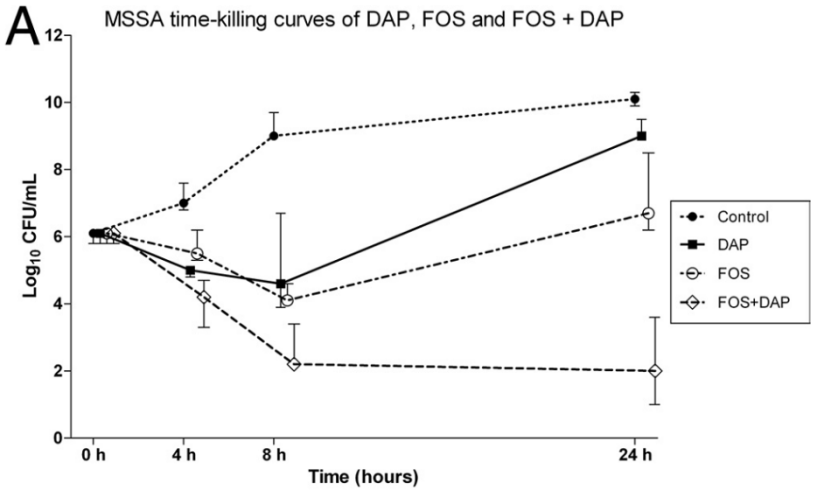

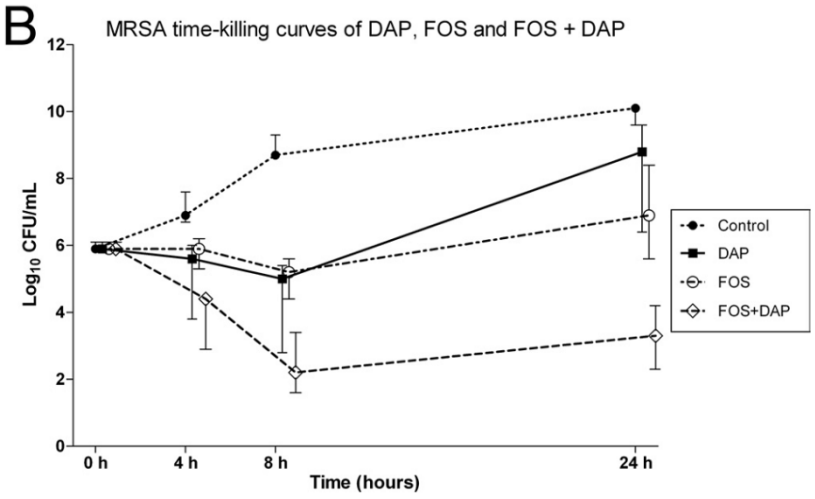

This combination was tested in vitro against 7 MSSA, 5 MRSA, and 2 intermediately glycopeptide-resistant S. aureus isolates and proved to be **synergistic against 11 (79%) strains** and **bactericidal against 8 (57%) strains**.

This combination deserves further clinical study.

Antimicrobial Agents and Chemotherapy p. 4511–4515

August 2012 Volume 56 Number 8

Summary: Fosfomycin combinations

- Very valuable option to compound other molecules
- No solid clinical end point data yet
- Sodium and water overload may be an issue in decompensated patients (cong heart failure, adv cirrhosis)

HLGR E.faecalis – prevalence of resistance

high-level resistance to gentamicin

< 1%
1% to < 5%
5% to < 10%
10% to < 25%
25% to < 50%
≥ 50%

VR E.faecium – prevalence of resistance

vancomycin

< 1%
1% to < 5%
5% to < 10%
10% to < 25%
25% to < 50%
≥ 50%

ESC 2015 guidelines for Enteroccal Endocarditis

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	4–6 2–6**	I I	B B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
	Paediatric doses:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses					
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses 4 g/day i.v. or i.m. in 2 doses	6 6	I I	B B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis. This combination is not active against *E. faecium*
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose	6 6	I I	C C		
	Paediatric doses:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above					

Habib G. *Eur Heart J* 2015

Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating *Enterococcus faecalis* Infective Endocarditis

Nuria Fernández-Hidalgo,[1] Benito Almirante,[1] Joan Gavaldà,[1] Mercè Gurgui,[2] Carmen Peña,[3] Arístides de Alarcón,[4] Josefa Ruiz,[5] Isidre Vilacosta,[6] Miguel Montejo,[7] Nuria Vallejo,[8] Francisco López-Medrano,[9] Antonio Plata,[10] Javier López,[11] Carmen Hidalgo-Tenorio,[12] Juan Gálvez,[13] Carmen Sáez,[14] José Manuel Lomas,[15] Marco Falcone,[18] Javier de la Torre,[16] Xavier Martínez-Lacasa,[17] and Albert Pahissa[1]

Table 3. Outcomes of 246 Episodes of *Enterococcus faecalis* Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin

Variable	Ampicillin + Ceftriaxone (n = 159)	Ampicillin + Gentamicin (n = 87)	*P* Value
Failures			
Death during treatment	35 (22%)	18 (21%)	0.81
Death during 3-mo follow-up	13 (8%)	6 (7%)	0.72
Adverse effects requiring treatment withdrawal	2 (1%)	22 (25%)	<0.001
Treatment failure requiring change of antimicrobials	2 (1%)	2 (2%)	0.54
Relapse	3/124 (3%)	3/69[a] (4%)	0.67

[a] These patients had received 28, 36, and 42 days of ampicillin plus gentamicin, respectively.

Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating *Enterococcus faecalis* Infective Endocarditis

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Table 2. Treatment and In-Hospital Mortality According to Antimicrobial Combination in 246 Episodes of *Enterococcus faecalis* Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin

Variable	Ampicillin + Ceftriaxone (n = 159)	Ampicillin + Gentamicin (n = 87)	*P* Value
Duration of antimicrobial treatment, d, median (IQR)			
Overall, in survivors	42 (39–46)	42 (35–44)	.122
Days until surgery	11 (6–22)	9 (3–22)	.34
Adverse events			
Overall	14 (9%)	38 (44%)	<.001
Overall obliging to withdraw treatment	2 (1%)	22 (25%)	<.001
Drug stopped due to rash/fever	1 (0.6%)	0	.46
Drug stopped due to leukopenia	1 (0.6%)	0	.46
Drug stopped due to new renal failure	0	20 (23%)	<.001
Drug stopped due to vestibular toxicity	0	2 (2%)	.055

Treatment choices for MDR Enterococci (Amp-R, HLGR, VRE)

Site of infection	First choice	Alternative
Bacteremia / Endocarditis	Daptomycin >10 mg/kg/day Linezolid, 600 mg bid	Daptomycin + Ampicillin Daptomycin + Ceftaroline Daptomycin + Linezolid
Urinary tract infections	Nitrofurantoin, 100 mg qid Fosfomycin, 3 g od, 2 doses	Ampicillin HD + Gentamycin
Intra-abdominal infections	Tygecycline, LD 100 mg > 50 mg bid	Teicoplanin, 12 mg/kg/day

Treatment of Vanco-R / Amp-R enterococcal IE (current guidelines)

Table 15. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Linezolid	600 mg IV or orally every 12 h	>6	*Class IIb; Level of Evidence C*	Linezolid use may be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions. Patients with IE caused by these strains should be treated by a care team including specialists in infectious diseases, cardiology, cardiac surgery, clinical pharmacy, and, in children, pediatrics. Cardiac valve replacement may be necessary for cure.
Or				
Daptomycin	10–12 mg/kg per dose	>6	*Class IIb; Level of Evidence C*	

IE indicates infective endocarditis, and IV, intravenous.
*Doses recommended are for patients with normal renal and hepatic function.

Baddour LM. *Circulation* 2015

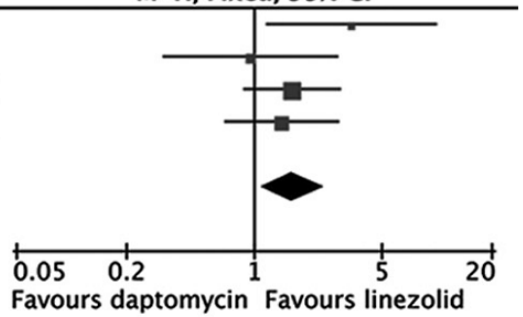
Systematic Review and Meta-Analysis of Linezolid versus Daptomycin for Treatment of Vancomycin-Resistant Enterococcal Bacteremia

Eleni P. Balli,[a] Chris A. Venetis,[b] Spiros Miyakis[a,c]

a)

Study or Subgroup	Daptomycin Events	Daptomycin Total	Linezolid Events	Linezolid Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Dubrovskaya et al., 2008	15	40	6	40	9.9%	3.40 [1.16, 10.00]
Kraft et al., 2011	10	43	7	29	16.9%	0.95 [0.32, 2.88]
McKinnell et al., 2011	32	86	28	104	41.9%	1.61 [0.87, 2.98]
Twilla et al., 2012	15	63	25	138	31.4%	1.41 [0.68, 2.91]
Total (95% CI)		**232**		**311**	**100.0%**	**1.61 [1.08, 2.40]**
Total events	72		66			

Heterogeneity: $Chi^2 = 2.84$, df = 3 (P = 0.42); $I^2 = 0\%$
Test for overall effect: Z = 2.36 (P = 0.02)



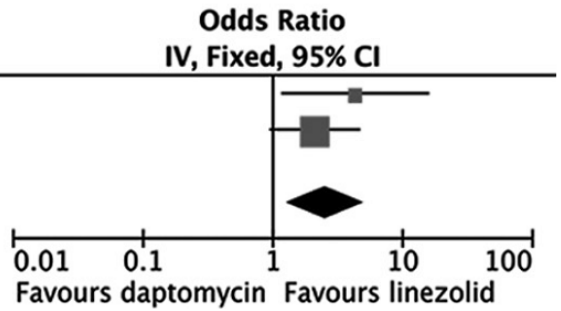
Unadjusted

30d mortality

b)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Dubrovskaya et al., 2008	1.458	0.668	27.5%	4.30 [1.16, 15.91]
McKinnell et al., 2011	0.74194	0.411	72.5%	2.10 [0.94, 4.70]
Total (95% CI)			**100.0%**	**2.56 [1.29, 5.08]**

Heterogeneity: $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0\%$
Test for overall effect: Z = 2.68 (P = 0.007)



Adjusted

Treatment of MDR Staph. aureus & Enterococci: SUMMARY

- A conservative, GL-based-approach relies rx on Vanco and Ampi
- There are still limited data supporting the superiority of alternative treatments / combinations
- The new options can be used though a cautious, patient-tailored approach, and can have some important advantages in terms of safety and easy of administration
- We do have rescue treatment options for ‘clinically’ recalcitrant infections
- We need more and more RCT on whose results base our daily practice