16:30 - 16:50 **La resistenza nei Gram-positivi** - *C. Tascini*

Prof Carlo Tascini

Direttore Clinica Malattie Infettive

ASUFC – Università di Udine

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Conflicts of interest:

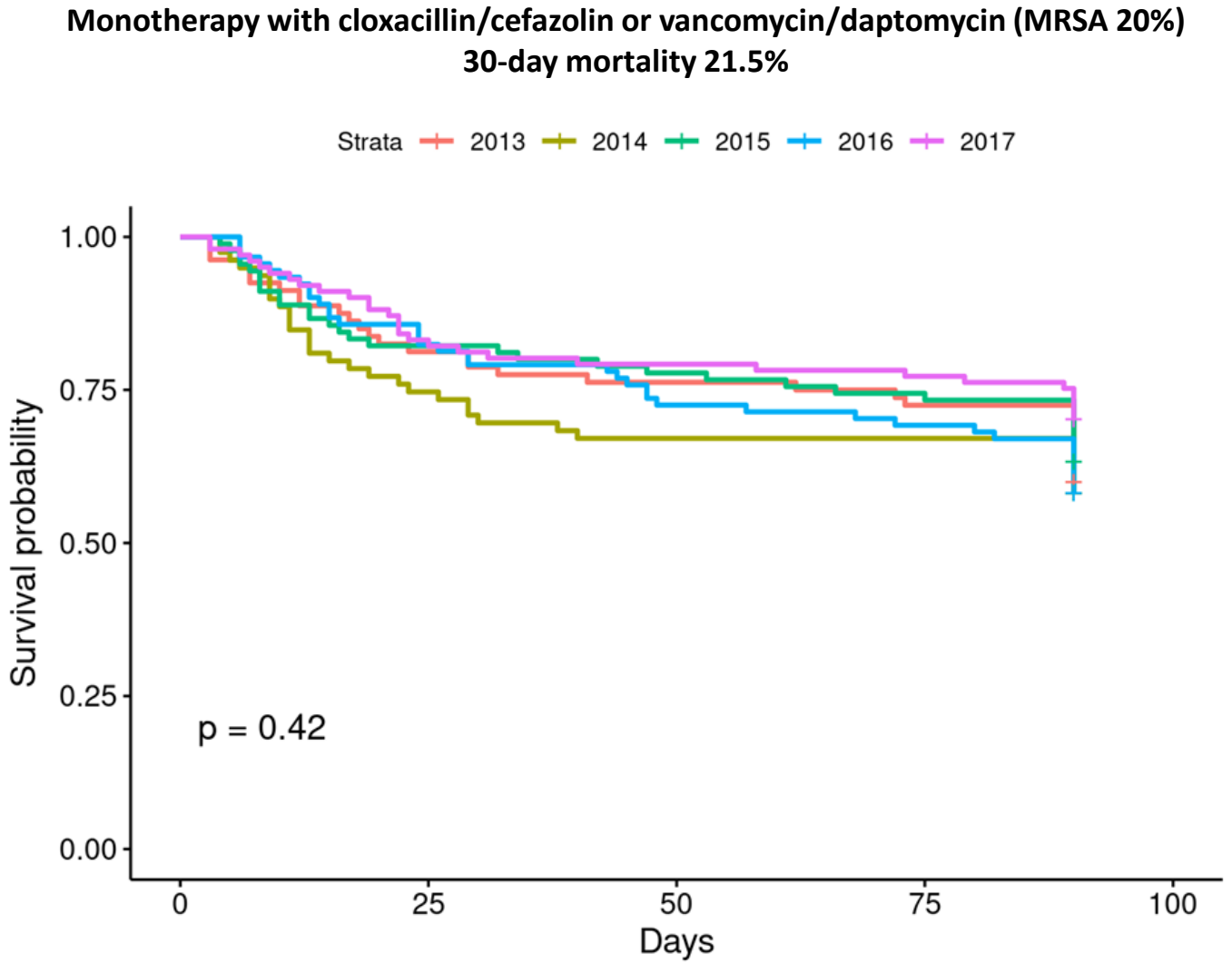
In the last two years I had direct financing relationships with the following subjects:

- *Menarini*
- *Merck*
- *Pfizer*
- *Advanz*
- *Angelini*
- *Gilead*
- *Novartis.*
- *Biomerieux*
- *Thermofisher*
- *Diasorin*
- *Zambon*
- *Hikma*
- *Avir Pharma*
- *Shionogi*
- *Biotest*

S. aureus

The introduction of penicillin into clinical practice in the late 1940s was followed by the emergence of penicillin-resistant *Staphylococcus aureus* strains harboring penicillinase encoded by plasmid-borne blaZ (29). Paralleling the arms race of the cold war of the second half of the 20th century, an antibiotic "arms race" between humans and *S. aureus* began, first with the development of semi-synthetic anti-staphylococcal penicillins, and, with the emergence of MRSA, the increased use of vancomycin (30).

Mortality in *Staphylococcus aureus* bacteraemia remains high despite adherence to quality indicators: secondary analysis of a prospective cohort study



Willekens R et al. J Infect. 2021 Dec;83(6):656-663

Clinical Infectious Diseases
MAJOR ARTICLE

Defining the Breakpoint Duration of *Staphylococcus aureus* Bacteremia Predictive of Poor Outcomes

Emi Minejima,[1,2] Nikki Mai,[1] Nancy Bui,[1] Melissa Mert,[3] Wendy J. Mack,[4] Rosemary C. She,[5] Paul Nieberg,[6] Brad Spellberg,[2,7] and Annie Wong-Beringer[1,8]

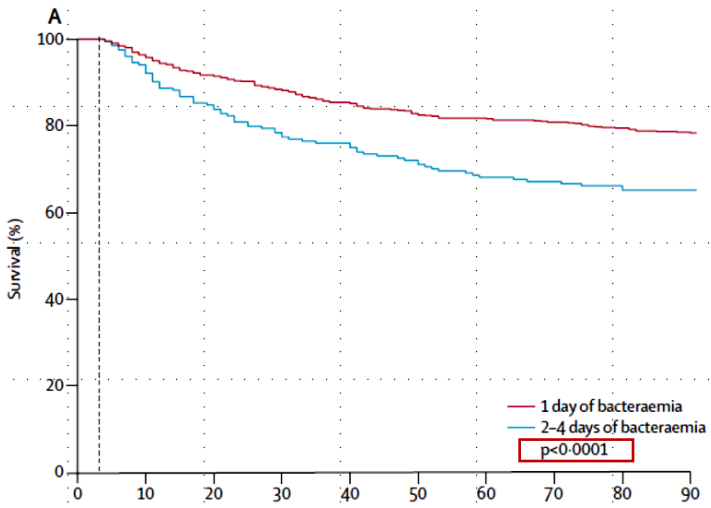
[1]Department of Clinical Pharmacy, University of Southern California (USC) School of Pharmacy, Los Angeles; [2]Los Angeles County and USC Medical Center; Departments of [3]Preventive Medicine and Clinical and Translational Science Institute, [4]Preventive Medicine of Keck School of Medicine and [5]Pathology, Keck School of Medicine at USC, Los Angeles; [6]Department of Medicine–Infectious Diseases, Huntington Hospital, Pasadena, California; [7]Department of Medicine, Keck School of Medicine at USC, Los Angeles; and [8]Department of Pharmacy, Huntington Hospital, Pasadena, California

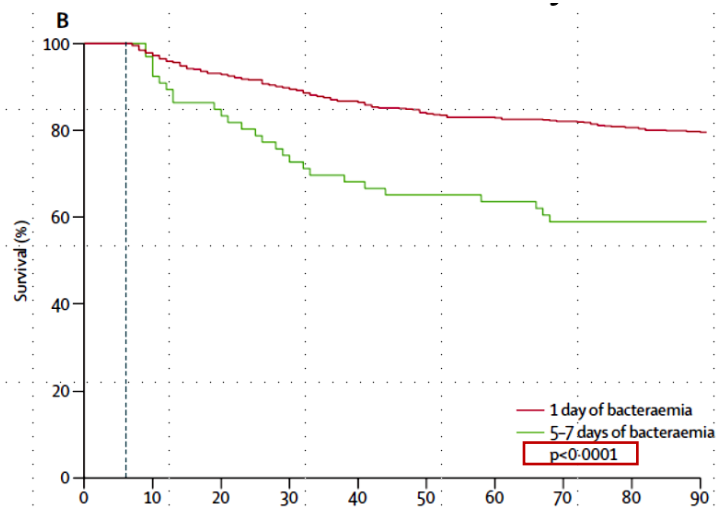
- 290 pts with MRSA bacteremia were on monotherapy.
- 124/290 pts (43%) > 2 days of bacteremia.

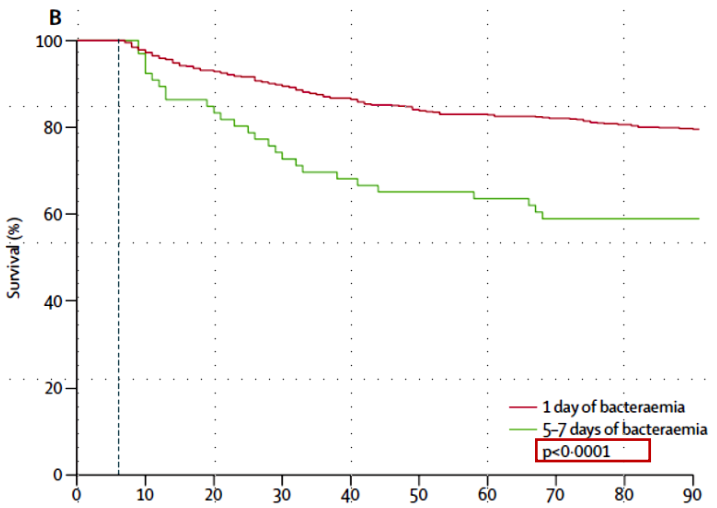
Defining persistent *Staphylococcus aureus* bacteraemia: secondary analysis of a prospective cohort study

*Richard Kuehl, Laura Morata, Christian Boeing, Isaac Subirana, Harald Seifert, Siegbert Rieg, Winfried V Kern, Hong Bin Kim, Eu Suk Kim, Chun-Hsing Liao, Robert Tilley, Luis Eduardo Lopez-Cortés, Martin J Llewelyn, Vance G Fowler, Guy Thwaites, José Miguel Cisneros, Matt Scarborough, Emmanuel Nsutebu, Mercedes Gurgui Ferrer, José L Pérez, Gavin Barlow, Susan Hopkins, Hugo Guillermo Ternavasio-de la Vega, M Estée Török, Peter Wilson, Achim J Kaasch, Alex Soriano, on behalf of the International Staphylococcus aureus collaboration study group and the ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis**

- 659/987 pts (67%) were on monotherapy.
- 192/315 pts (61%) with > 2 days of bacteremia were on monotherapy.

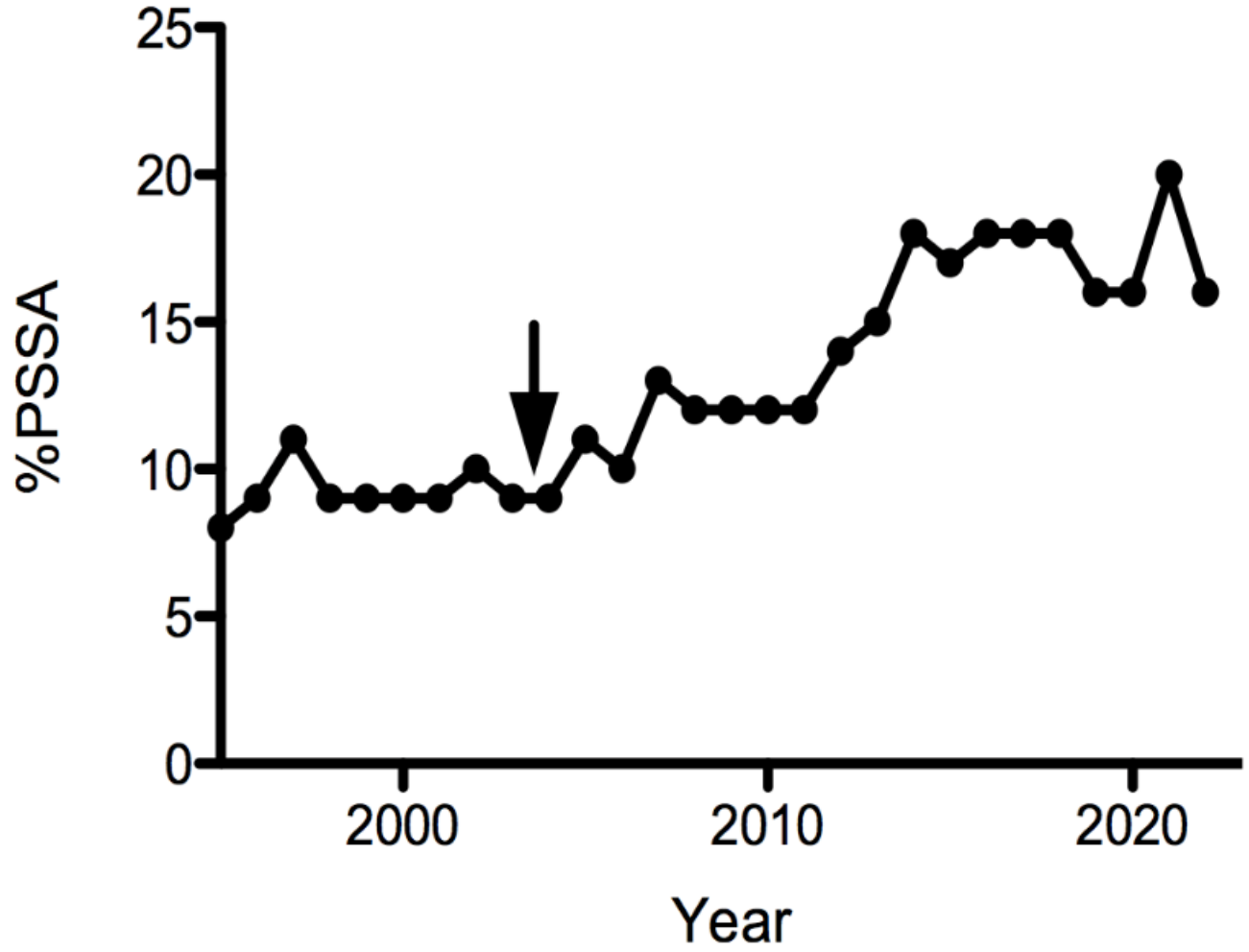






Minejima E et al Clin Infect Dis, 2019; Kuehl et al Lancet ID, 2020

S. aureus sensibile alla penicillina



AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Antimicrobial Chemotherapy | Minireview

Measuring beta-lactam minimum inhibitory concentrations in *Staphylococcus aureus* in the clinical microbiology laboratory: pinning the tail on the donkey

George Sakoulas,[1,2] Victor Nizet[2,3]

Daptomicina o peptidi naturali sono detergenti che fanno perdere la penicillinasi a *S. aureus*. Questi ceppi PSSA sono meno sensibili a peptidi naturali e daptomicina
Ed anche più virulenti

Given that penicillin-susceptibility may be a marker of virulence in endovascular *S. aureus* infections, we encourage labs to take the extra steps to quantify penicillin MIC in documented endovascular infections. Further investigation of these isolates is warranted. Clinician awareness of penicillin-susceptible *S. aureus* endocarditis would potentially offer potential therapeutic cues, including the avoidance of daptomycin monotherapy given that the pathway to daptomycin resistance may have already begun before daptomycin is even used. Such cases would potentially be treated with combination therapy. Given the shortcomings of disk testing, we recommend that labs serious about adopting penicillin therapy for PSSA use PCR for blaZ testing, although they are not commercially available.

Article

Emergence of methicillin resistance predates the clinical use of antibiotics

ence of other β-lactams was not investigated)[19]. This suggests that penicillin-producing *T. erinacei* isolates were circulating in European hedgehogs long before they were introduced into New Zealand in the late 1800s and that methicillin resistance first emerged in Europe as a co-evolutionary adaptation of *S. aureus* to colonization of hedgehogs.

hosts are highly localized. The finding that some human *mecC*-MRSA isolates probably originate from local hedgehog reservoirs indicates that *mecC*-MRSA has been a cause of sporadic infections in humans for the past 200 years, more than a century before MRSA was first identified in patients in 1960 (ref. [3]). The host interactions that lead to zoonotic

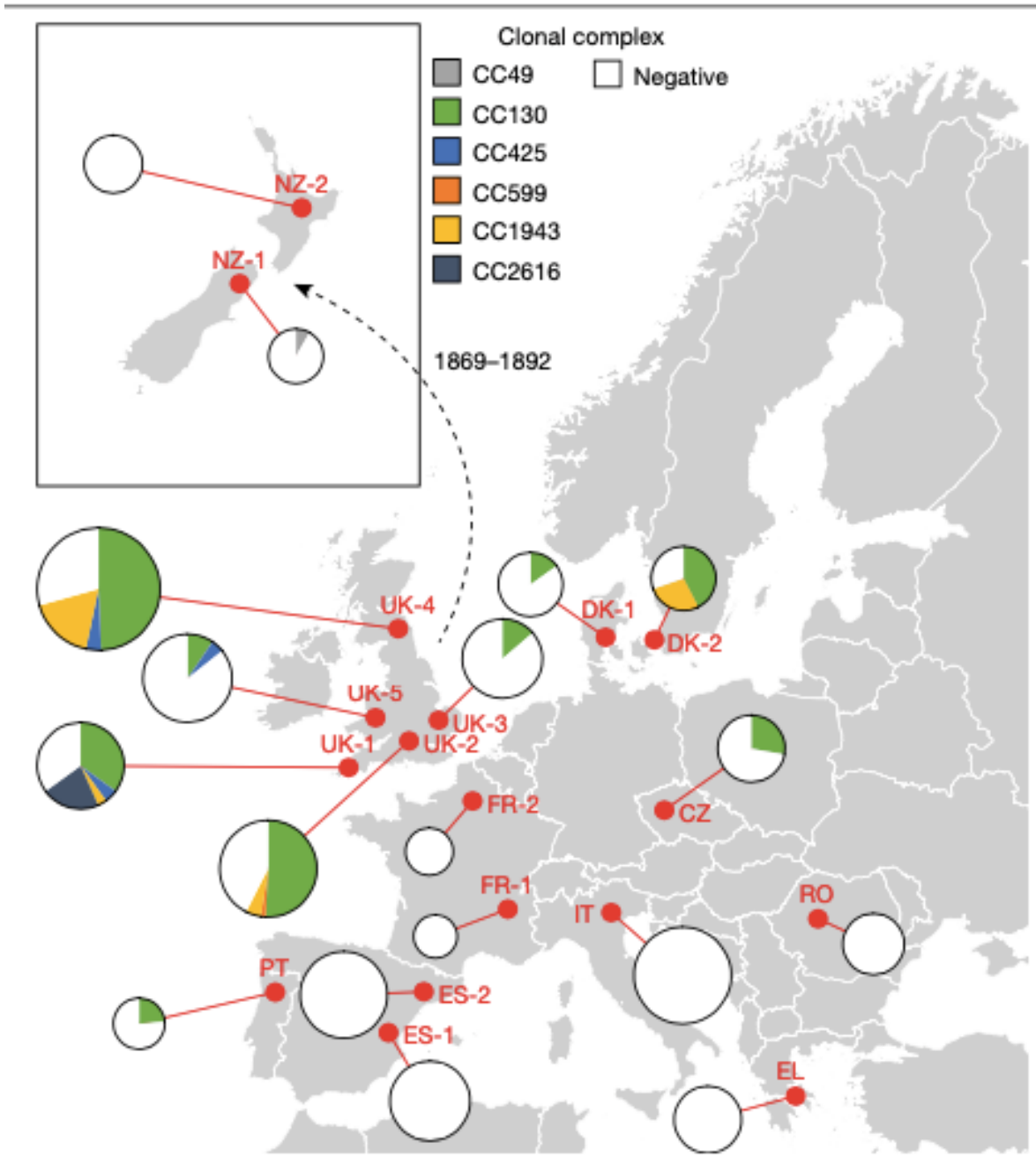
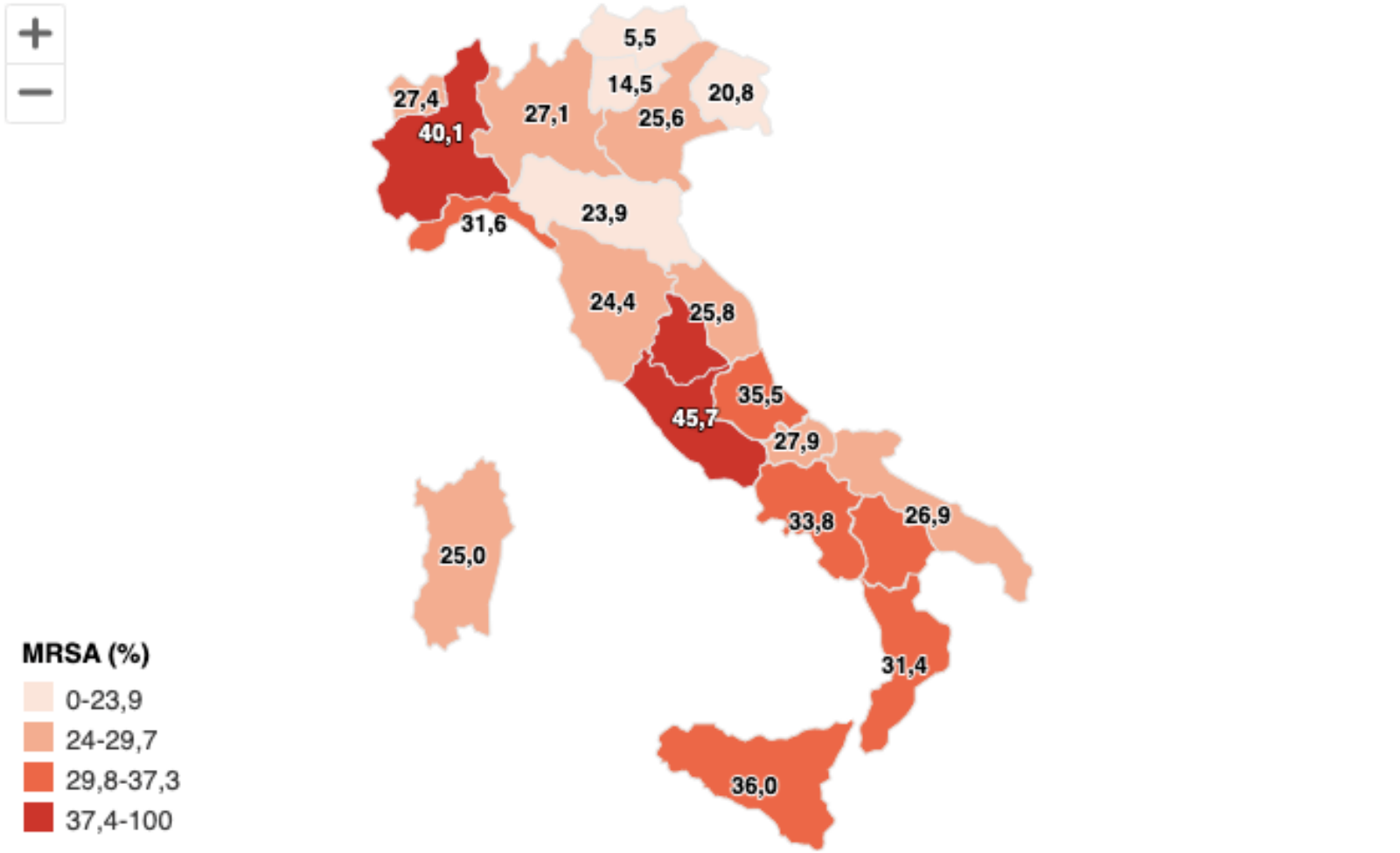


Fig. 1 | Distribution of *mecC*-MRSA clones in European and New Zealand hedgehog samples. The analysis included 828 samples from the nasal area,

Percentuali di resistenza delle principali combinazioni patogeno/antibiotico sotto sorveglianza per Regione, anno 2022*

MRSA (%)



AR-ISS

Le classi di intensità di resistenza sono identificate in base ai quartili della distribuzione nazionale

Recommended methods for detection of methicillin resistance in *S. aureus*

Staphylococcus aureus

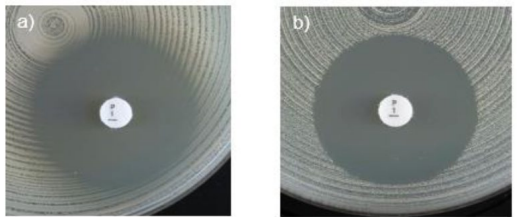
Cefoxitin screening

Assessment of antimicrobial susceptibility in physiologic media

BMD ≤ 4 mg/L
DD ≥ 22 mm

BMD > 4 mg/L
DD < 22 mm

PCR for *mecA/mecC*
latex agglutination for PBP2a protein



MSSA

MRSA

PSSA

BORSA
oxacillin MICs 1-8 mg/L

The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 14.0, 2024. http://www.eucast.org; The EUCAST guideline on detection of resistance mechanisms v 2.0 (2017-07-11) ; EUCAST Expert Rules v 3.2 February 2023

Borderline oxacillin-resistant *Staphylococcus aureus* (BORSA)

- Borderline strains that contain *mecA:*
  - extremely heterogeneous methicillin-resistant strains that produce PBP2a; the population contains a small fraction (10^{-6}) of highly resistant cells (MIC, >100 µg/ml)[1,2].
- Borderline resistance in *mecA*-negative strains (MRLMs):
  - modification of normal PBP genes with altered drug reactivities [1,2];
  - Hyperproduction of PBPs [1,3].
- Overproduction of beta-lactamase, which can by sheer high local amounts result in significant hydrolysis of beta-lactams (e.g., cefazolin) that are generally fairly resistant to hydrolysis (inoculum effect).

1 Chambers HF *Clin Microb Rev*, 1997; 2 Tomasz A et al. *AAC*, 1989; 3 Henze UU et al. *AAC*, 1995; Sakoulas G et al. J Clin Microbiol. 2024 Jan 17;62(1):e0036623; Lai L-Y et al. mBio. 2024 May 8;15(5):e0288923

BORSA with oxacillin MIC ≥ 4 mg/L: a therapeutic challenge

Mechanism of BORSA phenotype	Treatment
mecA gene	Treat as MRSA
Overproduction of beta-lactamases	Daptomycin, BPR, CPT, BL-BLIC (confirmed significant decrease in the MIC (≥ 2 doubling dilutions) or increase in disk diffusion zone size (≥ 5 mm) with the addition of a β-lactamase inhibitor; dalbavancin (if vanco S) and oritavancin
PBP mutations or overproduction	Vancomycin, daptomycin, daptomycin + beta-lactam combinations; dalbavancin (if vanco S) and oritavancin

Hryniewicz MM et al. J Med Microbiol. 2017 Oct;66(10):1367-1373; Skinner S et sl. J Clin Microbiol. 2009 Mar;47(3):859-61; Clinical and Laboratory Standards Institute. 2007. Performance standards for antimicrobial susceptibility testing; 17th informational supplement.M100-S17, vol. 27, no. 1. Clinical and Laboratory Standards Institute, Wayne, PA; Personal opinion

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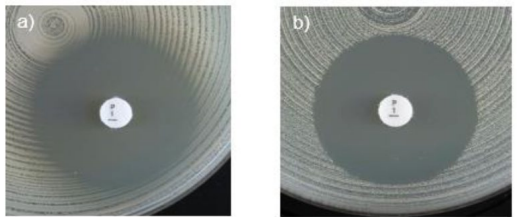

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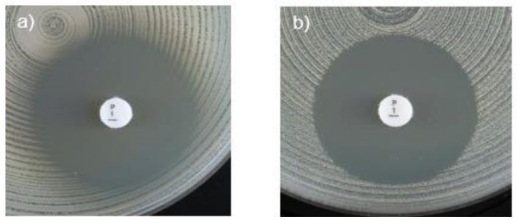

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Staphylococcus spp.

Expert Rules and Expected Phenotypes

For abbreviations and explanations of breakpoints, see the Notes sheet

MIC determination (broth microdilution according to ISO standard 20776-1 ~~except for fosfomycin where agar dilution is used~~)
Medium: Cation-adjusted Mueller-Hinton broth
Inoculum: 5x10^5 CFU/mL
Incubation: Sealed panels, air, 35±1ºC, 18±2h (for glycopeptides 24h)
Reading: Unless otherwise stated, read MICs at the lowest concentration of the agent that completely inhibits visible growth. See "EUCAST Reading Guide for broth microdilution" for further information.
Quality control: *Staphylococcus aureus* ATCC 29213. For agents not covered by this strain, see EUCAST QC Tables.

EBioMedicine 22 (2017) 26–27

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journal homepage: www.ebiomedicine.com

Commentary

The Accidental Orthodoxy of Drs. Mueller and Hinton

Victor Nizet [a,b,*]

[a] Division of Host Microbe Systems & Therapeutics, Department of Pediatrics, UC San Diego School of Medicine, La Jolla, CA, USA
[b] Skaggs School of Pharmacy & Pharmaceutical Sciences, UC San Diego, La Jolla, CA, USA

In the current issue of *EBioMedicine*, Ersoy et al. (2017) probe a simple but profound question. What if antibiotic testing were performed not in a classical enriched bacteriologic media such as MHB, but in a testing media designed to better resemble the chemical constitution of normal human body fluids? For example, a common medium used for

FORMULA DI HENDERSON - KASSIRER - BLEICH

$$[H^+] = K \frac{pCO_2}{[HCO_3^-]}$$

IN TERMINI NUMERICI

$$[H^+] = 24 \cdot \frac{40}{24} = 40$$

Fig. 1

EUCAST Clinical Breakpoint Tables v. 14.0, valid from 2024-01-01; Nizet V.. EBioMedicine. 2017 Aug;22:26-27

Antibiotic susceptibility performed in physiologic media better predicts activity *in vivo* compared to susceptibility testing performed in bacteriological media

Ersoy SC et al. EBioMedicine. 2017 Jun;20:173-181

"Susceptible" MIC
"Intermediate" MIC
"Resistant" MIC

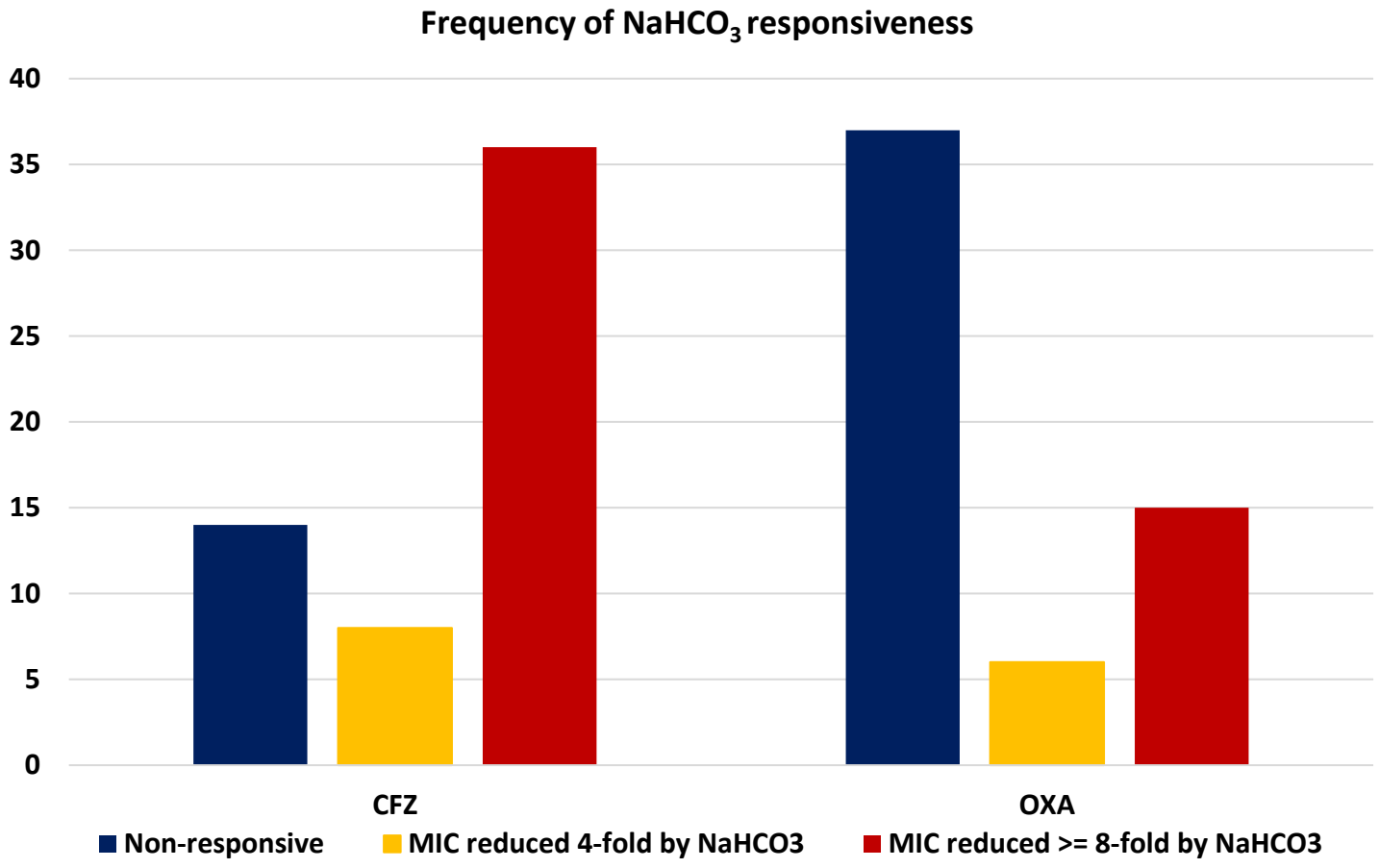
Supplementary Table 2A. Antimicrobial susceptibility test in media w/ and w/o $NaHCO_3$ (*Staphylococcus*)

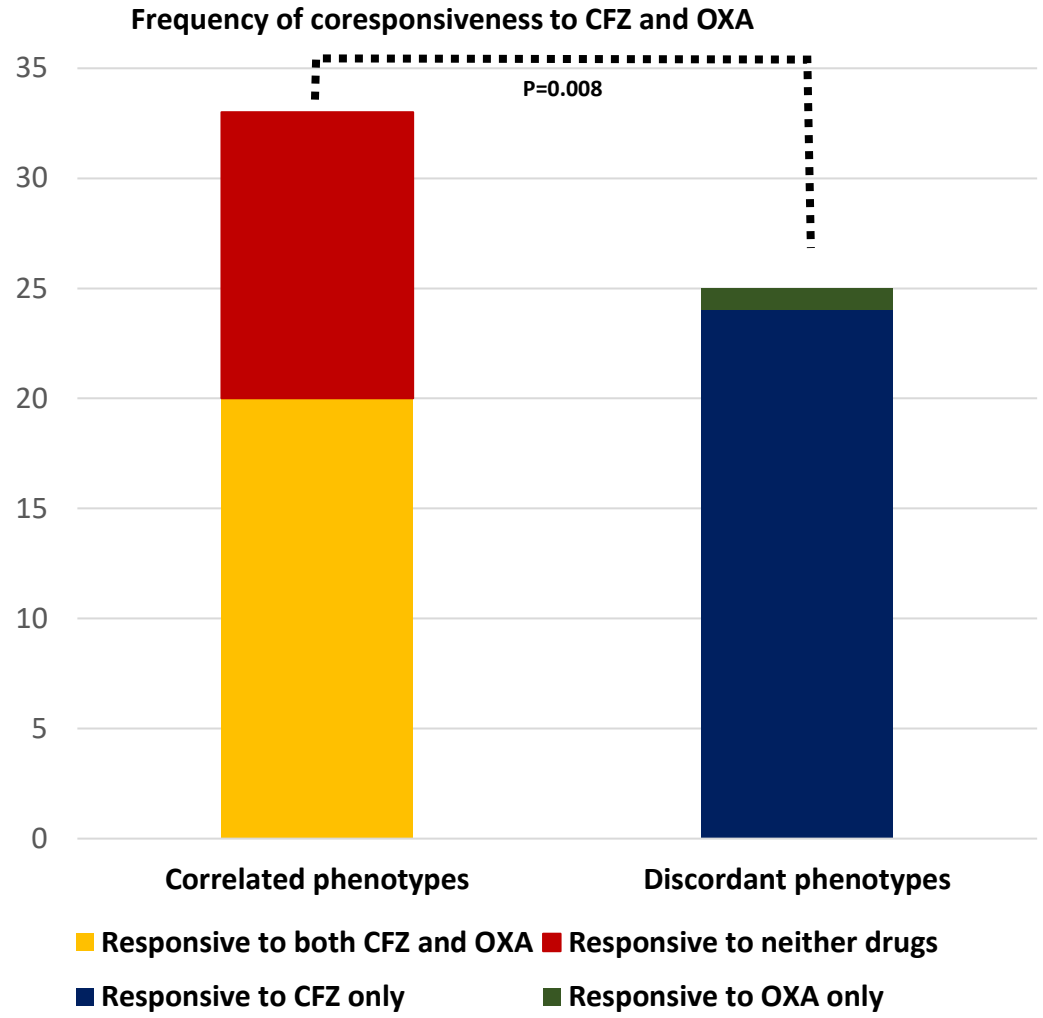
				Cephalothin MIC (µg/mL)
Clinical Breakpoints[a]:				S ≤ 8; I = 16; R ≥ 32[2]
Strain #	Strain Name	Ca-MHB pH 7.2	Ca-MHB 100 mM Tris pH 7.2	Ca-MHB 100 mM Tris 44 mM $NaHCO_3$ pH 7.4
MT3322	MRSA USA300	32	32	8
MT3315	MRSA Wound	8	4	1

				Ceftriaxone MIC (µg/mL)
Clinical Breakpoints:				S ≤ 8; I =16-32; R ≥ 64[2]
Strain #	Strain Name	Ca-MHB pH 7.2	Ca-MHB 100 mM Tris pH 7.2	Ca-MHB 100 mM Tris 44 mM $NaHCO_3$ pH 7.4
MT3322	MRSA USA300	512	256	16
MT3302	MRSA Blood	128	64	32
MT3315	MRSA Wound	64	64	32

				Oxacillin MIC (µg/mL)
Clinical Breakpoints:				S ≤ 2; R ≥ 4
Strain #	Strain Name	Ca-MHB pH 7.2	Ca-MHB 100 mM Tris pH 7.2	Ca-MHB 100 mM Tris 44 mM $NaHCO_3$ pH 7.4
MT3302	MRSA Blood	64	64	16
MT3315	MRSA Wound	32	64	32

Are MRSA really MRSA?: the curious case of “bicarbonate responder” MRSA



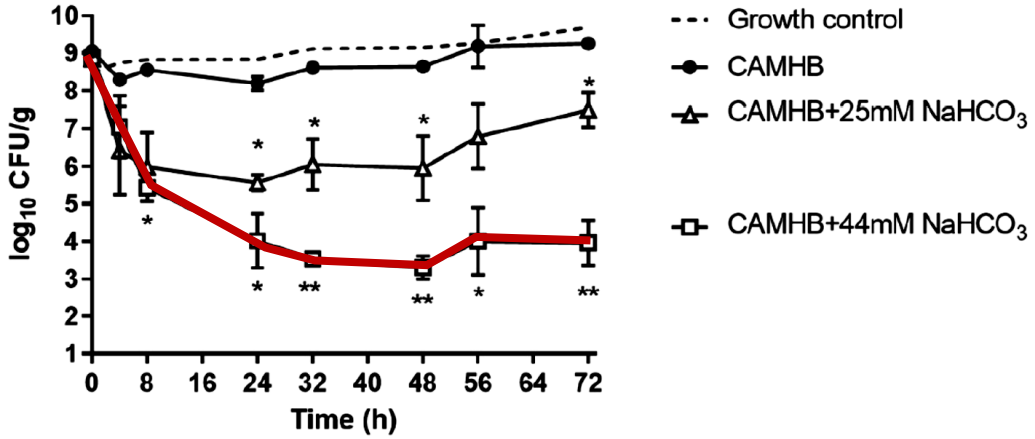


Ersoy SC et al. Antimicrob Agents Chemother. 2020 Apr 21;64(5):e02445-19.

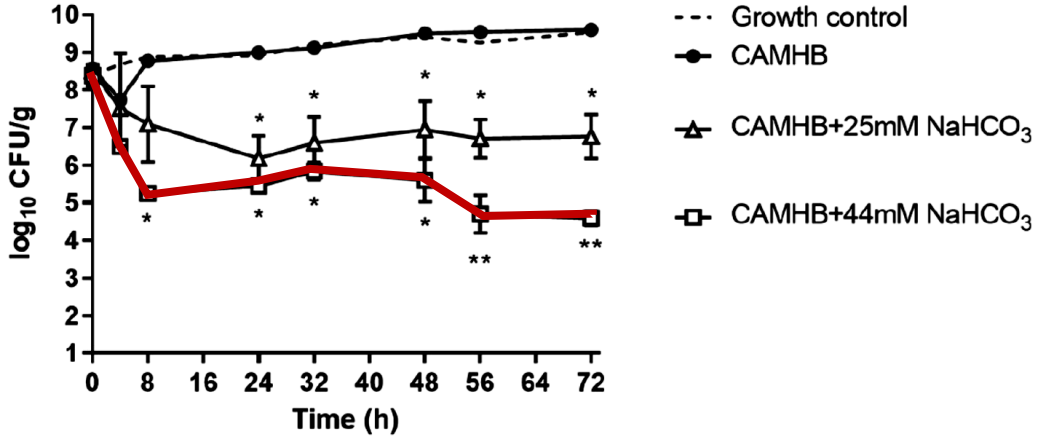
In an *ex-vivo* model of endocarditis bicarbonate-responsive MRSA can be effectively treated as MSSA with beta-lactams

Rose WE et al. Antimicrob Agents Chemother. 2020 Feb 21;64(3):e02072-19

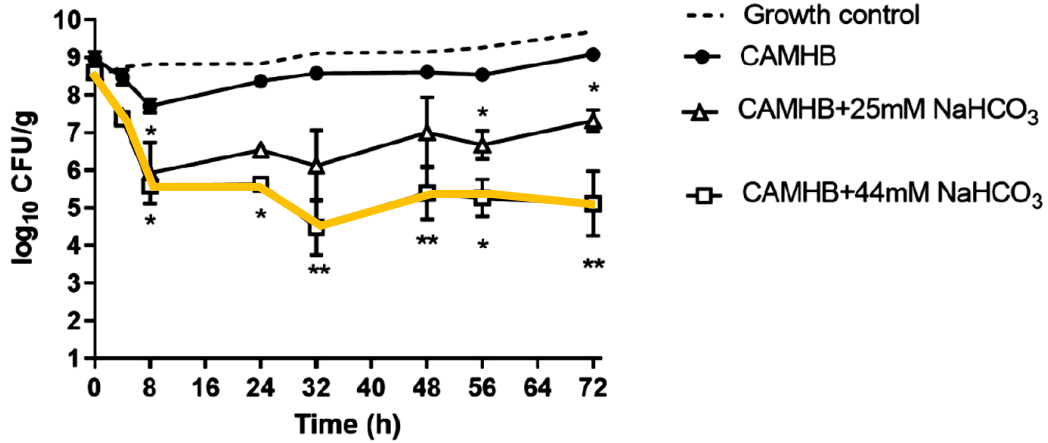
A. MRSA 11-11



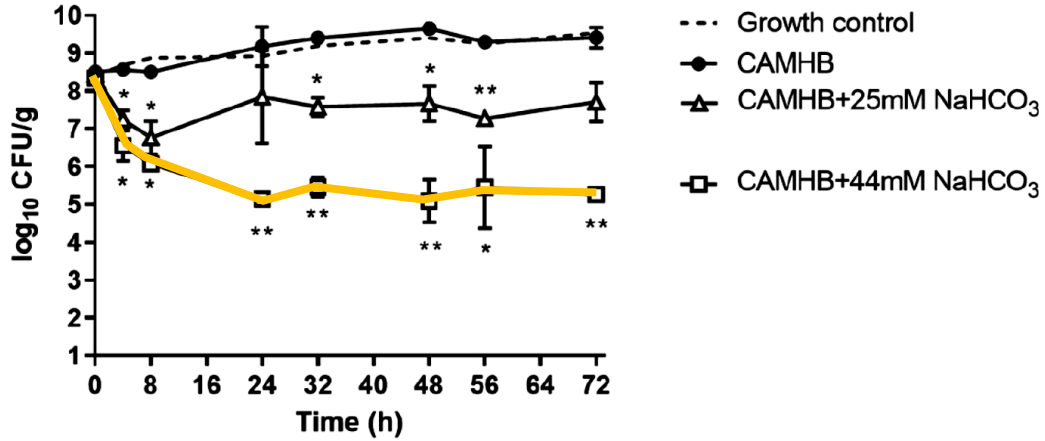
B. MRSA MW2



A. MRSA 11-11



B. MRSA MW2



CFZ 2 g q8h

OXA 2 g q6h

$NaHCO_3$ causes repression of PrsA, a cell membrane protein that is required for PBP2a full post-translational maturation and expression

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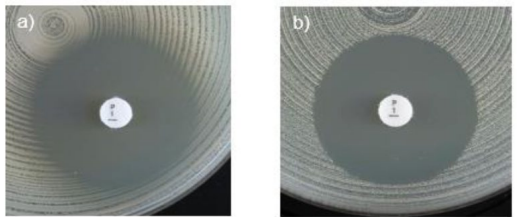


MSSA

MRSA

PSSA

VAN MIC > 2 mg/L

BORSA
oxacillin MICs 1-8 mg/L

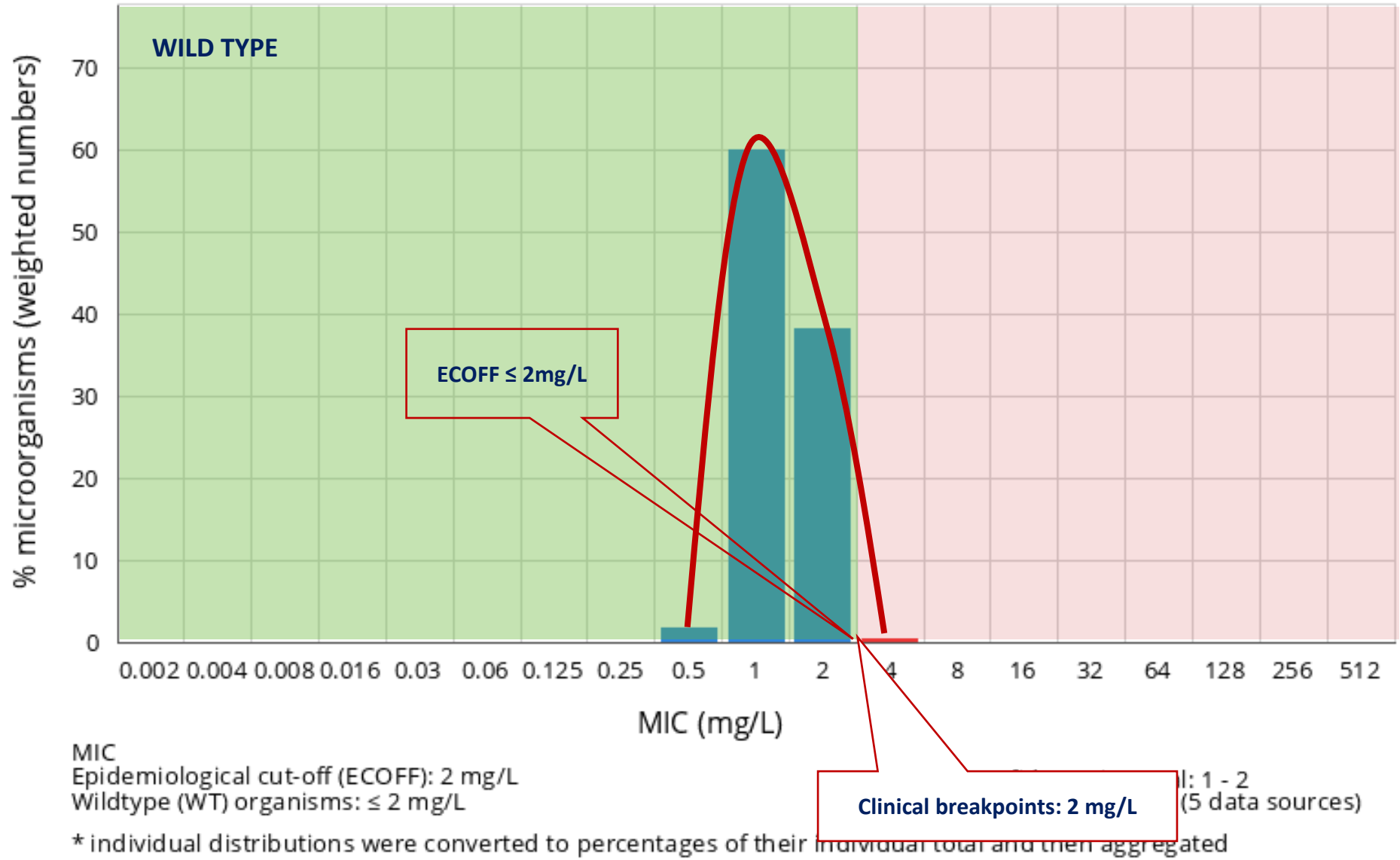
hVISA

VISA

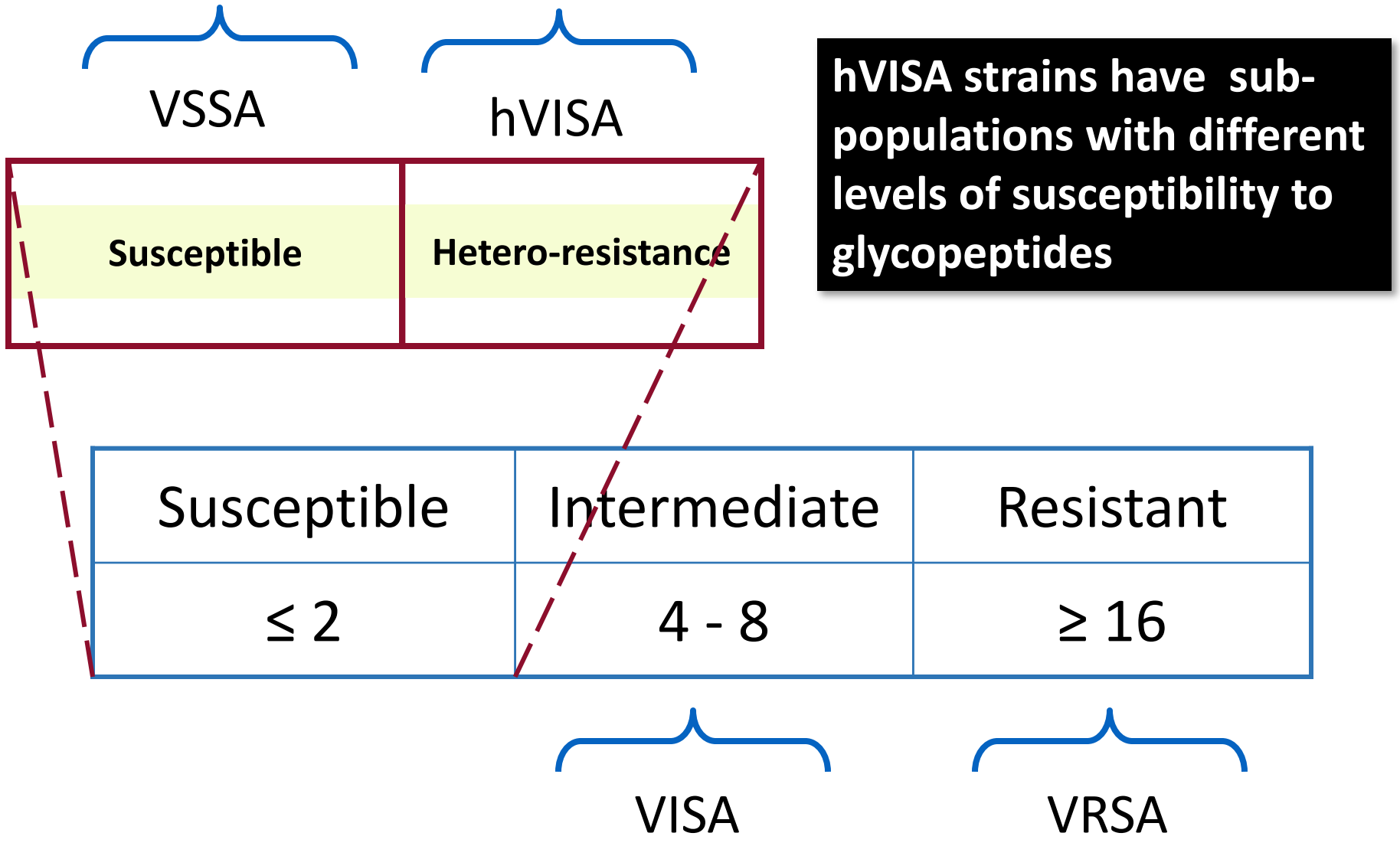
VRSA

The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 14.0, 2024. http://www.eucast.org; The EUCAST guideline on detection of resistance mechanisms v 2.0 (2017-07-11) ; EUCAST Expert Rules v 3.2 February 2023

Vancomycin MIC in MRSA

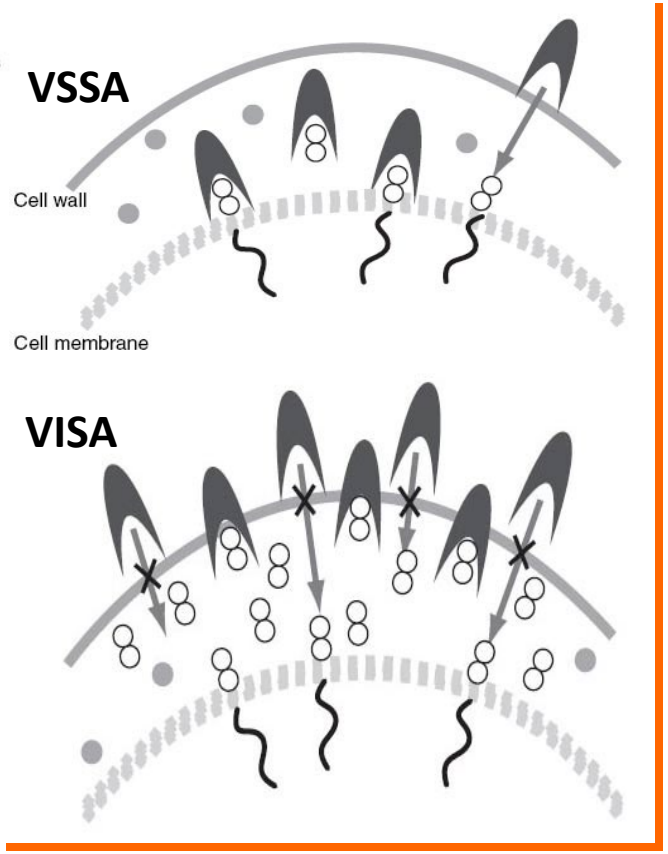


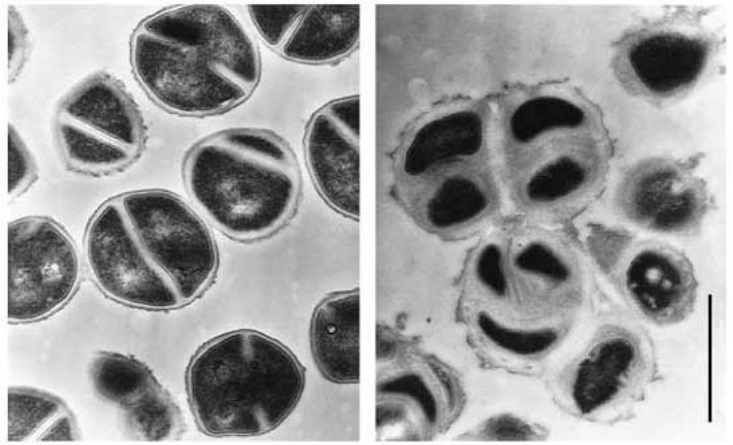
European Committee on Antimicrobial Susceptibility Testing. Data from the EUCAST MIC distribution website, last accessed 22 May 2024". http://www.eucast.org



VISA=Vancomycin-intermediate S. aureus
hVISA= heterogenous VISA

VISA: resistance mechanism





Glycopeptide Trapping at cell wall

Vanco MIC: >2 – <16 mg/L
Teico MIC: >8 – <32 mg/L

CLSI 2008; FDA 2008

Hetero-VISA

- *S. aureus* with MIC in the range of susceptibility (1-2 mg/L)
- Sub-populations with MIC of 4-8 mg/L, frequency 1 every 10^6-10^7 bacteria
- Routine tests performed with 10^4-10^5 bacteria: difficult to find

TOLLERANZA ALLA Vanco

Vancomycin tolerance is a state in which the bacteria are "stunned" or kept in check but not killed by vancomycin. That is manifested in the laboratory by a ratio of minimum bactericidal concentration to MIC greater than 32.

Microbiological Features of Vancomycin in t
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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.

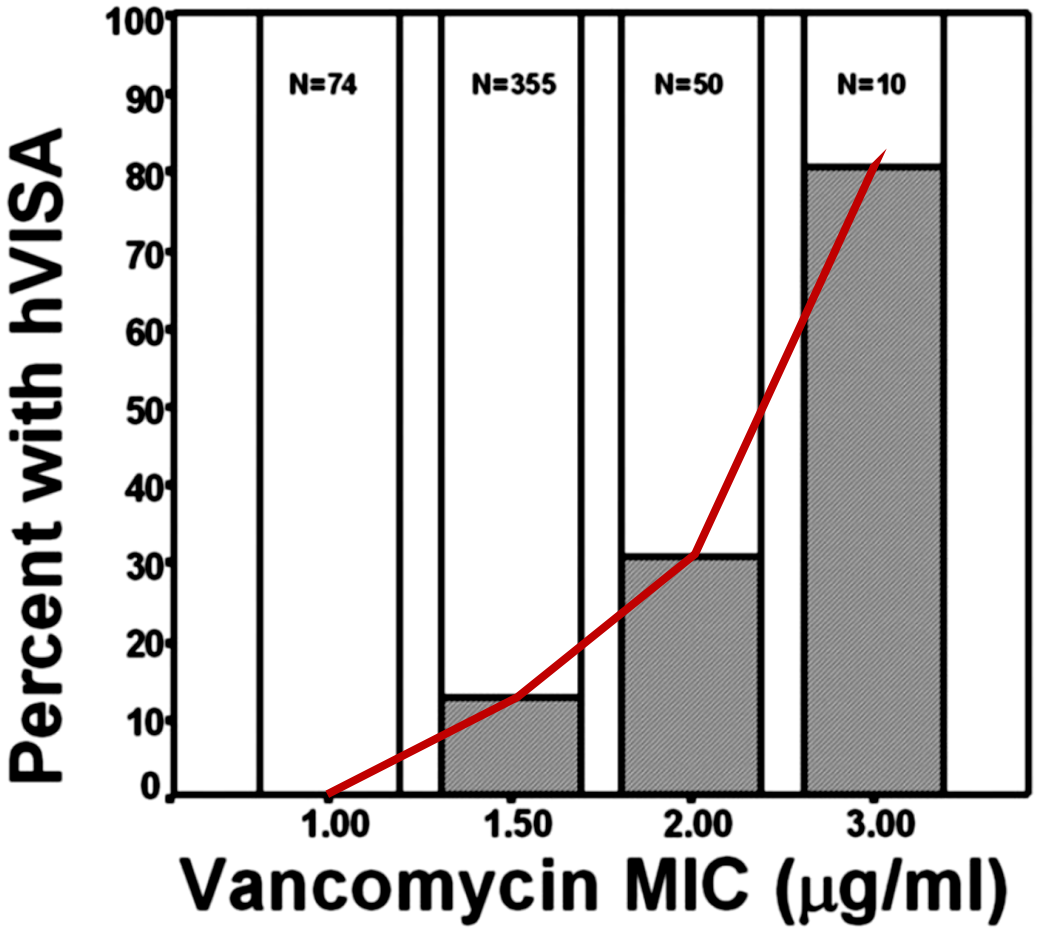
Strain	No. of isolates tested	No. of isolates, according to vancomycin MBC:MIC ratio					
		1	2	4	8	⩾16 + R[a]	⩾32
wt MRSA	105	42	21	11	15	7[b]	9[b]
hVISA	88	8	5	6	4	64[c]	1[c]
VISA	17	…	…	…	…	17[d]	…
VRSA	3	…	…	…	…	3[e]	…

[a] Denotes a ratio of ⩾16 with an associated resistant (R) MBC value of ⩾32 μg/mL.
[b] Strains conforming to a consensus definition of tolerance (15.2%) [77, 88].
[c] Tolerant strains (73.9%).
[d] Tolerant strains (100.0%).
[e] MBC results were >32 μg/mL; ratio was not determined.

The res ctivity against a
wide va enterococci, the
persiste cent discoveries
of vanc e use of vanco-
mycin. entration creep"
among quired resistance
to vanc recognize van-
comyci omycin-resistant
S. aure nitoring for ap-
propria comycin appear
to best aboratories. Im-
provem ycin bactericidal
assays to detect "tolerant" strains will be required to increase the value of vancomycin treatment or to refocus therapy toward the use of newer, alternative agents.

Clin Infect Disease. 2006 Jan 1;42 Suppl 1:S13-24

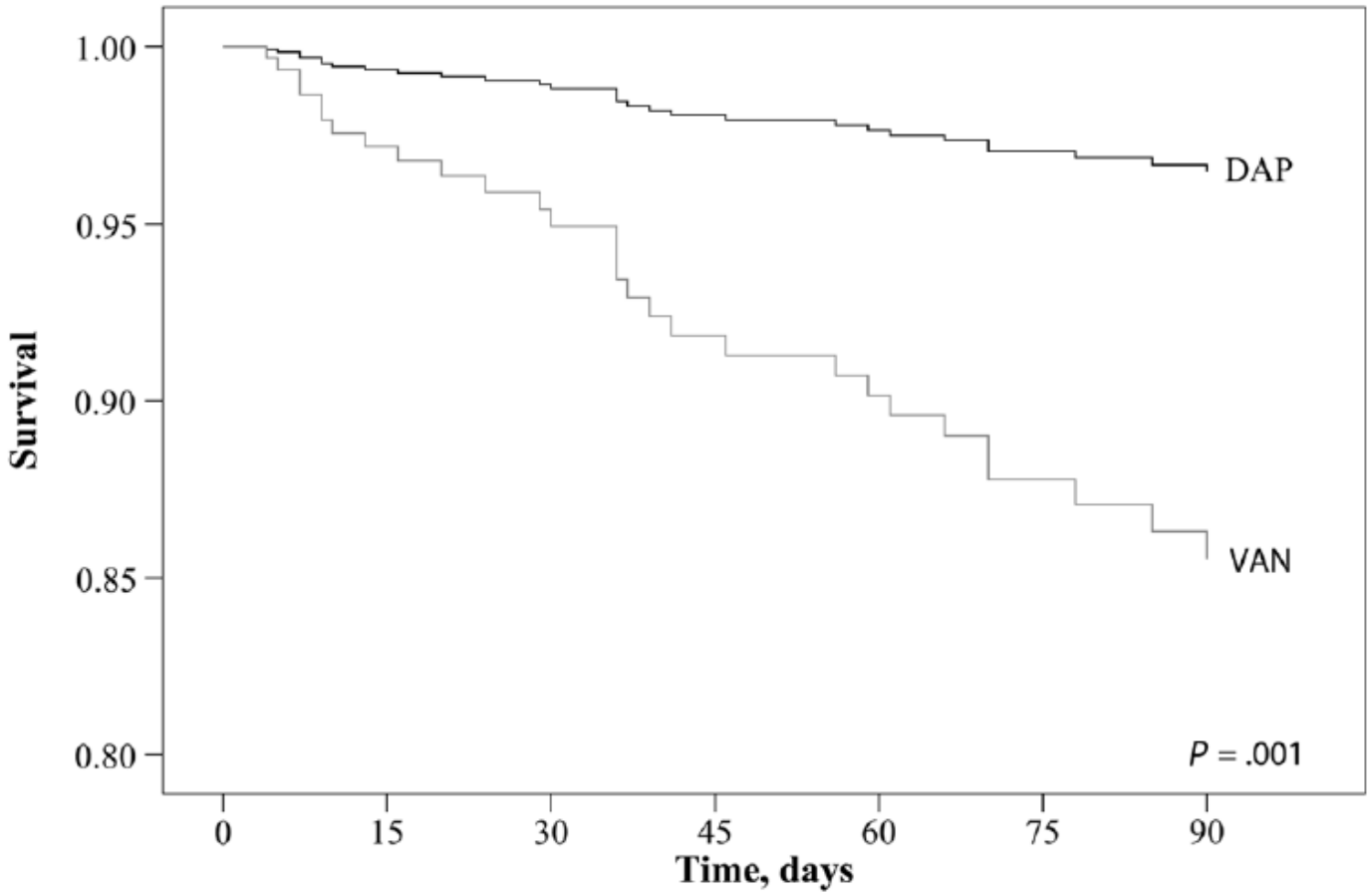
Frequency of hVISA among MRSA blood isolates saved intermittently between 1996 and 2006, stratified according to the vancomycin MIC.



Musta AC et al. J Clin Microbiol. 2009 Jun;47(6):1640-4

Early Use of Daptomycin Versus Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia With Vancomycin Minimum Inhibitory Concentration >1 mg/L: A Matched Cohort Study

Kyle P. Murray,[1] Jing J. Zhao,[1] Susan L. Davis,[3] Ravina Kullar,[3] Keith S. Kaye,[2] Paul Lephart,[4] and Michael J. Rybak[1,2,3]

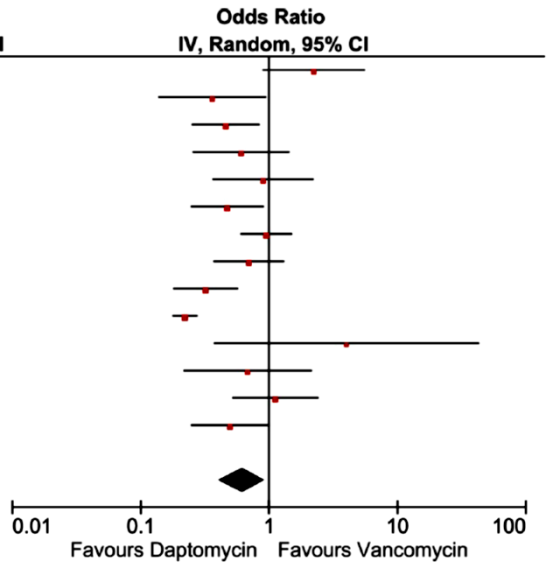


Prevention of clinical failure and persistent bacteremia

Clinical failure

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Arshad 2017	0.8	0.47	6.6%	2.23 [0.89, 5.59]
Cheng 2012	-1.022	0.495	6.4%	0.36 [0.14, 0.95]
Claeys 2016	-0.781	0.311	8.1%	0.46 [0.25, 0.84]
Fowler 2006	-0.505	0.443	6.9%	0.60 [0.25, 1.44]
Fox 2018	-0.107	0.462	6.7%	0.90 [0.36, 2.22]
Kullar 2013	-0.752	0.335	7.9%	0.47 [0.24, 0.91]
Lopez 2012	-0.051	0.234	8.8%	0.95 [0.60, 1.50]
Moise 2016	-0.365	0.324	8.0%	0.69 [0.37, 1.31]
Moore 2012	-1.139	0.297	8.2%	0.32 [0.18, 0.57]
Murray 2013	-1.514	0.115	9.5%	0.22 [0.18, 0.28]
Nichols 2021	1.386	1.216	2.3%	4.00 [0.37, 43.35]
Ruiz 2018	-0.386	0.587	5.6%	0.68 [0.22, 2.15]
Usery 2015	0.109	0.395	7.3%	1.12 [0.51, 2.42]
Weston 2014	-0.703	0.359	7.7%	0.50 [0.24, 1.00]
Total (95% CI)			**100.0%**	**0.62 [0.41, 0.94]**

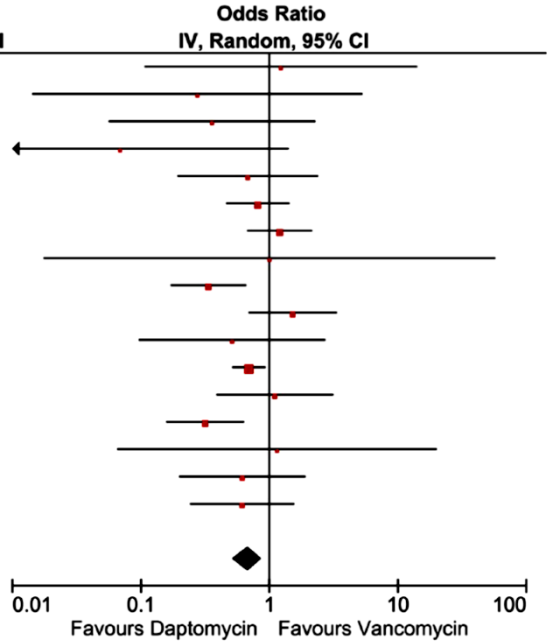
Heterogeneity: Tau² = 0.46; Chi² = 73.37, df = 13 (P < 0.00001); I² = 82%
Test for overall effect: Z = 2.28 (P = 0.02)



Persistent bacteremia

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Arshad 2017	0.201	1.248	1.1%	1.22 [0.11, 14.11]
Barlow 2021	-1.292	1.509	0.8%	0.27 [0.01, 5.29]
Carroll 2022	-1.03	0.944	1.9%	0.36 [0.06, 2.27]
Carugati 2013	-2.676	1.542	0.7%	0.07 [0.00, 1.41]
Cheng 2012	-0.389	0.641	3.8%	0.68 [0.19, 2.38]
Claeys 2016	-0.209	0.29	12.2%	0.81 [0.46, 1.43]
Fowler 2006	0.181	0.298	11.8%	1.20 [0.67, 2.15]
Kalimuddin 2018	0.0001	2.066	0.4%	1.00 [0.02, 57.36]
Kullar 2013	-1.095	0.344	9.9%	0.33 [0.17, 0.66]
Lopez 2012	0.416	0.404	7.9%	1.52 [0.69, 3.35]
Maeda 2016	-0.67	0.852	2.3%	0.51 [0.10, 2.72]
Moise 2016	-0.371	0.152	21.0%	0.69 [0.51, 0.93]
Moore 2012	0.096	0.535	5.1%	1.10 [0.39, 3.14]
Murray 2013	-1.153	0.354	9.5%	0.32 [0.16, 0.63]
Nichols 2021	0.134	1.461	0.8%	1.14 [0.07, 20.04]
Usery 2015	-0.488	0.578	4.5%	0.61 [0.20, 1.91]
Weston 2014	-0.49	0.476	6.2%	0.61 [0.24, 1.56]
Total (95% CI)			**100.0%**	**0.68 [0.52, 0.88]**

Heterogeneity: Tau² = 0.06; Chi² = 21.29, df = 16 (P = 0.17); I² = 25%
Test for overall effect: Z = 2.92 (P = 0.004)



Adamu Y et al. PLoS One. 2024 Feb 21;19(2):e0293423

Drug Resistance Updates 16 (2013) 73–79

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Reduced glycopeptide and lipopeptide susceptibility in *Staphylococcus aureus* and the "seesaw effect": Taking advantage of the back door left open?

Jessica K. Ortwine[a,**], Brian J. Werth[b,1], George Sakoulas[d,e], Michael J. Rybak[b,c,*]

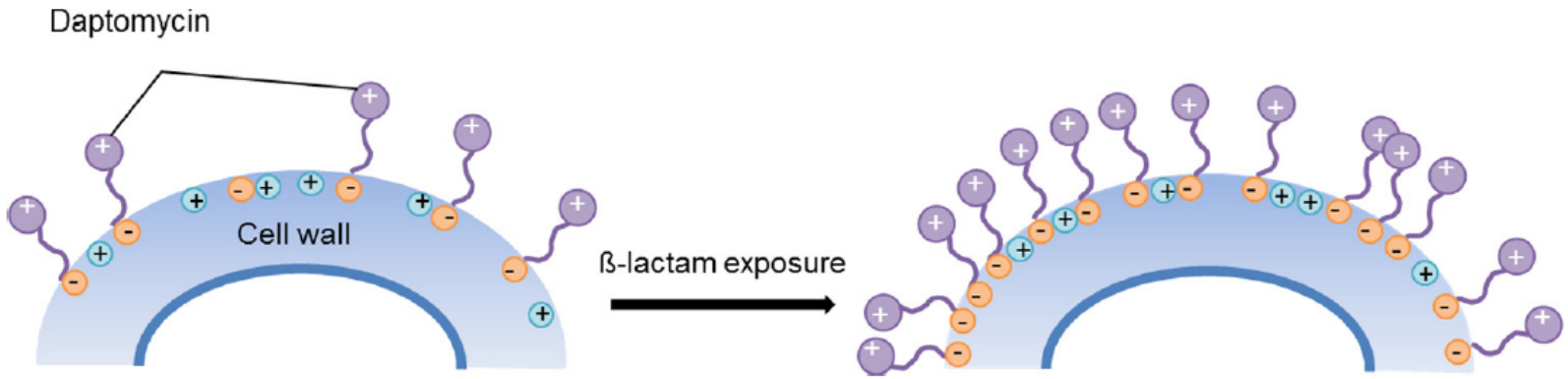


Figure 2. Proposed mechanisms for daptomycin and beta-lactam synergy. Daptomycin acts like a cationic peptide antibiotic and is attracted to the negative charge of the bacterial cell membrane. Once in contact with the cytoplasmic membrane (CM) daptomycin disrupts the CM causing a rapid release of electrolytes from the cytoplasm leading to depolarization and death of the cell. Exposure to beta-lactams increases the negative charge of the cell surface leading to an increase in daptomycin binding and improved bactericidal activity.


DAP
BPR


DAP
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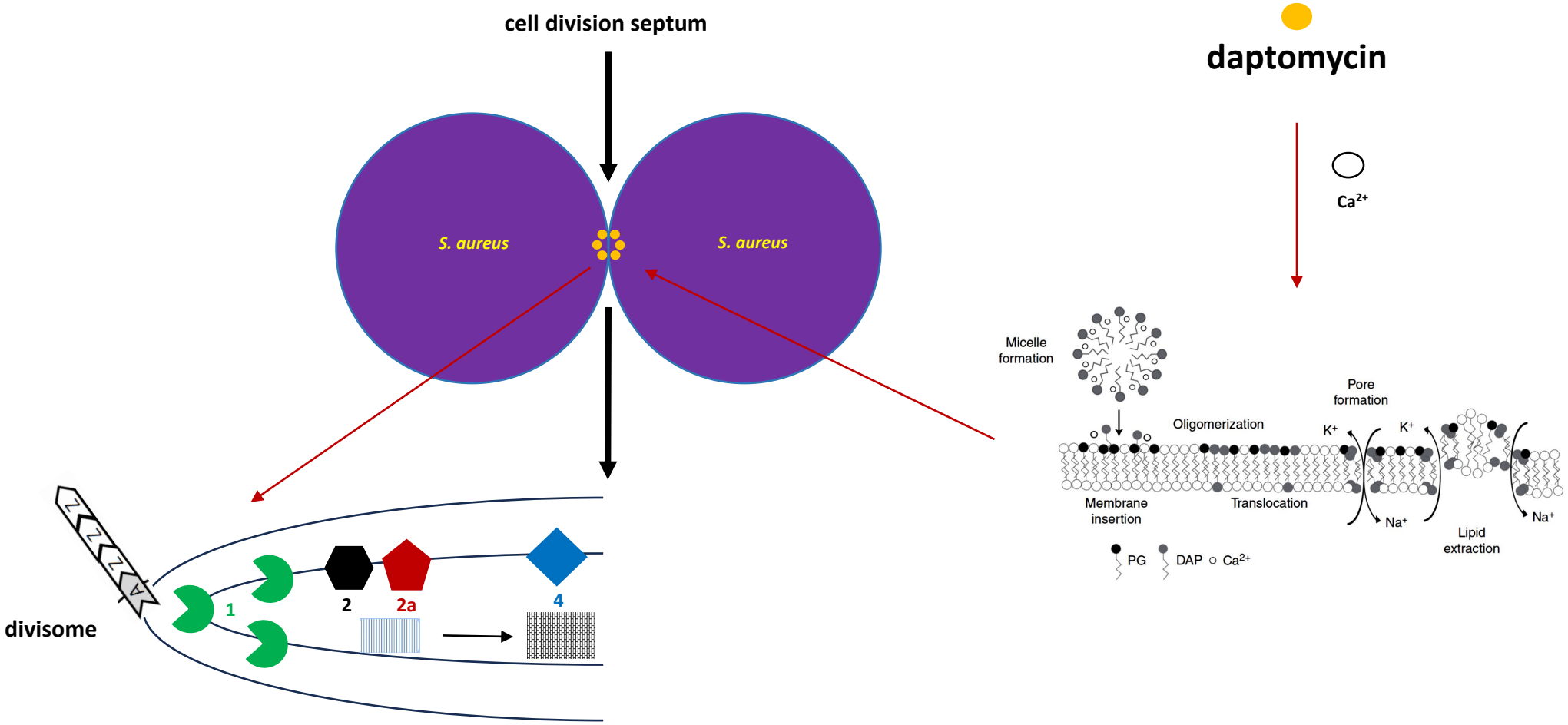

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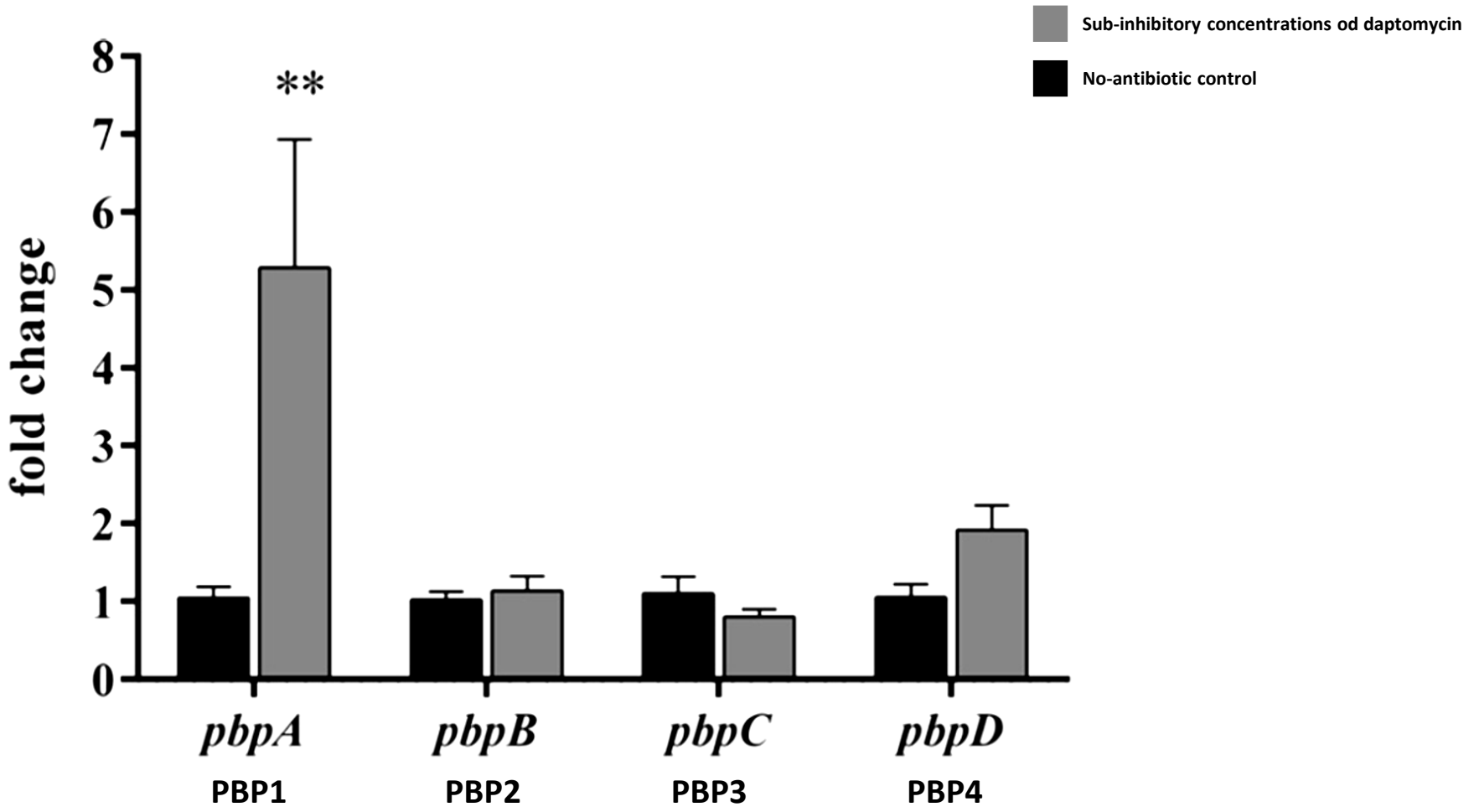
PBP1 is important in the compensatory response of *Staphylococcus aureus* to daptomycin-induced membrane damage



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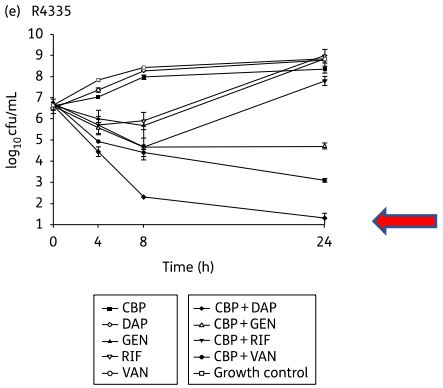
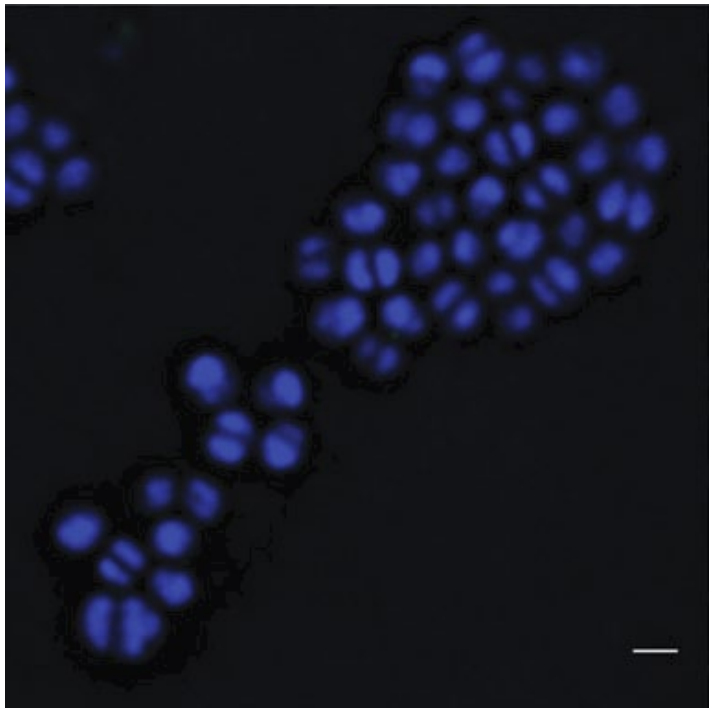
J Antimicrob Chemother 2014; **69**: 3006–3010
doi:10.1093/jac/dku236 Advance Access publication 1 July 2014

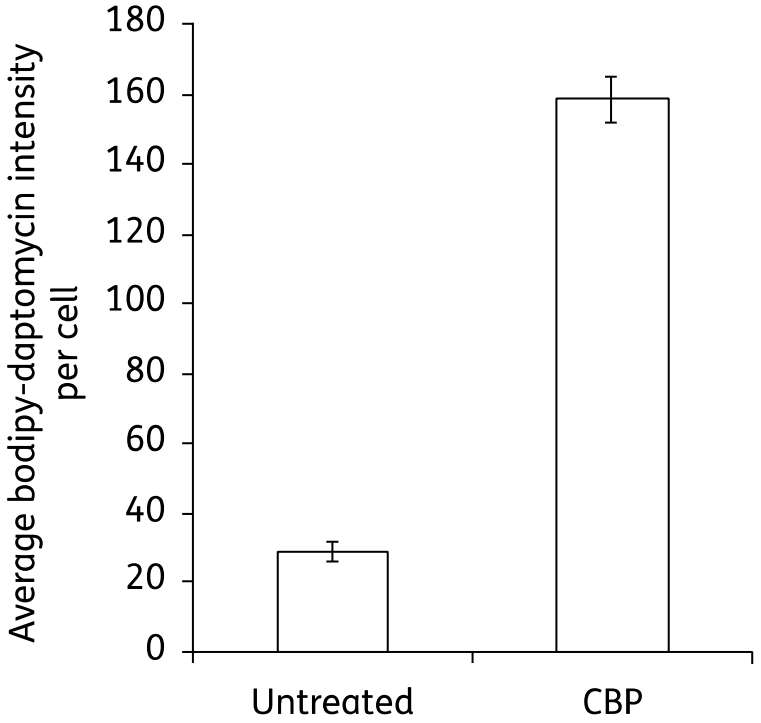
Potent synergy of ceftobiprole plus daptomycin against multiple strains of *Staphylococcus aureus* with various resistance phenotypes

Katie E. Barber[1], Brian J. Werth[1], Cortney E. Ireland[1], Nicole E. Stone[1], Poochit Nonejuie[2], George Sakoulas[3], Joseph Pogliano[2] and Michael J. Rybak[1,4]*

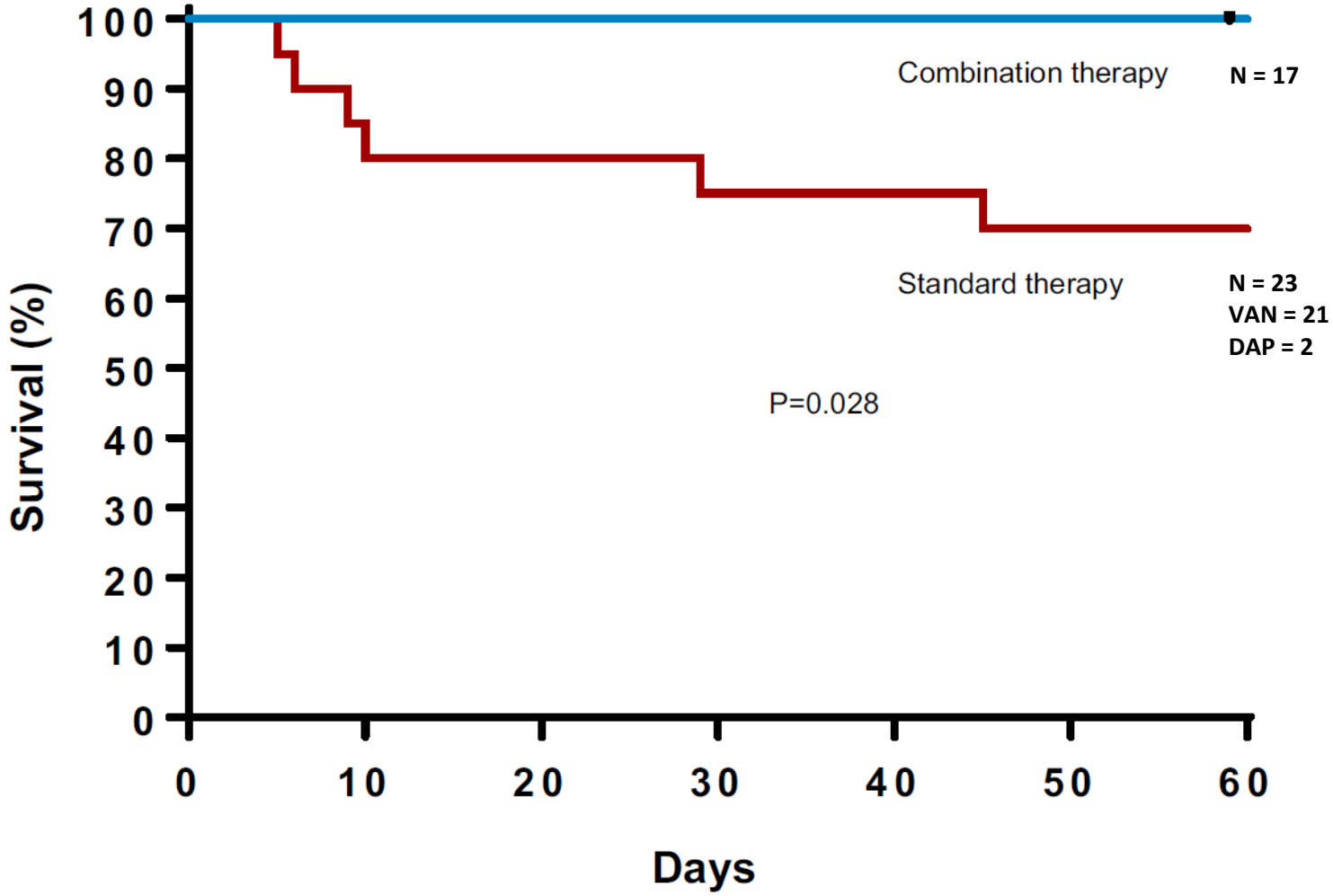




H-VISA



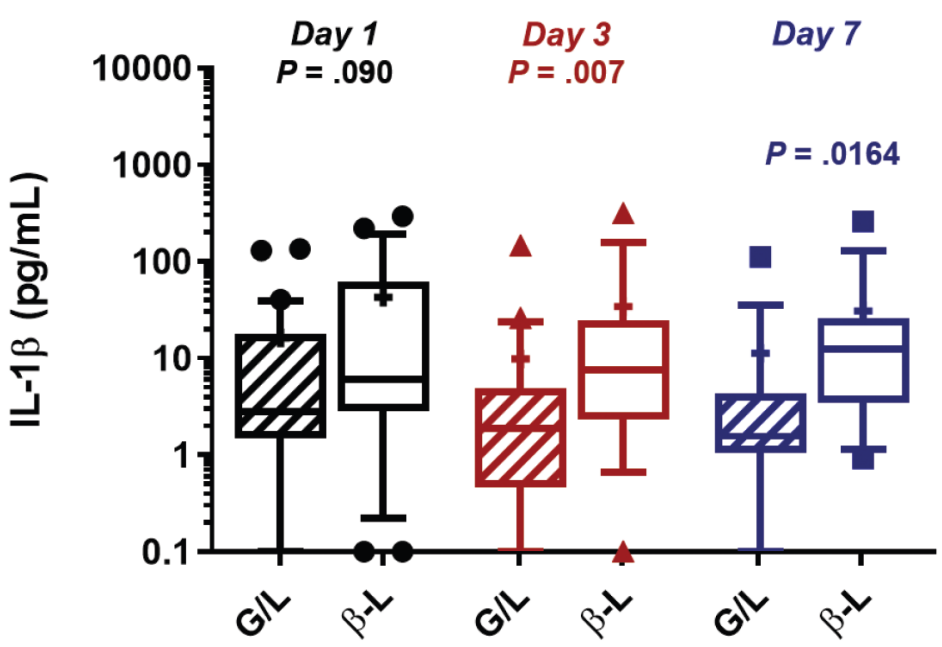
Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment MRSA bacteremia



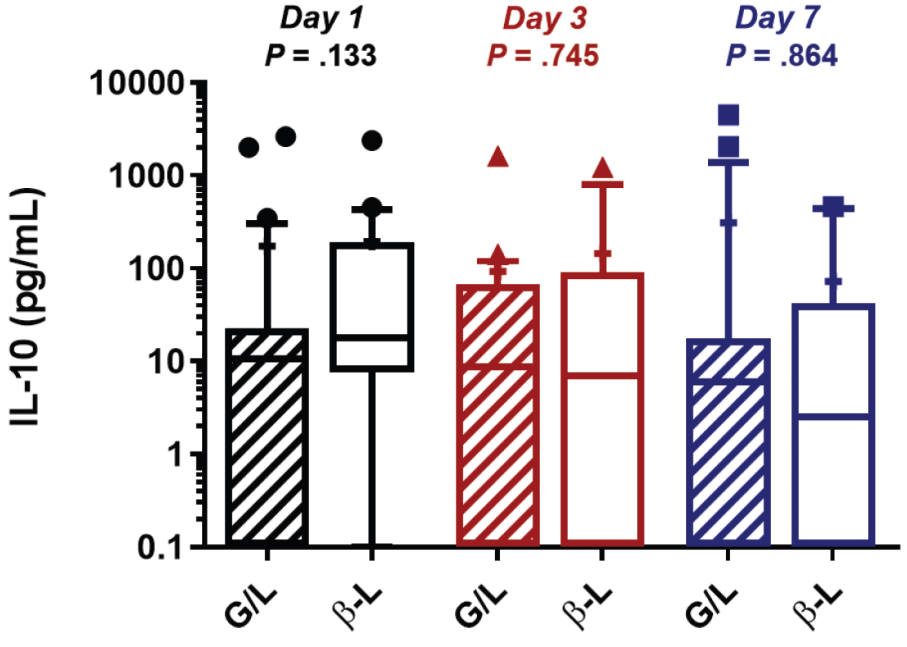
Geriak M et al. Antimicrob Agents Chemother. 2019 Apr 25;63(5):e02483-18

Interleukin (IL)-1β and IL-10 host responses in patients with SAB determined by antimicrobial therapy

IL-1β concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy.



IL-10 concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy.



Clinical Infectious Diseases 2020;70(12):2634–40

Synergistic enhancement of in vitro antimicrobial activity of imipenem and cefazolin, cephalothin, cefotiam, cefamandole or cefoperazone in combination against methicillin-sensitive and -resistant Staphylococcus aureus

T Uete [1], K Matsuo

Affiliations + expand

PMID: 7752453

Uete T, Matsuo K. Synergistic enhancement of in vitro antimicrobial activity of imipenem and cefazolin, cephalothin, cefotiam, cefamandole or cefoperazone in combination against methicillin-sensitive and -resistant Staphylococcus aureus. Jpn J Antibiot. 1995 Mar;48(3):402-8. PMID: 7752453.

Abstract

Synergistic enhancement of the in vitro antimicrobial activity of imipenem combined with cephalosporins against methicillin-resistant Staphylococcus aureus (MRSA) has been reported. In order to investigate which cephalosporin is more effective in enhancing the activity of imipenem against MRSA, the in vitro antimicrobial activities of imipenem, cefazolin, cephalothin, cefotiam, cefamandole and cefoperazone, alone and in combination, against methicillin-sensitive Staphylococcus aureus (MSSA) and MRSA were assessed. Using the checkerboard Mueller-Hinton agar dilution method, strong synergy was found in 97% to 100% of MRSA strains for imipenem and all tested cephalosporins except cefoperazone; fractional inhibitory concentration (FIC) indices were < or = 0.5. Among the cephalosporins studied, cefamandole most markedly increased the activity of imipenem against MRSA, followed, in order of decreasing effect, by cefotiam, cephalothin, cefazolin, and cefoperazone. The synergistic effect of imipenem combined with cefamandole or cefotiam was confirmed using the broth dilution method with 2% of NaCl.

Imipenem e molte cefalosporine
sono sinergiche contro MRSA
miglior combinazione con cefamandolo

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Cefazolin and Ertapenem, a Synergistic Combination Used To Clear Persistent *Staphylococcus aureus* Bacteremia

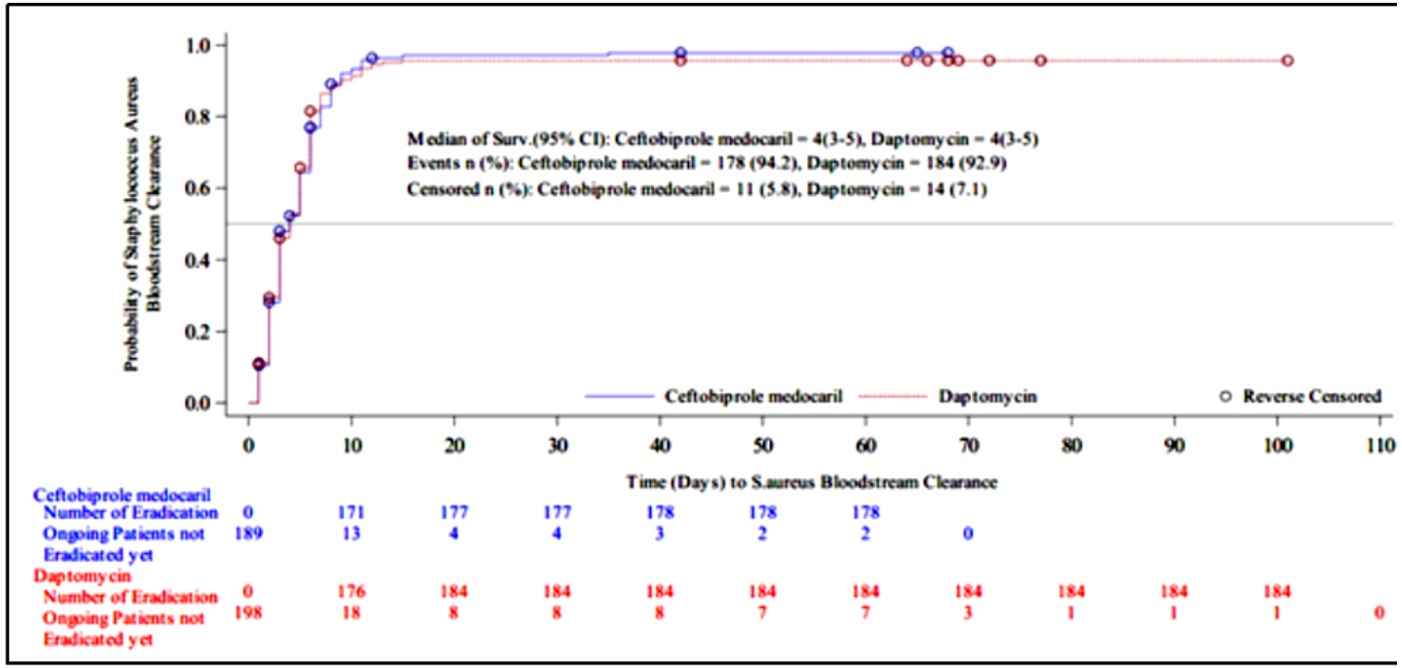
George Sakoulas,[a,b] Joshua Olson,[a] Juwon Yim,[c] Niedita B. Singh,[c] Monika Kumaraswamy,[a] Diana T. Quach,[d] Michael J. Rybak,[c] Joseph Pogliano,[d] Victor Nizet[a,e]

University of California San Diego School of Medicine, La Jolla, California, USA[a]; Sharp Healthcare System, San Diego, California, USA[b]; Eugene Appelbaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA[c]; Department of Biological Sciences, University of California San Diego, La Jolla, California, USA[d]; Skaggs School of Pharmacy, University of California San Diego, La Jolla, California, USA[e]

Ertapenem and cefazolin were used in combination to successfully clear refractory methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. In addition, recent work has demonstrated activity of combination therapy with beta-lactams from different classes against methicillin-resistant *S. aureus* (MRSA). The ertapenem-plus-cefazolin combination was evaluated for synergy *in vitro* and *in vivo* in a murine skin infection model using an index MSSA bloodstream isolate from a patient in whom persistent bacteremia was cleared with this combination and against a cadre of well-described research strains and clinical strains of MSSA and MRSA. Against the index MSSA bloodstream isolate, ertapenem and cefazolin showed synergy using both checkerboard (fractional inhibitory concentration [FIC] index = 0.375) and time-kill assays. Using a disk diffusion ertapenem potentiation assay, the MSSA isolate showed a cefazolin disk zone increased from 34 to 40 mm. *In vitro* pharmacokinetic/pharmacodynamic modeling at clinically relevant drug concentrations demonstrated bactericidal activity (>3 $\log_{10}$-CFU/ml reduction) of the combination but bacteriostatic activity of ether drug alone at 48 h. A disk diffusion potentiation assay showed that ertapenem increased the cefazolin zone of inhibition by >3 mm for 34/35 (97%) MSSA and 10/15 (67%) MRSA strains. A murine skin infection model of MSSA showed enhanced activity of cefazolin plus ertapenem compared to monotherapy with these agents. After successful use in clearance of MSSA bacteremia, the combination of ertapenem and cefazolin showed synergy against MSSA *in vitro* and *in vivo*. This combination may warrant consideration for future clinical study in MSSA bacteremia.

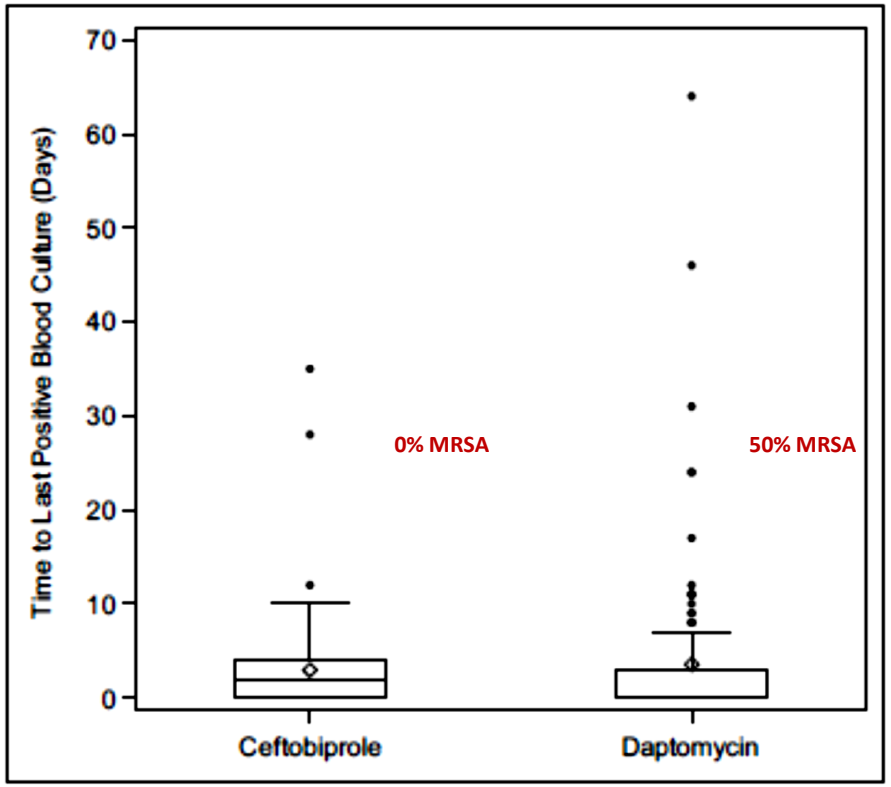
Blood culture clearance post-Day 10

Figure 1 Time to *S. aureus* bloodstream clearance (mITT population)



The Greenwood formula was used for confidence intervals of the Kaplan-Meier analysis.

Figure 2. Distribution of the time of last positive blood cultures for *S. aureus* (mITT population)†



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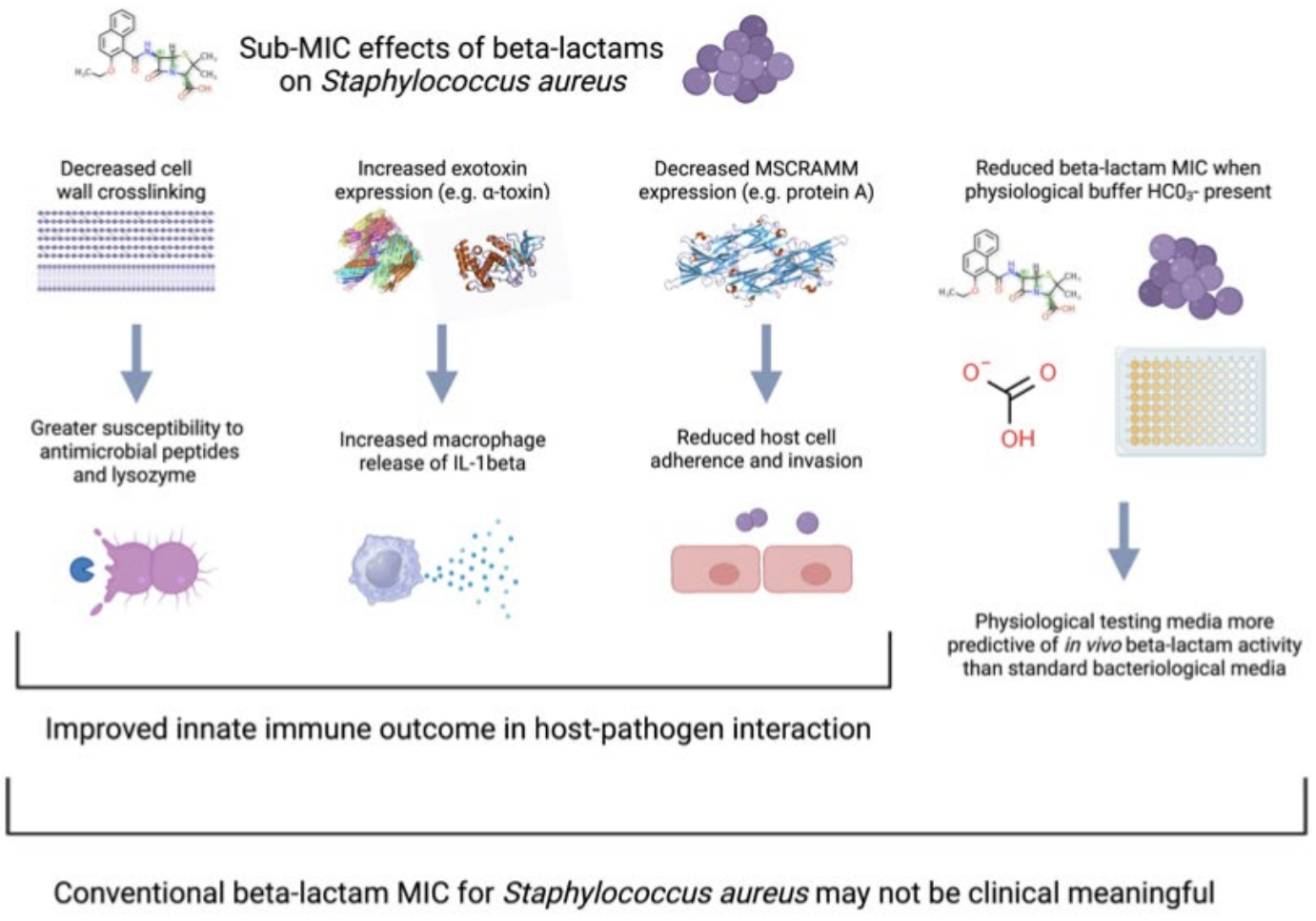
AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Antimicrobial Chemotherapy | Minireview

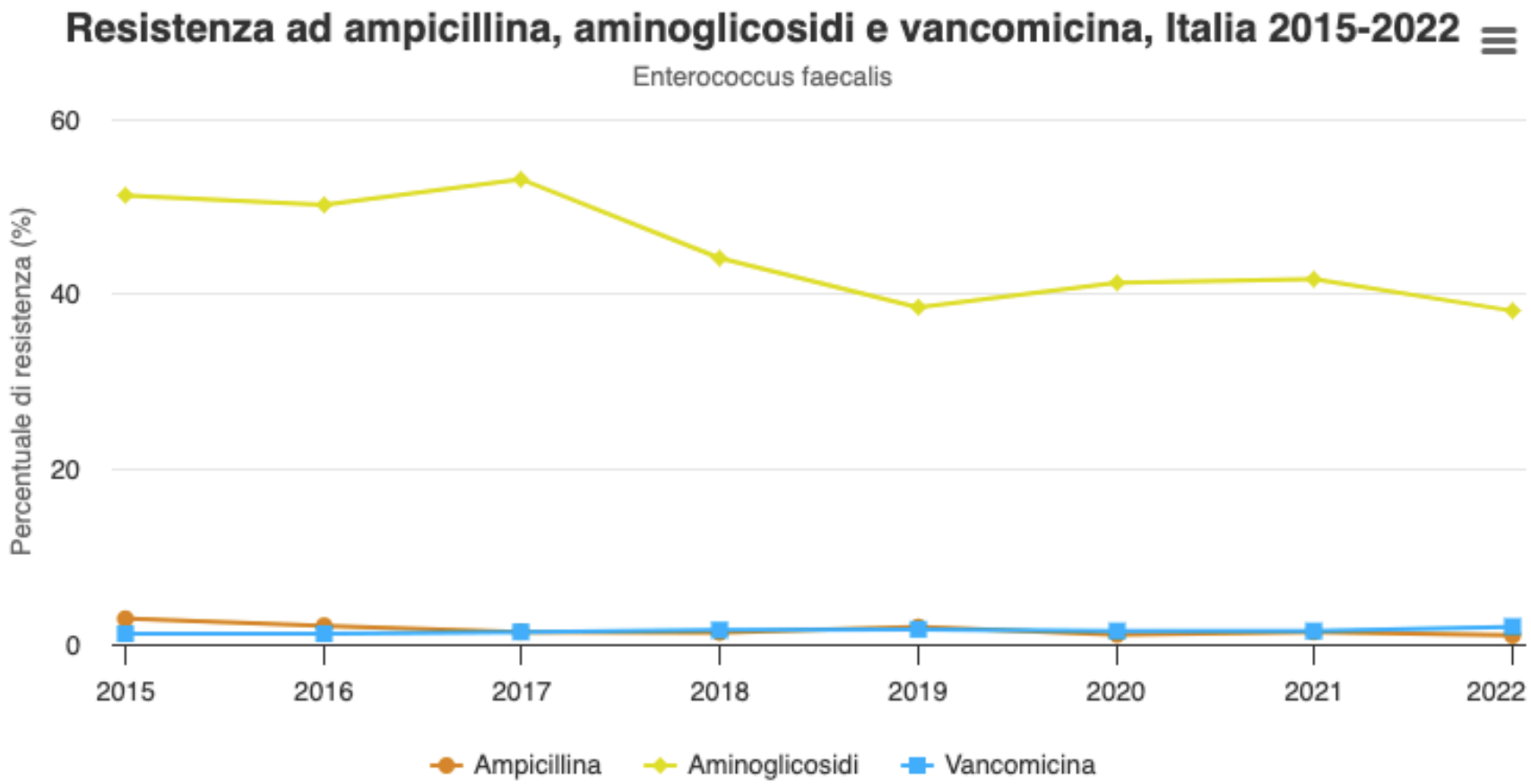
Measuring beta-lactam minimum inhibitory concentrations in *Staphylococcus aureus* in the clinical microbiology laboratory: pinning the tail on the donkey

George Sakoulas,[1,2] Victor Nizet[2,3]



Enterococcus faecalis

In Italia, dopo due anni di aumento nel 2020 e 2021, si osserva nel 2022 una diminuzione della percentuale di resistenza agli aminoglicosidi ad alto dosaggio (gentamicina, streptomicina) in *E. faecalis* (38,1%); inoltre, dai dati emerge che la resistenza alla vancomicina si è mantenuta bassa, non oltre il 2% (Figura).



State-of-the-Art Review: Persistent Enterococcal Bacteremia

Ralph Rogers and Louis B. Rice

Division of Infectious Diseases and Department of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

Streptococcus, and *Klebsiella* species [1]. Enterococcal bacteremia is associated with an imposing 20%–35% 30-day mortality rate, likely at least in some part due to the advanced age, multiple comorbid conditions, and/or underlying immunocompromised state typical among patients affected by enterococcal bacteremia [2–4]. Beyond the intrinsic antimicrobial

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https://doi.org/10.1093/jac/dkae032

Journal of Antimicrobial Chemotherapy

Differential *in vitro* susceptibility to ampicillin/ceftriaxone combination therapy among *Enterococcus faecalis* infective endocarditis clinical isolates

Kevin J. Westbrook[1], Gayatri Shankar Chilambi[1], Madison E. Stellfox[1], Hayley R. Nordstrom[1], Yanhong Li[1,2], Alina Iovleva[1], Niyati H. Shah[1], Chelsea E. Jones[1], Ellen G. Kline[1], Kevin M. Squires[1], William R. Miller[3,4], Truc T. Tran[3,4], Cesar A. Arias[3,4,5], Yohei Doi[1], Ryan K. Shields[1] and Daria Van Tyne[1,6]*

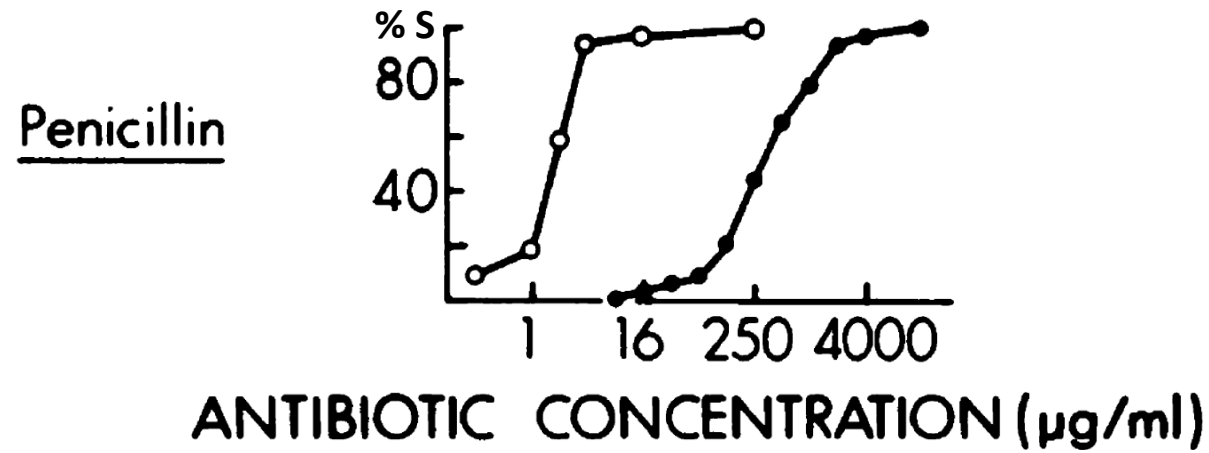
Fattori che influenzano la persistenza:
Immunodepressione
Virulenza degli isolati batterici
Fonte dell'infezione: emendabile o meno
Terapia antibiotica: tempestiva ed adeguata

ing.[4] Despite the use of *in vitro* active antibiotic combination therapy for at least 6 weeks, mortality from EFIE remains as high as 30%.[5,6]

TABLE 2. *Defective killing of group D streptococci*[a]

Antimicrobial agent	Enterococci		*S. bovis*		Viridans group streptococci	
	MBC/MIC	Median MIC	MBC/MIC	Median MIC	MBC/MIC	Median MIC
Penicillin	128	2.0	256	0.03	2	0.015
Cephalothin	≥256	31.0	256	0.12	2	0.06
Bacitracin	32	125.0	64	31.0	4	8.0
Cycloserine	≥128	250.0	≥64	125.0	4	125.0
Vancomycin	≥16,000	0.5	512	0.5	8	0.25

[a] The MBC/MIC is expressed as the median MBC/MIC ratio of all isolates tested, the median MICs are expressed in micrograms per milliliter, and defective killing is defined as an MBC/MIC ratio of ≥32 (13).



enterococcal isolates susceptible to growth inhibition (○) and killing (●) is plotted on the ordinate.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1980, p. 965–968
0066-4804/80/06-0965/04$02.00/0

Vol. 17, No. 6

Defective Killing of Enterococci: a Common Property of Antimicrobial Agents Acting on the Cell Wall

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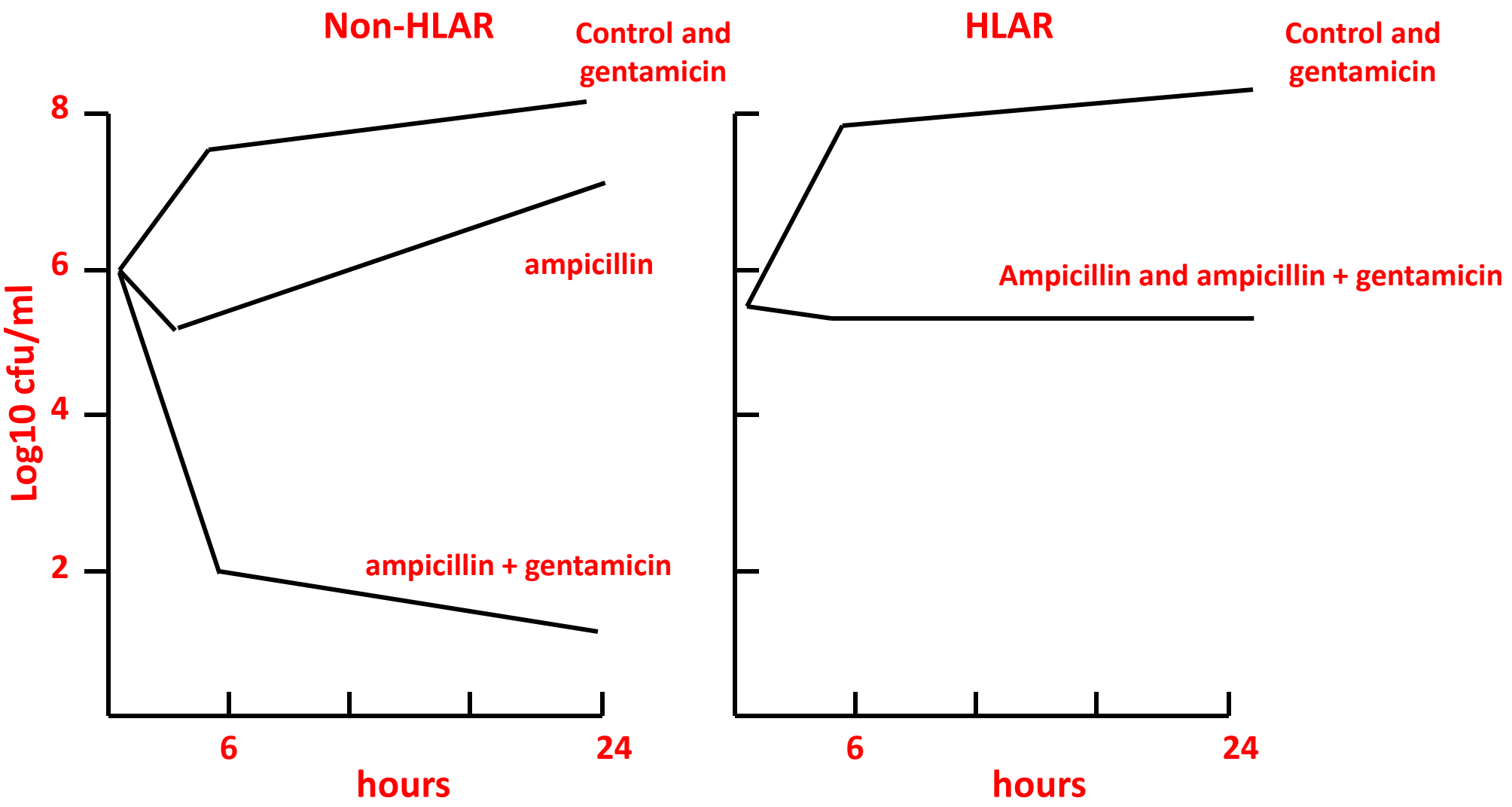
Departments of Medicine and Pathology, Barnes Hospital, Washington University School of Medicine, St. Louis, Missouri 63110

Ampicillin and gentamicin combination vs *Enterococcus* spp.



MAJOR ARTICLE

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

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

Fernández-Hidalgo N et al.. Clin Infect Dis. 2013 May;56(9):1261-8

Clinical Infectious Diseases
MAJOR ARTICLE

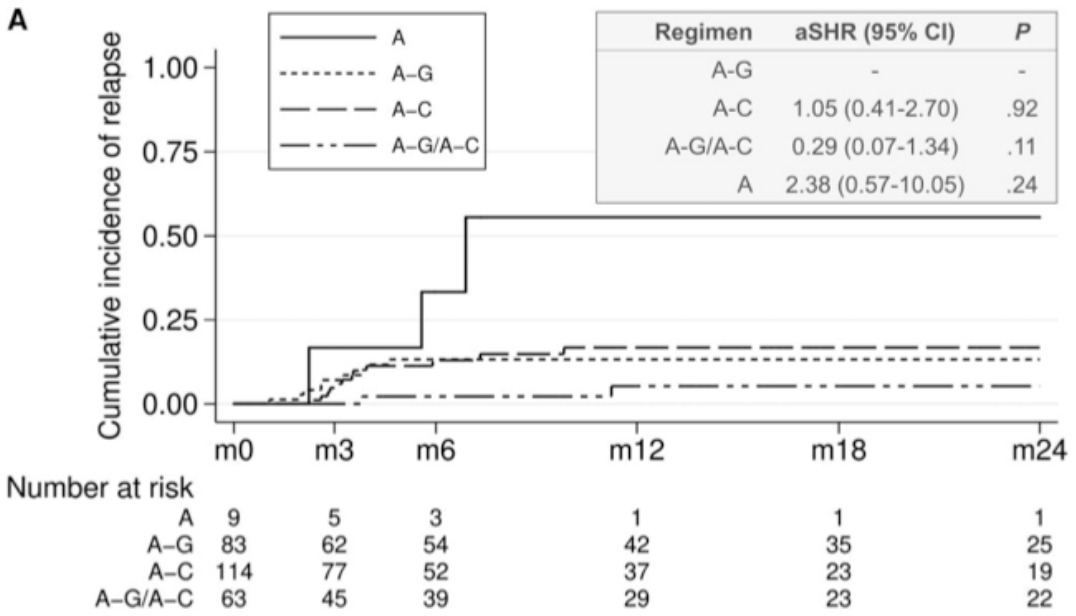
Impact of *Enterococcus faecalis* Endocarditis Treatment on Risk of Relapse

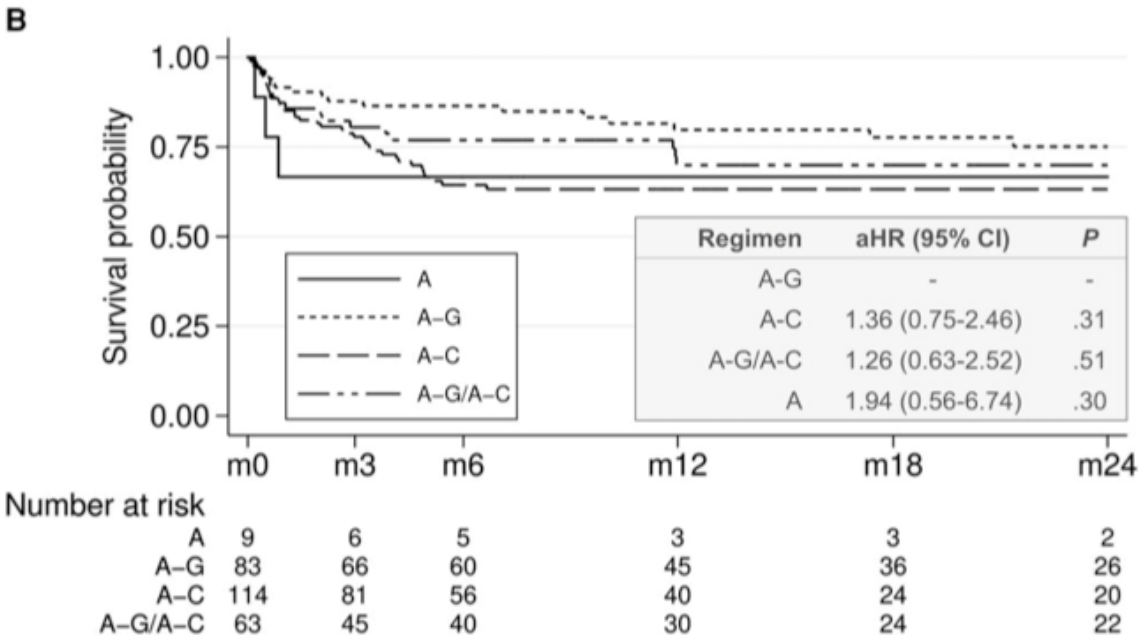
Pierre Danneels,[1,2] Jean-François Hamel,[3] Léa Picard,[4,2] Schéhérazade Rezig,[5,2] Pauline Martinet,[5,2] Aurélien Lorleac'h,[6,2] Jean-Philippe Talarmin,[7,2] Rodolphe Buzelé,[8,2] Thomas Guimard,[9,2] Gwenaël Le Moal,[10,2] Julia Brochard-Libois,[11,2] Aurélie Beaudron,[12,2] Julien Letheulle,[13,2] Cyrielle Codde,[14,2] Rachel Chenouard,[15,2] David Boutoille,[16,2] Adrien Lemaignen,[17,2] Louis Bernard,[17,2] Vincent Cattoir,[18,19,20] and Vincent Dubée,[1,2,21] the EFEMER study group[a]

The cumulative incidence of relapse 1 year after endocarditis was 46.2% for patients treated with amoxicillin, 13.4% with A-G, 14.7% with A-C, and 4.3% with A-G/A-C ($P \geq .05$ in multivariate analysis).

Conclusions. Relapses after treatment of EFIE are frequent, frequently asymptomatic, and may occur more than 6 months after the initial episode.

Keywords *E. faecalis*; endocarditis; relapse; amoxicillin; drug therapy combination





Beta-lactam binding to enterococcal PBPs in standard growth conditions

	PBP1	PBP2	PBP3	PBP4	PBP5	PBP6
Ceftobiprole	✓	✓	✓	✓↑	✓	∑
Ceftaroline	✓	✓	✓	✓	✓↑	∑
AMP/AMX	∑	∑	∑	✓ë	✓ë	ë

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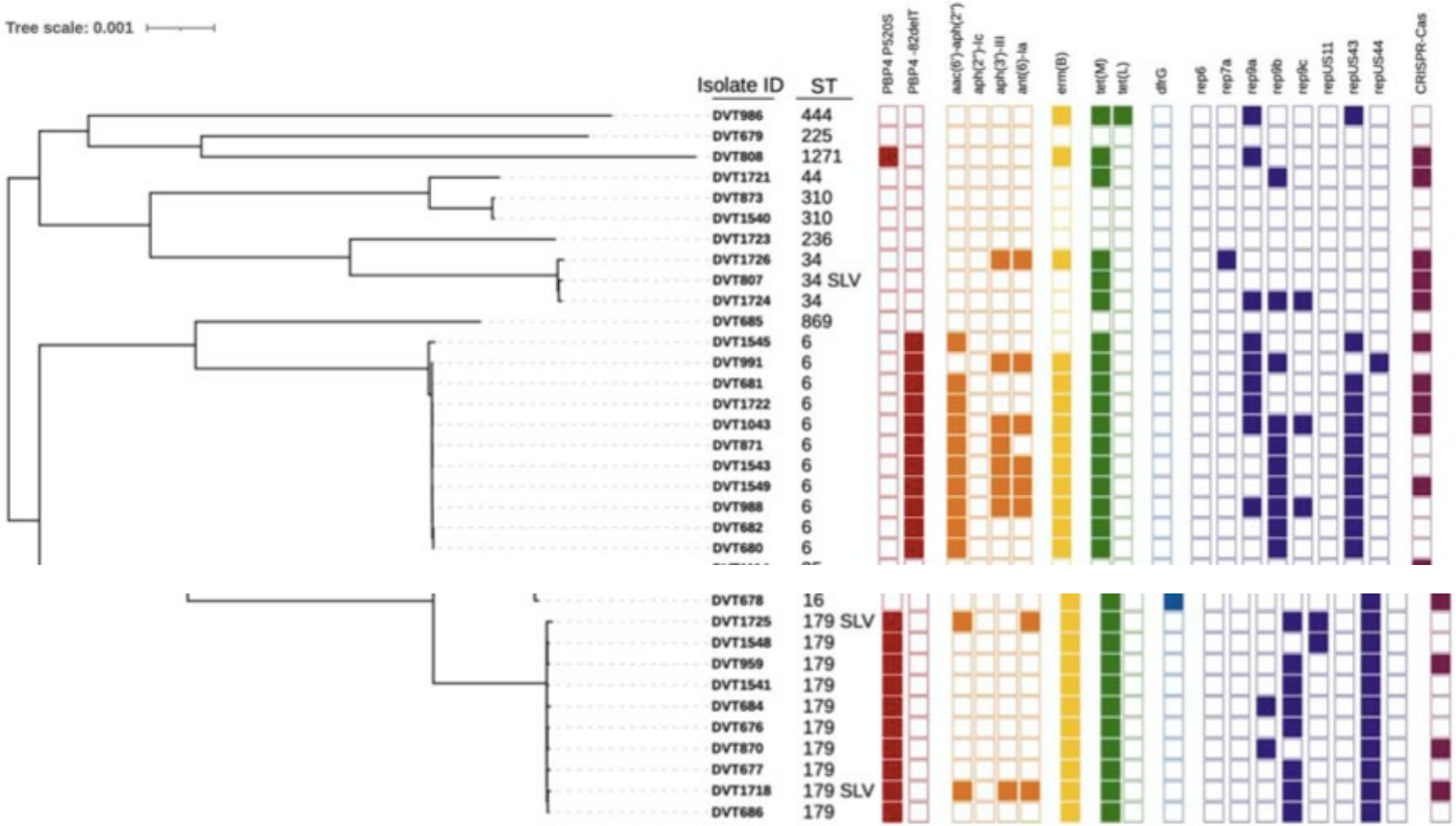
J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae032

Journal of Antimicrobial Chemotherapy

Differential *in vitro* susceptibility to ampicillin/ceftriaxone combination therapy among *Enterococcus faecalis* infective endocarditis clinical isolates

Kevin J. Westbrook[1], Gayatri Shankar Chilambi[1], Madison E. Stellfox[1], Hayley R. Nordstrom[1], Yanhong Li[1,2], Alina Iovleva[1], Niyati H. Shah[1], Chelsea E. Jones[1], Ellen G. Kline[1], Kevin M. Squires[1], William R. Miller [3,4], Truc T. Tran[3,4], Cesar A. Arias[3,4,5], Yohei Doi [1], Ryan K. Shields [1] and Daria Van Tyne [1,6]*



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Journal of Antimicrobial Chemotherapy

Differential *in vitro* susceptibility to ampicillin/ceftriaxone combination therapy among *Enterococcus faecalis* infective endocarditis clinical isolates

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shown to affect susceptibility to β-lactam agents.[28–30] We observed *pbp4* mutations in isolates belonging to ST6 and ST179 (Table S1, Figure 1). All ST6 isolates carried a single base deletion 82 nucleotides upstream of *pbp4* (–82delT), while all ST179 isolates as well as three additional isolates (two ST64 isolates and one ST1271 isolate) harboured a non-synonymous P520S mutation in *pbp4*. We also screened all genomes for acquired antimicrobial resistance genes using ResFinder[31] (Figure 1). Vancomycin resistance genes were absent, and no acquired β-lactamase genes nor β-lactamase production were identified in any isolate. Genes predicted to confer high-level aminoglycoside resistance were found in every ST6 isolate, while outside of ST6 they were rare except for ST16. Macrolide, tetracycline

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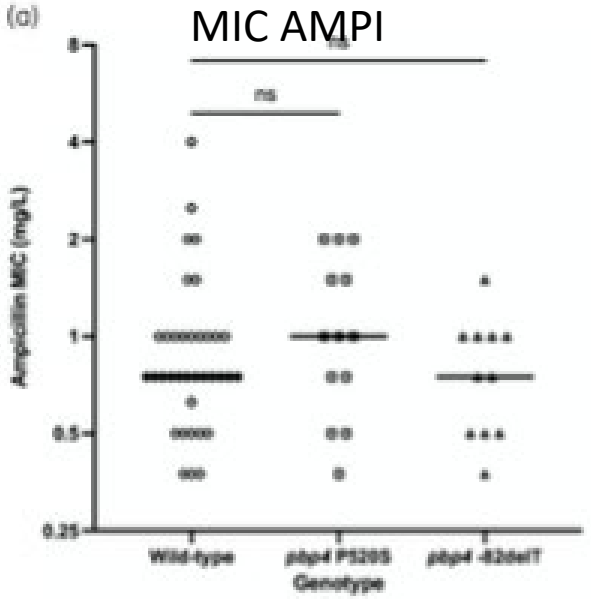
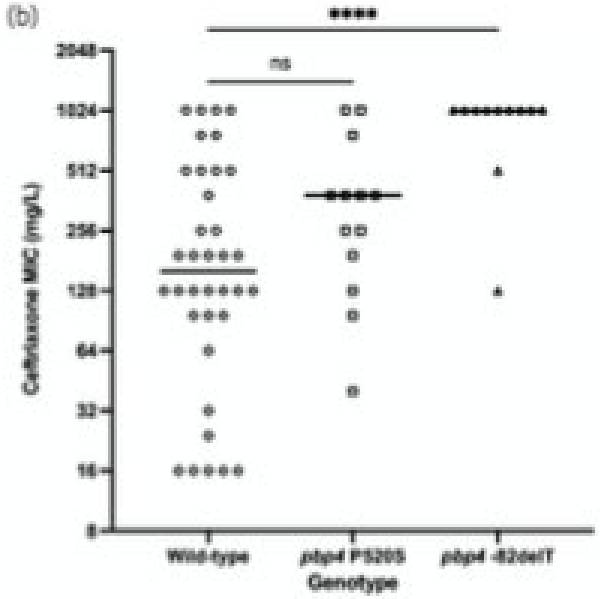
genotypes. Ampicillin MICs were ≤4 mg/L for all isolates and did not vary significantly between *pbp4* genotypes (Table S1, Figure 2a). Ceftriaxone MICs were more variable and ranged from 16 mg/L to 1024 mg/L. Median ceftriaxone MICs were higher for isolates encoding the *pbp4* P520S mutation compared to *pbp4* wild-type isolates; however, the difference was not statistically significant. ST6 isolates, all of which encoded the *pbp4* −82delT mutation, had higher ceftriaxone MIC values compared to wild-type isolates (mean ceftriaxone MIC = 896 mg/L versus 303 mg/L, $P < 0.0001$) (Figure 2b).

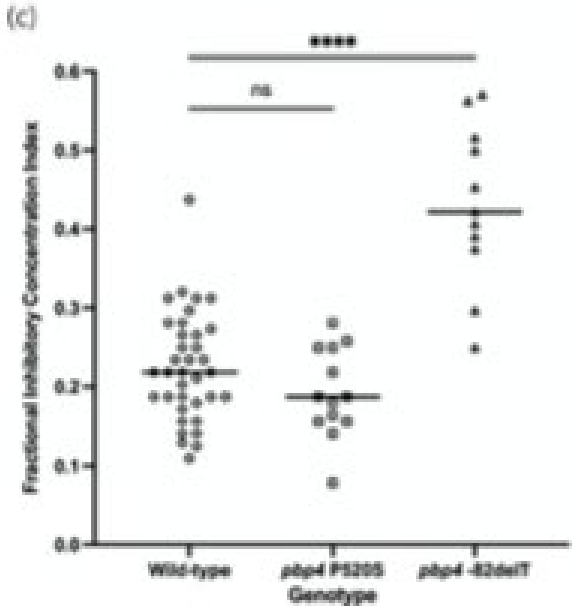
than *pbp4* wild-type isolates ($P < 0.0001$). We also examined average bacterial growth (OD_{600}) across the checkerboard assay plates among isolates encoding different *pbp4* mutations (Figure 2d). Bacterial growth was similar between *pbp4* wild-type and P520S isolates, whereas isolates encoding the *pbp4* −82delT mutation showed more growth in wells containing higher concentrations of both antibiotics. These data suggest that AC may be less active against ST6 isolates, perhaps due to the *pbp4* −82delT mutation they encode.

MIC AMPI

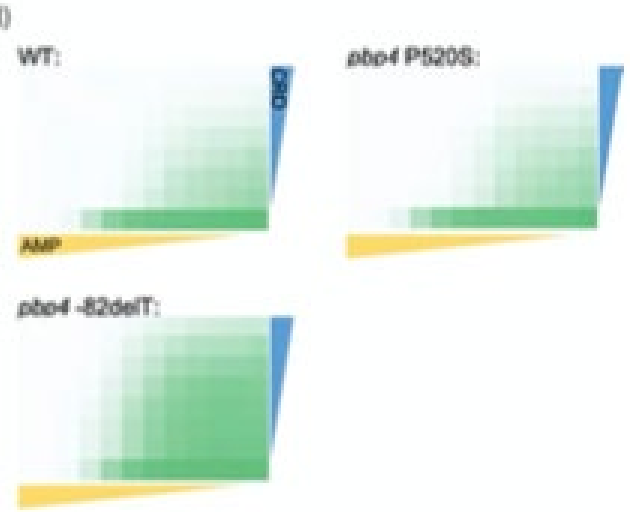




MIC CRO



SFICI



Crescita batterica:
Più è verde maggiore la crescita

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Table 2. AC susceptibility of OG1RF wild-type and isogenic *pbp4* mutant strains

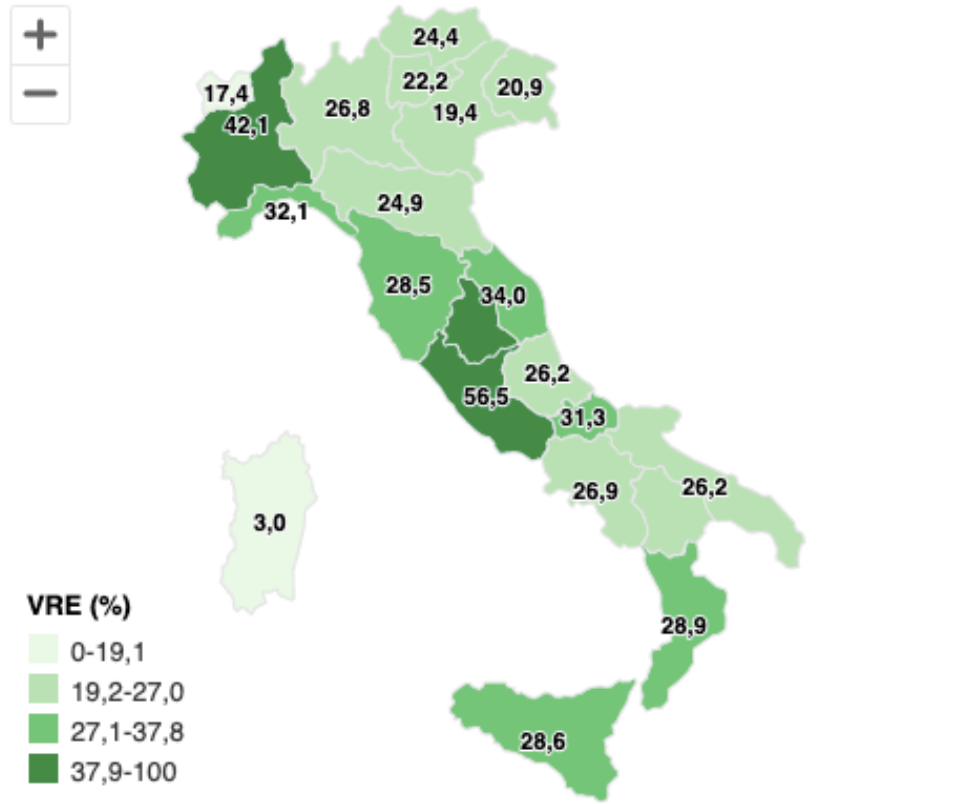
Strain background	*pbp4* genotype	Ampicillin MIC (mg/L)	Ceftriaxone MIC (mg/L)
OG1RF	Wild-type	1	16
OG1RF	P520S	1	8
OG1RF	–82delT	1	256

pbp4, penicillin-binding protein 4.

treated with AC, and no patients received AG. Our findings of variable *in vitro* susceptibility to ceftriaxone and diminished AC synergy among a subset of isolates suggest that AC may not be the optimal treatment for all patients with EFIE. The ST6 isolates

Percentuali di resistenza delle principali combinazioni patogeno/antibiotico sotto sorveglianza per Regione, anno 2022*

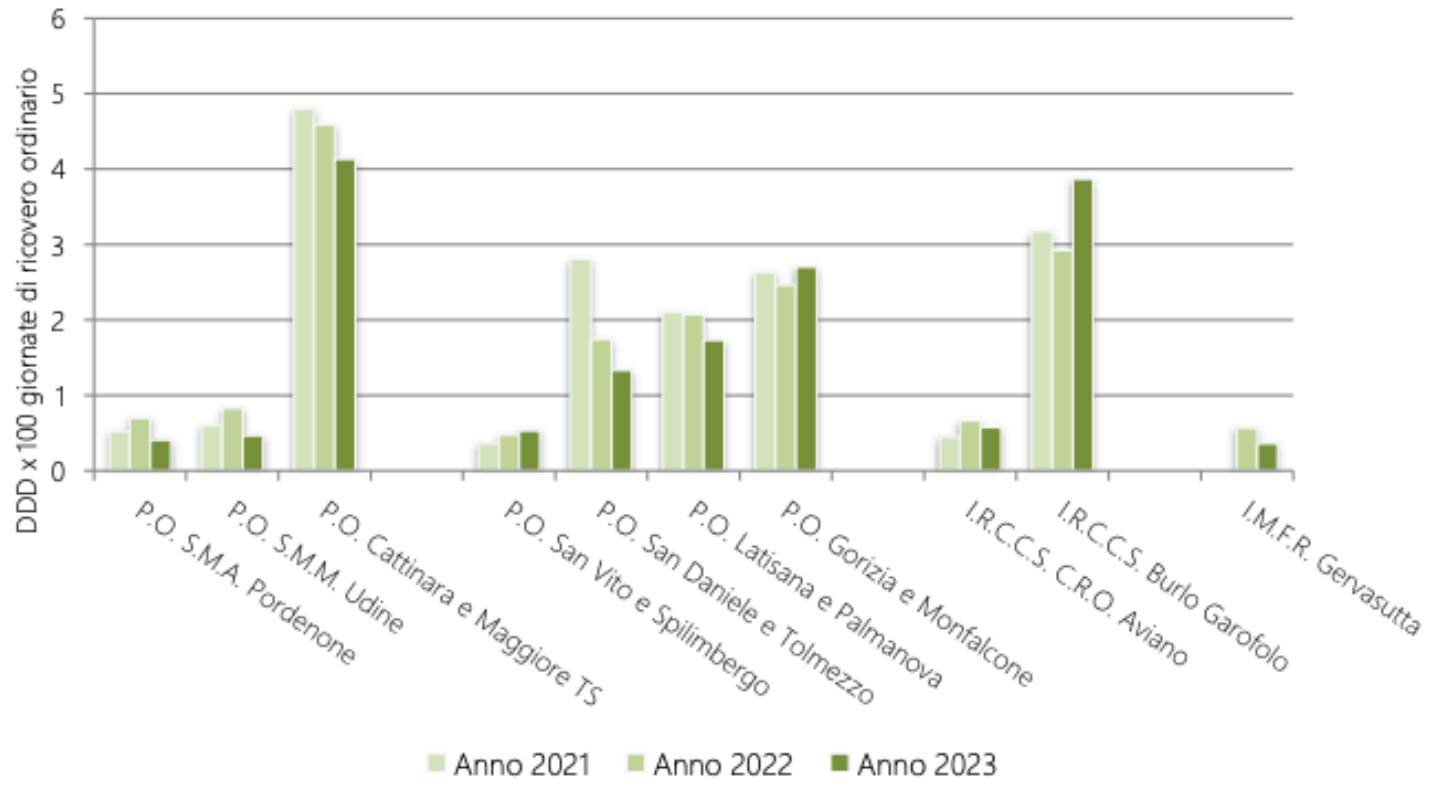
VRE-faecium (%)



AR-ISS

*Le classi di intensità di resistenza sono identificate in base ai quartili della distribuzione nazionale

Figura 20. Consumo ospedaliero (2021-2023) di **J01XA-Glicopeptidi** espresso in DDD x 100 giornate di ricovero ordinario.



Paziente trapiantato di fegato

- Problemi dell’anastomosi biliare con raccolta di 20 cm periepatica drenata
- Emocolture positive per VRE da Maggio a Novembre 2024 con nessun sintomo!!!!
- VRE marcatore di malattie non controllate

Surveillance of vancomycin-resistant enterococci reveals shift in dominating clones and national spread of a vancomycin-variable *vanA Enterococcus faecium* ST1421-CT1134 clone, Denmark, 2015 to March 2019

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TABLE 2

Regional occurrence of ST1421-CT1134 *vanA E. faecium*, Denmark, 2016–Q1 2019 (n = 268)

Region	2016 (n=2)	2017 (n=13)	2018 (n=176)	Q1 2019 (n=77)
Capital Region of Denmark	2	9	158	50
Region Zealand	ND	3	9	1
Region of Southern Denmark	ND	ND	9	23
Central Denmark Region	ND	ND	ND	2
North Denmark Region	ND	1	ND	1

Q1: first quarter.

Vancomycin variable Enterococci (VVE), sensibile al test fenotipico ma possiede gene VanA inducibile in vivo

TABLE 1

Description of the most common types of *vanA* and/or *vanB Enterococcus faecium* by MLST and cgMLST, Denmark, 2015–Q1 2019 (n = 1,910)

Types	2015 (n=369)		2016 (n=427)		2017 (n=425)		2018 (n=515)		Q1 2019 (n=174)	
	n	%	n	%	n	%	n	%	n	%
ST80-CT14 *vanA*	81	22	38	9	15	4	1	<1	ND	ND
ST80-CT24 *vanA*	23	6	19	4	11	3	2	<1	4	2
ST80-CT860 *vanA*	7	2	11	3	ND	ND	ND	ND	ND	ND
ST80-CT866 *vanA*	14	4	10	2	7	2	ND	ND	ND	ND
ST80-CT991 *vanA*	ND	ND	11	3	9	2	6	1	ND	ND
ST80-CT1160 *vanA*	ND	ND	ND	ND	7	2	10	2	ND	ND
ST80-CT1064 *vanA/vanB*	ND	ND	2	<1	8	2	23	5	4	2
ST80-CT1729 *vanA*	ND	ND	ND	ND	ND	ND	22	4	2	1
ST117-CT873 *vanA*	5	1	12	3	ND	ND	ND	ND	ND	ND
ST117-CT1180 *vanA*	ND	ND	ND	ND	9	2	30	6	7	4
ST117-CT36 *vanB*	ND	ND	ND	ND	ND	ND	2	<1	16	9
ST203-CT859 (subtypes CT1051 and CT1507) *vanA*	188	51	271	64	265	63	161	31	20	12
ST1421-CT1134 *vanA*	ND	ND	2	<1	13	3	176	34	77	44
Other types	51	14	51	12	81	19	82	16	44	25

CT: cluster type (cgMLST); MLST: multilocus sequence typing; ND: not detected; ST: sequence type (MLST); Q1: first quarter.

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Update on prevalence and mechanisms of resistance to linezolid, tigecycline and daptomycin in enterococci in Europe: Towards a common nomenclature

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A specific variant of VRE is represented by vancomycin-variable enterococci (VVE); these strains were noticed only very recently. VVE are vancomycin-susceptible enterococci with a *vanA* genotype (VVE-S), which can become resistant to vancomycin (VVE-R) upon exposure to vancomycin or teicoplanin (Coburn et al., 2014; Sivertsen et al., 2016). Development of vancomycin resistance in VVE-S can arise from different mechanisms and result in the expression of *vanHAX* genes, in either a restored vancomycin-inducible fashion (Sivertsen et al., 2016) or constitutively (Thaker et al., 2015). Outbreaks of VVE have been reported in Canada (Szakacs et al., 2014), Norway (Sivertsen et al., 2016) and Denmark (Hansen et al., 2018). Sporadic isolates of VVE have also been reported in other European countries (Jung et al., 2014; Loens et al., 2016; Sivertsen et al., 2017). Most of the reported VVE isolates have been *E. faecium*, but this phenomenon can also occur in *E. faecalis* (Sivertsen et al., 2016). The overall prevalence of VVE-S is unknown. Since the expression of vancomycin resistance genes is turned off in VVE-S, they are not easily detected with phenotypic methods. However, since vancomycin and teicoplanin exposure over days promote the development of resistance, VVE have caused treatment failure and could be considered an emerging threat (Downing et al., 2015; Sivertsen et al., 2016).

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A Silenced *vanA* Gene Cluster on a Transferable Plasmid Caused an Outbreak of Vancomycin-Variable Enterococci

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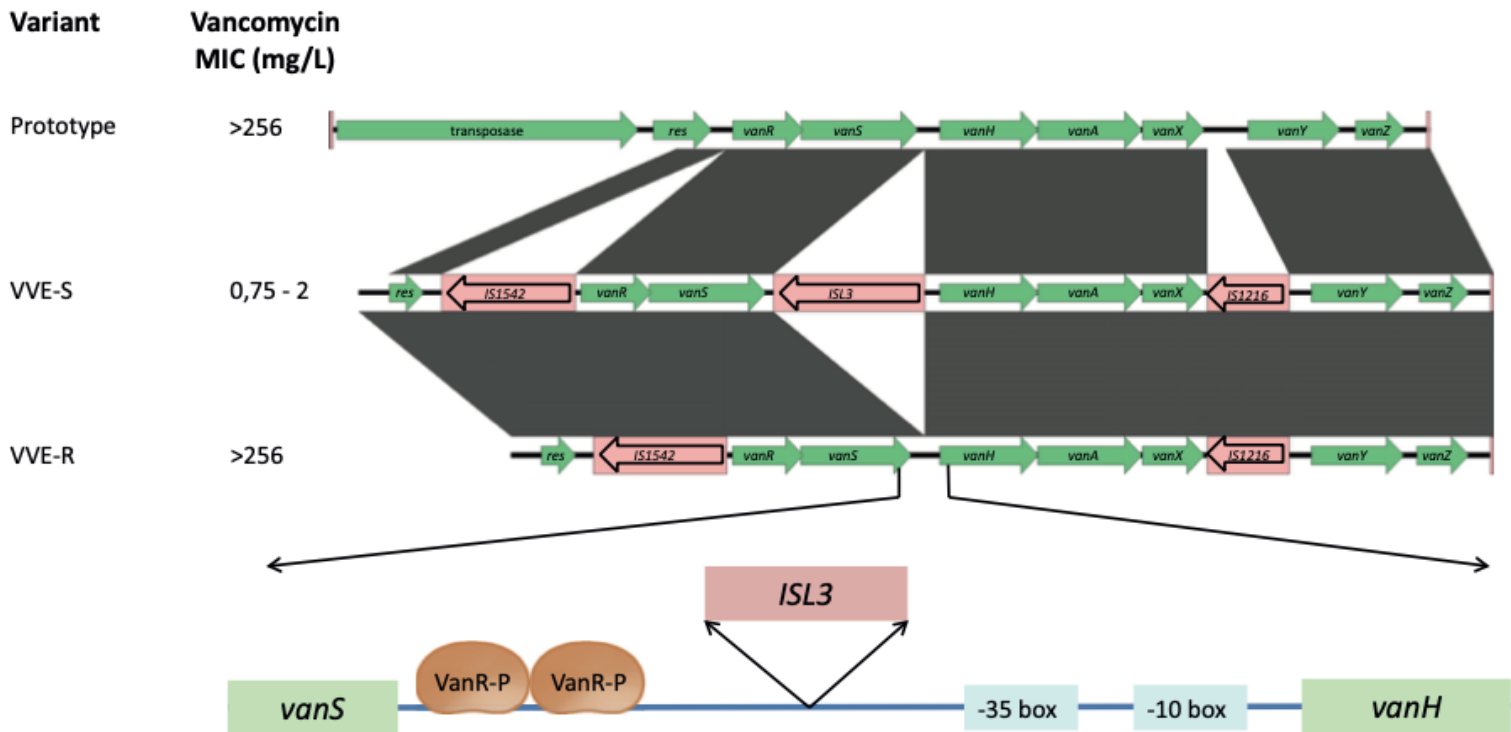

FIG 2 Insertion site of I*SL3* illustrated in a scaled alignment of *vanA* clusters from Norwegian clonal VVE-S and VVE-R to prototype Tn*1546* (GenBank accession no. M97297). In the zoomed view, the location of I*SL3* between the binding site of the VanR activator (VanR-P) and the *vanHAX* promoter (−35 and −10 boxes) is indicated.

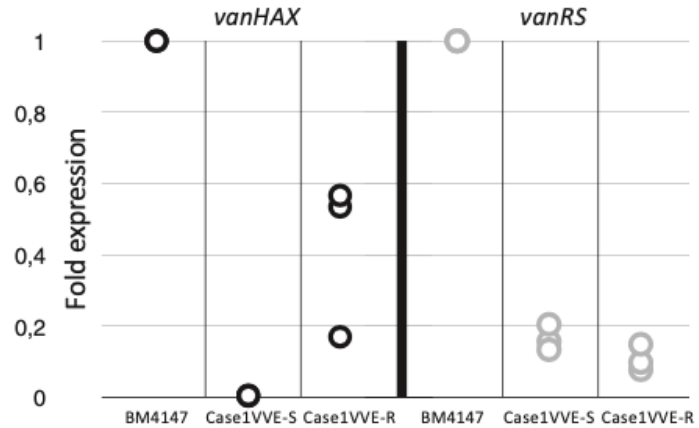

FIG 3 Expression levels of the *vanHAX* and *vanRS* operons in the VanA-silenced (Case1VVE-S) and resistant (Case1VVE-R) isolates relative to BM4147 (Tn*1546* prototype) assessed by RT-qPCR. Data points for three independent experiments are shown for each isolate. All measurements were normalized against the housekeeping gene glutamate dehydrogenase (*gdh*).

Conclusioni

- *S. aureus* sensibilità alla penicillina
- *S. aureus* casi gravi testare anche in bicarbonato
- hVISA
- (citokine?)
- *E. faecalis*: sequenziare i casi che hanno fallito ampi cefalosporine
- *E. faecium* VRE: verificare la virulenza