Prof Carlo Tascini
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08:45 -11:15 Focus sugli antibiotici recenti e futuri
Moderatori: *P. Grossi (Varese), C. Mastroianni (Roma)*

08:45 - 09:00 **Cefalosporine di 5ª generazione: quali novità nelle polmoniti e nelle batteriemie**
C. Tascini (Udine)

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*

Clinical Infectious Diseases

MAJOR ARTICLE

Interleukin (IL)-1β and IL-10 Host Responses in Patients With *Staphylococcus aureus* Bacteremia Determined by Antimicrobial Therapy

Cecilia F. Volk,[1] Sarah Burgdorf,[2] Graham Edwardson,[1] Victor Nizet,[2] George Sakoulas,[2] and Warren E. Rose[1]

[1]School of Pharmacy, University of Wisconsin–Madison; and [2]Department of Pediatrics, University of California–San Diego School of Medicine, La Jolla

clinical implications. Here, we demonstrate that monotherapy with vancomycin or daptomycin does not elicit a robust IL-1β response in patients. However, β-lactam therapy that includes oxacillin, cefazolin, or ceftaroline, either alone or in combination with vancomycin or daptomycin, enhanced IL-1β at days 3 and 7 of therapy. We suspect that the muted IL-1β response with non–β-lactam therapy may be a predisposing factor for the longer bacteremia that has been reported in MRSA compared to MSSA [19, 20].

Volk et al., CID 2020

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Table 2. Antibiotic Therapy Initiated Within 48 Hours of Presentation

	Glyco/Lipopeptide	β-Lactam
Antibiotic	n = 35	n = 24
Vancomycin	28	…
Daptomycin	7	…
Oxacillin	…	6
Cefazolin	…	2
Vancomycin plus oxacillin[a]	…	2
Daptomycin plus ceftaroline	…	14

[a] Vancomycin was discontinued after 48 hours due to definitive methicillin-sensitive *Staphylococcus aureus*, and oxacillin was continued for the duration of treatment of bacteremia.

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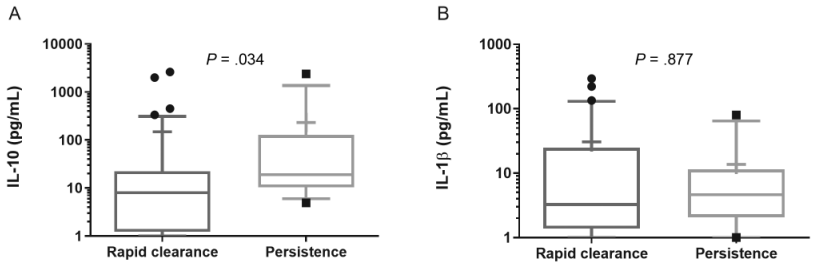

Figure 2. (*A*) IL-10 and (*B*) IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of rapid bacteremia clearance (≤4 days) or persistent bacteremia (>4 days). The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviation: IL, interleukin.

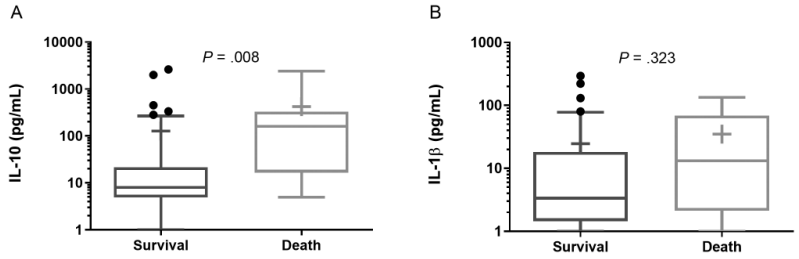

Figure 1. (*A*) IL-10 and (*B*) IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of 30-Day survival or mortality. The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviation: IL, interleukin.

Persistent bacteremia

Mortality

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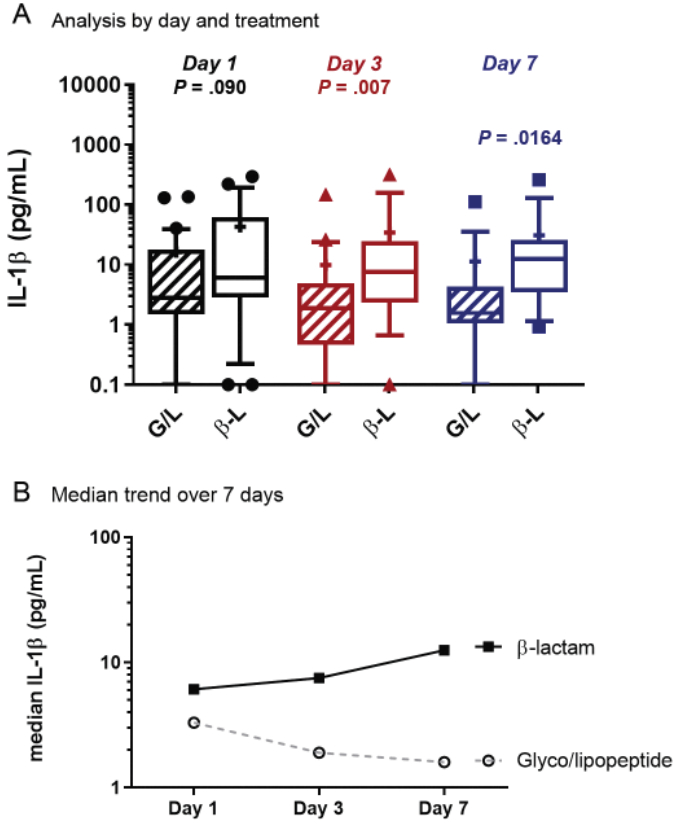


Figure 3. IL-1β concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy. The Mann-Whitney U test was used for statistical analysis. Median (line) and mean (+). Abbreviations: B-L, β-lactam; G/L, glyco/lipopeptide; IL, interleukin.

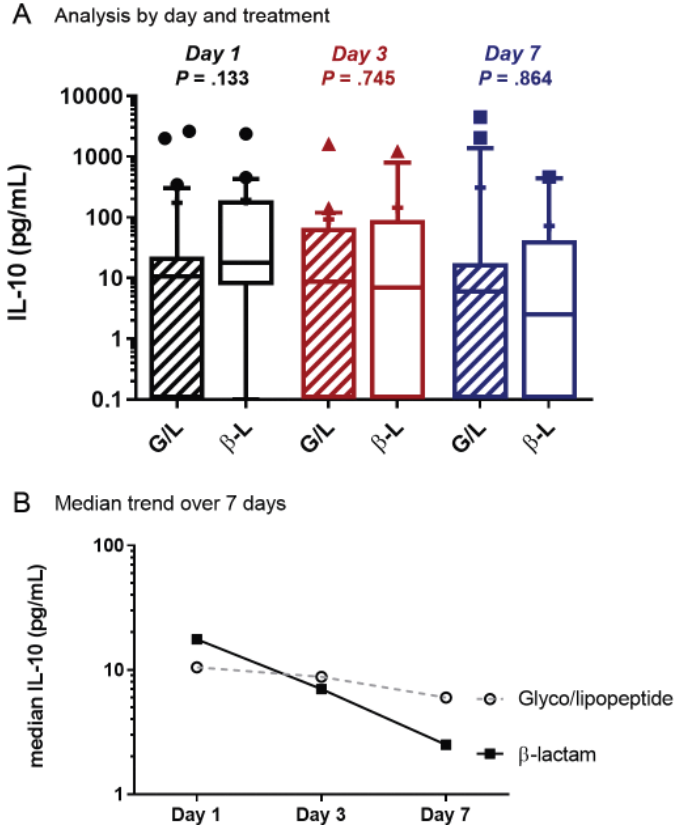
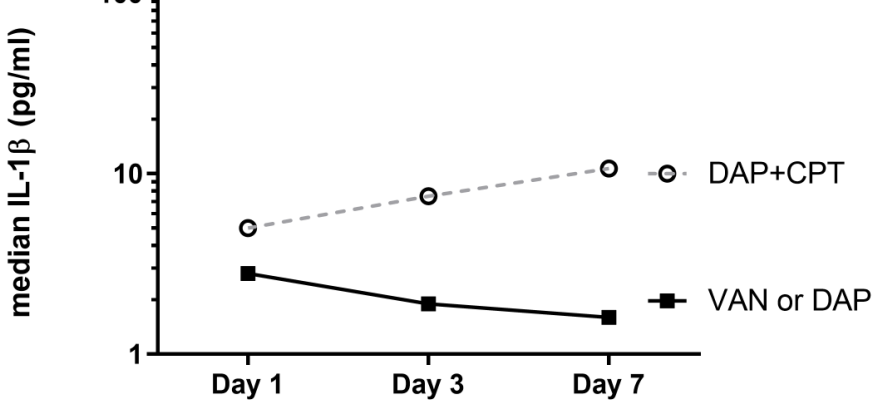


Figure 4. IL-10 concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy. The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviations: B-L, β-lactam; G/L, glyco/lipopeptide; IL, interleukin.



IL-1b trend in MRSA blood-stream infections

Volk et al., CID 2020

combination group and 25% (1/4) in the monotherapy group ($P = 1.0$). For an IL-10 concentration of >5 pg/ml, in-hospital mortality was 0% (0/14) in the combination therapy group versus 26% (5/19) in the monotherapy group ($P = 0.057$).

TABLE 4 Study outcomes

Outcome	Values by treatment type:		
	Combination therapy	Monotherapy	*P* value
Mortality, *n* (%)			
In hospital	0 (0)	6 (26)	0.02
30 day	0 (0)	6 (26)	0.02
90 day	0 (0)	7 (30)	0.03
Bacteremia duration, median (IQR) days	3 (1.5, 5.5)	3 (1, 5.3)	0.56
Length of stay, median (IQR) days	11 (6, 14)	12 (8, 23)	0.24

Clinical Infectious Diseases

STATE OF THE ART REVIEW

Contemporary Management of *Staphylococcus aureus* Bacteremia—Controversies in Clinical Practice

Daniel J. Minter,[1] Ayesha Appa,[1,2] Henry F. Chambers,[1,2] and Sarah B. Doernberg[1]

[1]Division of Infectious Diseases, Department of Medicine, University of California, San Francisco, San Francisco, California, USA; and [2]Division of HIV, Infectious Diseases, and Global Medicine at Zuckerberg San Francisco General Hospital, Department of Medicine, University of California, San Francisco, San Francisco, California, USA

Staphylococcus aureus bacteremia (SAB) carries a high risk for excess morbidity and mortality. Despite its prevalence, significant practice variation continues to permeate clinical management of this syndrome. Since the publication of the 2011 Infectious Diseases Society of America (IDSA) guidelines on management of methicillin-resistant *Staphylococcus aureus* infections, the field of SAB has evolved with the emergence of newer diagnostic strategies and therapeutic options. In this review, we seek to provide a comprehensive overview of the evaluation and management of SAB, with special focus on areas where the highest level of evidence is lacking to inform best practices.

Keywords. *Staphylococcus aureus* bacteremia.

Evaluation

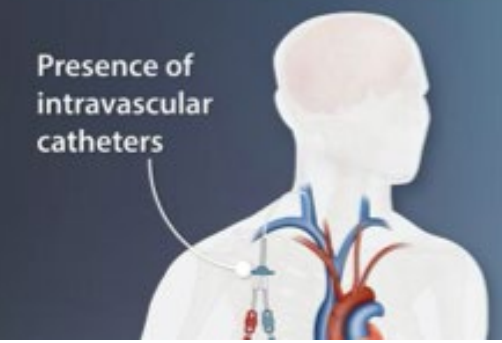
Minimum Evaluation

- Thorough history and physical exam
- Repeat blood cultures
- Transthoracic echocardiogram (TTE)
- Infectious diseases consultation

Additional evaluation (as clinically indicated)

- Transesophageal echocardiogram (TEE)
- Thoracoabdominal CT with contrast
- MRI spine
- PET/CT
- Symptom-based invasive diagnostics (e.g., arthrocentesis)

Physical exam



Management

Antibiotics

Agent

- Methicillin-resistant *Staphylococcus aureus* (MRSA) – vancomycin, daptomycin, ceftaroline/ceftobiprole (limited data)
- Methicillin-susceptible *Staphylococcus aureus* (MSSA) – cefazolin, nafcillin, daptomycin, vancomycin (β-lactams preferred)

Duration

- 2 weeks in those with low-risk *Staphylococcus aureus* bacteremia (SAB) and no metastatic sites
- 4-6 weeks in those with metastatic sites or higher-risk features

Persistent MRSA bacteremia or concern for antibiotic failure?

- Maximize source control
- Combination therapy with daptomycin + ceftaroline/ceftobiprole

Persistent MSSA bacteremia or concern for antibiotic failure?

- Maximize source control
- Optimal antibiotic management is unclear

Unable to complete 1st line parenteral antibiotics

- Long-acting infusions (e.g., dalbavancin)
- Oral step-down therapy

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

Ceftobiprole for the treatment of infective endocarditis: A case series

Carlo Tascini[a], Vittorio Attanasio[a], Marco Ripa[b], Antonio Carozza[c], Carlo Pallotto[d,e,*], Mariano Bernardo[f], Daniela Francisci[d], Chiara Oltolini[b], Giulia Palmiero[a], Paolo Scarpellini[b]

Table 1
Patients' characteristics and treatment history.

Patient (gender-age)	Year	Underlying conditions	Valve	Aetiology	Prior therapy	Indication for switch	Days on CBP	Concomitant antibiotics	Surgery	Time to apyrexia	Time to negative blood culture	Time to negative C-RP	Outcome
Pt 1 (F-39)	2016	IDU	T	MSSA	VAN + GEN + LFX	Persistent fever	35	DAPTO	Yes	30	na	na	Cured
Pt 2 (M-82)	2015	CIC, HTN, RI	A (BP) + M	Polymicrobial[a]	None	None	10	DAPTO	Yes	na	na	na	Cured
Pt 3 (M-76)	2018	PIE, CIC, AF, HTN	A (MP)	MSSA	CRO + LFX, DAPTO + CZA	Persistent fever and positive blood culture	9	DAPTO	No	Never but improving	2	Never but improving	exitus (fatal arrhythmia)
Pt 4 (M-77)	2018	CIC, AF, HTN	A (BP)	MRSE	None	None	8	DAPTO	No	5	2	Never but improving	Exitus (fatal arrhythmia)
Pt 5 (M-81)	2018	CIC, HTN, ictus cerebri	A (MP)	MR Staph. haemolyticus	DAPTO + MEM	Persistent fever	18	DAPTO	No	5	Negative before CBP	11	Cured
Pt 6 (M-46)	2018	IDU	T	MSSA	TCP + MEM	Persistent fever and positive blood culture	47	DAPTO	Yes	22	1	Never but improving	Cured
Pt 7 (M-92)	2018	CIC, AF, HTN	PMK	MSSA	DAPTO + CZA	Persistent fever, lung embolism	21	DAPTO	Yes	4	Negative before CBP	11	Cured
Pt 8 (F-20)	2016	SLE, HTN, APS, ictus cerebri, RI	M (MP)	Polymicrobial[b]	DAPTO + MEM	Concomitant pneumonia, persistent fever	18	None	No	1	Negative before CBP	Negative before CBP	Cured
Pt 9 (F-62)	2017	HTN, PMK	A (BP)	MRSE + MSSE	DAPTO + OXA	None	59	DAPTO + RIF	No	1	4	Never but improving	Cured
Pt 10 (F-69)	2016	RI, KT, vasculitis, ictus cerebri, AF	M	MRSA	PTZ	Concomitant pneumonia, RI	30	DAPTO	No	1	9	Never but improving	Cured
Pt 11 (M-66)	2015	RI, COPD, PIE	A (BP)	MRSA	DAPTO + PTZ	Persistent positive blood cultures	84	DAPTO	Yes	Afebrile before CBP	12	Never but improving	Cured
Pt 12 (F-76)	2015	DM, HTN, PMK, PIE	M (MP), PMK	MRSA	TMP/SMX + DAPTO + GEN	Increased vegetation size	28	TMP/SMX (later switched for FOF) + DAPTO	No	Afebrile before CBP	Negative before CBP	30	Cured

Abbreviations: Pt, patient; F, female; M, male; C-RP, C-reactive protein; IDU, intravenous drug user; CIC, chronic ischaemic cardiopathy; HTN, hypertension; RI, renal insufficiency; PIE, previous infective endocarditis; AF, atrial fibrillation; SLE, systemic lupus eritematosus; APS, anti-phospholipid syndrome; KT, kidney transplantation; DM, diabetes mellitus; T, tricuspid valve; A, aortic valve; M, mitral valve; BP, biologic prosthesis; MP, mechanic prosthesis; PMK, pace-maker; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSE, methicillin-resistant Staphylococcus epidermidis; VAN, vancomycin; GEN, gentamicin; LFX, levofloxacin; CRO, ceftriaxone; CZA, cefazolin; DAPTO, daptomycin; MEM, meropenem; CBP, ceftobiprole; TCP, teicoplanin; OXA, oxacillin; RIF, rifampin; PTZ, piperacillin-tazobactam; TMP-SMX, trimethoprim-sulfamethoxazole; FOF, fosfomycin; na, not available.

antibiotics

MDPI

Article

In Vitro Activities of Ceftobiprole, Dalbavancin, Tedizolid and Comparators against Clinical Isolates of Methicillin-Resistant *Staphylococcus aureus* Associated with Skin and Soft Tissue Infections

Sofia Maraki [1,*], Viktoria Eirini Mavromanolaki [2], Dimitra Stafylaki [1], Evangelia Iliaki-Giannakoudaki [1] and George Hamilos [1]

Table 2. Activity of antimicrobial agents against 124 MRSA isolates collected from patients with SSTIs in Greece (2020–2022).

Antibiotic	MIC_{50}	MIC_{90}	Range	S%
Vancomycin	1	2	0.38–2	100
Daptomycin	0.5	1	0.125–1.5	98.4
Ceftobiprole	0.38	1	0.064–1.5	100
Linezolid	0.38	1	0.125–2	100
Tedizolid	0.25	0.38	0.094–0.5	100
Dalbavancin	0.064	0.094	0.008–0.125	100

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

METHODS

In this phase 3, double-blind, double-dummy, noninferiority trial, adults with complicated *S. aureus* bacteremia were randomly assigned in a 1:1 ratio to receive ceftobiprole at a dose of 500 mg intravenously every 6 hours for 8 days and every 8 hours thereafter, or daptomycin at a dose of 6 to 10 mg per kilogram of body weight intravenously every 24 hours plus optional aztreonam (at the discretion of the trial-site investigators). The primary outcome, overall treatment success 70 days after randomization (defined as survival, bacteremia clearance, symptom improvement, no new *S. aureus* bacteremia–related complications, and no receipt of other potentially effective antibiotics), with a noninferiority margin of 15%, was adjudicated by a data review committee whose members were unaware of the trial-group assignments. Safety was also assessed.

ceftobiprole or daptomycin (modified intention-to-treat population). A total of 132 of 189 patients (69.8%) in the ceftobiprole group and 136 of 198 patients (68.7%) in the daptomycin group had overall treatment success (adjusted difference, 2.0 percentage points; 95% confidence interval [CI], –7.1 to 11.1). Findings appeared to be consistent between the ceftobiprole and daptomycin groups in key subgroups and with respect to secondary outcomes, including mortality (9.0% and 9.1%, respectively; 95% CI, –6.2 to 5.2) and the percentage of patients with microbiologic eradication (82.0% and 77.3%; 95% CI, –2.9 to 13.0). Adverse events were reported in 121 of 191 patients (63.4%) who received ceftobiprole and 117 of 198 patients (59.1%) who received daptomycin; serious adverse events were reported in 36 patients (18.8%) and 45 patients (22.7%), respectively. Gastrointestinal adverse events (primarily mild nausea) were more frequent with ceftobiprole.

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Categories of complicated *S. aureus* bacteremia — no. (%)‖			
Any complicated *S. aureus* bacteremia	189 (100.0)	198 (100.0)	387 (100.0)
Soft-tissue infections**	116 (61.4)	121 (61.1)	237 (61.2)
Osteoarticular infections††	32 (16.9)	35 (17.7)	67 (17.3)
Abdominal abscesses‡‡	26 (13.8)	29 (14.6)	55 (14.2)
Hemodialysis-associated *S. aureus* bacteremia§§	24 (12.7)	25 (12.6)	49 (12.7)
Persistent *S. aureus* bacteremia¶¶	16 (8.5)	16 (8.1)	32 (8.3)
Infective endocarditis on right side of heart	15 (7.9)	10 (5.1)	25 (6.5)
Estimated creatinine clearance <50 ml/min, excluding dialysis patients — no. (%)	17 (9.0)	14 (7.1)	31 (8.0)
Methicillin-resistant *S. aureus* bacteremia	45 (23.8)	49 (24.7)	94 (24.3)

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Table 2. Primary and Secondary Efficacy Outcomes (Modified Intention-to-Treat Population).*

Treatment Success or Failure and Secondary Outcomes	Ceftobiprole (N=189)	Daptomycin (N=198)	Adjusted Treatment Difference (95% CI)†
	no. of patients/total no. (%)		*percentage points*
Secondary outcomes			
Death through the post-treatment evaluation visit	17 (9.0)	18 (9.1)	–0.5 (–6.2 to 5.2)
Death due to *S. aureus* bacteremia	7 (3.7)	6 (3.0)	
Microbiologic eradication at the post-treatment evaluation visit	155 (82.0)	153 (77.3)	5.1 (–2.9 to 13.0)
Overall treatment success at the post-treatment evaluation visit in the per-protocol population**	127/163 (77.9)	130/167 (77.8)	0.6 (–8.3 to 9.5)
Development of new metastatic foci or other complications of *S. aureus* bacteremia after day 7	11 (5.8)	11 (5.6)	0.1 (–4.6 to 4.8)
Median time to *S. aureus* bloodstream clearance — days (95% CI)††	4 (3 to 5)	4 (3 to 5)	

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(Fig. 2). Among patients with MSSA, *S. aureus* bloodstream clearance appeared to be consistent between the trial groups (133 of 141 patients in the ceftobiprole group [94.3%] at a median of 3 days from the time of randomization and 139 of 146 patients in the daptomycin group [95.2%] at a median of 4 days). In patients with MRSA infection, clearance occurred at a median of 5 days in 42 of 45 patients (93%) in the ceftobiprole group and 43 of 49 patients (88%) in the daptomycin group (Fig. S2). The percentage of

Clinical Infectious Diseases
MAJOR ARTICLE

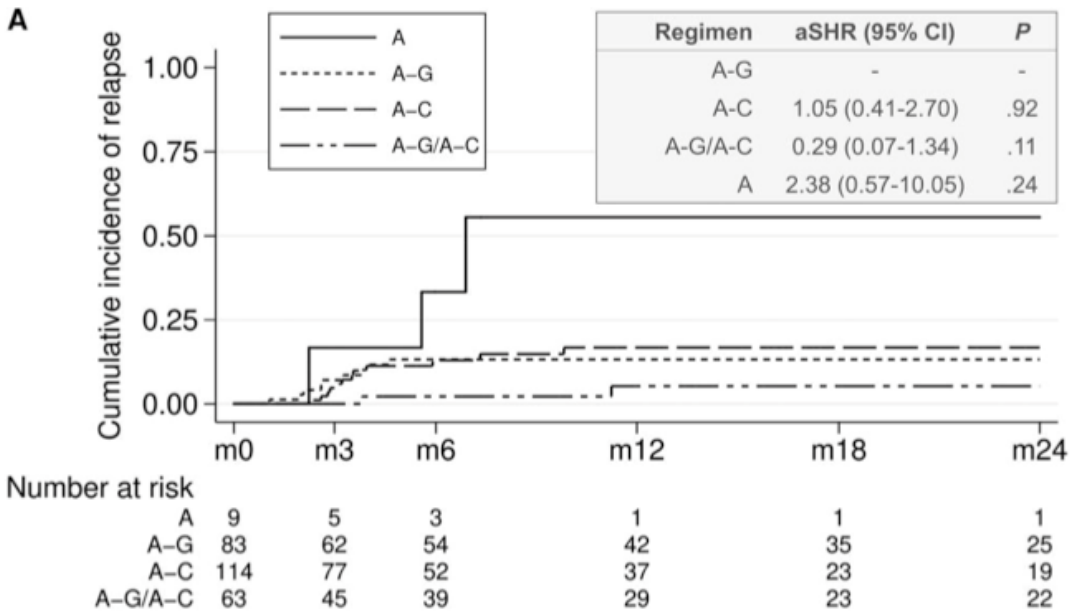
Impact of *Enterococcus faecalis* Endocarditis Treatment on Risk of Relapse

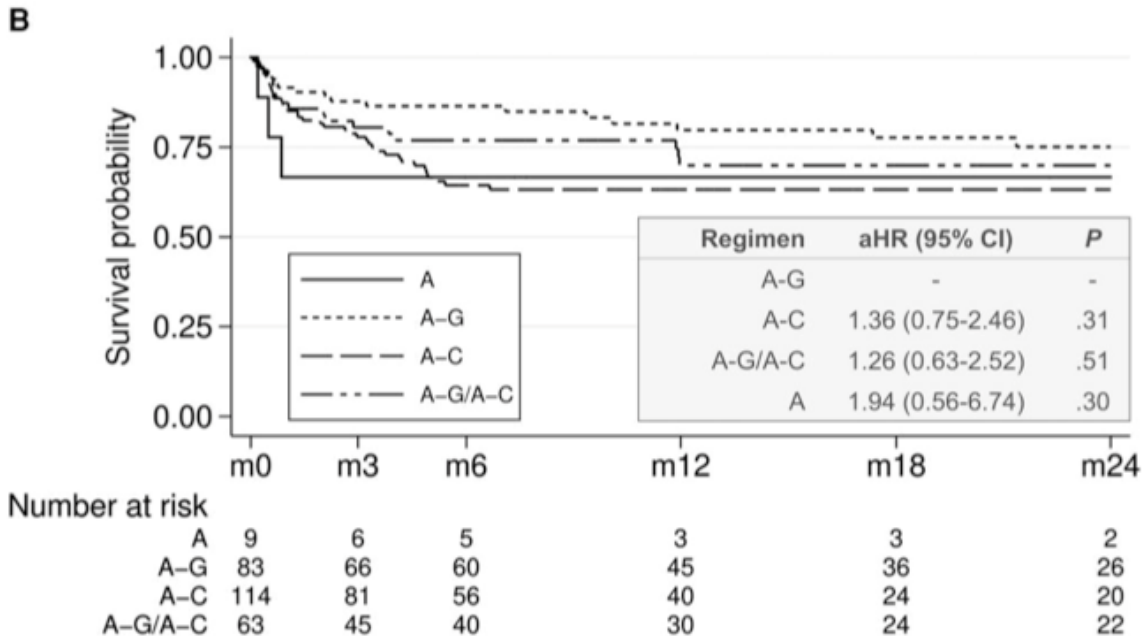
Pierre Danneels,[1,2] Jean-François Hamel,[3] Léa Picard,[4,2] Schéhérazade Rezig,[5,2] Pauline Martinet,[5,2] Aurélien Lorleac'h,[6,2] Jean-Philippe Talarmin,[7,2] Rodolphe Buzelé,[8,2] Thomas Guimard,[9,2] Gwenaël Le Moal,[10,2] Julia Brochard-Libois,[11,2] Aurélie Beaudron,[12,2] Julien Letheulle,[13,2] 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).

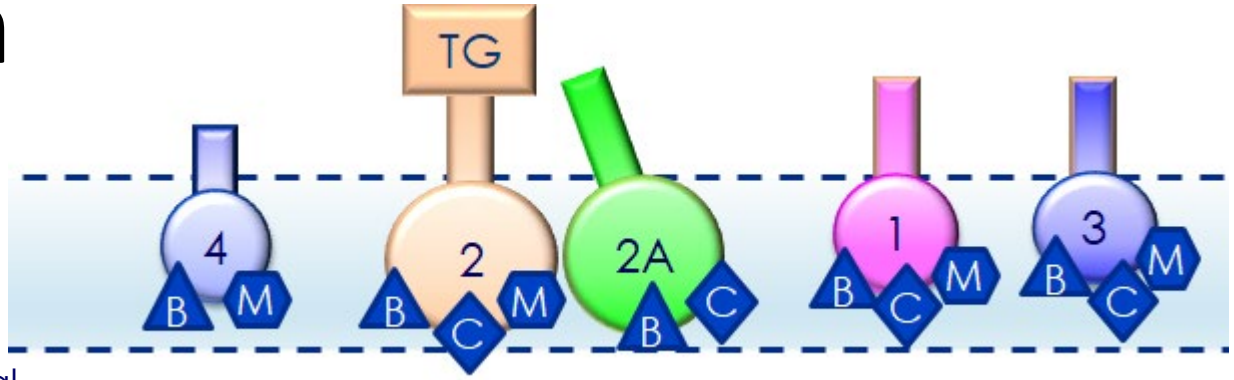
Conclusions. Relapses after treatment of EFIE are frequent, frequently asymptomatic, and may occur more than 6 months after the initial episode.

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





Ceftobiprole is unaffected by PBP4 overexpression

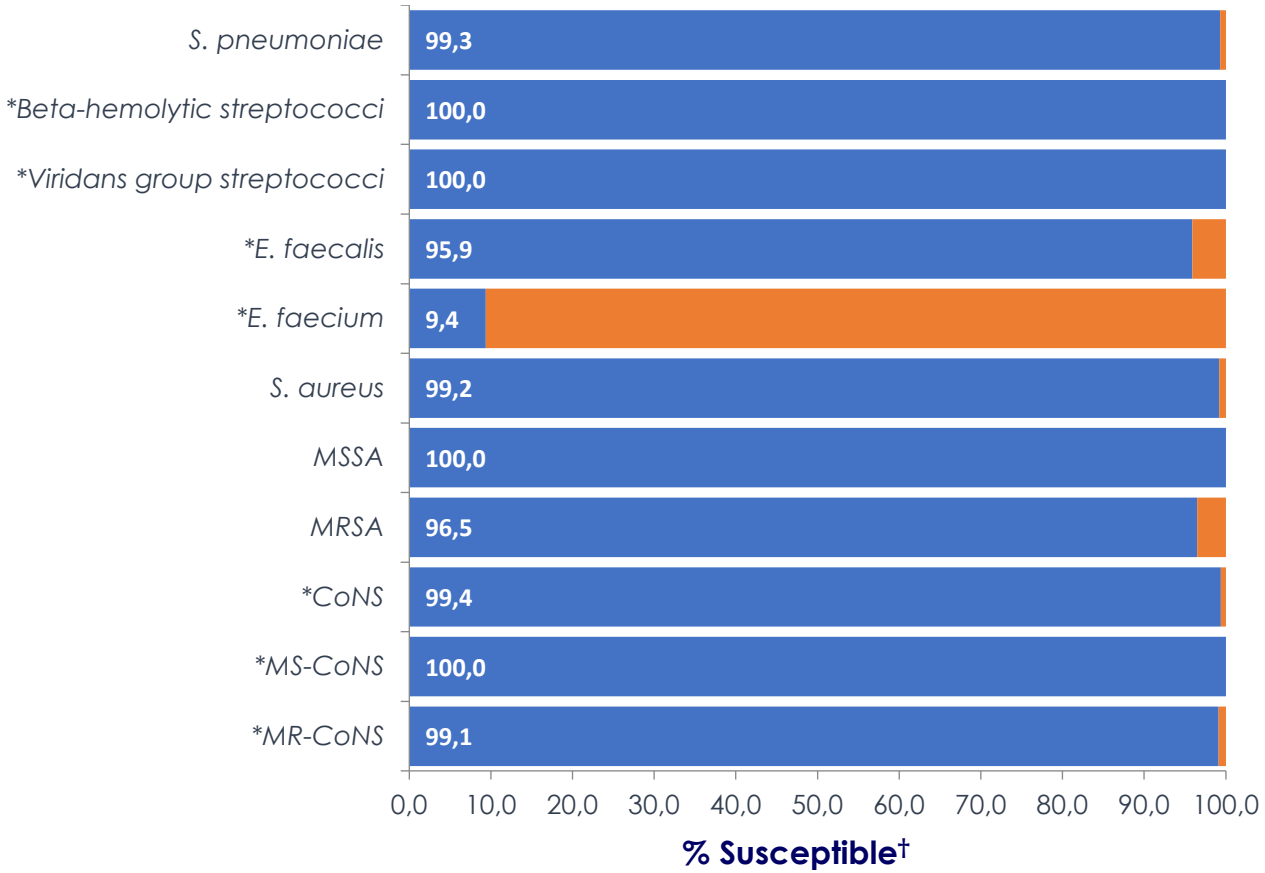


	PBP4	PBP2	PBP2a	PBP1	PBP3
Ceftaroline (C)		✓	✓	✓	✓
Ceftobiprole (B)	✓	✓	✓	✓	✓
Methicillin (M)	✓	✓			
Meropenem (M)	✓	✓		✓	✓
Ceftaroline + Meropenem	✓	✓	✓	✓	✓

TG: Transglycosylase domain
TP: transpeptidase domani
nPDB: non penicillin binding domain

Adapted from Lahiri SD, Alm RA. J Antimicrob Chemother 2016;

Activity of ceftobiprole vs Gram-positive pathogens: Europe, Turkey & Israel, 2015 (5355)



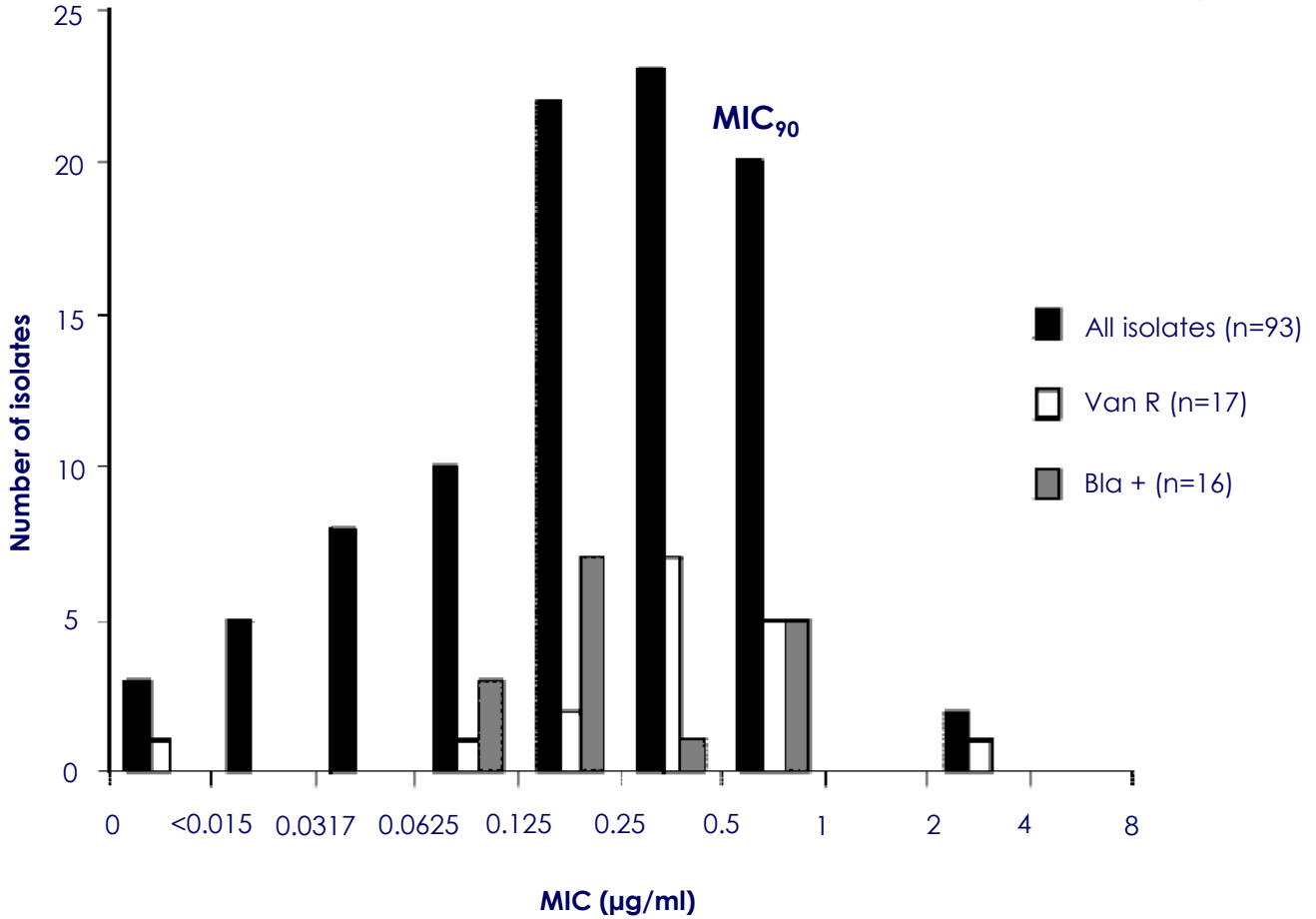
No. of strains	MIC_{90} (mg/L)
833	0.5
498	0.03
264	0.25
411	2
235	>4
2,588	2
2,009	0.5
579	2
526	2
190	0.5
336	4

†Using EUCAST breakpoints; *, indicates application of the PK/PD species non-specific breakpoint (4 mg/L)
MS, methicillin-sensitive; MR, methicillin-resistant; SA, *S. aureus;* CoNS, coagulase-negative staphylococci

Pfaller MA, et al. Diagn Microbiol Infect Dis; 91 (2018) 77–84

Ceftobiprole is active against clinical isolates of *E. faecalis*, including ampicillin- and vancomycin-resistant isolates

Arias et al., AAC 2007; 51: 2043-2047



concentrations as low as 1 µg/ml regardless of the production of β-lactamase or vancomycin resistance. A combination of ceftobiprole (0.5 µg/ml) and streptomycin (25 µg/ml) was synergistic against Bla$^+$ TX0630 and TX5070. Ceftobiprole (0.5 µg/ml) plus gentamicin (10 µg/ml) was synergistic against VanB isolate TX2484 and showed enhanced killing, but not synergism, against TX2784 (VanA), despite the absence of high-level resistance to gentamicin. In conclusion, ceftobiprole exhibited good in vitro activity against *E. faecalis*, including

Ceftobiprole for the treatment of invasive *Enterococcus faecalis* infections: ampicillin, "Should I Stay or Should I Go"?

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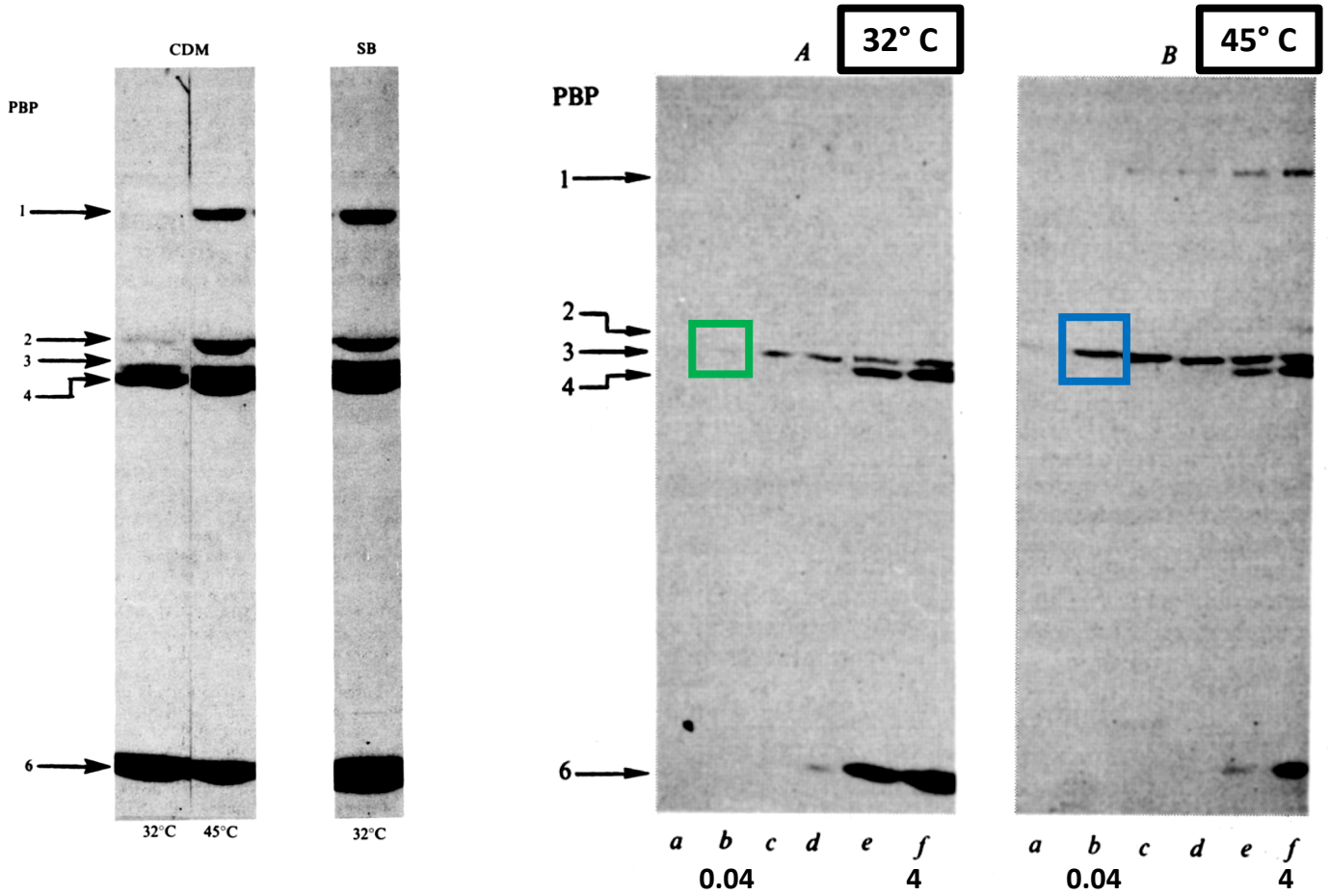
DAME, Università di Udine

Direct dependance of penicillin sensitivity of *E. faecalis* on growth rate

The higher the growth rate the lower the penicillin MIC is:

- 45°C (generation time 31.5 min): penicillin MIC 0.04 mg/l;
- 32° C (generation time 47.27 min): penicillin MIC 4 mg/l.

R Fontana et al. Nature. 1980 Sep 4;287(5777):70-2



Two different conditions (temperature and growth medium) associated with changes in growth rate are accompanied by changes in the physiological status of PBPs.

Table 2 Evaluation of the absolute amount of radioactivity bound to PBPs in cells growing in the presence of various ^{14}C-benzylpenicillin concentrations

^{14}C-benzyl-penicillin concentration ($\mu g\ ml^{-1}$)		Area of the peak (mm^2) corresponding to PBP 1	PBP 2	PBP 3	PBP 4	PBP 6
0.02	*A*	—	—	43	—	—
	B	—	—	100	—	—
0.04	*A*	—	—	53	—	—
	B	—	—	228	—	—
0.08	*A*	—	11	82	—	—
	B	48	40	252	—	—
0.32	*A*	6	15	112	32	54
	B	72	48	274	—	21
0.80	*A*	32	18	189	297	580
	B	105	57	280	324	63
4.00	*A*	25	20	200	352	804
	B	161	72	332	406	322

At 32êC and PEN concentration = PEN MIC:

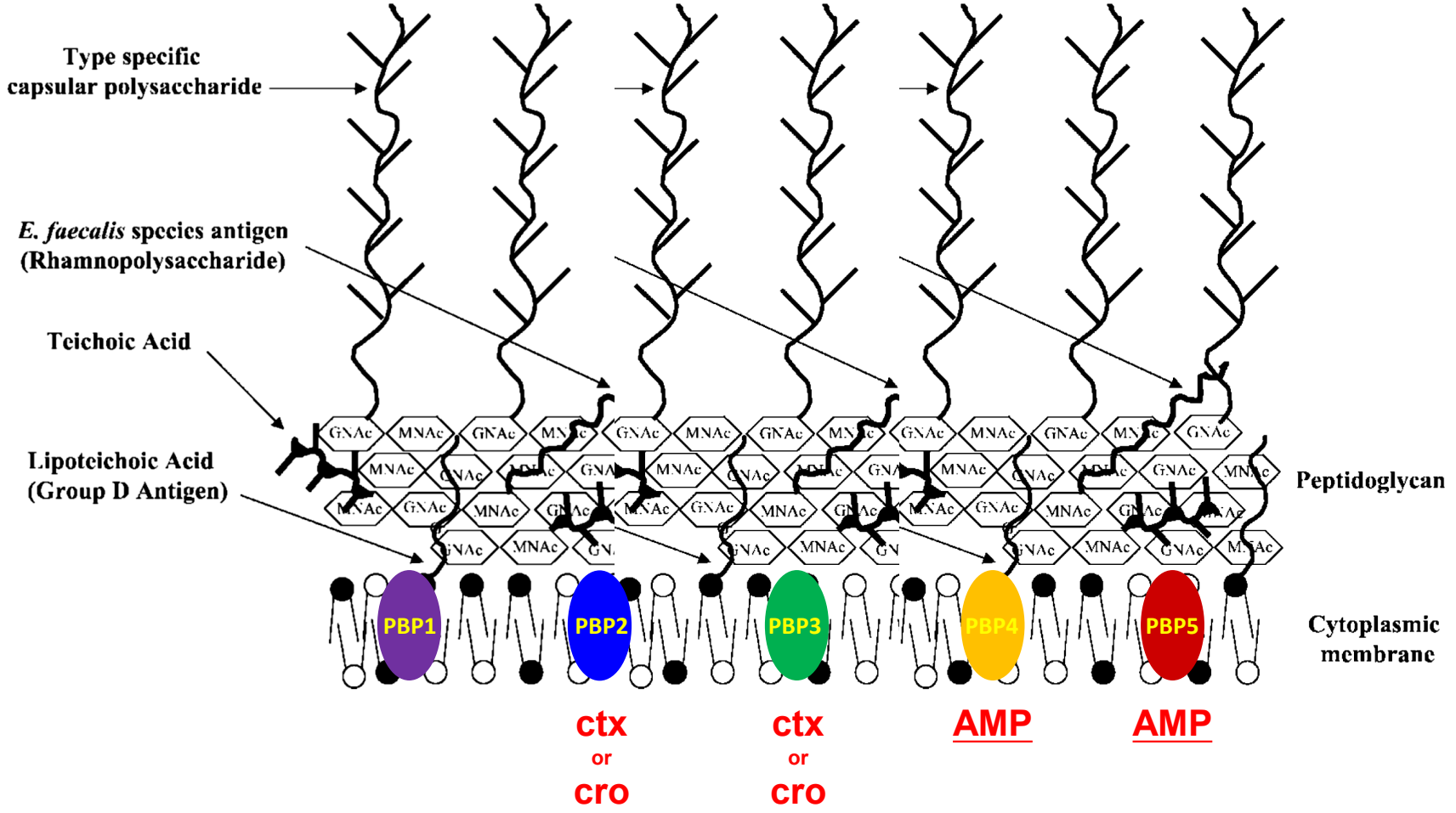
1. PBP3: same saturation observed in condition of optimal growth;
2. PBP3 could not be the only lethal target: this possibility is supported by the fact that the amount of penicillin bound to other PBPs also changes in this growth condition.

R Fontana et al. Nature. 1980 Sep 4;287(5777):70-2

The *critical* level of PBP saturation and inhibition might be like the critical mass of a fissile material required to initiate and sustain a nuclear chain reaction

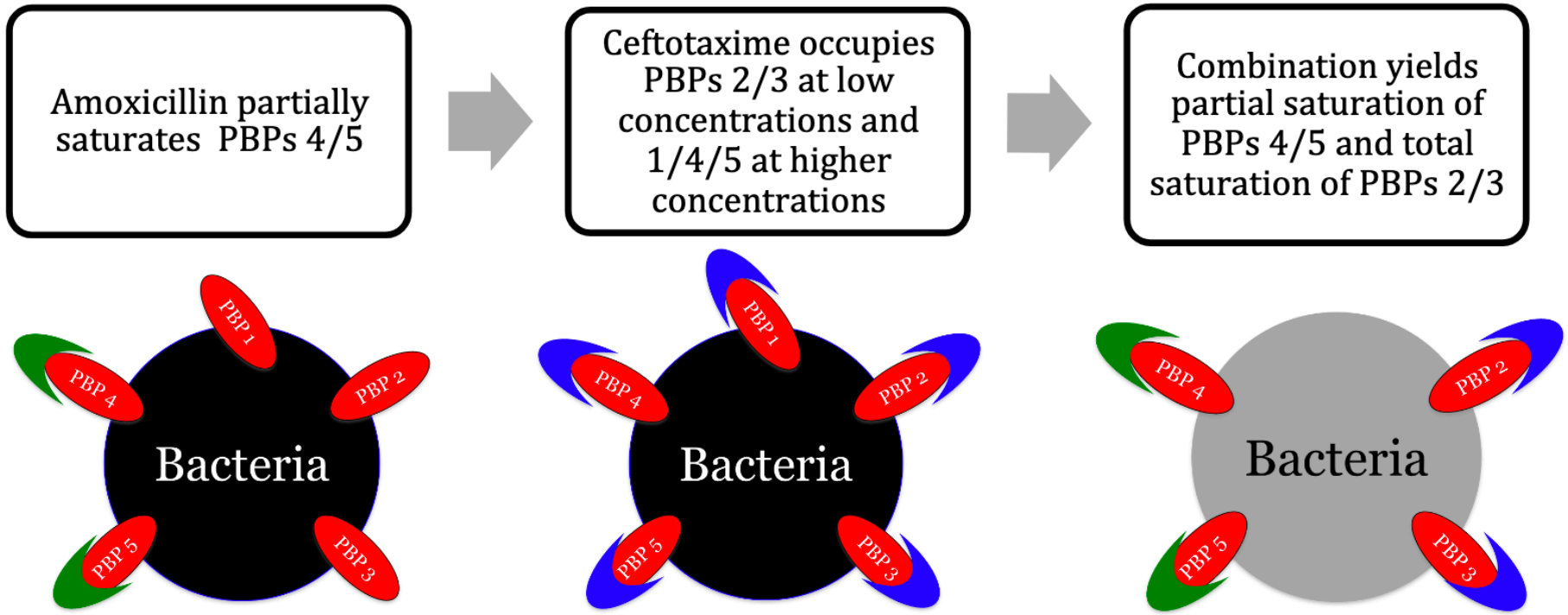
- Growth inhibition by beta-lactams is indirect and non constant and depends on which PBP is essential for growth in a certain physiologic status and on its affinity for the antibiotic.
- Whatever the crucial PBPs are for each growth condition, a *critical* level of PBP binding is required for cell killing. This *critical* level is a composite of beta-lactam affinity to the PBPs and number of PBPs bound.
- Hence beta-lactam and, at a greater extent, beta-lactam combinations, by binding to different PBP with various levels of affinity, can increase PBP saturation to the *critical* level necessary for bacterial killing.

Dual beta-lactam therapy: synergistic and bacteriocidal activity vs *Enterococcus faecalis*



Mainardi et al. Antimicrob Ag Chemother 1995; 39: 1984
Gavaldà et al. Antimicrob Ag Chemother 1999; 43; 639
Hancock LE et al. Proc Natl Acad Sci U S A. 2002 Feb 5;99(3):1574-9

Complete PBPs saturation: bactericidal synergy between aminopenicillin (AMX) and cephalosporins (CTX-CPT)



β-lactam activity with Ampicillin *plus* ceftriaxone → significant lower amoxicillin MICs

- Amoxicillin binds to essential PBP4/5, which leads to an upregulation of nonessential PBP2/3, which cefotaxime subsequently binds to and leads to total PBP saturation.

Mainardi, et al. AAC 1995; Gavaldà et al., JAC 2003; D'Arezzo S., et al., Microb Drug Resist. 2017

Beta-lactam binding to enterococcal PBPs in standard growth conditions

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

Mainardi JL et al. Antimicrob Agents Chemother. 1995 Sep; 39(9): 1984–1987.
Gavaldà J et al. Antimicrob Agents Chemother. 1999 Mar;43(3):639-46.
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Article

Ampicillin and Ceftobiprole Combination for the Treatment of *Enterococcus faecalis* Invasive Infections: "The Times They Are A-Changin"

Simone Giuliano [1], Jacopo Angelini [2,3], Denise D'Elia [1,*], Monica Geminiani [1], Roberto Daniele Barison [1], Alessandro Giacinta [1], Assunta Sartor [4], Floriana Campanile [5], Francesco Curcio [3,6], Menino Osbert Cotta [7,8], Jason A. Roberts [7,8,9,10], Massimo Baraldo [2,3] and Carlo Tascini [1]

- A retrospective analysis of our real-life experience in the treatment of *E. faecalis* invasive infections with ampicillin in combination with ceftobiprole (ABPR).
- Therapeutic drug monitoring (TDM) was always performed for ampicillin and ceftobiprole, and serum concentrations of both drugs were compared to the MICs of the different enterococcal isolates.
- To maximize the time-dependent antimicrobial properties of ceftobiprole and ampicillin, we administered ceftobiprole by a prolonged infusion over three hours and ampicillin by continuous infusion, adjusting the dosage with respect to renal function. This therapeutic strategy aimed to achieve the most effective pharmacodynamic and pharmacokinetic antimicrobial target represented by the highest plasmatic concentration of the antibiotic above the MIC (%T > MIC) for the longest time during the dosing interval.

Giuliano S et al. Antibiotics (Basel). 2023 May 9;12(5):879

ABPR for *E. faecalis* infections: I

- From January 2020 to December 2020, 21 patients with invasive *E. faecalis* infections.
- 13/21 (62%) left-sided infective endocarditis, 8/21 (38%) primary bacteremia (50% complicated, 50% uncomplicated).
- IE: 8/13 (62%) PVE; 5/13 (38%) NVE.
- IE: 3 periannular complications in PVE.
- IE: two cardioembolic events (1 PVE, 1 NVE).
- Microbiology: ampicillin MIC_{50} and MIC_{90} were 0.5 mg/l and 2 mg/l, respectively; ceftobiprole MIC_{50} and MIC_{90} were 0.5 mg/l and 1 mg/l, respectively.

Giuliano S et al. Antibiotics (Basel). 2023 May 9;12(5):879

ABPR for *E. faecalis* infections: II

- IE: the mean duration of the ABPR regimen was 27.8 ± 14.5 days.
- BSI: the mean duration of ABPR treatment was 20.4 ± 11.1 days.
- The mean duration of partial oral treatment was 19.0 ± 10.6 days.
- No patient developed a breakthrough infection.
- 2/21 patients (9%) experienced ABPR-related side effects such as seizure and a skin rash, respectively.
- A surgical procedure was performed on nine patients: eight of them (38%) underwent valve replacement, and one patient was managed with valve repair. The mean time to surgery was 18.4 ± 11.3 days.
- The mean length of hospital stay was 57.6 ± 44.3 days.

Giuliano S et al. Antibiotics (Basel). 2023 May 9;12(5):879

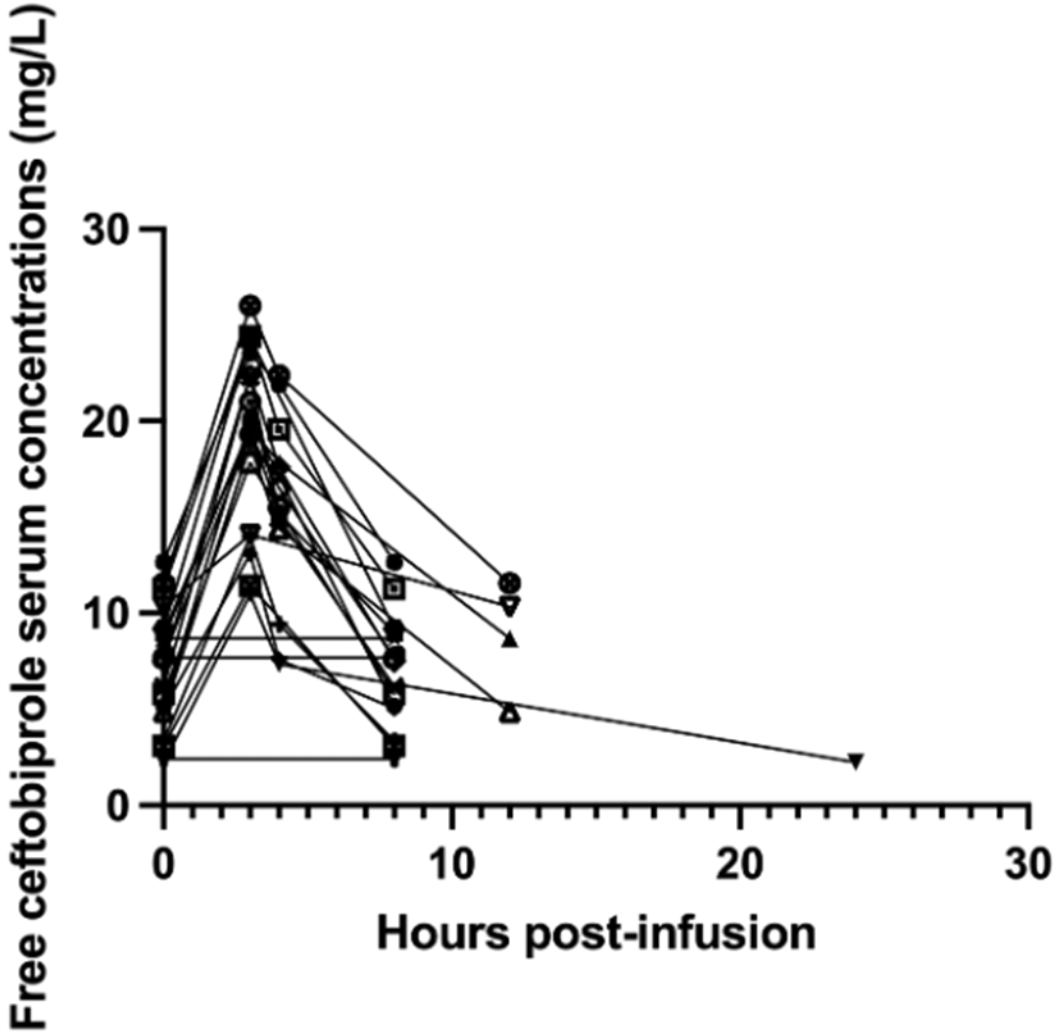
ABPR for *E. faecalis* infections: III

- Clinical cure: 81% of patients.
- Microbiological cure: 86% of patients.

Outline

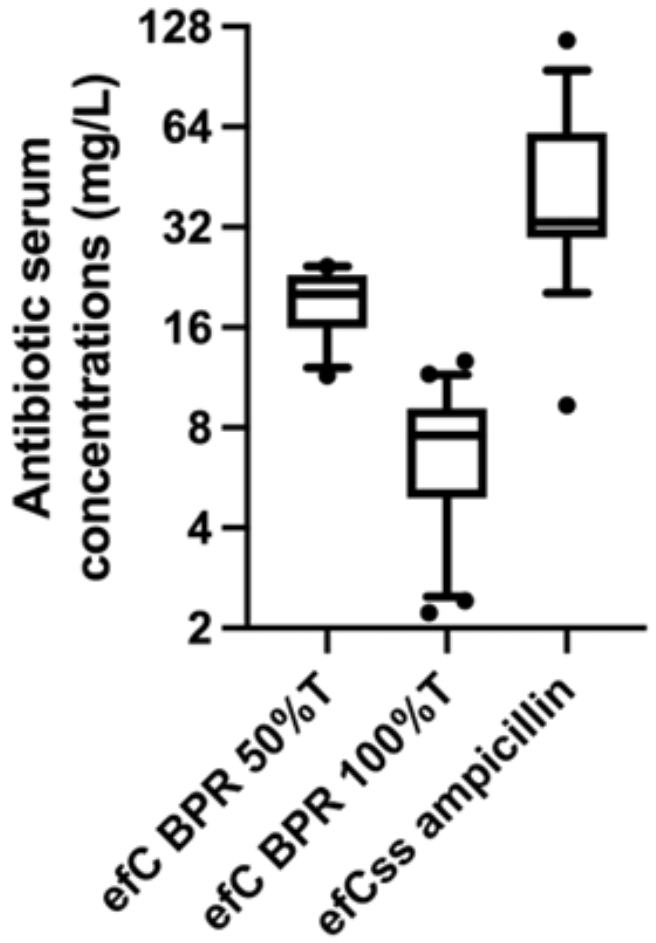
- Background.
- PK/PD of BPR and AMP.
- Time-kill experiments.
- Conclusions.

Spaghetti plot reporting the total estimated free serum concentrations of ceftobiprole from the 21 analyzed patients



Giuliano S, Angelini J, Campanile F et al. *Manuscript in preparation*

Estimated BPR and AMP serum concentrations



efC 50%T = estimated free serum concentration at 50% of dosing interval
efC100% T= estimated trough free serum concentration

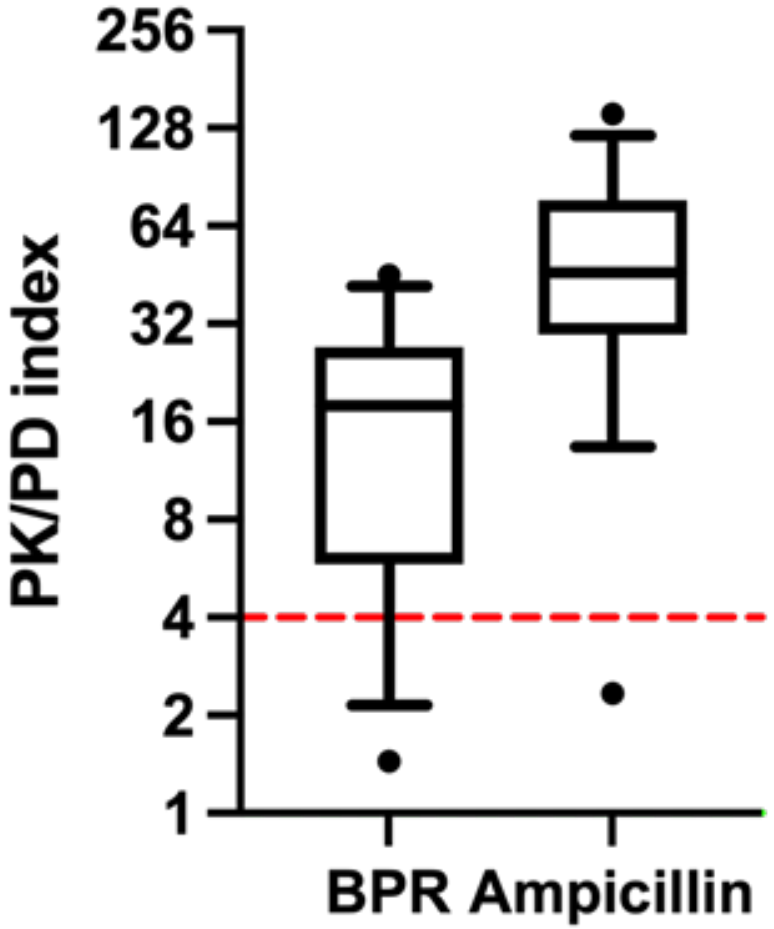
Giuliano S, Angelini J, Campanile F et al. *Manuscript in preparation*

Percentage of PK/PD target attainment

	Antibiotic	
PK/PD parameter	**BPR**	**AMP**
50%T>MIC	90.5%	-
50%T>4xMIC	71.0%	-
100%T>MIC	85.5%	81.0%
100%T>4XMIC	62.0%	76.0%

Giuliano S, Angelini J, Campanile F et al. *Manuscript in preparation*

Observed Pharmacokinetic/Pharmacodynamic (PK/PD) ratios at 100% of dosing interval (100% fT>MIC).

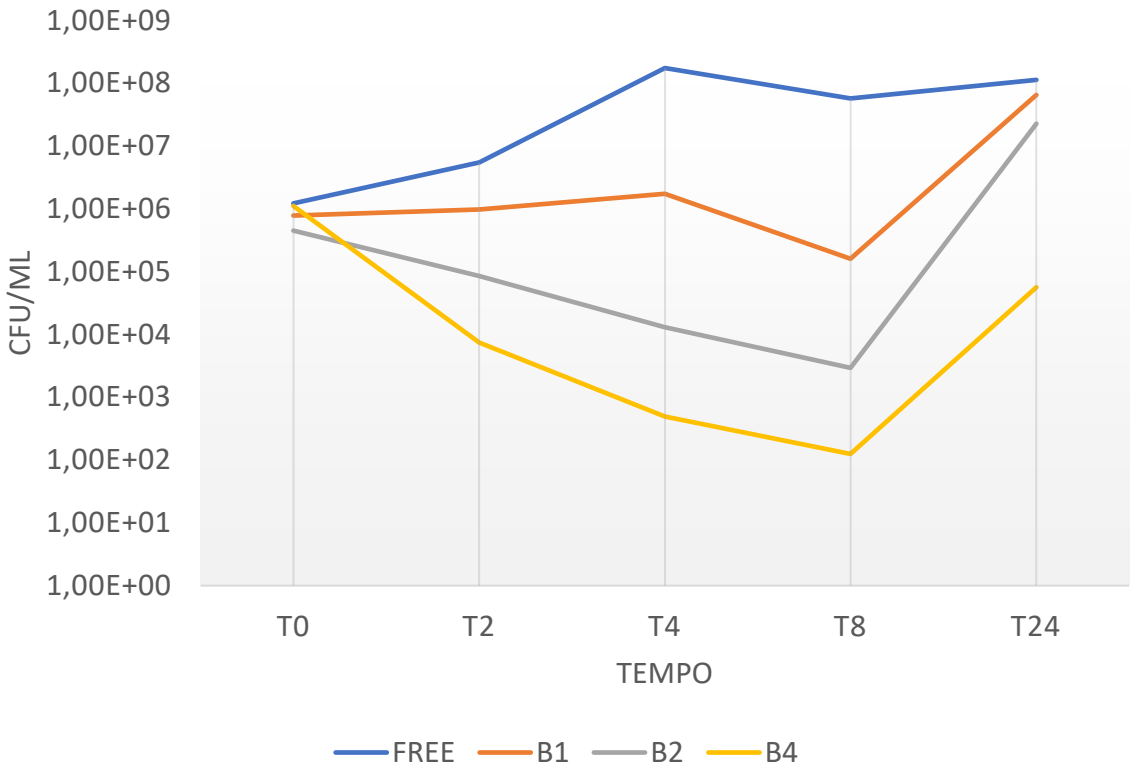


Giuliano S, Angelini J, Campanile F et al. *Manuscript in preparation*

Codice: 52194160

MIC BPR: 0.12 mg/L

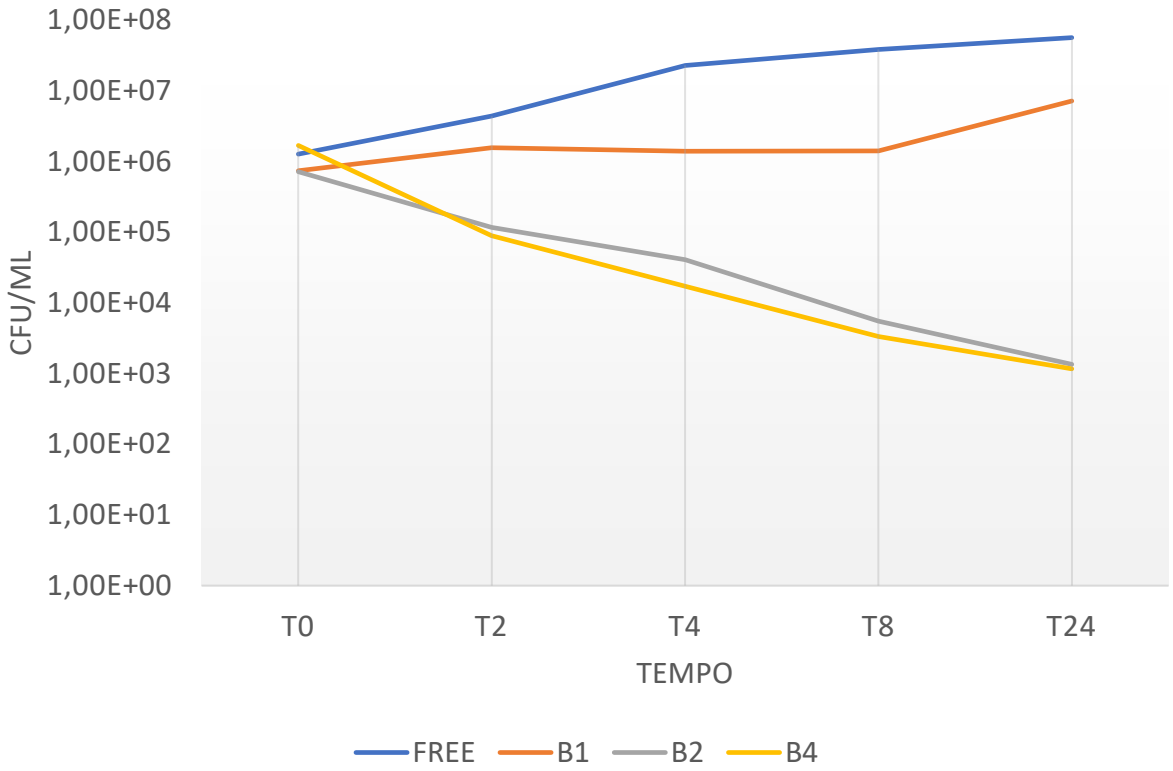
Condizioni	T0	T2	T4	T8	T24
FREE	1.2×10^6	5.4×10^6	1.7×10^8	5.7×10^8	1.1×10^8
B1	7.8×10^5	$9. \times 10^5$	1.7×10^6	1.6×10^5	6.5×10^7
B2	4.5×10^5	8.5×10^4	1.3×10^4	2.9×10^3	2.2×10^7
B4	1.1×10^6	7.4×10^4	4.9×10^2	1.2×10^2	5.6×10^4



Codice: 52599858

MIC BPR: 0.12 mg/L

Condizioni	T0	T2	T4	T8	T24
FREE	1.2×10^6	4.4×10^6	2.3×10^7	3.8×10^7	5.7×10^8
B1	7.4×10^5	1.5×10^6	1.4×10^6	1.4×10^6	7.2×10^7
B2	7.2×10^5	1.1×10^5	4.0×10^4	5.5×10^3	1.3×10^3
B4	1.7×10^6	8.9×10^4	1.7×10^4	3.3×10^3	1.1×10^3



Cortesia Prof Campanile, Università di Catania

Codice: 53906575 Data: 20/09/2023

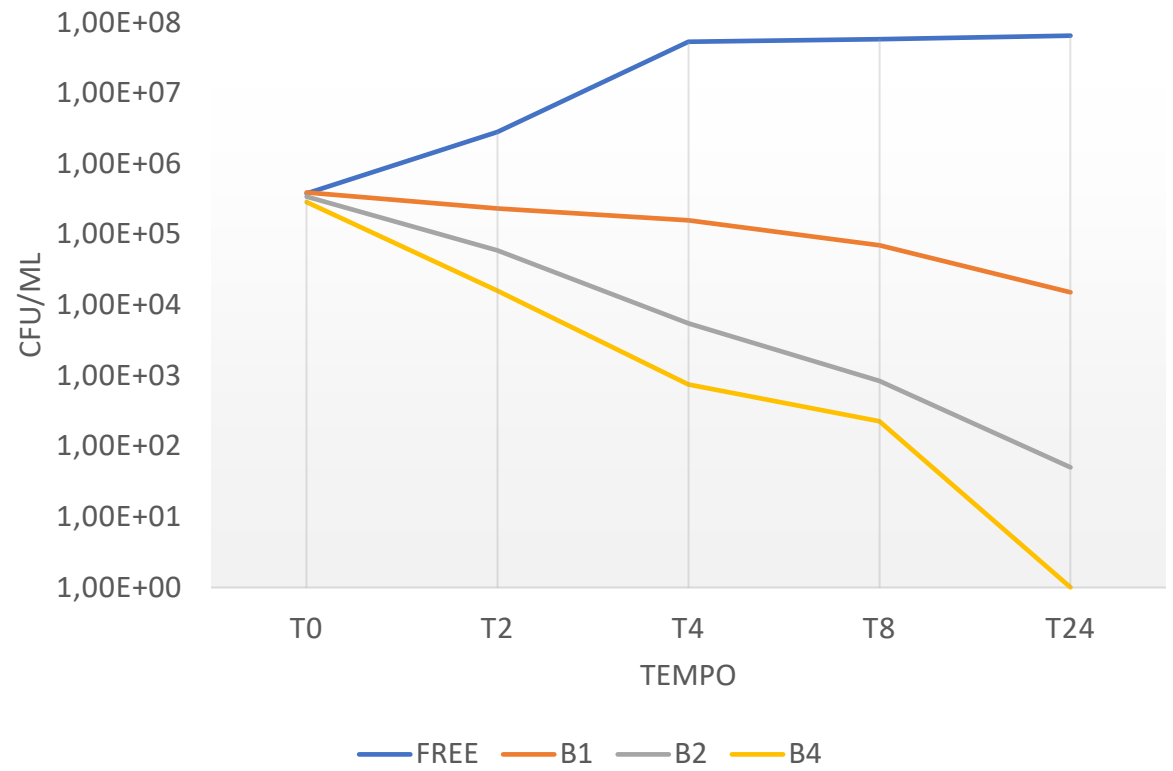
MIC BPR: mg/L 0.5 mg/L

Condizioni	T0	T2	T4	T8	T24
FREE	1,18E+06	1,61E+06	3,14E+07	2,70E+07	8,95E+07
B1	8,73E+05	1,11E+05	1,19E+05	1,21E+04	1,61E+07
B2	3,69E+05	9,45E+04	4,10E+03	1,12E+03	1,15E+02
B4	5,26E+05	1,10E+04	3,14E+03	6,30E+02	1,15E+02

Codice: 54281522

MIC BPR: 1 mg/L

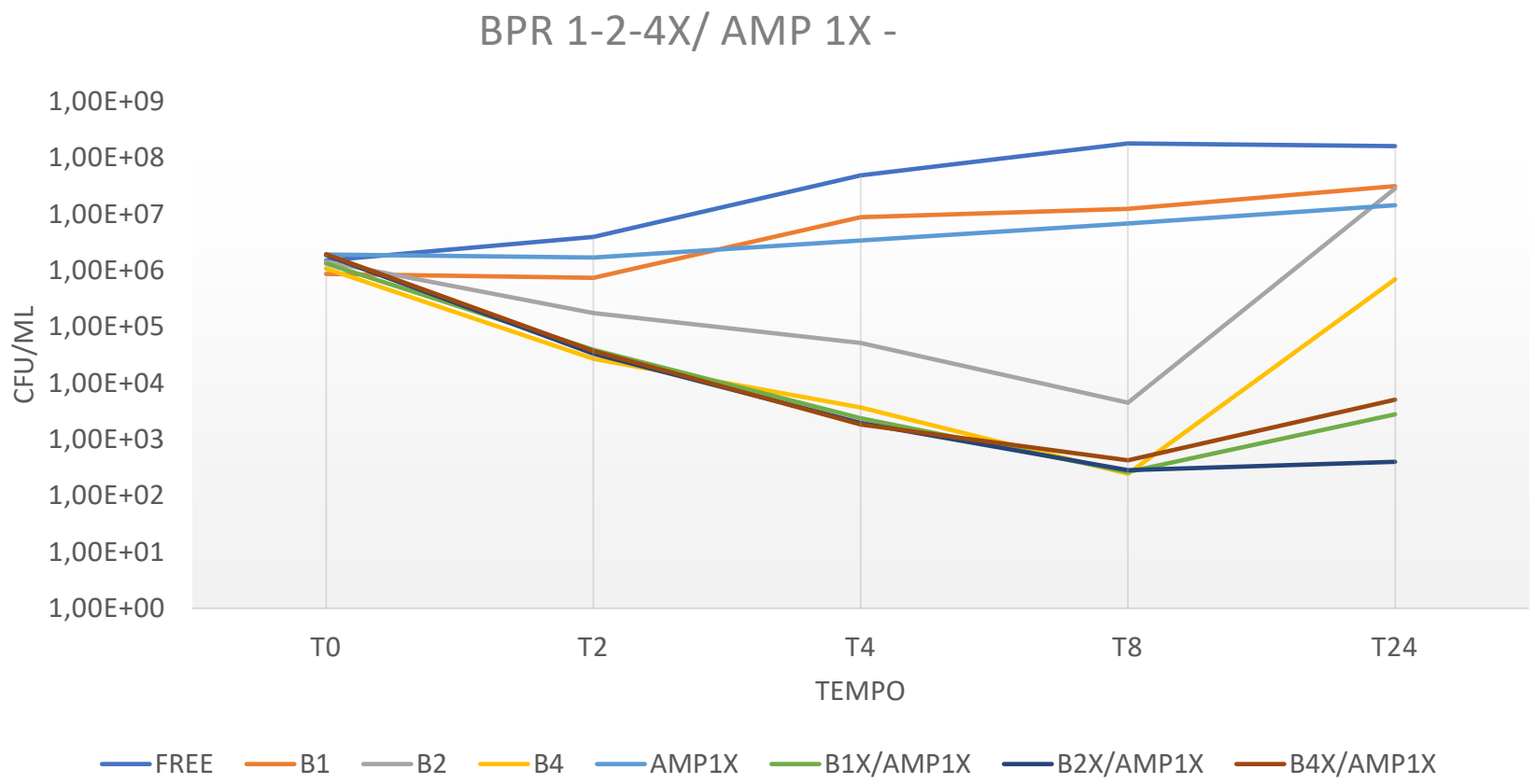
Condizioni	T0	T2	T4	T8	T24
FREE	3,78E+05	2,79E+06	5,34E+07	5,79E+07	6,49E+07
B1	3,89E+05	2,32E+05	1,58E+05	7,00E+04	1,50E+04
B2	3,43E+05	5,90E+04	5,50E+03	8,35E+02	5,00E+01
B4	2,86E+05	1,58E+04	7,50E+02	2,25E+02	1



Cortesia Prof Campanile, Università di Catania

Condizioni	T0	T2	T4	T8	T24
FREE	1,50E+06	3,93E+06	4,84E+07	1,79E+08	1,61E+08
B1	8,65E+05	7,35E+05	8,76E+06	1,24E+07	3,15E+07
B2	1,44E+06	1,74E+05	5,15E+04	4,50E+03	2,85E+07
B4	1,09E+06	2,70E+04	3,71E+03	2,45E+02	6,92E+05
AMP1X	1,90E+06	1,69E+06	3,39E+06	6,79E+06	1,43E+07
B1X/AMP1X	1,33E+06	3,92E+04	2,39E+03	2,65E+02	2,80E+03
B2X/AMP1X	1,86E+06	3,35E+04	1,97E+03	2,85E+02	4,00E+02
B4X/AMP1X	1,932E+06	3,70E+04	1,85E+03	4,25E+02	5,10E+03

Cortesia Prof Campanile, Università di Catania



Codice: 58438624

MIC BPR mg/L 0.06 mg/L

MIC AMP mg/L 0.5 mg/L

Conclusioni

- Cefalosporine di 5 generazione: farmaci ancora da studiare
- L’infiammazione, come la possiamo misurare e modulare
- Ceftobiprolo farmaco per le BSI da S. aureus (compreso MRSA)
- Forme complicate di BSI da S. aureus dapto più cefalosporine 5 generazione
- Ceftobiprolo farmaco per l’E. faecalis (compreso le endocarditi), al momento con ampicillina