Gram +: epidemiologia e strategie innovative

Dott. Matteo G. Lupi
U.O. Malattie Infettive - ASST Cremona

FOCUS DELLA PRESENTAZIONE:

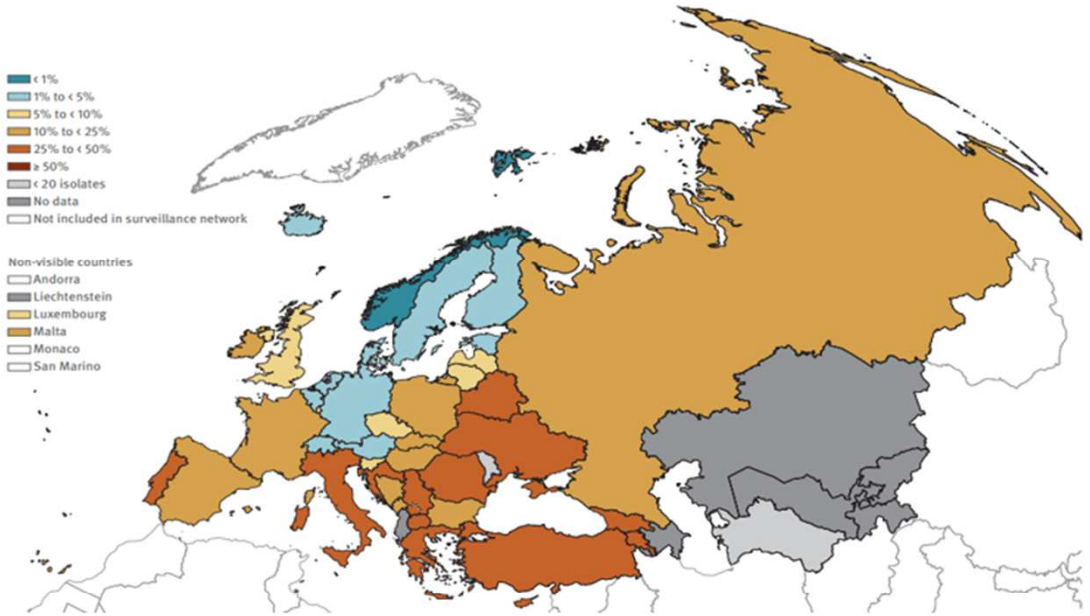
1. *Staphylococcus aureus*
2. *Enterococcus faecalis*
3. *Enterococcus faecium*

1. *Staphylococcus aureus*

Ancora oggi una delle sfide più ardue da affrontare

- elevata patogenicità
- elevata capacità di produzione di biofilm
- elevata capacità di acquisire resistenza antimicrobica
- frequente fallimento terapeutico (effetto inoculo, ''small colony variants'')

Fig. 8 *Staphylococcus aureus*. Percentage of invasive isolates resistant to meticillin (MRSA),[a] by country, WHO European Region, 2021



Total number of invasive isolates tested (n) and percentage of isolates with resistance phenotype (%)[a], by bacterial species and antimicrobial group/agent, 2021 EU/EEA range, population-weighted mean and trend, Italy, 2017–2021

Bacterial species	Antimicrobial group/agent	2017		2018		2019		2020		2021		2021 EU/EEA range and population-weighted mean[b]	Trend 2017–2021[c]
		n	%	n	%	n	%	n	%	n	%		
S. aureus	MRSA[f]	3591	33.9	8263	34.0	9681	34.3	10923	33.5	11344	30.0	15.8 (0.9–42.9)	↓*

MORTALITÀ CORRELATA AD ANTIMICROBICORESISTENZA

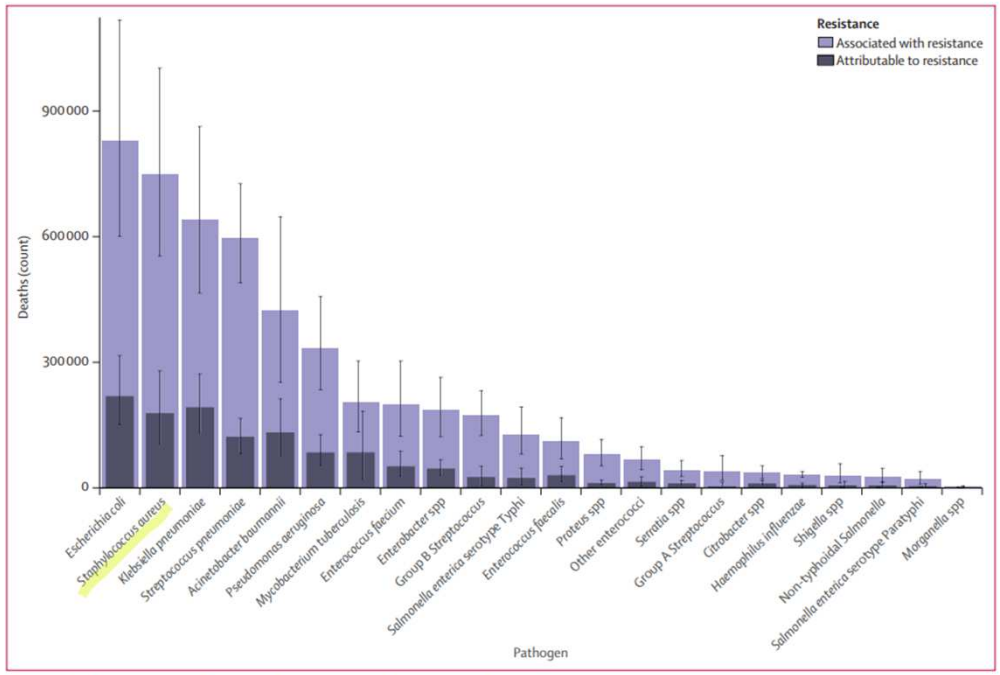


Figure 4: **Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019**
Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals.

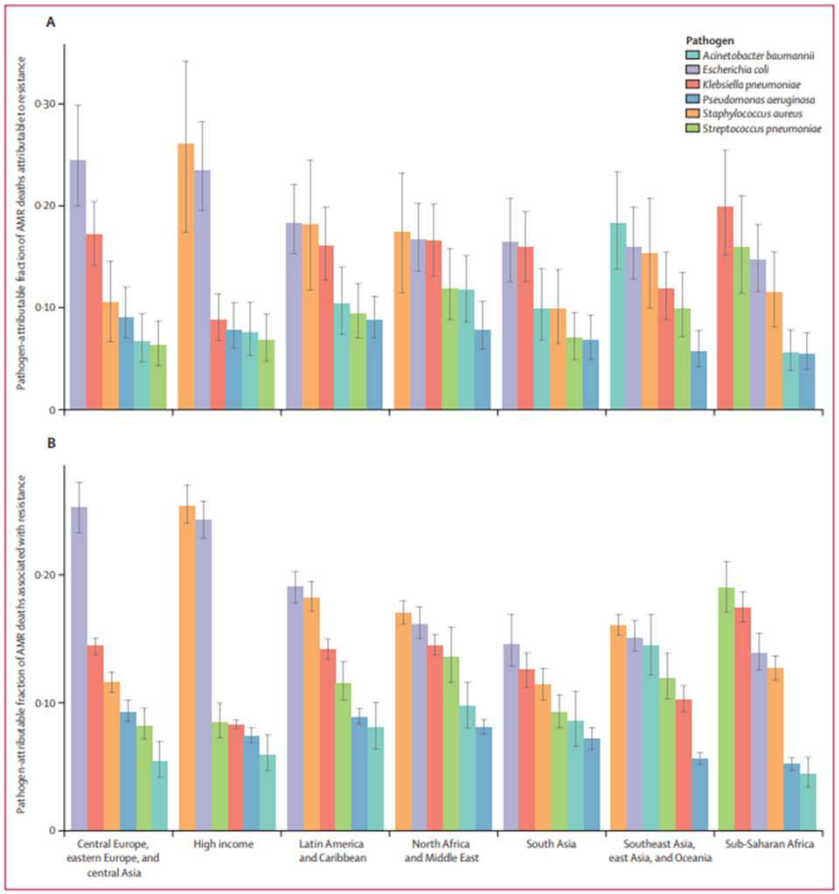


Figure 5: **Pathogen-attributable fraction of deaths attributable to (A) and associated with (B) bacterial AMR for the six leading pathogens by GBD super-region, 2019**
Error bars show 95% uncertainty intervals. AMR=antimicrobial resistance. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

''Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis''
Lancet 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19

GESTIONE TERAPEUTICA DELLA SEPSI DA MRSA
(sinossi di alcune linee guida ad oggi disponibili)

IDSA

Prima linea:

- **vancomicina o daptomicina (6mg/kg, 8-10mg/kg nelle infezioni complicate)**

Seconda linea o salvataggio:

- **daptomicina (10mg/kg) + (a scelta) gentamicina, rifampicina, linezolid, bactrim o un beta-lattamico)**

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children. .Clinical Infectious Diseases 2011;52(3):e18–e55

SIMIT-SITA-GISA-AMCLI-SIM

Prima linea:

- **daptomicina o vancomicina**
- **ceftarolina o ceftobiprolo** (se dapto o vanco non disponibili)

Seconda linea o salvataggio:

- **daptomicina** o **vancomicina + (**a scelta) fosfomicina o beta-lattamico

Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM)

BSAC

Prima linea:

- **vancomicina**
- **linezolid** (se vanco non disponibile)

Seconda linea o salvataggio:

- **daptomicina** o **teicoplanina**

Treatment of methicillin-resistant Staphylococcus aureus (MRSA): updated guidelines from the UK. Nicholas M Brown et al. JAC-Antimicrobial Resistance, Volume 3, Issue 1, March 2021, dlaa114, https://doi.org/10.1093/jacamr/dlaa114

Principali problemi relativi a:

- **sepsi**
- **infezioni dei dispositivi intracardiaci**
- **infezioni di protesi articolari**

Secondo l'AARP Public Policy Institute, circa **7,2 milioni di americani (2,2%) sono portatori di protesi articolari**, e **ogni anno** a circa **1 milione** vengono impiantate **protesi del ginocchio e dell'anca**. Inoltre, **ogni anno** negli Stati Uniti vengono impiantati quasi **370.000 pacemaker cardiaci**.

Understanding the market for implantable medical devices.
Washington, DC : AARP Public Policy Institute, August 2017

Elevata capacità di produzione di **biofilm**

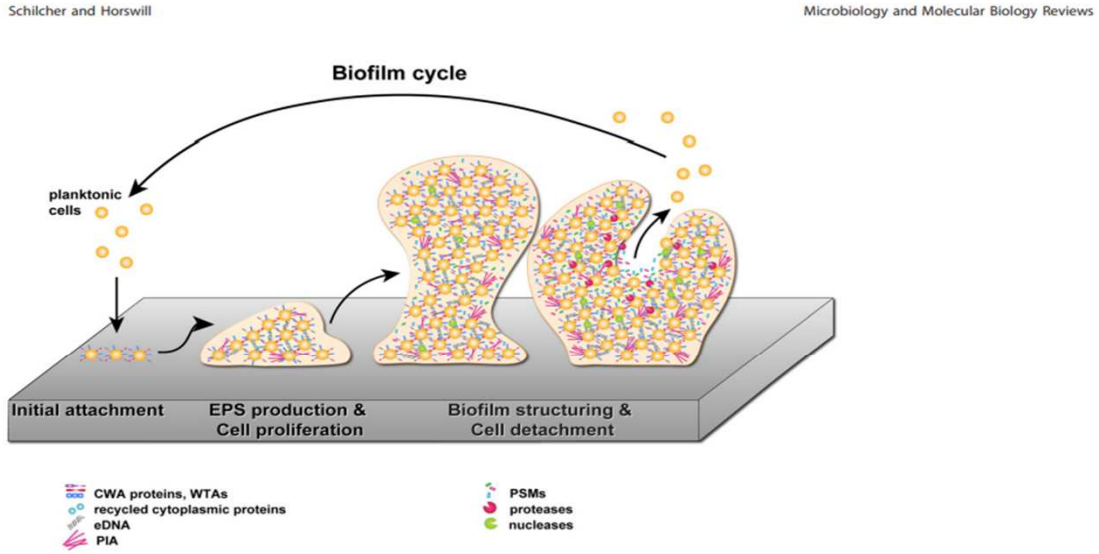


FIG 1 Staphylococcal biofilm cycle. During the first step of biofilm formation, planktonic staphylococcal cells attach to a surface with CWA proteins and WTAs (initial attachment). The production of PIA, eDNA, and adhesins to establish intercellular interactions is upregulated and leads to the formation of microcolonies on the surface (EPS production and cell proliferation). Cells within the growing biofilm express nucleases and PSMs, which are responsible for the formation of channels and towers in the matured biofilm. In the last step, the biofilm is dispersed by the action of PSMs and proteases, allowing the bacterial cells to detach from the biofilm to colonize new niches (biofilm structuring and cell detachment). The depiction of matrix components was inspired by Fig. 5 from the work of Hobley and colleagues (9).

Schilcher K, Horswill AR. 2020. Staphylococcal biofilm development: structure, regulation, and treatment strategies. Microbiol Mol Biol Rev 84:e00026-19. https://doi.org/10 .1128/MMBR.00026-19.

Table 2 In vitro MIC, MBIC and MBEC values for the antibiotics tested against *S. aureus* DFU isolates (*CLSI range susceptibility)

	Antimicrobial agents									
	FOX	CPT	CIP	CLI	DOX	ERY	GEN	LZD	MEM	VAN
MIC range	1.5–256	0.064–38	0.06- >32	0.015–0.06	0.064–0.125	0.12- >256	0.06–64	1–2	0.015–16	0.25–1
MBIC range	2–256	0.5–8	0.5–512	0.5–128	0.5–512	0.5- >256	0.5- >128	1- >1024	0.5–32	1–16
MBEC range	2–1024	0.5–1024	256–512	64- >1024	64–128	64- >1024	1- >256	4- >1024	0.5- >1024	8- >1024

FOX, cefoxitin (≤4 μg/ml*); CPT, ceftaroline (≤0.5 μg/ml *); CIP, ciprofloxacin (≤4 μg/ml *); CLI, clindamycin (≤0.25 μg/ml*); DOX, doxycycline (≤4 μg/ml*); ERY, erythromycin (≤8 μg/ml*); GEN, gentamicin (≤4 μg/ml*); LZD, linezolid (≤4 μg/ml*); MEM, meropenem (≤4 μg/ml*); VAN, vancomycin (≤2 μg/ml*)

"Susceptibility patterns of Staphylococcus aureus biofilms in diabetic foot infections''.
Mottola et al. BMC Microbiology (2016) 16:119 DOI 10.1186/s12866-016-0737-0

DALBAVANCINA nel BIOFILM

Table 1
Minimal inhibitory concentration (MIC), minimal biofilm inhibitory concentration (MBIC) and minimum biofilm bactericidal concentration (MBBC) of staphylococcal isolates in this study (number of isolates and percentage). MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; MRSE = methicillin-resistance *Staphylococcus epidermidis*; MSSE = methicillin-susceptible *S. epidermidis*.

	MIC (μg/mL)											MIC_{50}	MIC_{90}
	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16		
MRSA	3 (8.6)	28 (80)	3 (8.6)		1 (2.8)							0.03	0.06
MSSA	17 (27.4)	22 (35.5)	19 (30.6)	4 (6.5)								0.03	0.06
MRSE	18 (32.7)	21 (38.2)	6 (10.9)	6 (10.9)	4 (7.3)							0.03	0.12
MSSE	9 (47.3)	7 (36.8)	1 (5.3)	2 (10.6)								0.03	0.12
	MBIC (μg/mL)											$MBIC_{50}$	$MBIC_{90}$
	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16		
MRSA		10 (28.6)	12 (34.3)	8 (22.8)	4 (11.4)	1 (2.8)						0.06	0.25
MSSA		17 (27.4)	28 (45.2)	12 (19.3)	5 (8.1)							0.06	0.12
MRSE	2 (3.6)	18 (32.7)	13 (23.6)	9 (16.4)	5 (9.1)	6 (10.9)	2 (3.6)					0.06	0.5
MSSE		14 (73.7)	1 (5.3)		4 (21)							0.03	0.25
	MBBC (μg/mL)											$MBBC_{50}$	$MBBC_{90}$
	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16		
MRSA					1 (2.8)	1 (2.8)	24 (68.6)	7 (20)	2 (5.7)			1	2
MSSA				1 (1.6)	7 (11.3)	13 (21)	19 (30.6)	22 (35.5)				1	2
MRSE				6 (10.9)	2 (3.6)	6 (10.9)	16 (29.1)	17 (30.9)	8 (14.5)			1	4
MSSE							10 (52.6)	6 (31.6)	2 (10.5)	1 (5.3)		1	4

"In vitro activity of dalbavancin against biofilms of Staphylococci isolated from prosthetic joint infections".
Javier Fernandez et al. Diagn Microbiol Infect Dis .2016 Aug;85(4):449-51. doi: 10.1016/j.diagmicrobio.2016.05.009. Epub 2016 May 1

DALBAVANCINA vs VANCOMICINA nel BIOFILM

Table 1. Dalbavancin and vancomycin activity assessed on planktonic (MIC/MBC) and sessile conditions (MbIC/MbEC) on Calgary device and heart valve sections

	S. aureus clinical strain					
	Planktonic		Calgary device		Heart valve	
	MIC	MBC	cMbIC	cMbEC	vMbIC	vMbEC
DAL	<0.01	<0.01	<0.01	0.06	<0.01	0.03
VAN	1	16	28	>64	28	32

DAL, dalbavancin; VAN, vancomycin. Values are expressed in mg/L.

"Differential response to antibiotic therapy in staphylococcal infective endocarditis: contribution of an ex vivo model".
Sebastienne Lalanne et al. J Antimicrob Chemother 2023; 78: 1689–1693
https://doi.org/10.1093/jac/dkad155 Advance Access publication 30 May 2023

DALBAVANCINA NELLE ENDOCARDITI

Dalbavancin as sequential therapy for infective endocarditis due to Gram-positive organisms: a review

T. Fazili[a,*], E. Bansal[a], D. Garner[a], M. Gomez[a], N. Stornelli[b]

International Journal of Antimicrobial Agents
Volume 61, Issue 4, April 2023, 106749

- 12 case series + 4 case reports
- 175 pz (età media 48 anni con range 25-85aa)
- 83pz (49%) valvola nativa; 47pz (27%) valvola protesica; 20pz (12%) dispositivo intracardiaco
- Staphylococcus aureus *42%* di cui MRSA 46% e MSSA 54%
- Durata media terapia pre-dalba: 3 settimane
- Schema di somministrazione dalbavancina: 1500mg o 1000mg (LD) + 500mg per una o più settimane (durata massima 6 mesi in pz con ICD non rimuovibile)
- Efficacia complessiva del trattamento: 90%
- Rapporto costo-efficacia: 9000$ a paziente

DALBAVANCINA NELLE INFEZIONI ARTICOLARI

Outcome at last visit		
N. of patients included		401 (89.1%)
Success (n,%)		318 (79.3%)
Failure for persistent infection (n,%)		44 (11.0%)
Failure for relapse (n,%)		21 (5.2%)
Failure for need to switch therapy (n,%)		10 (2.5%)
Lost-to-follow-up (n,%)		5 (1.2%)
Infection-related death (n,%)		1 (0.2%)
Unrelated death (n,%)		2 (0.5%)
Outcome within and after 4 weeks since the end of treatment		
N. of patients included		12; 274 (60.9%)
	Outcome within 4 weeks	**Outcome after 4 weeks**
Success (n,%)	231 (84.3%)	212 (77.4%)
Failure-persistent infection (n,%)	37 (13.5%)	25 (9.1%)
Failure-relapse (n,%)	2 (0.7%)	20 (7.3%)
Failure-switch therapy (n,%)	0 (0.0%)	10 (3.6%)
Lost-to-follow-up (n,%)	4 (1.5%)	5 (1.8%)
Infection-related death (n,%)	0 (0.0%)	0 (0.0%)
Unrelated death (n,%)	0 (0.0%)	2 (0.7%)

Lovatti, S.; Tiecco, G.; Mulé, A.; Rossi, L.; Sforza, A.; Salvi, M.; Signorini, L.; Castelli, F.; Quiros-Roldan, E. Dalbavancin in Bone and Joint Infections: A Systematic Review. Pharmaceuticals 2023, 16, 1005.

ORITAVANCINA nel BIOFILM

Table 1
MIC, MBIC, and MBBC of staphylococcal isolates.

	MIC (μg/mL)												MIC$_{50}$ (μg/mL)	MIC$_{90}$ (μg/mL)
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
MRSA (n = 37)	5 (13.5)	9 (24.3)	6 (16.2)	10 (27)	7 (18.9)								0.03	0.12
MSSA (n = 67)	5 (7.5)	15 (22.4)	15 (22.4)	20 (29.9)	12 (17.9)								0.03	0.12

	MBIC (μg/mL)												MBIC$_{50}$ (μg/mL)	MBIC$_{90}$ (μg/mL)
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
MRSA (n = 37)	1 (2.7)				1 (2.7)	1 (2.7)	4 (10.8)	14 (37.8)	14 (37.8)	2 (5.4)			1	2
MSSA (n = 67)			1 (1.5)			1 (1.5)	9 (13.4)	29 (43.3)	22 (32.8)	5 (7.5)			1	2

	MBBC (μg/mL)												MBBC$_{50}$ (μg/mL)	MBBC$_{90}$ (μg/mL)
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
MRSA (n = 37)	1 (2.7)							9 (24.3)	15 (40.5)	12 (32.4)			2	4
MSSA (n = 67)			1 (1.5)				2 (3)	13 (19.4)	34 (50.7)	17 (25.4)			2	4

Data presented as number (%). MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; MRSE = methicillin-resistant *Staphylococcus epidermidis*; MSSE = methicillin-susceptible *S. epidermidis*.

Yan Q, et al, In vitro activity of oritavancin against biofilms of staphylococci isolated from prosthetic joint infection, Diagn Microbiol Infect Dis (2018), https://doi.org/10.1016/j.diagmicrobio.2018.05.010

ORITAVANCINA IN INFEZIONI COMPLICATE

Blood-Stream Infections						
First Author et al. [Ref]	**Type of Study**	**N. of Patients Treated**	**Dosing and Interval**	**Pathogen(s)**	**Outcome**	**Adverse Effects**
Stewart et al. (2017) [13]	Case Series	6 (10), isolated BSI	1200 single dose	4 MSSA, 1 enterococcus (Ampicillin-susceptible) and 1 CoNS	4 Favourable, 1 Failure and 1 Not evaluable	None
Ahiskali et al. (2020) [17]	Retrospective, observational	3 (24), isolated BSI	1200 single dose in 5 patients, 1200 weekly × 2 in 2 patient, 1200 weekly × 4 in 1 patient	5 MRSA and 4 MSSA	3 complete cure, 4 incomplete cure, 2 lost at FUP	NA
Redell et al. (2019) [20]	Retrospective, observational	7 (440), isolated BSI	1200 single dose	NA	NA	NA
Prosthetic Joint Infections						
First Author et al. [Ref]	**Type of Study**	**N. of Patients Treated**	**Dosing and Interval**	**Pathogen(s)**	**Outcome**	**Adverse Effects**
Van Hise et al. (2020) [21]	multicenter, retrospective, descriptive	134 ostheomyelitis, of which 24 prosthetic	1200 mg, then 800 mg weekly (4 to 5 doses)	71.9% MRSA	88.1% clinical success at the end of therapy	3 hypoglycemia, 1 tachycardia, 1 tachycardia with chest pain
Redell et al. (2019) [20]	retrospective, observational	438, of which 18 osteomyelitis and 3 prosthetic	1200 mg every 6–14 days (1–10 doses)	74% *S. aureus* of which 59.3% MRSA	93.8% cure or 30-days improvement	6.6% of patients reported an adverse event
Shulz et al. (2018) [18]	retrospective, observational	17 including osteomyelitis	1200 mg (2–18 doses)	NA	100% clinical success or improvement	24% of patients reported an adverse event
Delaportas et al. (2017) [22]	case report	1 ostheomyelitis	1200 mg weekly (6 doses)	MSSA	clinical cure	NA
Chastain et al. (2018) [23]	case series	9 chronic ostheomyelitis	1200 mg—variable time between doses (2–6 doses)	5 MRSA	100% clinical cure at 6-months follow up	None

Lupia, T.; De Benedetto, I.; Bosio, R.; Shbaklo, N.; De Rosa, F.G.; Corcione, S. Role of Oritavancin in the Treatment of Infective Endocarditis, Catheter- or Device-Related Infections, Bloodstream Infections, and Bone and Prosthetic Joint Infections in Humans: Narrative Review and Possible Developments. Life 2023, 13, 959. https://doi.org/10.3390/life13040959

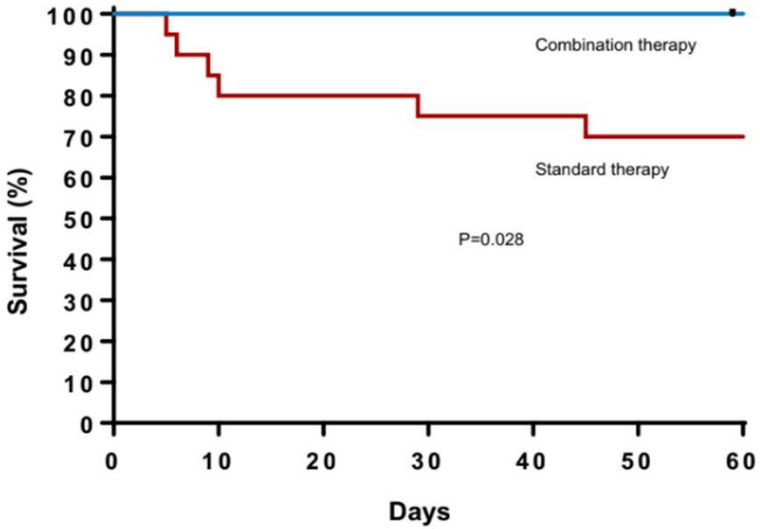
ALTERNATIVE PROMETTENTI

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Matthew Geriak,[a] Fadi Haddad,[b] Khulood Rizvi,[c] Warren Rose,[d] Ravina Kullar,[e] Kerry LaPlante,[f] Marie Yu,[b] Logan Vasina,[a] Krista Ouellette,[a] Marcus Zervos,[c] Victor Nizet,[f] George Sakoulas[a,g]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

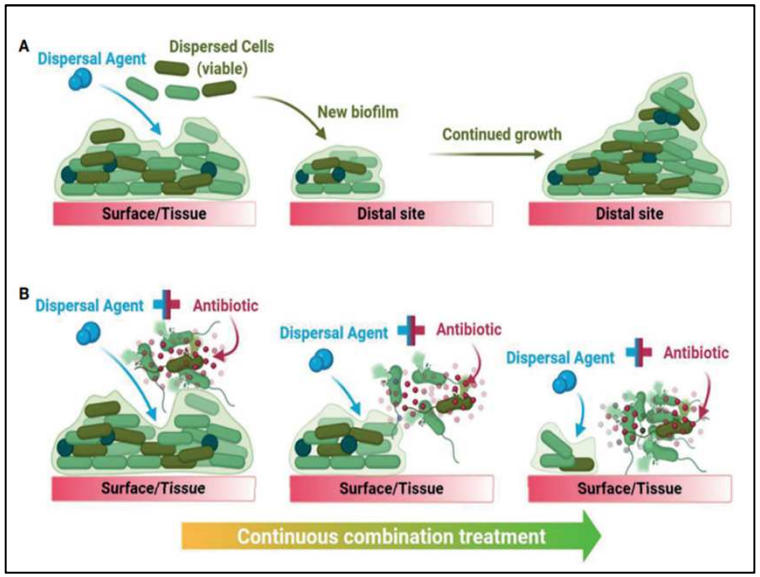
T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G.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

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*
Primary outcome			
Overall treatment success at the post-treatment evaluation visit	132 (69.8)	136 (68.7)	2.0 (−7.1 to 11.1)

STRATEGIE INNOVATIVE PER COMBATTERE IL BIOFILM

- Molecole ad azione dispersiva sul biofilm:
  - Quorum sensing inhibitors
  - NO (ossido nitrico)
  - Nitrossidi
  - Peptidi antimicrobici
  - Aminoacidi

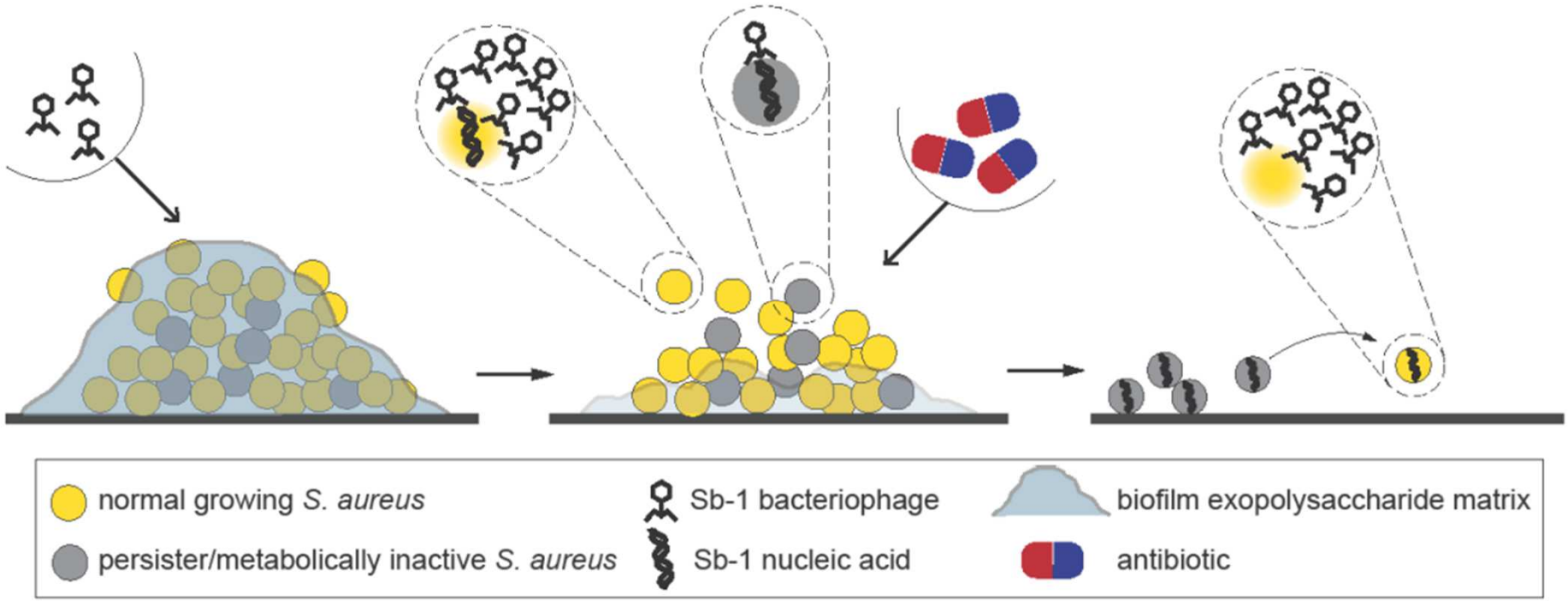
+ antibiotici patogeno-specifici



Hawas S, Verderosa AD and Totsika M (2022)
Combination Therapies for Biofilm Inhibition and Eradication: A Comparative Review of Laboratory and Preclinical Studies.
Front. Cell. Infect. Microbiol. 12:850030. doi: 10.3389/fcimb.2022.850030

BATTERIOFAGI:

- Virus in grado di attaccare direttamente i batteri
- Scoperti agli inizi del 1900, ma poi rapidamente dimenticati con l'avvento della terapia antibiotica
- Ogni fago è specifico per ciascuna specie batterica, e spesso per specifici individui all'interno della medesima specie
- Ad oggi il loro impiego è limitato all'uso compassionevole oppure all'interno di trial clinici



Bacteriophage Sb-1 enhances antibiotic activity against biofilm, degrades exopolysaccharide matrix and targets persisters of Staphylococcus aureus.
Tamta Tkhilaishvili , Lisa Lombardi et al. International Journal of Antimicrobial Agents

2. Enterococcus faecalis

- Incidenza di batteriemie ed infezioni complicate (in particolar modo endocarditi) in progressivo aumento

- Comunitario o associato all'ospedalizzazione (procedure invasive, interventi chirurgici)

- Fattori di rischio:
  - età
  - insufficienza renale cronica
  - malattia epatica avanzata
  - immunodeficienza (congenita o acquisita)
  - scompenso cardiaco congestizio

- Associazione con neoplasie colo-rettali

ENDOCARDITI DA *E.faecalis*

Agente eziologico di c.a il 15% di tutte le endocarditi infettive, in particolare:

- Responsabile di circa il 90% delle endocarditi da *Enterococcus spp*.
- Principalmente interessa il cuore sinistro, con predilezione per valvola aortica
- Più propenso all'adesione a materiale protesico rispetto ad altri streptococchi

Enterococcus faecalis endocarditis: what's next?
Nuria Fernandez-Hidalgo et al. Future Microbiol. (2020) 15(5), 349–364

OPZIONI TERAPEUTICHE - prima linea

Indication	Recommendation	Dosage and Route	Duration (Weeks)
Strains susceptible to Penicillin and Gentamicin in patients who can tolerate β-Lactam therapy	Ampicillin/amoxicillin	2 g IV every 4 h	4–6
	or		
	penicillin G	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6
	plus		
	gentamicin	3 mg/kg ideal body weight in 2–3 equally divided doses IV/IM [65] or in one dose [66]	2–6
	Ampicillin	2 g IV every 4 h	6
	plus		
	ceftriaxone	2 g IV/IM every 12 h	6
Strains susceptible to Penicillin and resistant to Aminoglycosides or Streptomycin-susceptible/ Gentamicin-resistant in patients able to tolerate β-Lactam therapy [65]	Ampicillin	2 g IV every 4 h	4–6
	or		
	penicillin G	18–30 million U/24 h IV either continuously or in 6 equally divided doses	4–6
	plus		
	Streptomycin #	15 mg/kg ideal body weight per 24 h IV or IM in 2 equally divided doses	4–6
Patients unable to tolerate β-Lactam or Penicillin-resistant *Enterococcus* species and Aminoglycoside-susceptible strains	Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6
	plus		
	gentamycin ¶	3 mg/kg per 24 h IV in 3 equally divided doses [65] or in a single dose [66]	6
Enterococcus species caused by strains resistant to Penicillin, Aminoglycosides, and Vancomycin	Linezolid	600 mg IV or orally every 12 h	>6
	or		
	Daptomycin (plus) Ampicillin	10–12 mg/kg IV per dose 200 mg/kg/day IV in 4–6 doses	>6

Herrera-Hidalgo, L.; Fernández-Rubio, B.; Luque-Márquez, R.; López-Cortés, L.E.; Gil-Navarro, M.V.; de Alarcón, A.
Treatment of Enterococcus faecalis Infective Endocarditis: A Continuing Challenge. Antibiotics 2023, 12, 704.
https://doi.org/10.3390/ antibiotics12040704

OPZIONI TERAPEUTICHE - alternative

Recommendation	Dosage and Route	Duration (Weeks)
Ceftobiprole or Ceftarolin With/without gentamycin	500–1000 mg/12 h IV 400 mg IV every 12 h 3 mg/kg/day IV or IM	6–9 2
		Lipo/Glucopeptides
Teicoplanin with/without gentamycin	6–10 mg/Kg/d IV or IM per dose 3 mg/kg/day IV or IM	6–8 2
Dalbavancin	1500 mg in a single dose IV, then 1000 mg every two weeks	6–8
Oritavancin	1200 mg in a single dose IV, then 800 mg every week	6–8
		Daptomycin-based regimens
Daptomycin plus ceftaroline or ceftobiprole	10–12 mg/kg IV per dose 400 mg IV every 12 h 500 mg IV every 8 h	 6–8
Daptomycin plus imipenem	10–12 mg/kg IV per dose 1 gr IV every 6 h	 6–8
Daptomycin plus Fosfomycin with/without gentamycin	10–12 mg/kg IV per dose 3 g IV every 6 h 3 mg/kg/day IV or IM	 6–8
Daptomycin plus Tigecycline	10–12 mg/kg IV per dose 50–100 mg/12 h	 6–8

Herrera-Hidalgo, L.; Fernández-Rubio, B.; Luque-Márquez, R.; López-Cortés, L.E.; Gil-Navarro, M.V.; de Alarcón, A. Treatment of Enterococcus faecalis Infective Endocarditis: A Continuing Challenge. Antibiotics 2023, 12, 704. https://doi.org/10.3390/ antibiotics12040704

DALBAVANCINA vs *Enterococcus faecalis*

Duration of Dalbavancin Therapy, wk	Patient No.	Types of IE	Pathogen	Therapy Before Dalbavancin (Duration, wk)	Reason for Change to Dalbavancin Therapy	Failure of Dalbavancin Treatment	Adverse Effects	Regimen (Once or Twice Weekly)
1 (n = 1)	1	Prosthetic valve	*Enterococcus faecalis*	Vancomycin (3)	Not documented	Death	No	Once
2 (n = 3)	2	Native valve	*Staphylococcus aureus*	Flucloxacillin and fosfomycin (2) cefazoline and daptomycin (4)	Poor venous access	No	No	Once
	3	Native valve	*S. aureus*	Flucloxacillin and daptomycin (5)	OPAT	No	No	Twice
	4	Native valve	*S. aureus*	Cefuroxime and daptomycin (4)	Poor venous access	No	No	Twice
4 (n = 5)	5	Native valve	*E. faecalis*	Ceftriaxone and ampicillin (2)	OPAT	No	No	Once
	6	Prosthetic valve	*Streptococcus equi*	Penicillin G (1)	OPAT	No	Nausea	Twice
	7	CDE	*Staphylococcus epidermidis*	Cefazoline and fosfomycin (4)	OPAT	No	No	Twice
	8	CDE	*S. epidermidis*	Daptomycin (4)	OPAT	No	No	Twice
	9	Native valve	*Streptococcus mitis*	Ceftriaxone and gentamycin (2)	OPAT	No	No	Twice
6 (n = 10)	10	Prosthetic valve	*S. aureus*	Flucloxacillin and rifampicin (2)	OPAT[a]	No	No	Once
	11	Native valve	*Staphylococcus hominis*	Flucloxacillin and daptomycin (2)	OPAT	No	No	Once
	12	CDE	*Streptococcus* spp., *S. epidermidis*	Daptomycin (5 d), vancomycin (2)	OPAT	No	No	Once
	13	Prosthetic valve	*Streptococcus equinus*	Penicillin G (1)	OPAT	No	No	Twice
	14	Suspected prosthetic valve	*Streptococcus sanguinis*	No	OPAT	No	RCI	Twice
	15	Native valve	*E. faecalis*	Ceftriaxone and ampicillin (1)	OPAT	No	No	Twice
	16	Native valve	*Aerococcus urinae*	Penicillin G (2)	OPAT	No	No	Twice
	17	Native valve	*S. aureus*	Flucloxacillin and daptomycin (1)	Poor venous access	No	No	Twice
	18	Native valve	*S. aureus*	Flucloxacillin and fosfomycin (1)	OPAT	No	No	Twice
	19	Native valve	*S. sanguinis, S. hominis*	Flucloxacillin and ampicillin (1)	OPAT	No	No	Twice
>6 (n = 8)	20	Native valve	*E. faecalis*	No	OPAT	No	No	Once

Tobudic S, Forstner C, Burgmann H et al.
Dalbavancin as primary and sequential treatment for Gram-positive infective endocarditis: 2-year experience at the General Hospital of Vienna.
Clin. Infect. Dis. 67(5), 795–798 (2018)

CEFTAROLINA E CEFTOBIPROLO

In vitro activity of ceftaroline and ceftobiprole against Gram-positive bacteria recovered from IE.

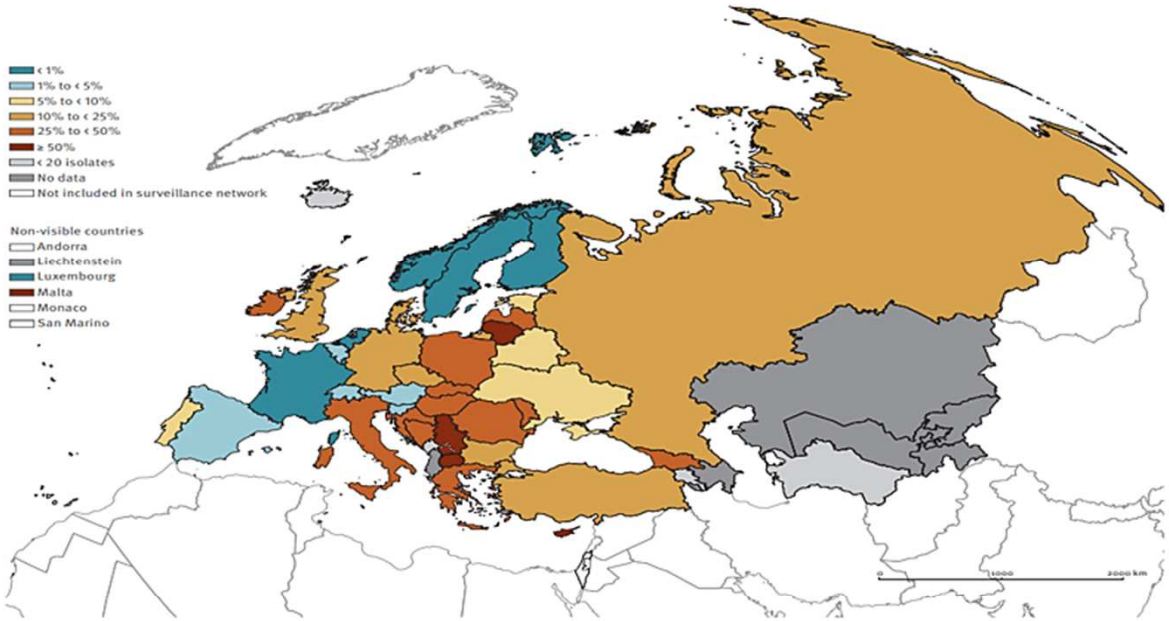
Bacterial species	*N*	No. (cumulative %) of isolates with the indicated MIC (μg/mL) CPT							No. (cumulative %) of isolates with the indicated MIC (μg/mL) CFTB								MIC_{50} (μg/mL) CPT	MIC_{50} (μg/mL) CFTB	MIC_{90} (μg/mL) CPT	MIC_{90} (μg/mL) CFTB	%[a] CPT	%[a] CFTB
		≤ 0.125	0.19	0.25	0.38	0.5	0.75	1.5	≤0.125	0.19	0.25	0.38	0.5	0.75	1	1.5						
Enterococcus faecalis	19		1 (5.3)	6 (36.8)	5 (63.1)	3 (78.9)	3 (94.7)	1 (100)	6 (31.5)	1 (36.8)	5 (63.1)	3 (78.9)	3 (94.7)			1 (100)	0.38	0.25	0.75	0.5	NA	NA

In vitro activity of ceftaroline and ceftobiprole against clinical isolates of Gram-positive bacteria from infective endocarditis: are these drugs potential options for the initial management of this disease?
Raquel Rodríguez-García a , María Ángeles Rodríguez-Esteban a , Enrique García-Carús b , Mauricio Telenti c , Javier Fernández c. Diagn Microbiol Infect Dis. 2020 Dec;98(4):115153. doi: 10.1016/j.diagmicrobio.2020.115153. Epub 2020 Jul 28.

3. Enterococcus faecium

- Incidenza in progressivo aumento
- Maggiore capacità di acquisire resistenze rispetto ad *E.faecalis*
- Batteriemie di difficile gestione per mancanza di strategie terapeutiche consolidate
- Infezioni gravate da elevata mortalità, anche perché più comuni nelle persone anziane e/o fragili

Fig. 10 *Enterococcus faecium*. Percentage of invasive isolates resistant to vancomycin, by country, WHO European Region, 2021



Total number of invasive isolates tested (n) and percentage of isolates with resistance phenotype (%)[a], by bacterial species and antimicrobial group/agent, 2021 EU/EEA range, population-weighted mean and trend, Italy, 2017–2021

Bacterial species	Antimicrobial group/agent	2017		2018		2019		2020		2021		2021 EU/EEA range and population-weighted mean[b]	Trend 2017–2021[c]
		n	%	n	%	n	%	n	%	n	%		
E. faecium	Vancomycin resistance	1049	14.6	2273	18.9	2839	21.3	4166	23.6	4736	28.2	17.2 (0.0–66.4)	↑*

Therapeutics for VRE Bloodstream Infections

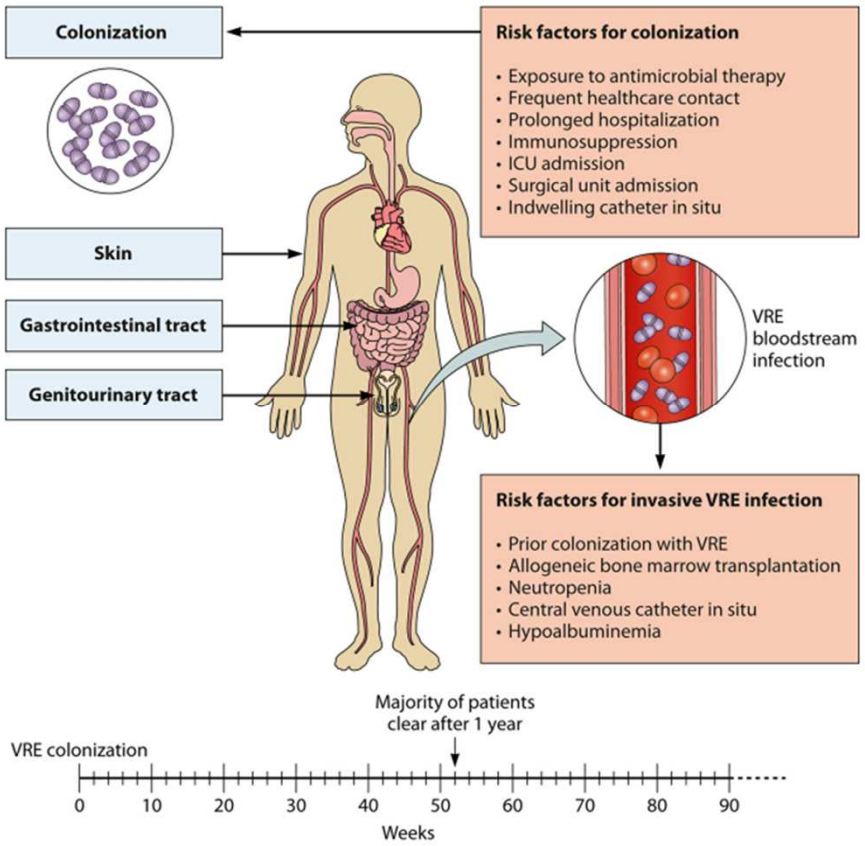


FIG 1 Role of VRE in colonization and infection.

"Therapeutics for Vancomycin-Resistant Enterococcal Bloodstream Infections." Kelly A Cairns et al. Clin Microbiol Rev. 2023 Jun 21;36(2):e0005922. doi: 10.1128/cmr.00059-22. Epub 2023 Apr 17

TRATTAMENTO

Farmaci attivi:

- DAPTOMICINA (>10mg/kg)
- LINEZOLID / TEDIZOLID
- TIGECICLINA
- ORITAVANCINA
- (-) teicoplanina se meccanismo di resistenza mediato da *VanB*

Nessuno tuttavia è di solito sufficiente in monoterapia per il trattamento delle infezioni complesse; vengono in aiuto altre molecole in combinazione:

- Beta-lattamici (AMPICILLINA, CEFTRIAXONE)
- FOSFOMICINA
- RIFAMPICINA

"Therapeutics for Vancomycin-Resistant Enterococcal Bloodstream Infections." Kelly A Cairns et al. Clin Microbiol Rev. 2023 Jun 21;36(2):e0005922. doi: 10.1128/cmr.00059-22. Epub 2023 Apr 17

DAPTOMICINA VS LINEZOLID

TABLE 3 Comparison of meta-analyses of daptomycin versus linezolid for VRE BSIs[b]

Authors (reference)	No. of studies	Daily dose(s)		Primary outcome	Findings
		Daptomycin (mg/kg/day)	Linezolid (mg/day)		
Shi et al. (90)	22	All patients, 3.4–11.5 Subgroup analysis, >6 (HD) (n = 3); irrespective of dose[a] (n = 18)	1,200 (n = 10), NR (n = 12)	Mortality as described in individual studies	All patients, ↑ mortality for daptomycin (OR = 1.27 [95% CI, 0.99–1.63]; I^2 = 42.9%) Subgroup analysis, comparable mortality when HD daptomycin was used (OR = 0.92 [95% CI, 0.46–1.84]; I^2 = 49.4%)
Zhao et al. (89)	11	Median, 6 (n = 9); median, 6.1 (n = 1); mean, 7.4 (n = 1); range, 6–11.5	1,200 (n = 8), NR (n = 3)	Crude overall mortality	Similar mortality rates (RR = 1.07 [95% CI, 0.83–1.37] [P = 0.61]; I^2 = 48%)
Chuang et al. (133)	13	Median, 6 (n = 4); median, 5.5 (n = 1); mean, 6.4 (n = 1); 6 (n = 2); NR (n = 5)	1,200 (n = 7), NR (n = 6)	Mortality	↑ mortality for daptomycin (OR = 1.43 [95% CI, 1.09–1.86] [P = 0.009]; I^2 = 0%)
Balli et al. (134)	10	Median, 6 (n = 6); median, 5.5 (n = 1); NR (n = 3)	1,200 (n = 6), NR (n = 4)	Mortality (30-day all-cause)	↑ mortality for daptomycin (OR = 1.61 [95% CI, 1.08–2.40]; fixed-effects model [heterogeneity P = 0.42])
Whang et al. (132)	9	Usual dose, 6; range, 3.4–10.4	1,200 (n = 4), NR (n = 5)	Mortality as defined by the study investigators	↑ survival with linezolid (OR = 1.3 [95% CI, 1.0–1.8]; I^2 = 0 [P = 0.053])

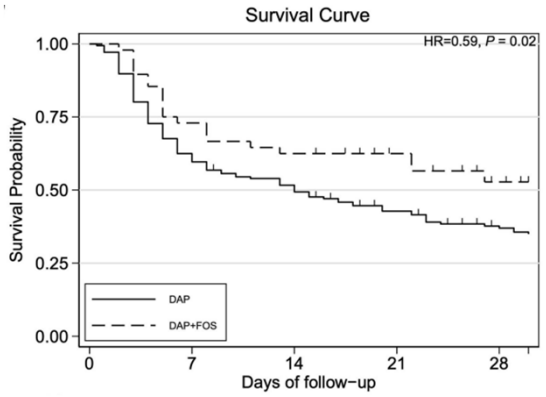
[a]Studies that did not provide dose data or did not meet the criteria for high-dose daptomycin dosing.
[b]HD, high dose; NR, not reported; RR, risk ratio; OR, odds ratio; CI, confidence interval.

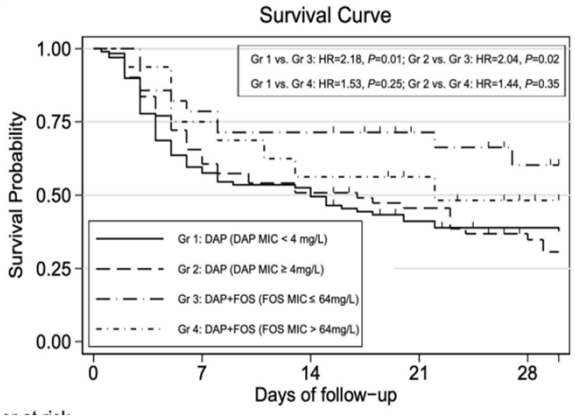
Infect Dis Ther (2023) 12:589–606
https://doi.org/10.1007/s40121-022-00754-1

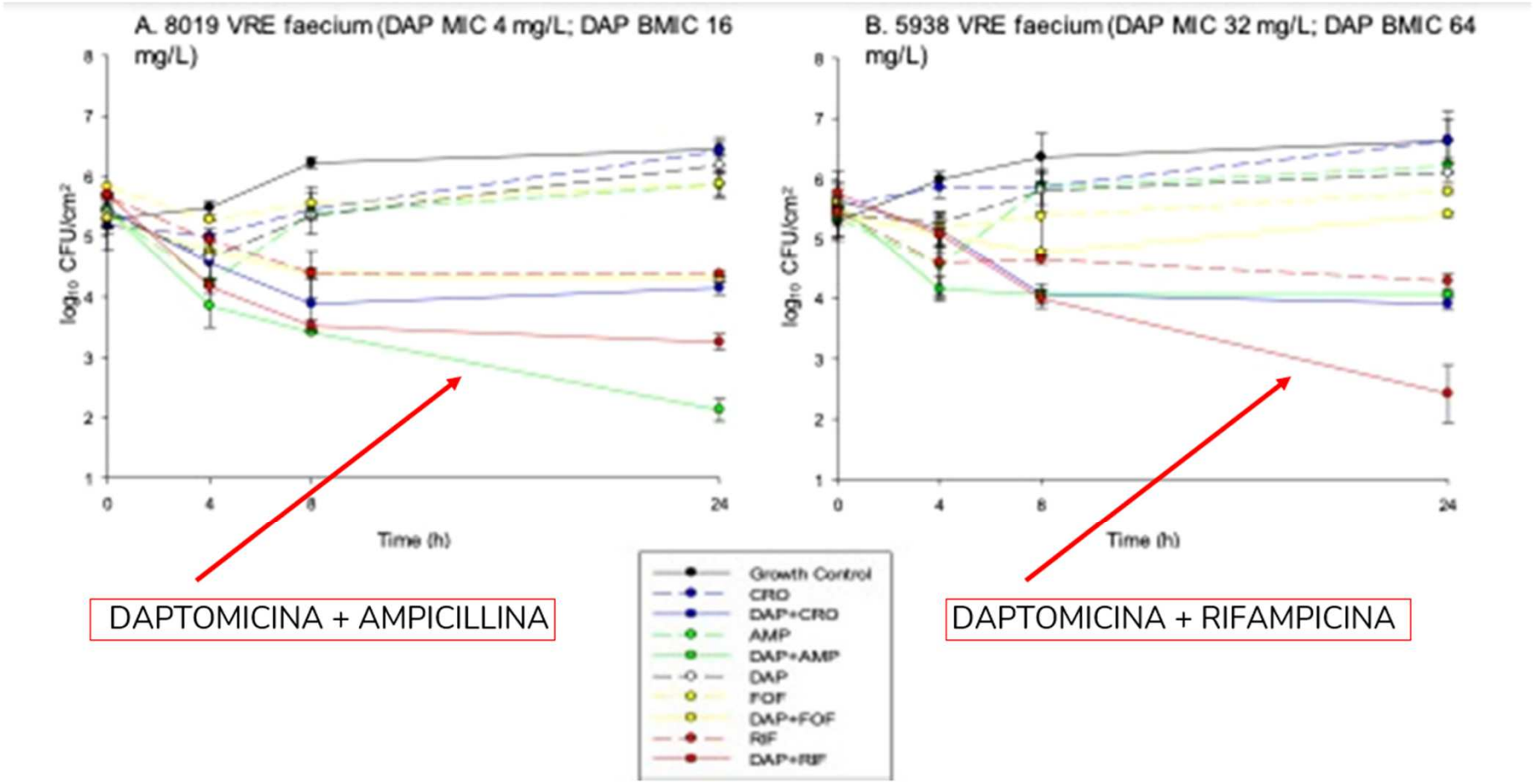
ORIGINAL RESEARCH

The Combination of Daptomycin with Fosfomycin is More Effective than Daptomycin Alone in Reducing Mortality of Vancomycin-Resistant Enterococcal Bloodstream Infections: A Retrospective, Comparative Cohort Study

Tai-Chung Tseng · Yu-Chung Chuang · Jia-Ling Yang · Chi-Ying Lin · Sung-Hsi Huang · Jann-Tay Wang · Yee-Chun Chen · Shan-Chwen Chang







Biofilm Time-Kill Curves to Assess the Bactericidal Activity of Daptomycin Combinations against Biofilm-Producing Vancomycin-Resistant Enterococcus faecium and faecalis.
Katie E. Barber et al. Antibiotics (Basel). 2021 Aug; 10(8): 897

ORITAVANCINA

- Lipoglicopeptide semi-sintetico a lunga emivita

- Azione mirata su batteri Gram positivi, con buona efficacia contro:
  - *Staphylococcus aureus* resistente a meticillina (MRSA)
  - *Staphylococcus aureus* resistente a vancomicina (VRSA)
  - *Staphylococcus aureus* con sensibilità intermedia a vancomicina (VISA)
  - *Enterococcus faecium* resistente a vancomicina (VRE) -sia vanA che vanB-
  - Diversi streptococchi e gram+ anaerobi

- Approvato per infezioni della cute e dei tessuti molli

ORITAVANCINA + BETA-LATTAMICI

TABLE 2 MICs of ORI alone and in combination with beta-lactams against VRE[a]

VRE strain[b]	Range of MICs (μg/ml) of ORI in combination with:							
	ORI alone	AMP	CRO	CPT	FEP	PIP	MEM	ERT
E. faecium	0.03–0.12	<0.01–0.12	<0.01–0.12	0.03–0.12	0.03–0.12	0.03–0.12	0.03–0.12	0.02–0.06
E. faecalis	0.12 (all)	<0.01–0.12	0.02–0.12	<0.01–0.03	0.02–0.12	0.06–0.12	<0.01–0.12	<0.01–0.06

[a] ORI, oritavancin; AMP, ampicillin; CRO, ceftriaxone; CPT, ceftaroline; FEP, cefepime; PIP, piperacillin; MEM, meropenem; ERT, ertapenem.
[b] Five isolates of each strain type were tested.

"Oritavancin Combinations with -Lactams against Multidrug-Resistant Staphylococcus aureus and Vancomycin-Resistant Enterococci". Jordan R Smith et al. Antimicrob Agents Chemother. 2016 Apr; 60(4): 2352–2358. Published online 2016 Mar 25.
Prepublished online 2016 Feb 1. doi: 10.1128/AAC.03006-15

ORITAVANCINA NELLE INFEZIONI COMPLESSE

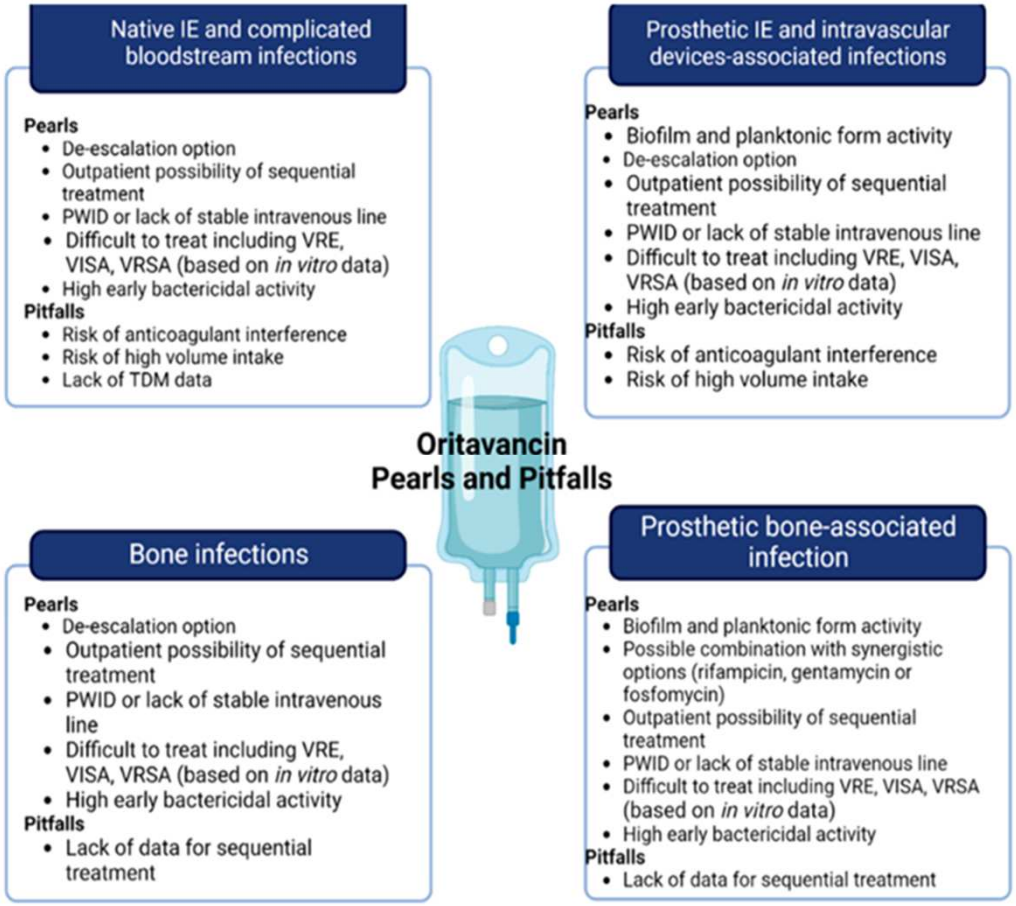
ENDOCARDITI

Infective Endocarditis						
First Author et al. (Year) [Ref]	**Type of Study**	**N. of Patients Treated, Type of Infection**	**Dosing and Interval**	**Pathogen (s)**	**Outcome**	**Adverse Effects**
Johnson et al. (2015) [12]	Case Report	1 (1), PVE	1200 q48h × 3; 1200 twice weekly for 6 wks; After recurrence 2 wks twice weekly in combination with gentamicin (4 days) and then linezolid and tigecicline; 10 wks after surgery 1200 twice weekly (in the first ten days in addition with linezolid and tigecycline)	VRE	Favourable after surgical valve replacement	Increased aPTT; nausea and anorexia (during combination therapy with linezolid and tigecycline)

INFEZIONI DELL'OSSO

Dahesh et al. (2019) [25]	case report	1 prosthetic vertebral ostheomyelitis	1200 mg weekly (2 doses), then 800 mg weekly (8 doses) plus ampicillin	vancomycin-resistant *E. faecium*	clinical cure	NA

Lupia, T.; De Benedetto, I.; Bosio, R.; Shbaklo, N.; De Rosa, F.G.; Corcione, S. Role of Oritavancin in the Treatment of Infective Endocarditis, Catheter- orDevice-Related Infections, Bloodstream Infections, and Bone and Prosthetic Joint Infections in Humans: Narrative Review and Possible Developments. Life 2023, 13, 959. https://doi.org/10.3390/life13040959



''Role of Oritavancin in the Treatment of Infective Endocarditis, Catheter- or Device-Related Infections, Bloodstream Infections, and Bone and Prosthetic Joint Infections in Humans: Narrative Review and Possible Developments''
Tommaso Lupia, Ilaria De Benedetto, Roberta Bosio, Nour Shbaklo, Francesco Giuseppe De Rosa and Silvia Corcione. Life 2023, 13,959.
https://doi.org/10.3390/life13040959

CONCLUDENDO…

Staphylococcus aureus

- Dalbavancina e oritavancina vs biofilm e infezioni complesse (?)
- Batteriofagi e “biofilm dispersal agents” vs biofilm (?)
- Nuove cefalosporine opzione anche per le sepsi (?)

Enterococcus faecalis

- Ceftobiprolo e ceftarolina come prima linea per endocarditi (?)

Enterococcus faecium

- Daptomicina + fosfomicina per le sepsi
- Daptomicina + ampicillina/daptomicina + rifampicina per biofilm(?)
- Oritavancina + ampicillina alternativa nelle infezioni complesse (?)

Grazie per l'attenzione

