SITA
Società Italiana di Terapia Antinfettiva
Antibatterica Antivirale Antifungina

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Presidente SITA:
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Comitato Organizzatore:
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Infezioni e terapia da MRSA e VRE

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Conflicts of interest

- Investigator-initiated grants (Pfizer, Gilead Italia, bioMérieux, Shionogi)
- Personal fees for speaker/consultant (Pfizer, Tillotts Pharma, Menarini)

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MRSA

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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)

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Tiseo et al. International Journal of Antimicrobial Agents 60 (2022) 106611

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Search strategy 1

- Drugs approved by EMA and/or AIFA
- Many drugs with anti-MRSA activity approved for indication by site
- Large RCTs (>200 patients) → indirect evidence for efficacy, direct solid evidence for safety (to be subjected to GRADE)

Search strategy 1

SSTI/ABSSSI

- Recommendation #1
- *Ceftaroline, dalbavancin, daptomycin, delafloxacin, linezolid, oritavancin, and tedizolid are all possible alternative to glycopeptides* for the treatment of skin and soft tissue infections caused by MRSA; the choice should not be exclusively based on costs, and should be tailored to any single patient according to the characteristics of the different available drugs (availability of oral formulation, adherence to outpatient treatment, possibility of outpatient treatment or early discharge, toxicity profile)***

- * The lack of recent efficacy data from large RCTs for teicoplanin should be taken into account when making treatment choices, with other agents remaining preferential if not contraindicated.
- ** Source control should also be obtained whenever indicated. Favorable efficacy results for the treatment of acute bacterial skin and skin structure infections from a recent phase 3 RCT are also available for ceftobiprole, that could be considered as an additional alternative, provided it is authorized for the treatment of skin and skin structure infections by AIFA. In selected cases when other agents are not indicated, telavancin could be considered as an alternative for the treatment of MRSA skin and skin structure infections, although a possible increased risk of nephrotoxicity should be taken into account. Tigecycline may be considered for non-severe skin and skin structure infections. Finally, omadacycline also showed favorable efficacy results in phase 3 RCTs, but the application for EMA approval has recently been withdrawn.

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SSTI/ABSSSI

- Recommendation #1 – Certainty HIGH – Strength STRONG

Number of studies	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
25 studies	Randomized controlled trials	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged reasonable to extrapolate evidence from large RCTs *per* indication, see discussion of search strategy in the manuscript)	No serious imprecision	No other considerations	High

Tiseo et al. International Journal of Antimicrobial Agents 60 (2022) 106611

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Table 2. Clinical conditions for which antibiotic therapy should be always considered for patients suffering from skin abscess

Single abscesses at least 2 cm
Multiple comorbidities and/or immunosuppressive status
Extensive area of associated cellulitis
Signs of sepsis or septic shock
Inadequate clinical response after incision and drainage alone
Presence of a permanent medical device (such as prosthetic joint, vascular graft or pacemaker)
High risk of endocarditis (previous infective endocarditis, prosthetic valve or perivalvular prosthetic material, congenital heart defect or valve dysfunction)

Russo A et al. Curr Opin Infect Dis. 2022 Apr 1;35(2):120-127

SSTI/ABSSSI

- Recommendation #2
- *Trimethoprim/sulfamethoxazole or clindamycin could be considered for outpatient treatment of mild, uncomplicated skin infections (after drainage of skin abscesses, if necessary).*

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SSTI/ABSSSI

- Recommendation #2 – Certainty MODERATE – Strength WEAK

Number of studies	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
5 studies	Randomized controlled trials	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged reasonable to extrapolate evidence from large RCTs *per* indication, see discussion of search strategy in the manuscript)	No serious imprecision (although some included studies were possibly underpowered)	No other considerations	Moderate

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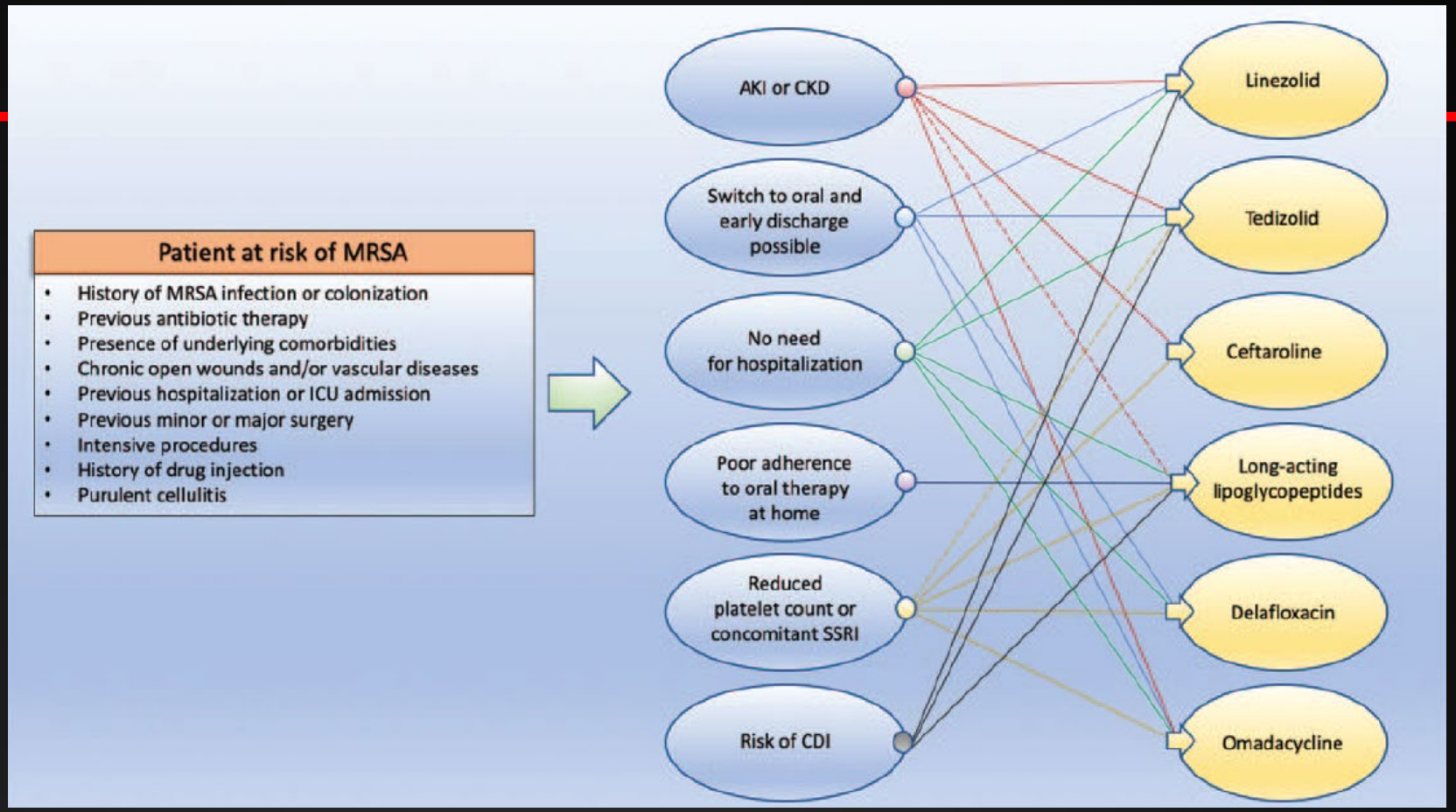
ABSSSI



Bassetti et al. Curr Opin Infect Dis 2020

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Pneumonia

- Recommendation #3
- *Ceftobiprole, ceftaroline, linezolid, or vancomycin are recommended for the treatment of community-acquired pneumonia caused by MRSA; the choice should not be exclusively based on costs and should be tailored to any single patient according to the drug toxicity profile and susceptibility test results.*

- BEST PRACTICE RECOMMENDATION* based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

- * Very few proven MRSA infections are registered in large RCTs in patients with community-acquired pneumonia, therefore sufficient evidence for providing GRADE-based recommendation could not be extrapolated. The panel considered appropriate to support the use of drugs with anti-MRSA activity approved for the treatment of community-acquired pneumonia, including also lefamulin or delafloxacin when the other agents are contraindicated.

Pneumonia

- Recommendation #4
- *Linezolid, ceftobiprole, or vancomycin are recommended for the treatment of hospital-acquired MRSA pneumonia in non-ventilated patients; the choice should not be exclusively based on costs and should be tailored to any single patient according to the drug toxicity profile and susceptibility test results.*

Pneumonia

- Recommendation #4 – Certainty HIGH – Strength STRONG

Number of studies	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
6 studies	Randomized controlled trials	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged reasonable to extrapolate evidence from large RCTs *per* indication, see discussion of search strategy in the manuscript)	No serious imprecision	No other considerations	High

Pneumonia

- Recommendation #5
- *Linezolid or vancomycin are recommended for the treatment of ventilator-associated pneumonia caused by MRSA; the choice should not be exclusively based on costs and should be tailored to any single patient according to the drug toxicity profile and susceptibility test results.*

Pneumonia

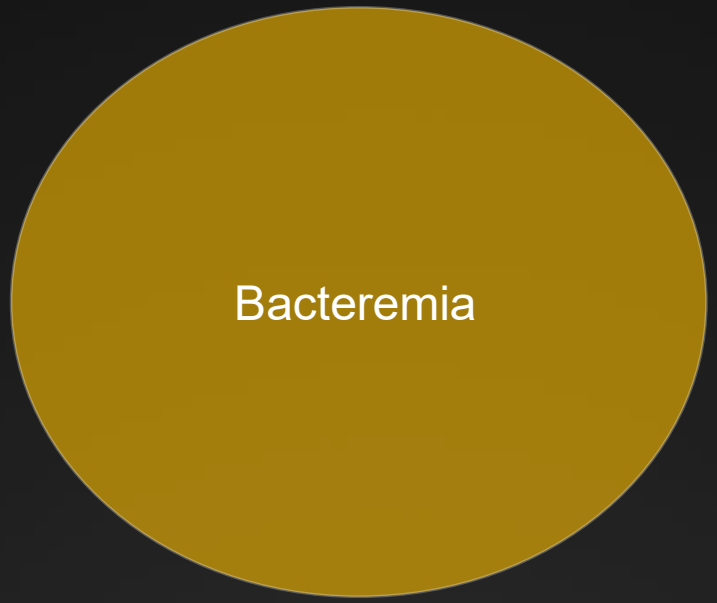
- Recommendation #5 – Certainty HIGH – Strength STRONG

Number of studies	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
6 studies	Randomized controlled trials	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged reasonable to extrapolate evidence from large RCTs *per* indication, see discussion of search strategy in the manuscript)	No serious imprecision	No other considerations	High

Search strategy 2

- Drugs approved by EMA and/or AIFA
- More than 50 patients with MRSA infection *per* indication in RCTs
- Sufficient evidence for efficacy (to be subjected to GRADE)

Search strategy 2



Bacteremia

- Recommendation #6
- *Daptomycin or vancomycin are recommended for the treatment of MRSA bacteremia; the choice should not be exclusively based on costs and should be tailored to any single patient according to the drug toxicity profile and susceptibility test results.*

Bacteremia

- Recommendation #6 – Certainty MODERATE – Strength STRONG

Number of studies	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
2 studies	Randomized controlled trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Direct comparison of daptomycin and vancomycin only in one study	Moderate

Bacteremia

- Recommendation #7
- *Other anti-MRSA agents could be considered for the treatment of bacteremia when daptomycin or vancomycin are contraindicated.*

- BEST PRACTICE RECOMMENDATION* based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

Bacteremia

- Recommendation #8
- *Pending further evidence from RCTs, addition of fosfomycin to daptomycin, or of antistaphylococcal penicillins (or other beta-lactams) to vancomycin or daptomycin for the treatment of MRSA bacteremia are reasonable choices for salvage treatment. The panel suggests that in selected cases of complicated MRSA bacteremia combination therapy could be considered as first-line treatment, although the current evidence remains inconclusive*.*
- BEST PRACTICE RECOMMENDATION based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)
- * A possible increased toxicity risk of these combinations, to be confirmed in further RCTs, should also be taken into account

General recommendations

- Recommendation #9
- *Trimetoprim/sulfametoxazole monotherapy should not be used for severe MRSA infections.*

General recommendations

- Recommendation #9 – Certainty LOW – Strength STRONG

Number of studies	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
1 study	Randomized controlled trial	No serious risk of bias	No serious inconsistency	Serious indirectness (heterogeneous types of infections)	Serious imprecision (it should be noted that the effect was apparently the largest in the bacteremia subgroup)	The included study was open label	Low

Future perspectives

- Other indications
- Companion agents in necrotizing MRSA pneumonia
- Duration of treatment specific for MRSA infections
- New agents
- Future agents

Table 2. Characteristics of published studies on the use of dalbavancin for indications other than acute bacterial skin and skin structure infections[a]

Reference	Type of study	Type of infections other than ABSSSI treated with dalbavancin (no. patients)	Outcome/s data	Safety data AE (no. patients)
Bouza *et al.* [15]	Retrospective Multicenter	Prosthetic joint infection (20) Osteomyelitis (12) CRBSI (8) Endocarditis (7) Intra-abdominal infection (3) Other endovascular infections (2) Septic arthritis (1) Sinusitis (1)	*Successful clinical outcome* Prosthetic joint infection (80%, 16/20) Osteomyelitis (91.7%, 11/12) CRBSI (75%, 6/8) Endocarditis (85.7%, 6/7) Intra-abdominal infection (100%, 3/3) Septic arthritis (100%, 1/1)	*Assessed in the entire cohort, n = 69, including also patients with ABSSSI* Any AE (9) Mild AE (7) Severe AE (2) *Type of AE* Rash (2) Tachycardia (2) Impaired renal function (2) Nausea (1) Rectal bleeding (1) Candidiasis (1)
Nair *et al.* [80]	Retrospective Single center	Endocarditis (2) Osteomyelitis (5) BSI (5) Septic shock with puerperal sepsis (1)	*Outcome assessed in the entire cohort, n = 52, including also patients with ABSSSI* Complete resolution or improvement observed in 44/52 patients (84.6%)	*Assessed in the entire cohort, n = 52, including also patients with ABSSSI* Red man type reaction (2)
Tobudic *et al.* [81]	Retrospective Single center	Endocarditis (27)	Microbiological and clinical success observed in 25/27 patients (92.6%), with the note that dalbavancin was used after clearance of blood cultures in 24/27 cases (88.9%)	Nausea and vomiting (1) Increase in serum creatinine levels (1)

Bassetti M., et al. Curr Opin Infect Dis. 2021 Apr 1;34(2):96-108

Reference	Type of study	Type of infections other than ABSSSI treated with dalbavancin (no. patients)	Outcome/s data	Safety data AE (no. patients)
Dinh *et al.* [75]	Retrospective Multicenter	BJI (48) Endocarditis (19) Vascular infection (5) Catheter line infection (4) BSI (3) Mediastinitis (2) Disseminated disease (19)	*Cure at last visit (exclusion of patients lost to follow-up)* BJI (76.1%, 35/46) Endocarditis (72.2%, 13/18) Vascular infection (100%, 5/5) Catheter line infection (100%, 2/2) BSI (100%, 1/1) Mediastinitis (50%, 1/2)	Erythematous rash, chills and fever (2) Headache (1) Self-resolving hypereosinophilia (1) Local inflammatory signs (1)
Almangour *et al.* [82]	Retrospective Multicenter	Osteomyelitis (36)	Clinical success at 3-month after the end of antibiotic course equal to 90% (28/31, missing 5)	No AE
Bartoletti *et al.* [83]	Retrospective Multicenter	DSWI (15)	At 6-month follow-up, 14/15 patients (93%) showed no relapse, did not received further coursed of antibiotics, and were not readmitted	NA
Bork *et al.* [84]	Retrospective Multicenter	Osteomyelitis (13) Endovascular infection (6) BSI (4) Septic arthritis (1) Prosthetic joint infection (1) Cardiac device infection (1) MRSA pneumonia (1) Pyelonephritis (1)	Clinical cure at 30-day was 71% (15/21 patients with available follow-up)	Acute kidney injury (2) Pruritus and rash (1)
Bryson-Cahn *et al.* [85]	Retrospective Single center	MSSA endocarditis (2) MRSA endocarditis (7) Osteomyelitis (7) Uncomplicated or complicated BSI (14) Septic arthritis (2)	Clinical response observed in 18/32 patients (56%)	NA
Buzón Martín *et al.* [86]	Retrospective Single center	Prosthetic joint infection (16)	Infection resolved in 12/16 patients (75%)	Mild skin rash (1) Mild transient leukopenia (1)

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Hidalgo-Tenorio *et al.* [87]	Retrospective Multicenter	Endocarditis (34) Uncomplicated or complicated BSI (49)	*Clinical cure of dalbavancin as consolidation therapy* Endocarditis (100%, 34/34) Uncomplicated or complicated BSI (100%, 49/49)	Asthenia (1) Self-limited rash (1) Fever with self-limited shivering (1) Impaired renal function (1)
Morata *et al.* [88]	Retrospective Multicenter	BJI with orthopedic implant (45) BJI without orthopedic implant (19)	*Success or improvement (missing = 1)* BJI with implant retention (100%, 23/23) BJI with implant removal (95.2%, 20/21) BJI without implant (89.5%, 17/19)	Gastrointestinal (3) Self-limited rash (1) Phlebitis (1) Self-reported asthenia (1) Increase of serum creatinine (1)
Morrisette *et al.* [52,53]	Retrospective Multicenter	*Numbers include both dalbavancin-treated and oritavancin-treated patients:* Osteomyelitis (15) Endocarditis (5) CRBSI (2) Pneumonia (2) Various other infections (14)	*Numbers include both dalbavancin-treated and oritavancin-treated patients for whom outcome data was available:* 92% clinical success (11/12) for osteomyelitis, 100% (3/3) for endocarditis, and 100% (2/2) for CRBSI	*The following mild AE include both dalbavancin-treated and oritavancin-treated patients:* Infusion reaction (1) Nausea (1) Chest tightness (1) Line infiltration with edema (1) Acute kidney injury (1) Headache (1)
Streifel *et al.* [89]	Retrospective Single center	Osteomyelitis (11) Joint infection (4) Uncomplicated or complicated BSI (12) Endocarditis (2)	*Outcome assessed in the entire cohort, n = 37, including also patients with ABSSSI* 30-day readmission for any reason (24%, 9/37) 30-day readmission due to recurrence of infection or potential AE of dalbavancin (5%, 2/37) Recurrence of infection (3%, 1/37)	*Assessed in the entire cohort, n = 37, including also patients with ABSSSI* Thrombophlebitis at the peripheral intravenous insertion site (1) Pruritus (1) Chest pain and acute on chronic increase in serum creatinine (1)

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Table 1. Characteristics of published studies on the use of oritavancin for indications other than acute bacterial skin and skin structure infections[a]

Reference	Type of study	Type of infections other than ABSSSI treated with oritavancin (no. patients)	Outcome/s data	Safety data AE (no. patients)
Stewart *et al.* [50]	Retrospective Single center	MSSA BSI (5) MRSA bursitis (1) Group B streptococcal BSI with infective endocarditis (1) CoNS bacteremia (1) MSSA deep tissue infection (1) *Enterococcus* spp. BSI (1)	7/10 Patients (70%) were successfully treated	Nausea (2) Hearing loss (1)
Co *et al.* [43]	Retrospective Single center	Cardiac device infection (7) Diabetic foot infection (3) Osteomyelitis (8) Bacteremia (3)	No readmission within 14 days	NA
Schulz *et al.* [51]	Retrospective Single center	MRSA pneumonia (2) Osteomyelitis (4) VRE hepatic abscess (1) *Staphylococcus lugdunensis* endovascular graft infection (1) VRE bacteremia (1)	Success or improvement in 9/9 cases (100%)	*Assessed in the entire cohort, n = 17, including also patients with ABSSSI* Infusion-related infections (2) Anemia and leukopenia (1)
Chastain and Davis [16]	Retrospective Single center	Osteomyelitis (9)	Clinical cure in 9/9 cases (100%) at 6-month follow-up	No treatment-emergent AE reported
Morrisette *et al.* [52,53]	Retrospective Multicenter	*Numbers include both dalbavancin-treated and oritavancin-treated patients:* Osteomyelitis (15) Endocarditis (5) CRBSI (2) Pneumonia (2) Various other infections (14)	*Numbers include both dalbavancin-treated and oritavancin-treated patients for whom outcome data was available:* 92% clinical success (11/12) for osteomyelitis, 100% (3/3) for endocarditis, and 100% (2/2) for catheter-related bacteraemia	*The following mild AE include both dalbavancin-treated and oritavancin-treated patients:* Infusion reaction (1) Nausea (1) Chest tightness (1) Line infiltration with edema (1) Acute kidney injury (1) Headache (1)

Bassetti M., et al. Curr Opin Infect Dis. 2021 Apr 1;34(2):96-108

Table 1 (*Continued*)

Reference	Type of study	Type of infections other than ABSSSI treated with oritavancin (no. patients)	Outcome/s data	Safety data AE (no. patients)
Brownell *et al.* [42]	Retrospective Single center	Osteomyelitis/septic arthritis (10) Diabetic foot infection (3) Endocarditis (4) Line infection (2) Pneumonia (5) Prosthetic device infection (4) Sepsis (5) Surgical wound infection (12) Other (5)	*Clinical cure or improvement* Osteomyelitis/septic arthritis (100%, 10/10) Diabetic foot infection (100%, 3/3) Endocarditis (100%, 4/4) Line infection (100%, 2/2) Pneumonia (100%, 5/5) Prosthetic device infection (3/3, 100%, 1 missing) Sepsis (3/5, 60%) Surgical wound infection (11/12, 91.7%) Other (4/5, 80%)	Any AE (5) The most frequent AE was back pain (3/75, including also patients with ABSSSI at the denominator)
Van Hise *et al.* [55]	Retrospective Multicenter	Osteomyelitis (134)	Clinical success at the end of treatment (118/134, 88.1%) Relapse or persistent infection (13/134, 9.7%)	Hypoglycemia (3) Tachycardia (1) Tachycardia with chest pain (1)
Redell *et al.* [48]	Retrospective Multicenter	Primary bacteremia (5) Osteomyelitis (18) Septic Arthritis/synovitis (4) Prosthetic joint infection (3) Infected bursa (3) Catheter exit site (1) Maxillary sinus infection (1) Hardware, posterior lumbar tissue (1) Lymphadenitis (1)	In patients with osteomyelitis receiving single-dose oritavancin for completion of treatment, clinical success or improvement was observed in 9/10 cases (90%) Clinical success in patients receiving oritavancin for joint infections was 71.4% (5/7)	*Assessed in the entire cohort, n = 440, including also patients with ABSSSI* Any AE (29) Pruritus (14) *Six AE leading to discontinuation* Infusion site reaction (2) Pruritus, urticaria, and headache (1) Urticaria and pruritus (1) Headache and throat tightness (1) Back pain and flushing (1)
Ahiskali and Rhodes [54]	Retrospective Single center	Bone or joint infections (14) Endocarditis (2) Isolated BSI (3)	*Outcome includes also patients with ABSSSI* Clinical cure was observed in 19/24 patients (79%)	*Assessed in the entire cohort, n = 24, including also patients with ABSSSI* Infusion-related reaction (1) Abdominal pain (1)

Bassetti M., et al. Curr Opin Infect Dis. 2021 Apr 1;34(2):96-108

ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

- Population: 387 patients with complicated *S. aureus* BSI
- Design: phase 3, double blind, double dummy, non-inferiority
- Intervention: Ceftobiprole 500 mg q6h (q8h from day 9) vs. daptomycin 6-10 mg/kg/die; optional aztreonam;
- Primary endpoint: treatment success at day 70 (survival, bacteremia clearance, symptom improvement, no new *S. aureus* bacteremia–related complications, and no receipt of other potentially effective antibiotics)

Holland TL, et al. N Engl J Med 2023;389:1390-1401.

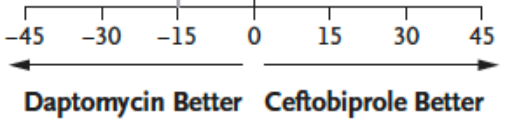
ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

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)

Holland TL, et al. N Engl J Med 2023;389:1390-1401.

Subgroup	Ceftobiprole	Daptomycin	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
All patients	132/189 (69.8)	136/198 (68.7)	2.0 (–7.1 to 11.1)
Age at written informed consent			
18 to <65 yr	98/131 (74.8)	101/135 (74.8)	0.6 (–9.8 to 10.9)
≥65 yr	34/58 (59)	35/63 (56)	6.9 (–10.5 to 24.3)
Sex			
Male	93/128 (72.7)	92/140 (65.7)	8.0 (–2.8 to 18.8)
Female	39/61 (64)	44/58 (76)	–11.3 (–27.7 to 5.1)
Baseline category of complicated *S. aureus* bacteremia			
Soft-tissue infection	81/116 (69.8)	80/121 (66.1)	4.5 (–7.3 to 16.3)
S. aureus bacteremia excluding soft-tissue infection	51/73 (70)	56/77 (73)	–1.7 (–15.9 to 12.6)
Osteoarticular infection	23/32 (72)	24/35 (69)	2.9 (–19.7 to 25.6)
Abdominal abscess	18/26 (69)	22/29 (76)	–9.7 (–33.3 to 13.9)
Hemodialysis	13/24 (54)	15/25 (60)	–4.6 (–32.5 to 23.3)
Persistent *S. aureus* bacteremia	8/16 (50)	8/16 (50)	–0.0 (–35.9 to 35.9)
Infective endocarditis on right side of heart	10/15 (67)	7/10 (70)	–6.6 (–40.1 to 27.0)
Baseline *S. aureus* infection			
Methicillin-susceptible	100/141 (70.9)	97/146 (66.4)	4.8 (–5.9 to 15.5)
Methicillin-resistant	31/45 (69)	38/49 (78)	–8.3 (–25.3 to 8.6)
Previous antibiotic use			
Yes	92/139 (66.2)	85/134 (63.4)	2.9 (–8.4 to 14.2)
No	40/50 (80)	51/64 (80)	–0.2 (–15.0 to 14.6)
Trial cohort			
Cohort 1	68/97 (70)	62/96 (65)	7.6 (–5.6 to 20.8)
Cohort 2	64/92 (70)	74/102 (72.5)	–3.4 (–16.1 to 9.3)



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Holland TL, et al. N Engl J Med 2023;389:1390-1401.

Investigational agent	Phase II studies for ABSSSI	Other indications (development phase)
Brilacidin	X	Oral mucositis (II)/Ulcerative colitis (I-II)
Lefamulin	X	CABP (FDA approved)
Afabicin	X	Staphylococcal BJI (II)
CG-400549	X	
Delpazolid		Pulmonary tuberculosis (II)
Radezolid	X	Acne vulgaris (I)
Contezolid	X	ABSSSI (III in China)
Levonadifloxacin		ABSSSI (III in India)
Avarofloxacin	X	
TNP-2092	X	
Gepotidacin	X	uUTI (III), urogenital gonorrhoea (III)
Cefilavancin	X	
Exebacase		*S. aureus* BSI/right-sided endocarditis (II)
SAL200		Persistent *S. aureus* BSI (II)
Monoclonal antibodies		Various (see text)

Bassetti et al. Expert Opinion on Investigational Drugs 2020, DOI: 10.1080/13543784.2020.1750595

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Table 1. mAbs and vaccines for planktonic and biofilm *S. aureus* infections in clinical development.

Agent	Molecular target	Sponsor(s)	Clinical trial identifier	Study design	Number of patients	Status	Indication
mAbs							
AR-301	Alpha-toxin	ARIDIS Pharmaceutical	NCT01589185	Interventional, randomized, double-blind	48	Phase 1/2—completed	Pneumonia
			NCT03816956	Interventional, randomized, double-blind	240	Phase 3—completed	
MEDI4893	Alpha-toxin	MedImmune	NCT02296320	Interventional, randomized, double-blind	213	Phase 2—completed	Pneumonia
			NCT05331885	Interventional, randomized, double-blind	564	Phase 3—ongoing	
ASN100	Cytotoxins	Arsanis Inc	NCT02940626	Interventional, randomized, double-blind	155	Phase 2—halted	Pneumonia
DSTA4637S	Wall teichoic acid	Genentech	NCT02596399	Interventional, randomized, double-blind	30	Phase 1—completed	Not available
			NCT03162250	Interventional, randomized, double-blind	27	Phase 1b—completed	
Pagibaximab	Lipoteichoic acid	Biosynexus/GSK/MedImmune	NCT00646399	Interventional, randomized, double-blind	1579	Phase 3—failed	Staphylococcal sepsis
Altastaph	Capsular polysaccharide	Nabi Biopharmaceuticals	NCT00066989	Interventional, randomized, double-blind	200	Phase 2—halted	Bacteremia
514G3	Immunoglobulin binding protein, SpA	Xbiotech	NCT02357966	Interventional, randomized, double-blind	52	Phase 2—completed	Bacteremia
Tefibazumab	ClfA	Inhibitex	NCT00198289	Interventional, non-randomized, dose escalation	30	Phase 2—completed	Bacteremia, cystic fibrosis
F598	Poly-*N*-acetyl-glucosamine	Alopexx Pharmaceuticals	Not available	Not available	Not available	Phase 2—completed	Pneumonia
TRL1068	Extracellular DNA	Trellis Bioscience	NCT04763759	Interventional, randomized, double-blind	18	Phase 1—on-going	Prosthetic joint infections

Chung PI, et al. Pathogens and Disease 2023; 81: 1–10

VRE

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Synergistic Killing of Vancomycin-Resistant Enterococci of Classes A, B, and C by Combinations of Vancomycin, Penicillin, and Gentamicin

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Using both high and low inocula for time-kill curves, we examined the antibiotic killing of clinical isolates of glycopeptide-resistant enterococci (*Enterococcus faecium*, *E. faecalis*, and *E. gallinarum*) belonging to phenotypic resistance classes A, B, and C. None were resistant to high levels (>500 mg/liter) of gentamicin. Vancomycin-penicillin-gentamicin resulted in 2 or more logs of killing above that of the most effective two-antibiotic combination for all strains except two of three *E. gallinarum* (VanC) strains and a constitutive mutant of a VanB strain. This strategy may be useful clinically.

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.

Cairns KA, et al. Clin Microbiol Rev 2023; doi:10.1128/cmr.00059-22

Table 2. Cumulative fraction of response (%) of linezolid for various dosing regimens that met each pharmacokinetic/pharmacodynamic target

Dosing regimens	Infusion time (hour)	CFR (%)				C_{trough} ≥9 μg/mL (%)
		AUC/MIC		*f*T>MIC		
		≥80	≥100	85%	100%	
600 mg q 12 h	0.5	80.1	66.5	80.3	74.9	14.3
600 mg q 12 h	2	80.6	67	83.7	78.2	16.1
600 mg q 12 h	3	80.7	67	85.7	80.4	17.1
600 mg q 12 h	4	80.8	67.2	87.9	82.7	18.1
1,200 mg q 24 h	0.5	79.9	66.1	58.5	48.4	7.0
1,200 mg q 24 h	24	99.9	99.8	100	100	99.6
600 mg q 8 h	0.5	94.7	88.2	94.1	92.5	40.7

Color codes: Strongly recommended dose based on ≥90% PTA or ≥90% CFR.

Moderately recommended dose based on 80 - 89% PTA or 80 - 89% CFR.

CFR, Cumulative fraction of response; AUC, area under the curve; MIC, minimum inhibitory concentration; *f*T, time of free drug concentrations; C_{trough}, trough concentration; h, hour; mg, milligram; q, every; PTA, probability of target attainment.

Santimaleeworagun W, et al. Infect Chemother 2021; 53:503-511.

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Journal of Antimicrobial Chemotherapy

Influence of daptomycin doses on the outcomes of VRE bloodstream infection treated with high-dose daptomycin

Yu-Chung Chuang[1]*†, Hsin-Yi Lin[2], Jia-Ling Yang[1], Chi-Ying Lin[3], Sung-Hsi Huang[4], Jann-Tay Wang[1]†, Yee-Chun Chen[1] and Shan-Chwen Chang[1]

- Population: 661 treated with daptomycin ≥8 mg/kg/die for VRE BSI
- Design: multicenter, observational, prospective
- Results: 28-day mortality was 45.1%. The 8 to <11 and ≥11 mg/kg doses of daptomycin differed in the 28 day mortality in the higher MIC group (≥2 mg/L) (49.4% versus 33.3%; P=0.004), but not in the lower MIC group (≤1 mg/L) (29.3% versus 29.4%; P=0.99).

Daptomycin area under the curve to minimum inhibitory concentration ratio by broth microdilution for predicting the outcome of vancomycin-resistant *Enterococcus* bloodstream infection

Yu-Chung Chuang [a,*], Hsin-Yi Lin [b], Jann-Tay Wang [a], Jia-Ling Yang [a], Chi-Ying Lin [c], Sung-Hsi Huang [d], Yee-Chun Chen [a], Shan-Chwen Chang [a]

- 393 VRE bacteremia treated with daptomycin ≥8 mg/kg/die
- Using Monte Carlo simulation, none of the doses had a probability of target attainment of ≥50% with an MIC of ≥2 mg/L

Chuang YC, et al. Biomedicine & Pharmacotherapy 2022; 155:113710

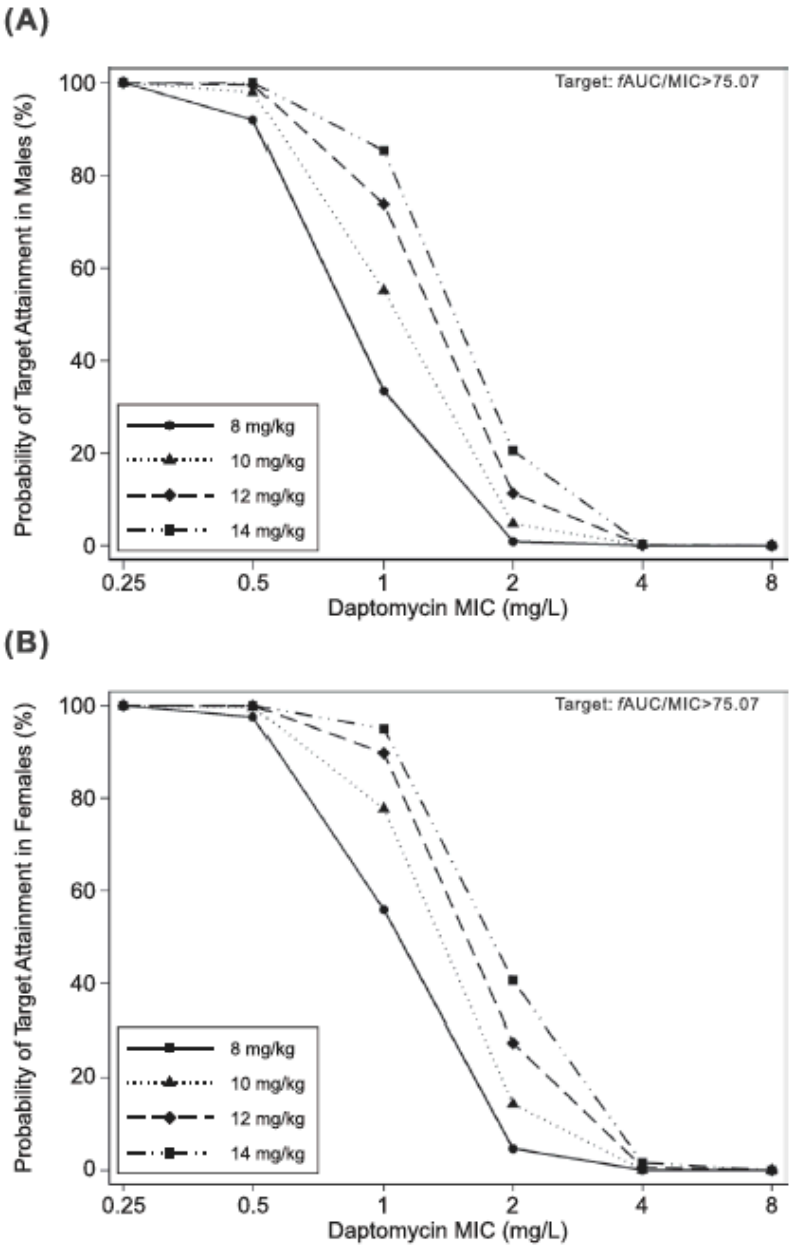

Fig. 3. Monte Carlo simulation of the probability of target attainment in (A) males and (B) females. The pharmacodynamic target was an *f*AUC/MIC for BMD > 75.07. Abbreviations: BMD, broth microdilution; *f*AUC, area under the concentration–time curve for the free drug; MIC, minimal inhibitory concentration.

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A retrospective clinical comparison of daptomycin vs daptomycin and a beta-lactam antibiotic for treating vancomycin-resistant *Enterococcus faecium* bloodstream infections

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	Adjusted Model 1[a]			Adjusted Model 2[c,d]	
	Hazard ratio (95% CI)	*P*		Hazard ratio (95% CI)	*P*
Steroid use	2.86 (1.42–5.79)	0.003	Steroid use	3.28 (1.64–6.57)	0.001
Pitt bacteremia score	1.17 (1.05–1.30)	0.004	Pitt bacteremia score	1.17 (1.05–1.30)	0.005
Platelet count ($\times 10^4/\mu L$)	0.96 (0.92–0 0.99)	0.02	Platelet count ($\times 10^4/\mu L$)	0.96 (0.92–0.99)	0.02
Treatment regimens					
DAP dose (mg/kg)	0.74 (0.58–0.93)	0.01	DAP dose ≥9 mg/kg with BLA	Reference	
DAP + BLA	0.90 (0.41–1.96)	0.79[b]	DAP dose <9 mg/kg without BLA	5.16 (1.34–19.89)	0.02
			DAP dose <9 mg/kg with BLA	5.39 (1.62–17.93)	0.006
			DAP dose ≥9 mg/kg without BLA	19.01 (2.96–121.95)	0.002

Table 3. Multivariable Cox Proportional Hazards Model of Factors Associated with Mortality. Abbreviations: BLA, beta-lactam antibiotic; CI, confidence interval; DAP, daptomycin. [a]Test of proportional-hazards assumption: $P = 0.92$. [b]DAP + BLA was forced as an independent variable in the final adjusted model 1. [c]Test of proportional-hazards assumption: $P = 0.73$. [d]Interactions between daptomycin dose and beta-lactam combinations were considered in the final adjusted model 2.

Chuang YC, et al. Scientific Reports 2018; 8:1632.

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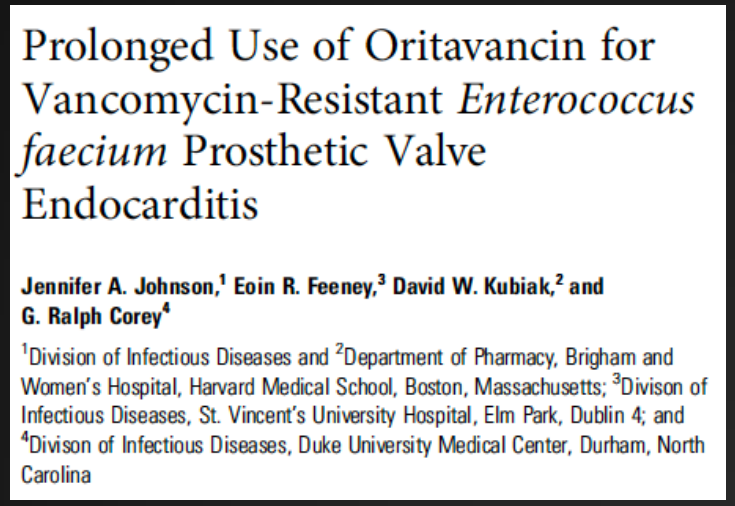
Long-acting lipoglycopeptides

- Dalbavancin: active against *vanB* VRE
- Oritavancin: active against *vanA* and *vanB* VRE



Prolonged Use of Oritavancin for Vancomycin-Resistant *Enterococcus faecium* Prosthetic Valve Endocarditis

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Zhanel GG, et al. Drugs 2010; 70:859–886.
Smith JR, et al. Infect Dis Ther 2015; 4:245–258.
Johnson JA, et al. Open Forum Infect Dis 2015; 2:ofv156.

Other agents

- Tigecycline, eravacycline, omadacycline, doxycycline, minocycline, fosfomycin, chloramphenicol

TABLE 4 VRE-active agents in the development pipeline[a]

Drug (reference)	Class	Mechanism	Progress in pipeline (reference[s])
PS-757 (194)	Ring-fused 2-pyridone antibiotics (GmPcides)	Bacteriostatic against dividing cells, bactericidal against nondividing cells via autolysin	Preclinical
VRELysin	Bacteriophage cocktail	Cell lysis	Phase 1/2a study for VRE colonization (275)
Contezolid (7)	Oxazolidinone	Protein synthesis inhibitor	Phase 2 study for ABSSSI completed (276); approved in China in 2021 for cSSTI (277)
Delpazolid (7)	Oxazolidinone	Protein synthesis inhibitor	Phase 2a study for MRSA BSI (278)
Iclaprim (279)	Diaminopyrimidine	Dihydrofolate reductase inhibitor	Completed 2 phase 3 trials for ABSSSI (280) and 2 phase 3 trials for cSSTI (281, 282); a phase 2 trial for HAP/VAP was terminated (283)

[a]VRE, vancomycin-resistant enterococci; ABSSSI, acute bacterial skin and skin structure infection; cSSTI, complicated skin and skin structure infection; MRSA, methicillin-resistant *S. aureus*; BSI, bloodstream infection; HAP/VAP, hospital-associated pneumonia/ventilator-associated pneumonia.

Cairns KA, et al. Clin Microbiol Rev 2023; doi:10.1128/cmr.00059-22

Resp. Scientifici: Matteo Bassetti, Daniele R. Giacobbe

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- 3 study ongoing
- 1 study published
- 2 studies starting in April 2024

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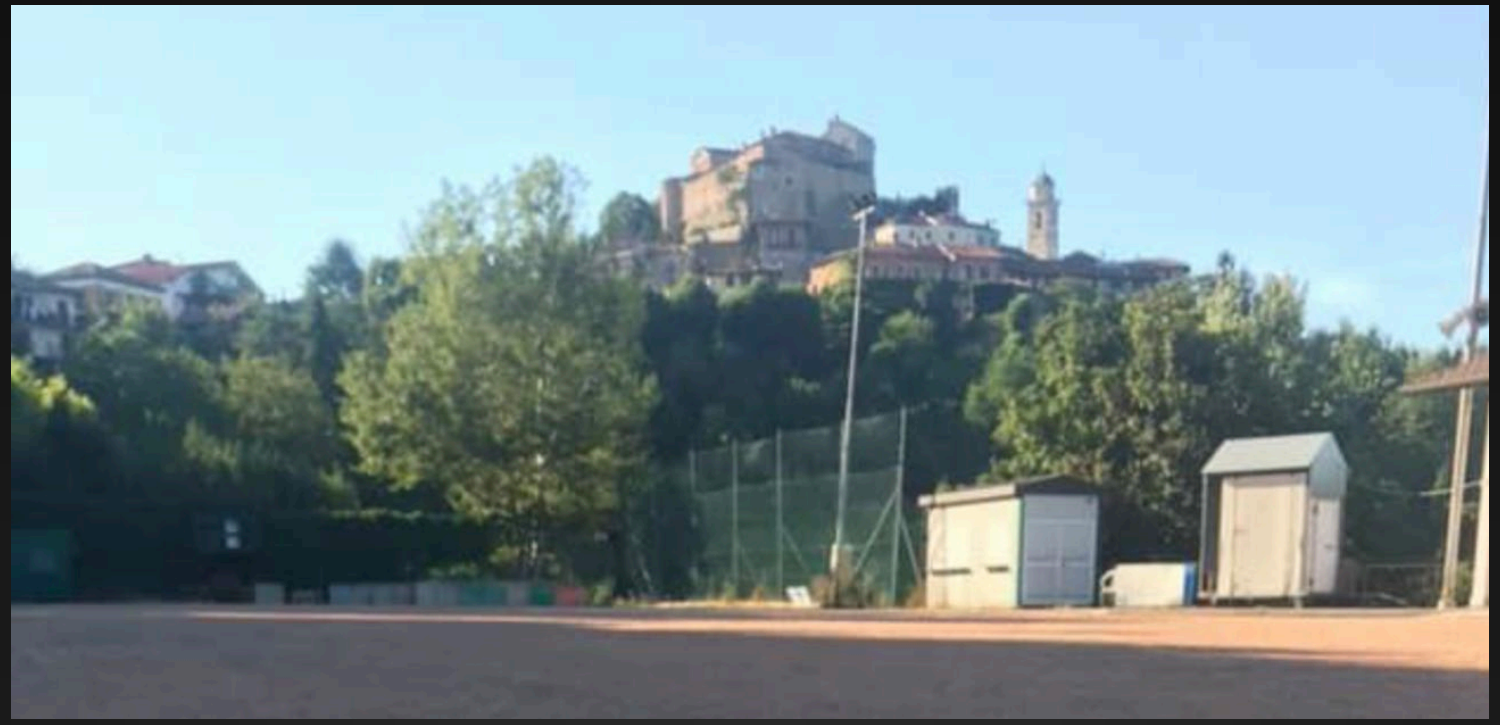
Thank you



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