Nuovi approcci terapeutici nelle infezioni da batteri gram-positivi

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UNIVERSITÀ DEGLI STUDI DI MILANO

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Outline

1. Duration of therapy in uncomplicated SAB
2. Carbapenem combination therapy in persistent MSSA BSI
3. Daptomycin vs lipopeptides against G+
4. Cotrimoxazole for BJI

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Duration of therapy in uncomplicated SAB

> Clin Microbiol Infect. 2024 Oct;30(10):1254-1260. doi: 10.1016/j.cmi.2024.05.015. Epub 2024 May 30.

Long versus short course anti-microbial therapy of uncomplicated Staphylococcus aureus bacteraemia: a systematic review

Martin Schnizer [1], Paul Schellong [1], Norman Rose [1], Carolin Fleischmann-Struzek [1], Stefan Hagel [1], Mohamed Abbas [2], Brendan Payne [3], Rebecca N Evans [4], Mathias W Pletz [1], Sebastian Weis [5]

- Patients are typically considered to have an uncomplicated SAB in the **absence of deep-seated infection, septic metastasis, or infective endocarditis** (IE), **negative follow-up blood cultures,** and **defervescence within 72 hours** after initiation of effective anti-microbial therapy.
- Some authors also include the mere presence of **implanted foreign material** as an indicator of a complicated infection, but this view is controversially discussed.
- Current recommendations request that patients with uncomplicated SAB should receive targeted anti-infective therapy for **at least 14 days.**
- Reducing duration of treatment in patients with SAB without increasing relapses or mortality could limit length of hospital stay while simultane

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- To assess the current strength of evidence for the recommendation of treatment duration for patients with uncomplicated SAB.
- All clinical studies comparing the DOT (long vs. short) for adult patients with uncomplicated SAB regardless of design, publication status, or language were eligible for inclusion.
- SAB defined as any blood culture positive for *Staphylococcus aureus*, not considered a contaminant.
- **"short" DOT compared to control "long" DOT.**
- Studies applying bundle approaches (such as additional infectious disease expert consultation), were excluded.
- Only data from studies that have **adjusted their results for potential confounding factors** such as age, sex, or severity of disease and which reported adjusted effect sizes for mortality were included in the final review.

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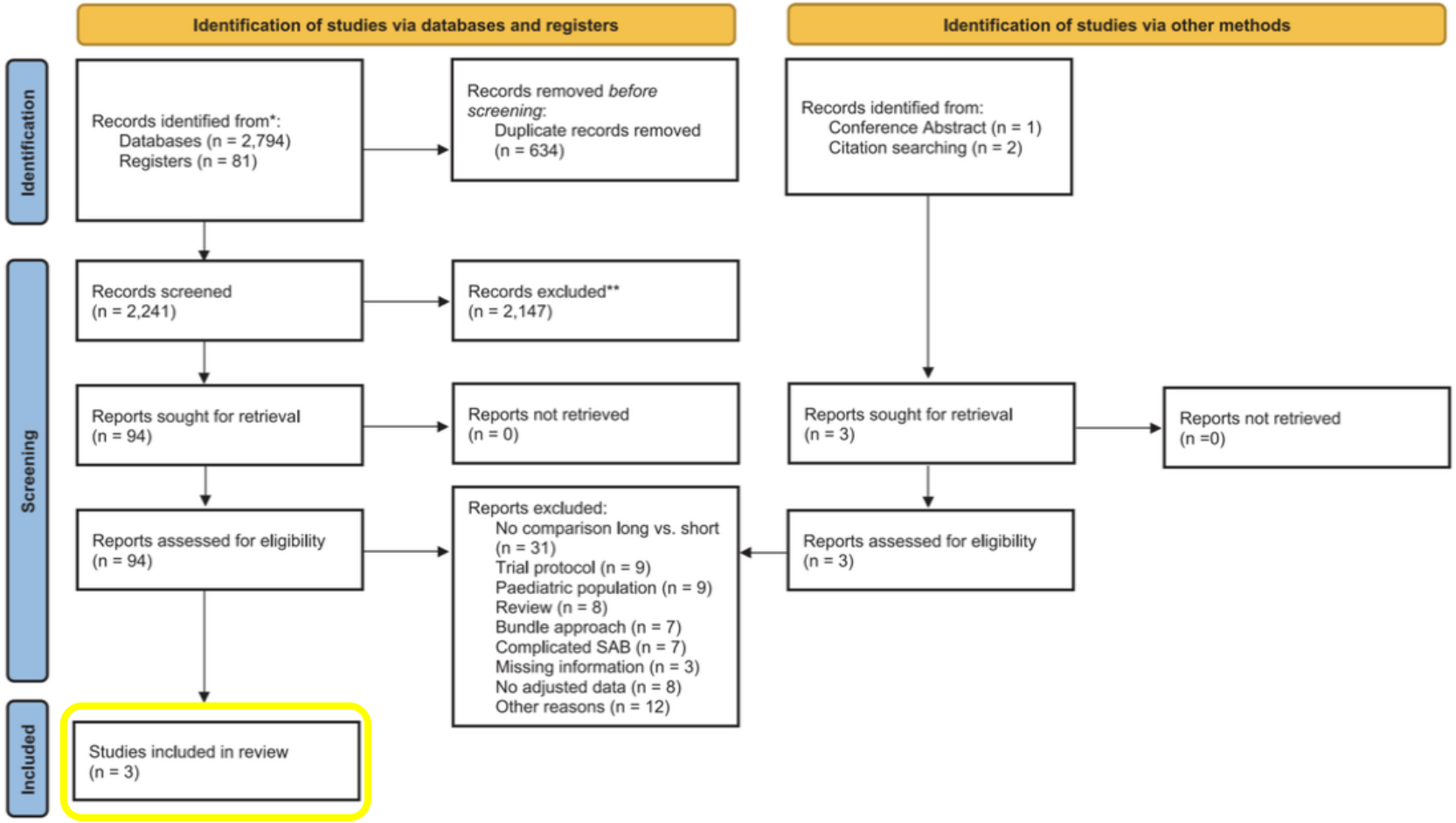

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Study	Abbas et al. [13], 2020	Evans et al. [16], 2022	Thorlacius-ussing et al. [16], 2021
Design	Retrospective, observational cohort study	Retrospective, observational cohort study	Retrospective, observational cohort study
Country	Switzerland MRSA/MSSA	UK MRSA/MSSA	Denmark MSSA
No. of centres	1	5	6
Study period	01/2010–12/2015	11/2010–05/2012	01/2009–12/2018
Treatment comparison	Short DOT (≤14 d) vs. long DOT (>14 d)	Short DOT (10–18 d) vs. long DOT (>18 d)	Short DOT (6–10 d) vs. long DOT (11–16 d)
(median dot short)	total population: 20 days	(NS)	(8 d)
(median dot long)		(NS)	(14 d)
Primary outcome	90-day mortality	28-day mortality	90-day mortality
Secondary outcome	30-day mortality 90-day relapse		Relapse
Sample size	225	425	1005
Adjusted variables in analysis	Age Nosocomial Acquisition of SAB Child C cirrhosis Prior prednisone use Active cancer Lower respiratory tract focus of SAB Complicated SAB	Age Source of infection Neutrophil count on day of blood culture eGFR systolic BP on IV fluids on ventilation on vasopressor on systemic corticosteroids Baseline neutrophil count Daily temperature measurement	Age Sex Charlson-Comorbidity-Index score Acquisition of SAB Primary focus of SAB Pitt score C-reactive protein

DOT, duration of therapy; NS, not specified; SAB, *Staphylococcus aureus* bacteraemia.

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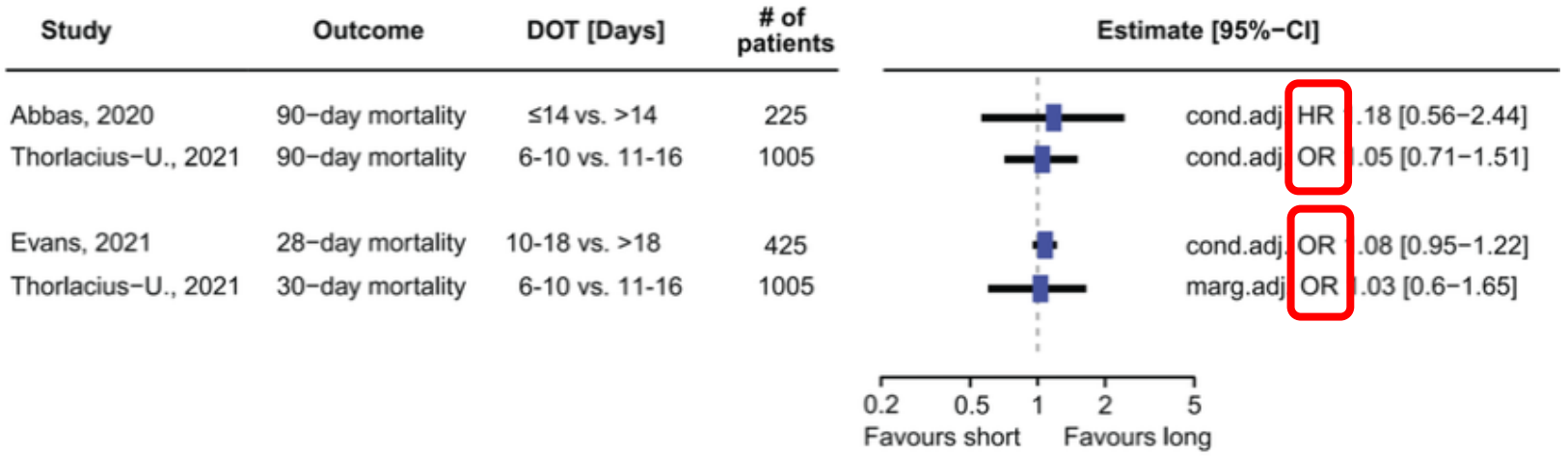

- For uncomplicated SAB, current guidelines recommend treatment durations of at least 14 days. We could not find sound evidence that would support this, a shorter, or a longer treatment duration.
- **The available data suggest that there is simply not enough evidence available to inform a decision.**
- Well-designed prospective randomized clinical studies overcoming the limitations inherent in observational studies assessing treatment duration are needed to determine the necessary treatment durations in patients with uncomplicated SAB.

Duration of therapy in uncomplicated SAB

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Carbapenem combination therapy in persistent MSSA BSI

Comparative Study > J Antimicrob Chemother. 2024 Aug 1;79(8):1990-1997.
doi: 10.1093/jac/dkae198.

Carbapenem combination therapy versus standard of care for persistent methicillin-susceptible Staphylococcus aureus bacteraemia

Sunish Shah [1 2], Lloyd G Clarke [1 2], Justin Ludwig [3], Sarah Burgdorf [4], Ricardo D Arbulu Guerra [4], Ryan K Shields [1 4]

- Standard treatment of MSSA bacteraemia with anti-staphylococcal penicillins or cefazolin is generally effective; however, persistent bacteraemia is associated with an increased risk of metastatic infection and death.
- Several **antimicrobial combinations** have been studied to shorten the duration of MSSA bacteraemia, but **none has been shown to be more effective than standard treatment with β-lactam monotherapy**.
- Successful use of **carbapenems in combination with either cefazolin or oxacillin for persistent MSSA infections** has been described.
  - The proposed rationale for this combination is **complete**

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- To **compare carbapenem combination therapy with standard treatment for persistent MSSA bacteraemia.**
- Retrospective study of consecutive adult patients with MSSA bacteraemia for >48 h between July 2019 and October 2023.
- **Standard treatment** was defined as monotherapy with cefazolin, oxacillin or nafcillin. **Combination therapy** was defined as the addition of ertapenem or meropenem to standard treatment for at least 24 h.
- Patients were excluded if they had polymicrobial infections or if they received a carbapenem following blood culture sterilization.
- Outcomes:

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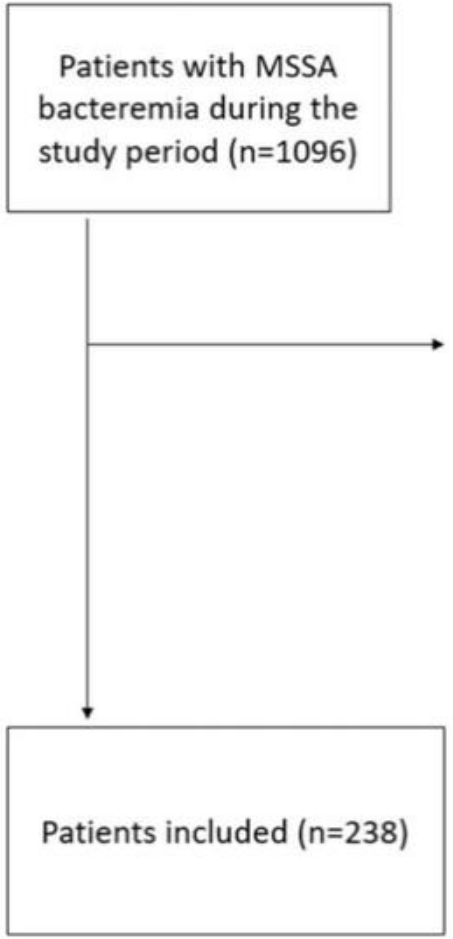

Reasons for exclusion	Total n=858
<48 hours of positive blood cultures	658
Carbapenem added after blood culture sterilization	43
Alternative treatment for MSSA bacteremia	24
Standard treatment employed for <72 hours	15
Polymicrobial infection	75
Death prior to repeat blood cultures	41
Empiric carbapenem treatment in patients receiving standard care	1
Age <18 years	1

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	Standard treatment (*n*=157)	Combination therapy (*n*=81)	*P* value
Patient demographics and underlying diseases			
Age, years, median (IQR)	60.3 (43.1–72.1)	51.7 (39.4–64.8)	**0.012**
Female gender, *n* (%)	71 (45.2)	42 (51.9)	0.332
CCI, median (IQR)	2 (1–4)	2 (0–3)	0.202
Immunocompromised, *n* (%)	18 (11.5)	7 (8.6)	0.656
PWID, *n* (%)	42 (26.8)	29 (35.8)	0.148
Patient-directed discharge, *n* (%)	11 (7)	9 (11.1)	0.280
Infection characteristics and source control			
Pitt bacteraemia score, median (IQR)	1 (0–3)	1 (0–3)	0.664
Definitive endocarditis, *n* (%)	57 (36.3)	41 (50.6)	**0.034**
Spinal infection, *n* (%)	45 (28.7)	33 (40.7)	0.059
Source control procedure, *n* (%)	25 (56)	15 (45)	0.492
Time to source control, days, median (IQR)	2 (0.88–6)	5.7 (4.1–8.7)	**0.016**
Source control for non-spinal infections, *n* (%)[a]	84 (53.5)	29 (35.8)	**0.009**
Source control procedure, *n* (%)	68 (81)	23 (79)	1.000
Time to source control, days, median (IQR)	3 (1.4–5)	4.4 (1.7–11.7)	0.137
Treatment characteristics			
Empirical antibiotic regimen			0.892
Vancomycin monotherapy, *n* (%)	33 (22)	15 (18.5)	
Vancomycin plus β-lactam, *n* (%)	110 (70.1)	59 (72.8)	
Other, *n* (%)	14 (8.9)	7 (8.6)	
Time to empirical treatment, hours, median (IQR)	2.16 (0.48–11.04)	1.92 (0.24–13.44)	0.962
Initial targeted regimen selected			0.264
Oxacillin/nafcillin, *n* (%)	93 (59.2)	54 (66.7)	
Cefazolin, *n* (%)	64 (40.8)	27 (33.3)	
Time to targeted treatment, hours, median (IQR)[b]	64.8 (43.2–79.2)	57.6 (36–72)	**0.024**
Concomitant anti-staphylococcal antibiotic, *n* (%)[c]	16 (10.2)	8 (9.9)	0.939

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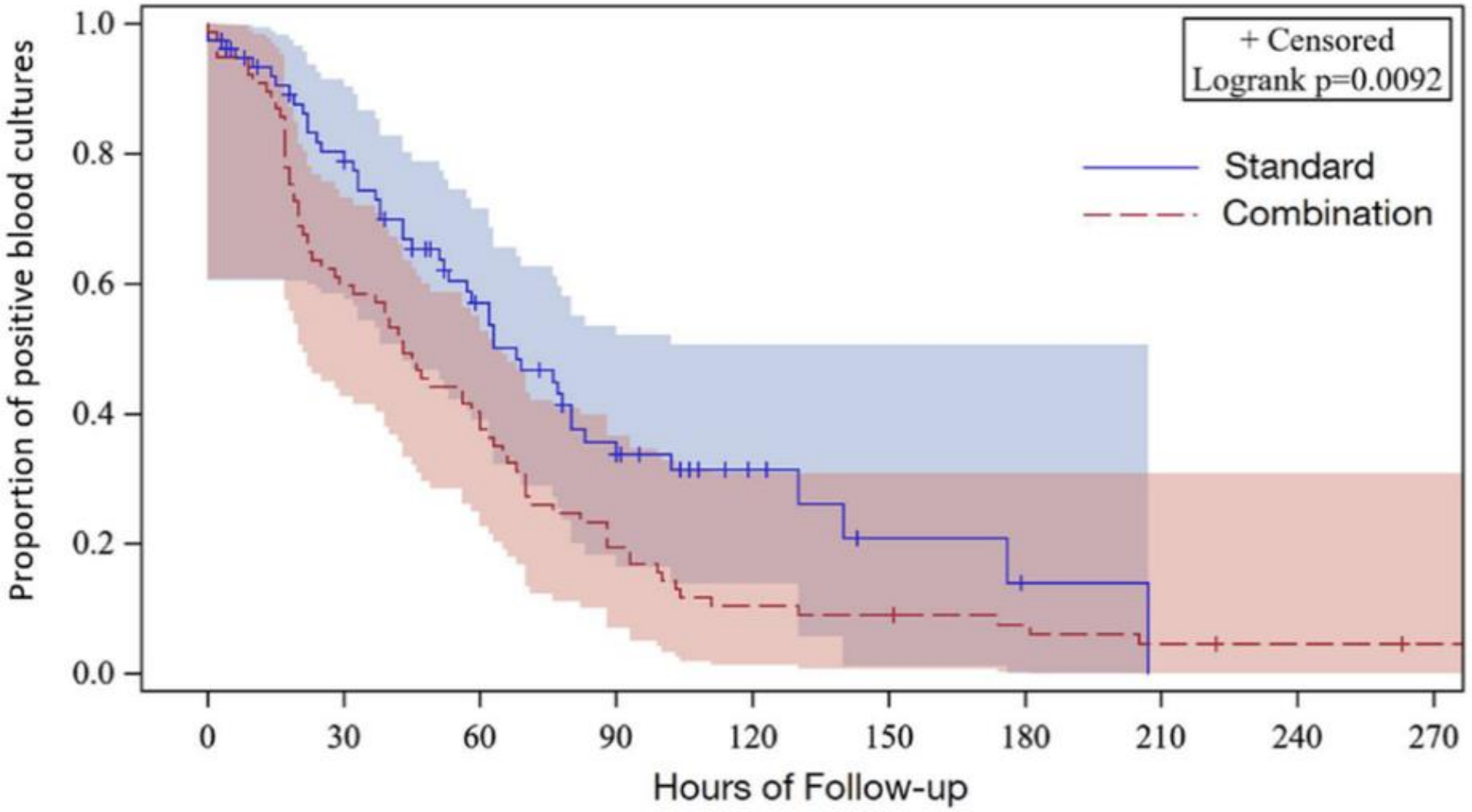

Combination therapy: 25h faster clearance of blood cultures

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Overall

Time to negative blood cultures in favour of combination therapy: [HR = 1.618 (95%CI; 1.119–2.339) P = 0.011

Equal mortality: combination therapy [24.7% (19/77)] versus matched controls [22.1% (17/77); HR = 1.267 (95% CI; 0.610–2.678), P = 0.61]

Cefazolin vs oxacillin

No differences in time to negative blood cultures: 1.8 versus 1.7 days, P = 0.731

<96h vs >96h since BSI detection

No differences in time to negative blood cultures: 1.6 versus 1.8 days, P = 0.224
Equal mortality: 33.3% versus 24.1%; P = 0.395

Endocarditis

No differences in time to negative blood cultures: [HR = 1.667 (95% CI; 0.776–3.739), P = 0.215].

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Daptomycin vs lipopeptides against G+

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Comparison of daptomycin and glycopeptide efficacy and safety for the treatment of Gram-positive infections: a systematic review and meta-analysis

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- Methicillin-resistant strains of *S. aureus* and CoNS are primarily treated with vancomycin. However, vancomycin is known to be difficult to handle as its use often causes adverse events.
- Daptomycin is increasingly used off-label for left-sided endocarditis and has been recommended in the IDSA guideline for the treatment of PJI.
- **Limited information exists on its efficacy and safety compared with vancomycin**, as only a limited number of clinical trials evaluated the safety and efficacy of daptomycin compared with [illegible]eptides.

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- A **systematic review and meta-analysis**, aiming at assessing the **efficacy and safety profile of daptomycin compared with those of glycopeptides.**
- To be included, studies had to be published in English or French, be an RCT, and use **daptomycin in the experimental arm and glycopeptides in the control arm (either vancomycin or teicoplanin)** irrespective of schemes, doses or the estimates of concentration samples, **monotherapy only.**
- Outcomes:
  - **All-cause mortality**
  - **Safety, defined as any major adverse event (at least grade 3)**
  - **Clinical and microbiological success** (resolution or improvement of signs and symptoms compared with baseline, and eradication of all base line pathogens, respectively)

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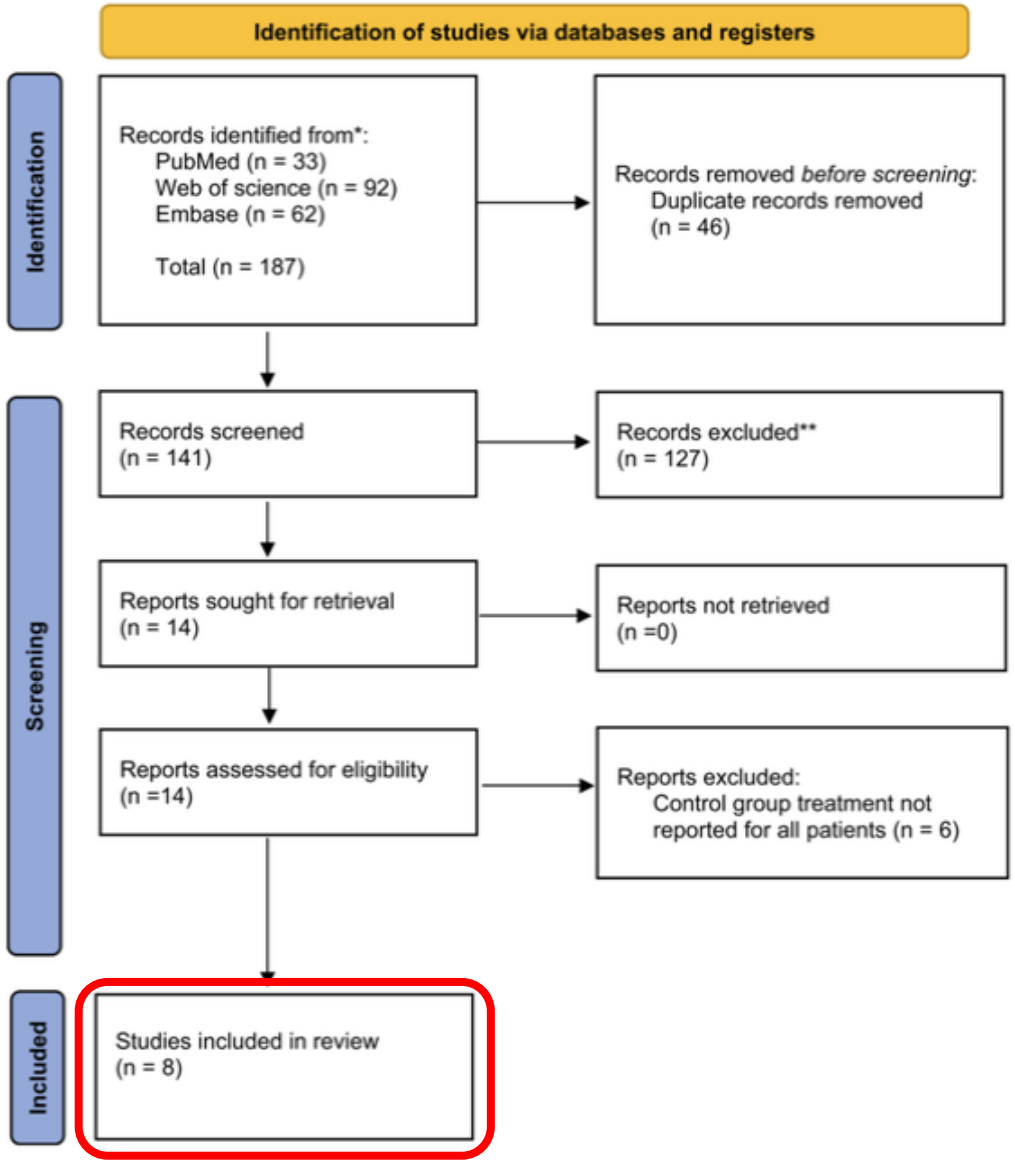

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Study	Design	Risk of bias	Indication	*N*	Population characteristics, age (years)[a]	Female ratio	Treatment: Daptomycin[b]	Treatment: Glycopeptides[c]
Byren *et al.*, 2012[19]	Multicentre open-label RCT	Some concerns	Prosthetic joint infection	DAP6: 25 DAP8: 24 GLY: 25	DAP6: 63.5 ± 13.3 DAP8: 60.4 ± 13.2 GLY: 61.2 ± 12.7	DAP6 : 0.56 DAP8: 0.42 GLY: 0.44	6 or 8 mg/kg	VAN 1 g or TEC 6 mg/kg
Arbeit *et al.*, 2004[37]	Multicentre blinded RCT	Low	cSSSI	DAP: 111 GLY: 172	[d]DAP: 51.5 ± NR	[d]DAP: 0.45	4 mg/kg	VAN 1 g
Quist *et al.*, 2012[38]	Multicentre blinded RCT	Some concerns	cSSSI	DAP: 97 VAN: 46 TEC: 46	NR	NR	4 mg/kg	VAN 1 g or TEC: loading dose of 400 mg q12h on Day 1, followed by 400 mg once daily
Kalimuddin *et al.*, 2018[39]	Multicentre open-label RCT phase 2B	Low	BSI	DAP: 7 GLY: 7	DAP: 65 (50–71) VAN: 70 (64–71)	DAP: 0.285 VAN: 0.285	6 or 8 mg/kg	VAN 15 mg/kg
Shaw *et al.*, 2015[40]	Monocentre open-label RCT	Low	cSSSI	DAP: 50 VAN: 50	DAP: 42 ± 12 VAN: 38 ± 13	DAP: 0.42 VAN: 0.3	4 mg/kg	VAN 15 mg/kg
Kauf *et al.*, 2015[41]	Multicentre open-label RCT	Low	cSSSI	DAP: 118 VAN: 106	DAP: 47.2 ± 15.2 VAN: 50 ± 13.5	DAP: 0.458 VAN: 0.462	4 mg/kg	Dosed at the investigator's discretion
Pertel *et al.*, 2009[42]	Multicentre blinded RCT	Some concerns	cSSSI	DAP: 50 VAN: 51	DAP: 57 (22–79) VAN: 55 (21–86)	DAP: 0.66 VAN: 0.51	4 mg/kg	Not specified
Aikawa *et al.*, 2013[43]	Multicentre open label RCT	Low	cSSSI	DAP: 88 VAN: 22	DAP: 69 (22–92) VAN: 70 (29–82)	DAP: 0.466 VAN: 0.318	4 mg/kg	VAN 1 g

1095 patients
570 DAP, 478 VAN, 47 TEC

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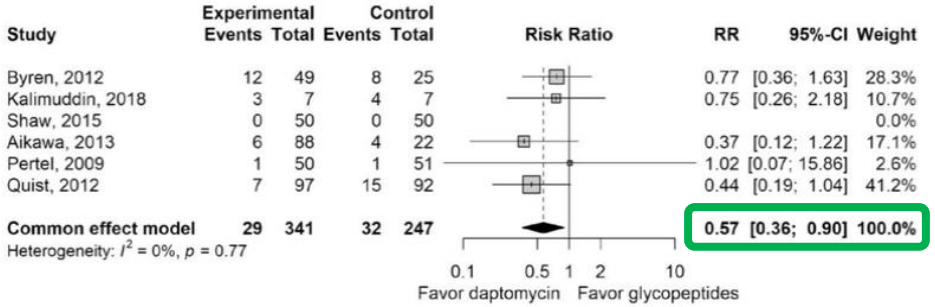
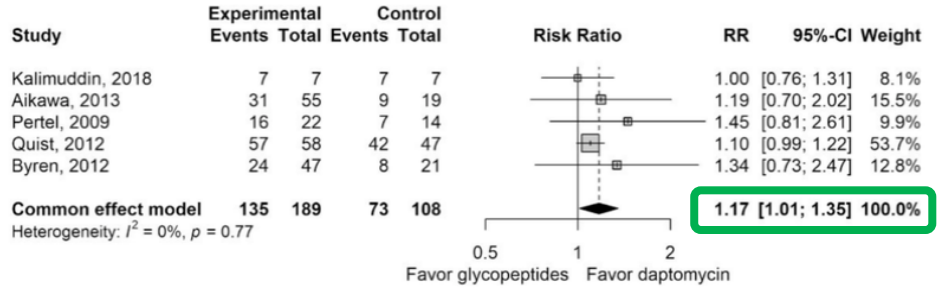
- **All-cause mortality was not significantly different** across groups [RR = 0.32 (95% CI 0.09–1.14); P = 0.078; I2 = 0%]. (Reported only in two trials)

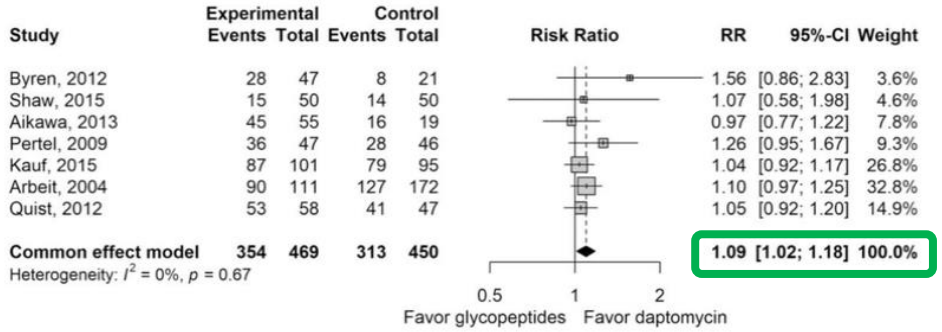
SAEs



Microbiological success



Clinical success



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Cotrimoxazole for BJI

Efficacy and safety of co-trimoxazole in device-related bone and joint infections: a CRIOGO multicentre case–control study

Raphaël Lecomte ✉, Colin Deschanvres, Amandine Le Bourgeois, Géraldine Bart, Rafaël Mahieu, Gwénaël Le Moal, Séverine Ansart, Nathalie Asseray, Louise Ruffier d'Epenoux, Stéphane Corvec ... Show more
Author Notes

Journal of Antimicrobial Chemotherapy, dkae328, https://doi.org/10.1093/jac/dkae

- Bone and joint infections (BJIs) are associated with a **high morbidity**, particularly when they occur on devices. Treatment is based on surgery, followed by prolonged antibiotic therapy, associated with numerous adverse effects.
- For the treatment of G+ infections, a rifampicin-based regimen is recommended, but its use is limited by numerous drug interactions and adverse effects.
- Co-trimoxazole has good bioavailability, which allows oral administration and is an economic alternative.
- In BJI, co-trimoxazole use is uncommon for two main reasons:
  - (i) there are very **few efficacy data published in the literature**, particularly for device-associat
  - (ii) the duration of treatment is particularly long for

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- The study objective of this study was to compare the outcome of patients with **device-related BJI treated with an antibiotic regimen including co-trimoxazole** versus a regimen without cotrimoxazole, in terms of efficacy and safety.
- **Retrospective case-control study** was performed using patient data from four University hospitals of the CRIOGO network.
- Clinical signs and symptoms of BJI associated with a positive bacteriological culture of the surgical samples.
- Each included patient receiving **at least one dose of co-trimoxazole** was included in the co-trimoxazole group and was matched with two control patients.
- **: death or treatment failure dur**
  follow-up

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	Co-trimoxazole group (N=50)	Control group (N=100)	P value
Age, years, median (IQR)	64 (48-83)	65 (49-76)	0.39
Male sex, *n* (%)	30 (60)	62 (62)	0.81
Comorbidity			
Charlson CI, median (IQR)	3 (1-5)	2.5 (1-4)	0.62
Diabetes, *n* (%)	5 (10)	9 (9)	0.84
Malignancy, *n* (%)	5 (10)	15 (15)	0.40
Obesity, *n* (%)	4 (8)	9 (9)	0.84
Chronic renal failure, *n* (%)	3 (6)	7 (7)	0.82
Cardiopathy, *n* (%)	11 (22)	15 (15)	0.29
Microorganisms, *n* (%)			
S. aureus	15 (30)	46 (46)	0.06
CoNS	13 (26)	15 (15)	0.10
Enterococcus sp.	4 (8)	4 (4)	0.30
Streptococcus sp.	2 (4)	7 (14)	0.47
Gram-negative bacteria	20 (40)	24 (24)	0.04
Enterobacter sp.	12 (24)	8 (8)	0.01
Escherichia coli	5 (10)	9 (9)	0.99
P. aeruginosa	0	7 (7)	0.13
Proteus sp.	5 (10)	2 (2)	0.08
Other Gram-negative bacteria	2 (4)[a]	5 (5)[b]	0.99
Other	9 (9)	22 (22)	0.57
Polymicrobial	15 (30)	26 (26)	0.60
Surgical treatment, *n* (%)			
Prosthetic joints	25 (50)	38 (38)	0.16
Debridement with implant retention	9 (18)	11 (11)	0.23
One-stage exchange	8 (16)	16 (16)	0.99
Two-stage exchange	6 (12)	8 (8)	0.58
Permanent removal	2 (4)	3 (3)	0.75
Osteosynthesis[c]	25 (50)	62 (62)	0.16
Removal	12 (24)	30 (30)	0.44
Exchange	5 (10)	12 (12)	0.72
Debridement with retention	8 (16)	18 (18)	0.76
Antibiotic treatment (definitive treatment)			
Bitherapy[d], *n* (%)	49 (98)	91 (91)	0.11
Fluoroquinolone, *n* (%)	24 (48)	76 (76)	<0.01
Rifampicin, *n* (%)	13 (26)	43 (43)	0.04
Clindamycin, *n* (%)	4 (8)	25 (50)	0.01
Duration, days, median (IQR)	95 (80-106)	91 (58-109)	0.25

In patients with normal renal function (n = 40), co-trimoxazole dosage was:

- 320/1600 mg/day for 23 patients (57.5%)
- 480/2400 mg/day for 11 patients (27.5%)
- 640/3200 mg/day for 6 patients (15%)

Cotrimoxazole for BJI

	Co-trimoxazole group (*N* = 50)	Control group (*N* = 100)	*P* value
Primary outcome, *n* (%)			
Death or treatment failure	9 (18)	21 (21)	0.66
Secondary outcomes, *n* (%)			
Treatment failure	7 (14)	17 (17)	0.64
Death	2 (4)	4 (4)	0.99
Major sequelae	8 (16)	8 (8)	0.13
Adverse events[a]	17 (34)	18 (18)	**0.03**
PAD	7 (14)	12 (12)	0.73
Adverse events, *n* (%)	17 (34)[a]	18 (18)[b]	**0.03**
Grade I[c]	7 (14)	9 (9)	0.35
Grade II[c]	9 (18)	8 (8)	0.07
Grade III or more[c]	1 (2)[d]	1 (2)[e]	0.61
PAD, *n* (%)	7 (14)	12 (12)	0.73
Type of adverse events, *n* (%)			
Gastrointestinal disturbance	2 (6)	3 (2)	0.75
Renal impairment	4 (6)	0	**0.01**
Skin rash	4 (8)	6 (6)	0.64
Elevated hepatic enzymes	1 (2)	3 (3)	0.72
Haematotoxicity	9 (18)	4 (4)	**0.01**
Musculoskeletal disorders	0	3 (3)	0.55
Delay of adverse events, days, median (IQR)	28 (17.5–50)	29 (24–51)	0.42

Efficacy and safety of co-trimoxazole in device-related bone and joint infections: a CRIOGO multicentre case–control study

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Table 3. Comparison of the primary outcome (death or failure) according to antibiotic regimen (co-trimoxazole or control group) and surgical management of the device-associated infection

	Co-trimoxazole group (*N* = 50)	Control group (*N* = 100)[a]	*P* value
Removal, *n*/*N* (%)	0/14 (0)	6/33 (18)	0.09
Exchange, *n*/*N* (%)	6/19 (32)	10/36 (28)	0.42
Debridement with retention, *n*/*N* (%)	3/17 (18)	5/29 (17)	0.97

Conclusions

- For **uncomplicated SAB**, current guidelines recommend treatment durations of **at least 14 days**. The available data suggest that there is simply **not enough evidence available to inform a decision.**
- In MSSA BSI, combination therapy with a carbapenem leads to a 25h **faster clearance of blood cultures**. No evidence of lower mortality, shorter lengths of stay, or decreased rates of recurrence.
- Daptomycin vs glycopeptides for the treatment of infections due to G+: **similar rates of all-cause mortality and clinical success, higher rate of micro-biological success** in patients who received daptomycin. Those also exhibited a **lower incidence of SAEs.**
- Co-trimoxazole **could be an effective alternative for the treatment of BJI**, even when it occurs on a device. Nevertheless, the safety profile requires **c**
  monitoring of adverse effects throughout the course of