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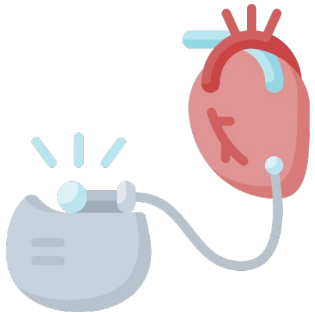
SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI
PANDORA ID - 23
TIME TO WEBINAR IN INFECTIOUS DISEASES
PROGETTO DI FORMAZIONE

I.R.C.C.S. Ospedale San Raffaele
Gruppo San Donato

Terapia antibiotica empirica o mirata nei pazienti che vanno incontro a rimozione dei devices cardiaci



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Outline

1. Introduction
2. Guidelines
3. Empirical and definitive therapy
4. Antibiotic timing
5. Oral and long-acting therapy
6. Conclusions

Introduction

Epidemiology

Table 2 Incidence and incidence rate of device-related infection in the Danish CIED population 1982–2018

Variable	Devices	Device years	Events	Overall incidence			Incidence rate /1000 DY		
					95% CI			95% CI	
Total	128 045	566 275	1827	1.43%	1.36	1.49	3.23	3.08	3.38
Sex									
Female	51 484	241 524	505	0.98%	0.90	1.07	2.09	1.92	2.28
Male	76 561	324 750	1322	1.73%	1.64	1.82	4.07	3.86	4.30
Operation & Device Type									
Pacemaker									
Total	100 374	460 196	1194	1.19%	1.12	1.26	2.59	2.45	2.75
First	79 318	364 744	744	0.94%	0.87	1.01	2.04	1.90	2.19
Replacement	17 265	77 742	359	2.08%	1.87	2.30	4.62	4.16	5.12
Up-/downgrade	3791	17 708	91	2.40%	1.94	2.94	5.14	4.18	6.31
ICD									
Total	16 718	69 766	320	1.91%	1.71	2.13	4.59	4.11	5.12
First	12 037	52 040	200	1.66%	1.44	1.91	3.84	3.35	4.41
Replacement	3959	15 015	92	2.32%	1.88	2.84	6.13	4.99	7.52
Up-/downgrade	722	2711	28	3.88%	2.59	5.56	10.33	7.13	14.96
CRT-P									
Total	4630	15 848	101	2.18%	1.78	2.64	6.37	5.24	7.75
First	2991	10 965	48	1.60%	1.19	2.12	4.38	3.30	5.81
Replacement	769	2249	26	3.38%	2.22	4.91	11.56	7.87	16.97
Up-/downgrade	870	2632	27	3.10%	2.05	4.48	10.26	7.03	14.96
CRT-D									
Total	6323	20 464	212	3.35%	2.92	3.83	10.36	9.05	11.85
First	3386	12 131	82	2.42%	1.93	3.00	6.76	5.44	8.39
Replacement	1339	3537	67	5.00%	3.90	6.31	18.94	14.91	24.07
Up-/downgrade	1598	4795	63	3.94%	3.04	5.02	13.14	10.26	16.82

Olsen T et al. Eur Heart J. 2019.

Clinical scenarios and microbiology

Signs of Pocket Infection?	Lead or Valvular Vegetations on Echocardiogram?		
	Yes	No	Blood Cultures?
Yes	Pocket infection with lead/valvular endocarditis	Isolated Pocket Infection	-
		Pocket Infection with bacteremia	+
No	CIED-related endocarditis without pocket infection	Occult bacteremia with presumable cardiac implantable electronic device (CIED) infection	

Table 2: Pathogens isolated in patients undergoing interventions for device infection from three large patient cohorts in North America, Europe, and Asia

Pathogen	Percentage of isolates		
	North America [16]	Europe [17]	Asia [18]
Coagulase-negative staphylococci		69	45.2
Methicillin-*resistant*	18.8		
Methicillin-*sensitive*	18.8		
S. aureus		13.8	4.1
Methicillin-*sensitive*	15.8		
Methicillin-*resistant*	15.0		
Streptococcus spp.	2.5		
Enterococcus spp.			
Vancomycin-sensitive	2.8		
Vancomycin-resistant	1.4		
Cutibacterium spp. (previously *Propionibacterium* spp.)		2.5	
Corynebacterium		5	
Gram-negative bacteria	8.9	6.1	9.1
Enterobacteriaceae		3	3.2
Non-fermentative bacilli, incl. *Pseudomonas* spp.		1.5	5.9
Anaerobes	1.6		
Fungi	0.9	1	0.9
Mycobacteria	0.2		

Palmeri NO et al. JACC Clin Electrophysiol. 2021; Blomström-Lundqvist C et al. Eur Heart J. 2020.

Microbiology - Gram-negatives

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Table 3
Multinomial logistic regression of infection development (not infected = base outcome).

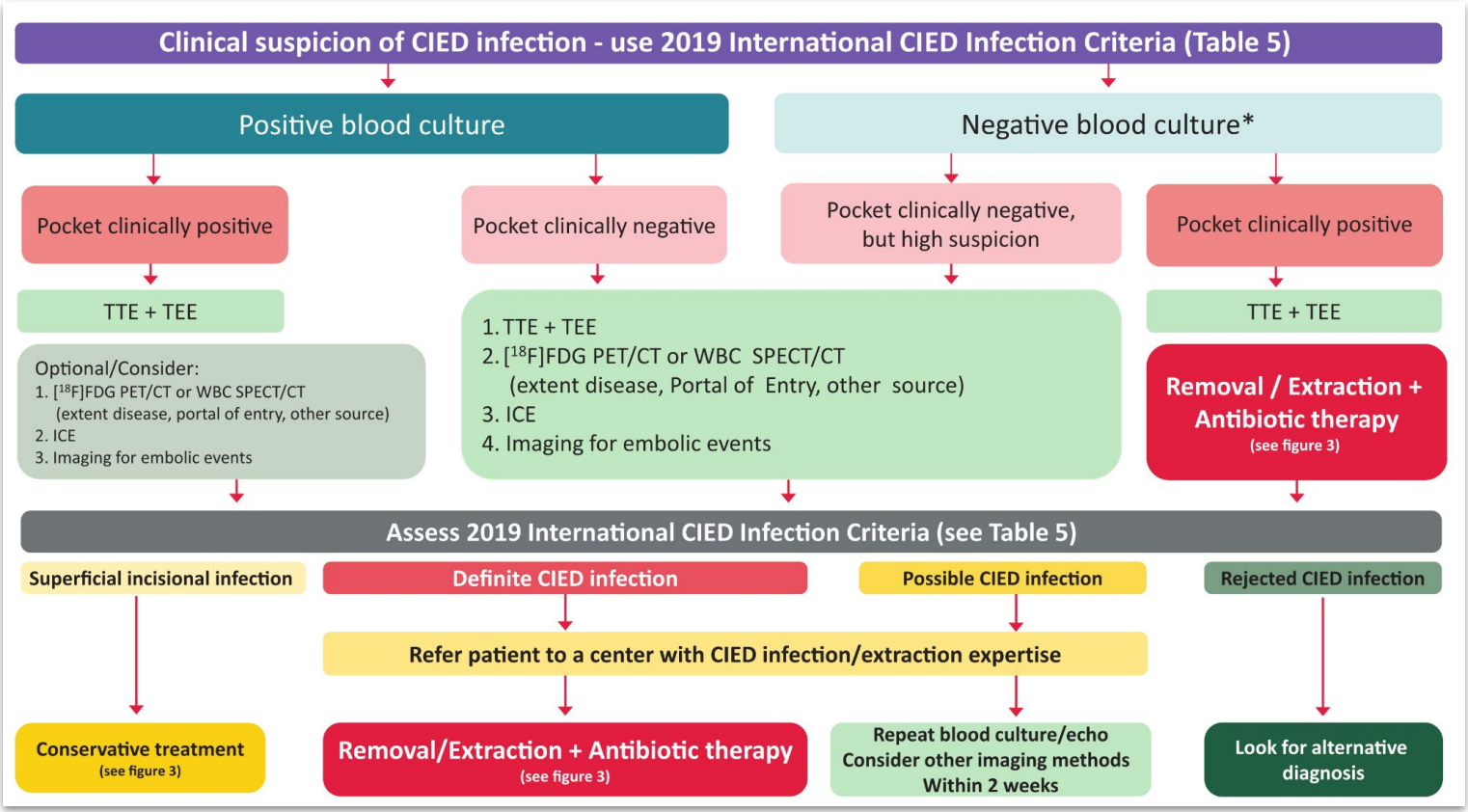
Gram-negative CIED infection risk	RRR	95% CI	*P*-value
Males	0.869	0.425 – 1.776	0.700
Age at device implantation	1.015	0.987 – 1.044	0.303
Charlson Index Score	1.211	1.045 – 1.404	0.011
Obesity	5.122	1.536 – 17.085	0.008
PM-VVI	3.027	1.372 – 6.680	0.006
CRT-D	1.267	0.408 – 3.936	0.682
Right subclavian vein site of implantation	5.014	1.665 – 15.101	0.004
Shariff score	1.270	0.882 – 1.830	0.199
constant	0.315	0.170 – 0.585	< 0.001
Gram-positive CIED infection risk			
Males	3.617	1.576 – 8.301	0.002
Age at device implantation	1.031	1.001 – 1.063	0.041
Charlson Index Score	0.920	0.819 – 1.033	0.159
Obesity	0.987	0.301 – 3.240	0.983
PM-VVI	3.032	1.058 – 8.691	0.039
CRT-D	2.692	1.706 – 4.249	< 0.001
Right subclavian vein site of implantation	1.435	0.448 – 4.601	0.543
Shariff score	1.682	1.234 – 2.293	0.001
constant	0.112	0.050 – 0.250	< 0.001

Abbreviations: CIED, cardiac implantable electronic devices; CRT-D, cardiac resynchronisation therapy devices; RRR, relative risk ratio; PM-VVI, ventricular-pacing ventricular-sensing inhibited-response pacemaker.
RRR for constant was estimated with respect to all covariates at their reference value.

Blomström-Lundqvist C et al. Eur Heart J. 2020; Pascale R et al. Int J Antimicrob Agents. 2023.

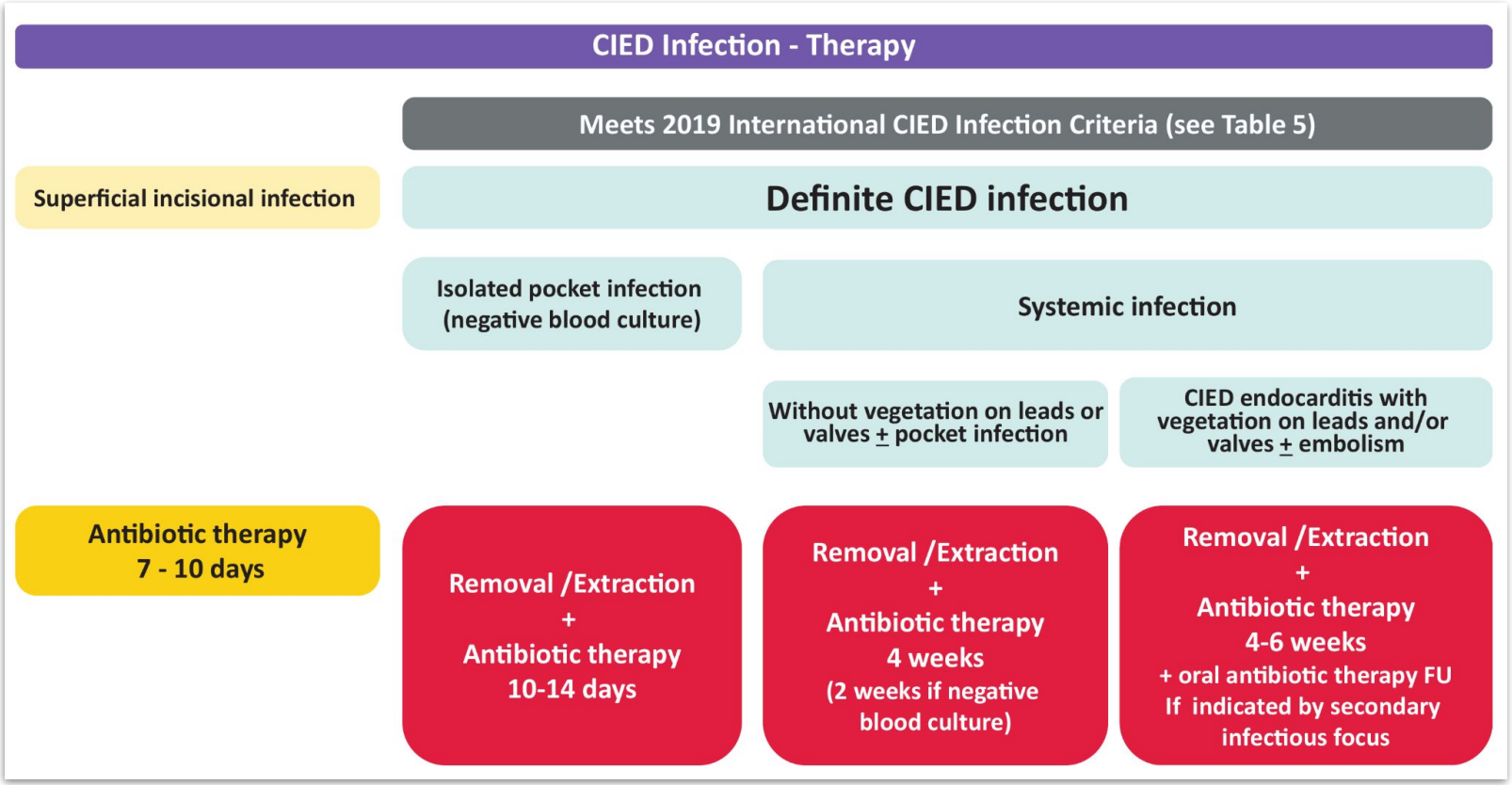
Guidelines

Management guidelines



Blomström-Lundqvist C et al. Eur Heart J. 2020.

Management guidelines



Blomström-Lundqvist C et al. Eur Heart J. 2020.

Management guidelines

Table 9: International consensus recommendations for antibiotic therapy including long-term suppressive therapy

Consensus statement		Statement class	Scientific evidence coding	References
Superficial incisional infection				
Empirical treatment: Oral antibiotic treatment covering *S. aureus* Flucloxacillin oral (amoxicillin-clavulanate is an alternative) If high MRSA prevalence: Trimethoprim-sulfamethoxazole, Clindamycin, Doxycyclin, Linezolid To be adjusted after culture result Duration: 7–10 days	Flucloxacillin p.o. 1 g every 6–8 h (amoxicillin-clavulanate standard dose)		O, R	[19, 65]
Isolated pocket infection (negative blood cultures)				
Empirical treatment: Directed at methicillin-resistant coagulase-negative staphylococci (CoNS) and *S. aureus*: Vancomycin (Daptomycin is an alternative)	Vancomycin: 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg i.v. od)		O, R	[19, 59, 65]
If systemic symptoms: For additional Gram-negative coverage, combine with 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin To be adjusted after culture result	+/- Cephalosporin: standard dose Gentamicin 5–7 mg/kg i.v od**			
If sensitive staphylococcus: Flucloxacillin (1st generation cephalosporin as an alternative) Partial oral treatment often used Duration post-extraction: 10–14 days	Flucloxacillin: 8 g/d i.v. in 4 doses or (1st generation cephalosporin standard dose)			
Systemic infections				
Without vegetation on leads or valves ± pocket infection Empirical treatment: (directed at methicillin-resistant staphylococci and Gram-negative bacteria): Vancomycin (Daptomycin is an alternative)	Vancomycin: 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg od)		O, R	[19, 59, 65, 81]
+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin To be adjusted after culture result	+ Cephalosporin: standard dose i.v or Gentamicin 5–7 mg/kg i.v. od[b]			
If sensitive staphylococcus: Flucloxacillin i.v. (1st generation cephalosporin i.v. as an alternative) Duration post-extraction: 4 weeks (2 weeks if negative blood culture, see text)	Flucloxacillin i.v. dosages as above. (1st generation cephalosporin standard dose i.v.)			

Blomström-Lundqvist C et al. Eur Heart J. 2020.

Management guidelines

CIED endocarditis with vegetation on leads and/or valves ± embolism				
Empirical treatment: Vancomycin (Daptomycin is an alternative)	Vancomycin; 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg od) +		O, R	[59]
+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin Adjust to culture result according to ESC endocarditis guidelines 2015	Cephalosporin; standard dose or Gentamicin 5–7 mg/kg i.v. od[b]			
If prosthetic valve and staphylococcal infection: Rifampicin to be added after 5–7 days Duration for native valve infective endocarditis: 4 weeks post extraction, for prosthetic valve endocarditis: (4-) 6 weeks, for isolated lead vegetation: 2 weeks therapy after extraction may be sufficient (in total 4 weeks) except for *S. aureus* infection, see text	Rifampicin: 900–1200 mg/day orally (or i.v.) in 2 doses			
Bacteraemia in a CIED patient without signs of pocket infection or echocardiographic evidence of lead or valve involvement				
According to pathogen specific treatment guidelines, see text			O, R	[119, 120]
Attempted salvage therapy and long-term suppressive therapy				
I.v. antibiotics as in prosthetic valve endocarditis for 4–6 weeks Stop antibiotic therapy under close follow-up or continue individualized long-term suppressive oral therapy, see text			E	[103, 118]

[a]Treatment regimens differ between countries depending on prevalence of MRSA and other circumstances—see text. Dosage recommendation needs to be adjusted for kidney function.

[b]For patients with normal renal function.

d: day; E: expert opinion; H: hour; i.v.: intravenous; M: meta-analysis; MRSA: methicillin-resistant *Staphylococcus aureus*; O: observational studies; od: once daily; p.o.: per oral; R: randomized trials.

Blomström-Lundqvist C et al. Eur Heart J. 2020.

Empirical and definitive therapy

Empirical therapy

- No clinical trials available
- Adequate anti-gram positive coverage
    - Including methicillin-resistant pathogens
- Include anti-gram negative
- Preferably bactericidal (?)
- Preferably with anti-biofilm activity

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Holubar et al. Infect Dis Clin N Am. 2016; Jacqueline et al. J Antimicrob Chemother. 2014; Blomström-Lundqvist C et al. Europace. 2020.

Empirical therapy

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Agent	MIC Breakpoint for *S aureus* (μg/mL)	PK-PD Indices Associated with Efficacy	Activity Against *S aureus*
Vancomycin	≤2	AUC/MIC	Bactericidal
Daptomycin	≤1	AUC/MIC	Bactericidal
Ceftaroline	≤1	T > MIC	Bactericidal
Dalbavancin	≤0.12	AUC/MIC	Bactericidal
Oritavancin	≤0.12	AUC/MIC	Bactericidal
Telavancin	≤0.12	AUC/MIC	Bactericidal
Tedizolid	≤0.5	AUC/MIC	Bacteriostatic
Linezolid	≤4	AUC/MIC	Bacteriostatic
Tigecycline	≤0.25	AUC/MIC	Bacteriostatic

Antibiotics	Inhibition of biofilm formation (adhesion)	Biofilm penetration	Bactericidal activity in biofilm
Vancomycin	+	++[16,17]	+[16,17]
Linezolid	+	++[24,29]	+[24]
Daptomycin	+	+++[15]	++[21,24]

Holubar et al. Infect Dis Clin N Am. 2016; Jacqueline et al. J Antimicrob Chemother. 2014; Blomström-Lundqvist C et al. Europace. 2020.

Anti-gram-positive - MSSA

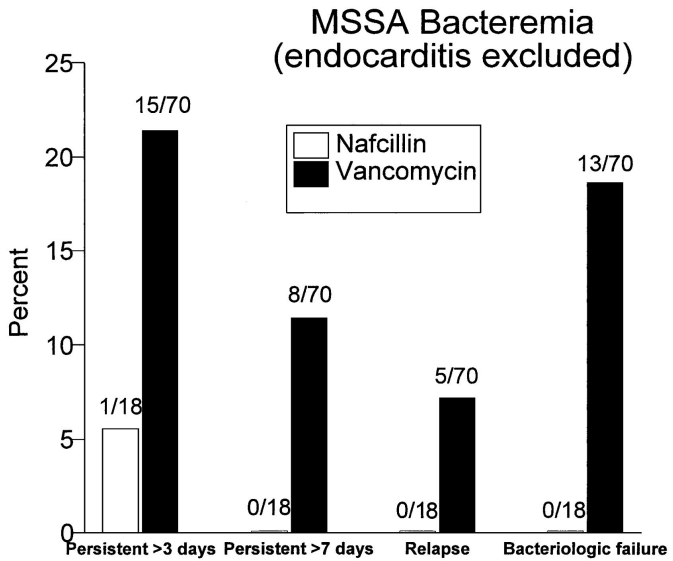


TABLE 2. Variables associated with *S. aureus*-related mortality in 294 patients with MSSA-B (cohort study)

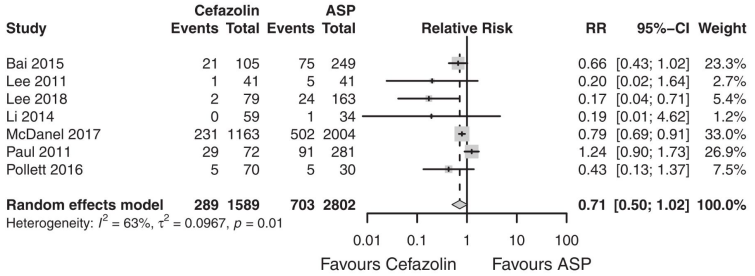
Characteristic	Univariate analysis		Multivariate analysis[a]		Multivariate analysis[b]	
	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Old age (≥65 yr)	1.4 (0.8–2.5)	0.29				
Male gender	1.0 (0.6–1.8)	0.98				
Community-acquired infection	1.2 (0.7–2.2)	0.52				
McCabe classification (ultimately fatal or rapidly fatal)	7.3 (2.8–19.0)	<0.001	2.7 (0.9–7.7)	0.06	2.7 (0.9–7.7)	0.06
Underlying diseases						
Solid tumor	6.8 (3.6–13.1)	<0.001	4.7 (2.2–9.9)	<0.001	4.8 (2.2–10.3)	<0.001
Hematologic malignancy	0.4 (0.2–1.0)	0.06				
Liver cirrhosis	4.5 (2.4–8.6)	<0.001	3.4 (1.6–7.3)	0.002	3.4 (1.6–7.4)	0.002
End stage renal disease	0.4 (0.1–1.2)	0.09				
Cardiovascular disease	0.8 (0.3–2.5)	0.75				
Primary sites of infection						
Unknown	3.0 (1.7–5.4)	0.001				
Catheter-related infection	0.1 (0.0–0.4)	0.002				
Pneumonia	2.6 (1.1–6.0)	0.03	2.7 (0.9–7.3)	0.046	2.7 (0.9–7.3)	0.06
Soft tissue infection	0.6 (0.2–1.5)	0.30				
Surgical wound infection	0.8 (0.2–3.9)	0.81				
Eradicated foci of infection	0.2 (0.1–0.4)	<0.001	0.3 (0.1–0.7)	0.006	0.3 (0.1–0.7)	0.006
Infection acquired in intensive care unit	1.6 (0.6–4.4)	0.34				
Inappropriate empirical treatment	1.0 (0.4–2.3)	0.98				
Vancomycin treatment	2.8 (1.2–6.4)	0.02	3.4 (1.2–9.3)	0.02	3.3 (1.2–9.5)	0.02

[a] Adjusted for the variables associated with *S. aureus*-related mortality.
[b] Adjusted for the variables associated with *S. aureus*-related mortality and the propensity score of each patient's likelihood of being treated with vancomycin.

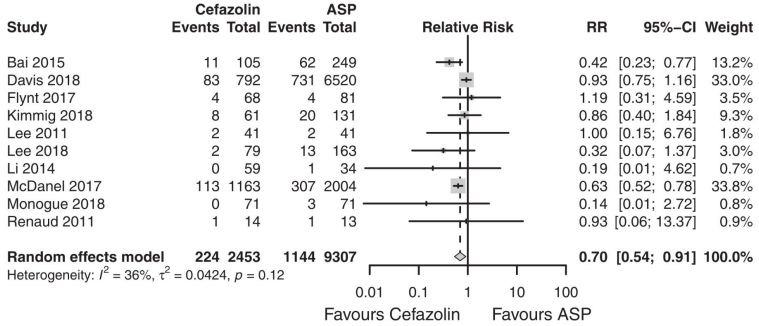
Kim SH et al. Antimicrob Agents Chemother. 2008; Chang FY et al. Medicine (Baltimore). 2003; McDanel JS et al. Clin Infect Dis. 2015.

Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemia

(a) 90−day all−cause mortality



(b) 30−day all−cause mortality



Weis S et al. Clin Microbiol Infect. 2019.

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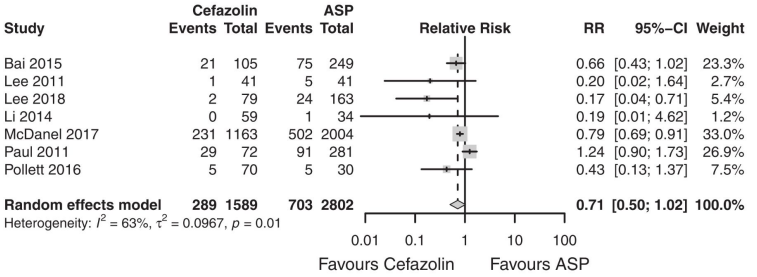

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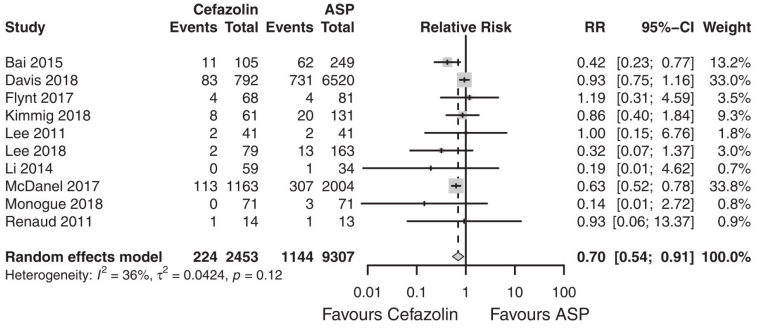
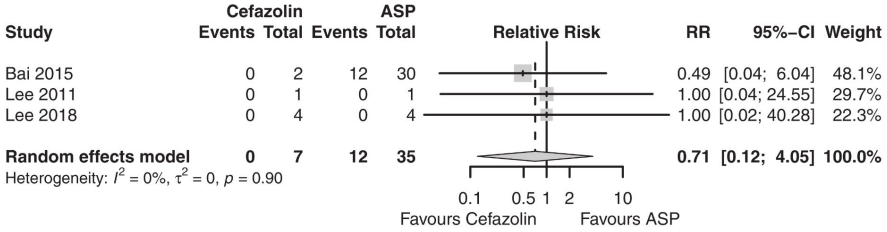
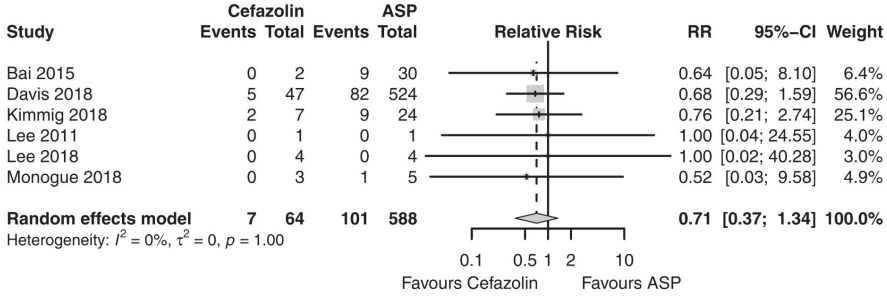


(a) 90-day all-cause mortality in patients with endocarditis



(b) 30-day all-cause mortality in patients with endocarditis



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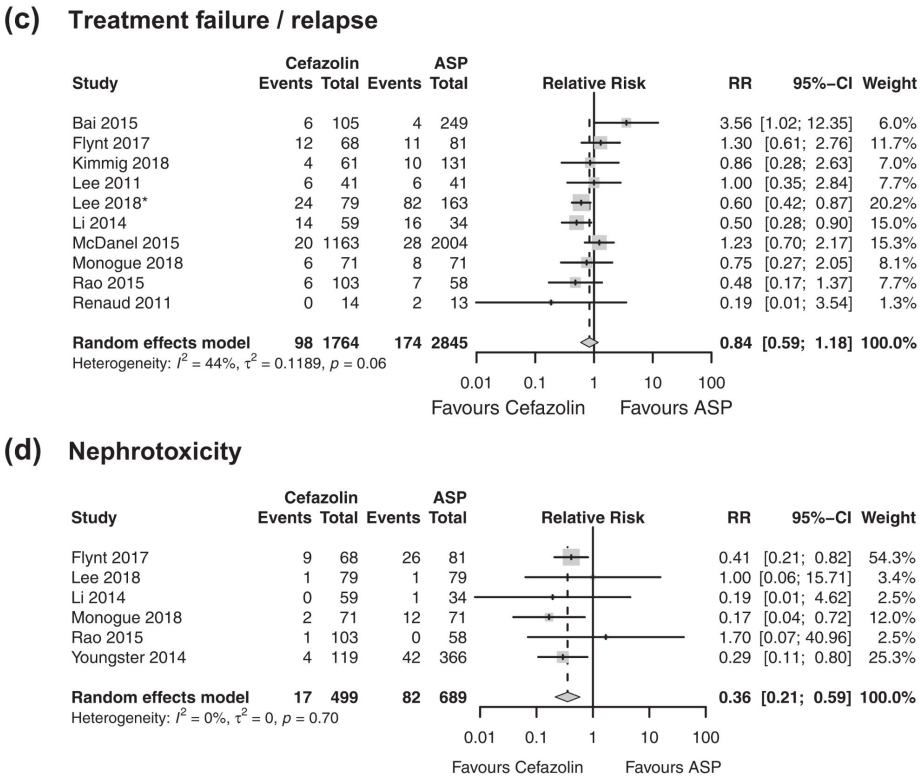

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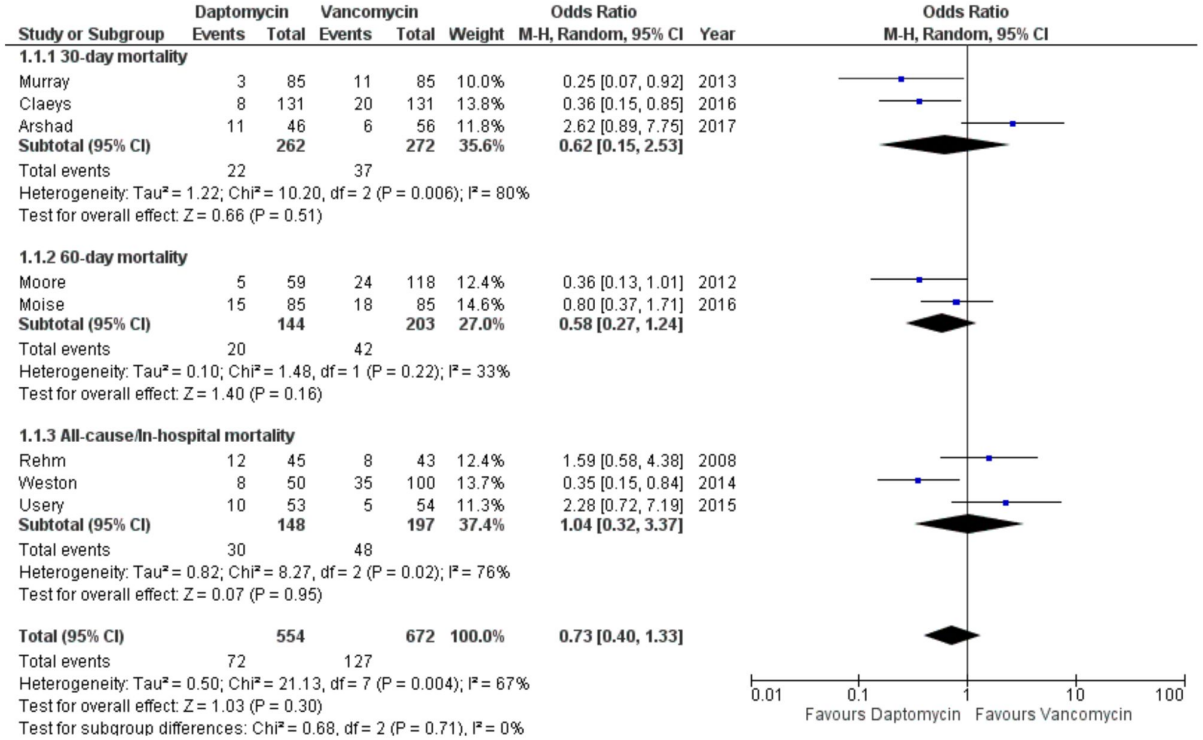
Anti-gram-positive - MRSA



Maraolo AE et al. Antibiotics (Basel). 2021.

Anti-gram-positive - MRSA

Study or Subgroup	Daptomycin Events	Daptomycin Total	Vancomycin Events	Vancomycin Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Rehm	25	45	29	43	11.4%	0.60 [0.25, 1.44]	2008
Moore	10	59	37	118	12.4%	0.45 [0.20, 0.98]	2012
Murray	17	85	41	85	13.9%	0.27 [0.14, 0.53]	2013
Weston	17	50	51	100	13.5%	0.49 [0.24, 1.00]	2014
Usery	11	53	9	54	10.1%	1.31 [0.49, 3.48]	2015
Moise	38	131	59	131	16.4%	0.50 [0.30, 0.83]	2016
Claeys	9	85	20	85	11.5%	0.38 [0.16, 0.90]	2016
Arshad	15	46	10	56	10.7%	2.23 [0.89, 5.59]	2017
Total (95% CI)		**554**		**672**	**100.0%**	**0.58 [0.38, 0.89]**	
Total events	142		256				

Heterogeneity: Tau² = 0.22; Chi² = 17.35, df = 7 (P = 0.02); I² = 60%

Test for overall effect: Z = 2.52 (P = 0.01)

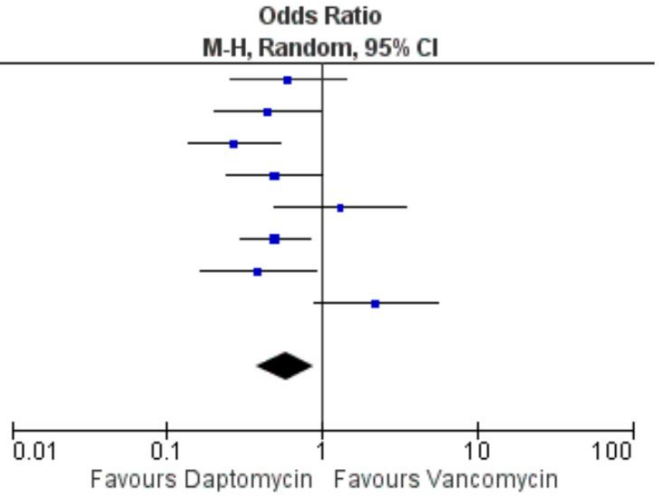


Figure 3. Forest plot depicting the odds ratio of clinical failure of patients receiving daptomycin vs. vancomycin.

Maraolo AE et al. Antibiotics (Basel). 2021.

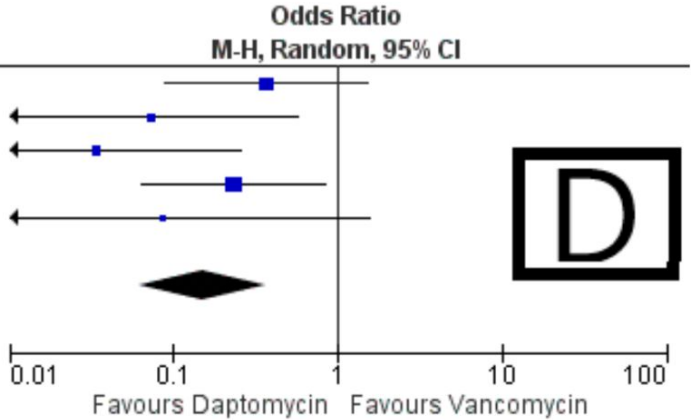
Anti-gram-positive - MRSA

Discontinuation due to safety issues

Study or Subgroup	Daptomycin Events	Total	Vancomycin Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Rehm	3	45	7	43	28.0%	0.37 [0.09, 1.53]	2008
Moore	1	59	13	68	15.5%	0.07 [0.01, 0.58]	2012
Murray	1	85	22	85	16.0%	0.03 [0.00, 0.26]	2013
Claeys	3	131	12	131	32.1%	0.23 [0.06, 0.84]	2016
Moise	0	85	5	85	8.4%	0.09 [0.00, 1.57]	2016
Total (95% CI)		**405**		**412**	**100.0%**	**0.15 [0.06, 0.36]**	
Total events	8		59				

Heterogeneity: Tau² = 0.20; Chi² = 4.96, df = 4 (P = 0.29); I² = 19%

Test for overall effect: Z = 4.22 (P < 0.0001)



Maraolo AE et al. Antibiotics (Basel). 2021.

Anti-gram-positive - MRSA

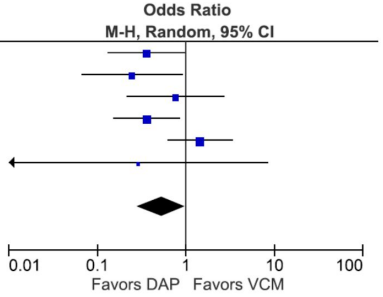
Vancomycin MIC >1mg/L

Mortality

(A)

Study or Subgroup	DAP Events	DAP Total	VCM Events	VCM Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Moore 2012	5	59	24	118	19.8%	0.36 [0.13, 1.01]	2012
Murray 2013	3	85	11	85	14.5%	0.25 [0.07, 0.92]	2013
Cheng 2013	4	26	10	52	15.2%	0.76 [0.21, 2.72]	2013
Claeys 2016	8	131	20	131	23.5%	0.36 [0.15, 0.85]	2016
Moise 2016	15	85	11	85	23.9%	1.44 [0.62, 3.35]	2016
Kalimuddin 2018	0	7	1	7	3.1%	0.29 [0.01, 8.39]	2018
Total (95% CI)		**393**		**478**	**100.0%**	**0.53 [0.29, 0.98]**	
Total events	35		77				

Heterogeneity: Tau² = 0.23; Chi² = 8.42, df = 5 (P = 0.13); I² = 41%
Test for overall effect: Z = 2.03 (P = 0.04)

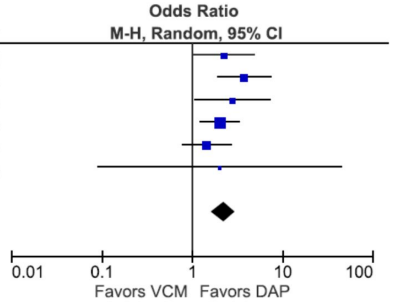


Treatment success

(B)

Study or Subgroup	DAP Events	DAP Total	VCM Events	VCM Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Moore 2012	49	59	81	118	14.5%	2.24 [1.02, 4.90]	2012
Murray 2013	68	85	44	85	19.2%	3.73 [1.89, 7.36]	2013
Cheng 2013	16	26	19	52	9.4%	2.78 [1.05, 7.34]	2013
Claeys 2016	93	131	72	131	34.0%	2.01 [1.20, 3.34]	2016
Moise 2016	59	85	52	85	22.0%	1.44 [0.76, 2.72]	2016
Cubist 2018	6	7	3	4	0.9%	2.00 [0.09, 44.35]	2018
Total (95% CI)		**393**		**475**	**100.0%**	**2.20 [1.63, 2.96]**	
Total events	291		271				

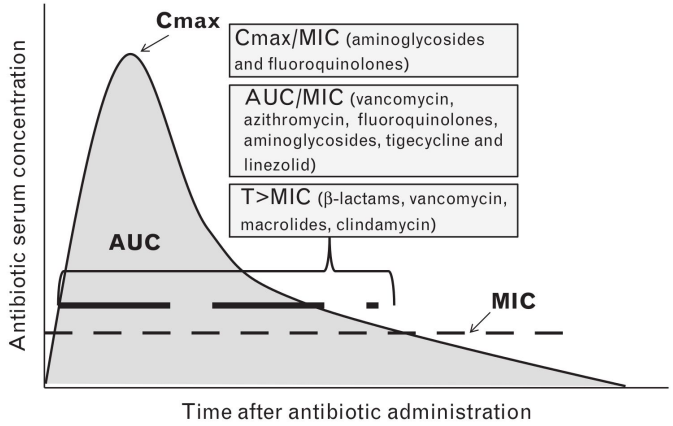
Heterogeneity: Tau² = 0.00; Chi² = 4.37, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 5.19 (P < 0.00001)



Samura M et al. Pharmaceutics. 2022.

Anti-gram-positive - MRSA - PK/PD

- Vancomycin
  - Penetration
    - Soft tissue/plasma concentration 0.5
    - Lung/plasma 0.6
  - Target AUC/MIC 400-600
    - Need for TDM
      - Two samples preferred if intermittent infusion
      - One sample if continuous infusion
      - Difficult to reach for MIC >1
- Daptomycin
  - Penetration
    - Soft tissues/plasma about 0.8-1.2
    - Inactivated by surfactant
  - Target AUC/MIC >600
    - Likely with doses >8-10mg/kg



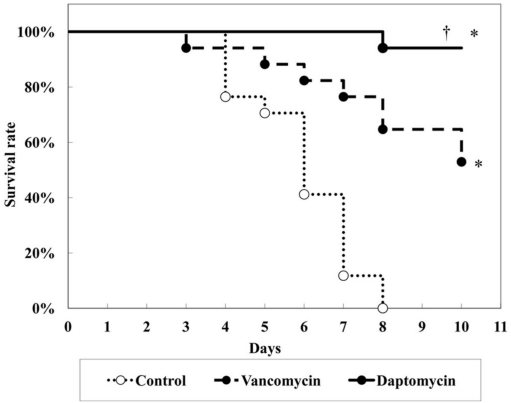
Finazzi S et al. Antibiotics (Basel). 2022; Rybak MJ et al. Am J Health Syst Pharm. 2020; Falcone M et al. Clin Infect Dis. 2013.

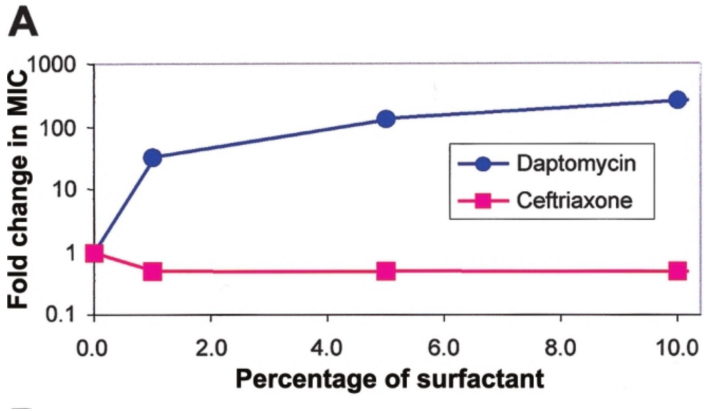
Daptomycin - Lung infection

Table 1. Daptomycin efficacy in pulmonary infection models.

Model	Organism	Daptomycin		Comparator	
		Dose, mg/kg	Log reduction	Drug (dose, mg/kg)	Log reduction
Mouse BAP	*S. pneumoniae*	100	0.1 ± 0.13	Ceftriaxone (50)	4.5 ± 0.28
Mouse BAP	MRSA	100	0 ± 0.4	…	…
Rat HP	MRSA	50	2.1 ± 0.56	Vancomycin (100)	1.3 ± 1.19
Rat HP	*S. aureus*	75	2.2 ± 1.0	Nafcillin (150)	1.5 ± 0.62

NOTE. Data are expressed as reduction in bacterial burden in the infected organ, compared with that in untreated, infected controls. For bronchial-alveolar pneumonia (BAP), mice were treated at 1 and 4 h after infection, and lungs were harvested 24 h after infection. For hematogenous pneumonia (HP), rats were treated once daily (daptomycin and vancomycin) or twice daily (nafcillin) for 6 days after infection, and lungs were harvested on day 7. MRSA, methicillin-resistant *Staphylococcus aureus*; *S. pneumoniae, Staphylococcus pneumoniae.*





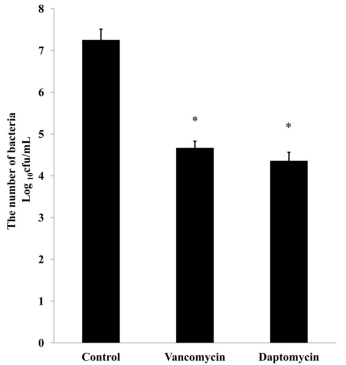


FIG 4 The number of viable bacteria in the lungs on day 3. The numbers (means ± SEMs) of bacteria in the control and vancomycin- and daptomycin-treated groups were 7.25 ± 0.26, 4.67 ± 0.17, and 4.36 ± 0.20 $\log_{10}$ CFU/ml ($n = 6$ for all groups), respectively (*, $P < 0.01$ versus control).

Crass RL et al. Diagn Microbiol Infect Dis. 2019; Silverman JA et al. J Infect Dis. 2005; Harada Y et al. Antimicrob Agents Chemother. 2013.

Reimplantation and Repeat Infection After Cardiac-Implantable Electronic Device Infections

Experience From the MEDIC (Multicenter Electrophysiologic Device Infection Cohort) Database

Table 2. Six-Month Outcomes According to Device Management Strategy

Management Strategy	Therapy Complete—No Sign of CIED Infection	Chronic Suppression—No Sign of CIED Infection	Repeat Infection	Patient Deceased
Original device maintained (n=53)	18 (34.0)	15 (28.3)	6 (11.3)	14 (26.4)
Device removed, not reimplanted (n=161)	123 (76.4)	7 (4.3)	1 (0.6)	30 (18.6)
Reimplanted same day (n=23)	16 (69.6)	2 (8.7)	1 (4.3)	4 (17.4)
Reimplanted in 1–7 days (n=59)	51 (86.4)	2 (3.4)	2 (3.4)	4 (6.8)
Reimplanted in 8–14 days (n=68)	58 (85.3)	3 (4.4)	0 (0.0)	7 (10.3)
Reimplanted in 15–21 days (n=28)	23 (82.1)	1 (3.6)	0 (0.0)	4 (14.3)
Reimplanted after 21 days (n=42)	35 (83.3)	0 (0.0)	1 (2.4)	6 (14.3)

Values are mean±SD or n (%). CIED indicates cardiovascular-implantable electronic device.

Blomström-Lundqvist C et al. Eur Heart J. 2020.

Re-implantation

Table 10: Recommendations for preventive strategies after device implantation and for new re-implantations including alternative novel devices

Consensus statement	Statement class	Scientific evidence coding	References
After device extraction, re-assessment of the indication for re-implantation is recommended		O	[38, 122]
Whenever possible, re-implantation may be avoided or delayed until symptoms and signs of systemic and local infection have resolved		O	[38, 123]
A temporary pacemaker with ipsilateral active fixation strategy may be considered in pacemaker-dependent patients requiring appropriate antibiotic treatment before re-implantation		O	[124–127]
Preferred access sites for replacement device are the contralateral side, the femoral vein, or epicardially		E, O	[38, 128, 129]
Temporary pacing in patients who are not pacemaker dependent		O	[28]
Replacement device implantation ipsilateral to the extraction site		E	[38]
Alternative novel devices as LPM and S-ICD may be considered in selected patients with high infective risk or in patients in whom these devices are considered better options after an CIED infection		O	[129–133]

CIED: cardiac implantable electronic device; E: expert opinion; LPM: leadless pacemaker; M: meta-analysis; O: observational studies; R: randomized trials; S-ICD: subcutaneous implantable cardiac defibrillator.

Blomström-Lundqvist C et al. Eur Heart J. 2020.

Re-implantation

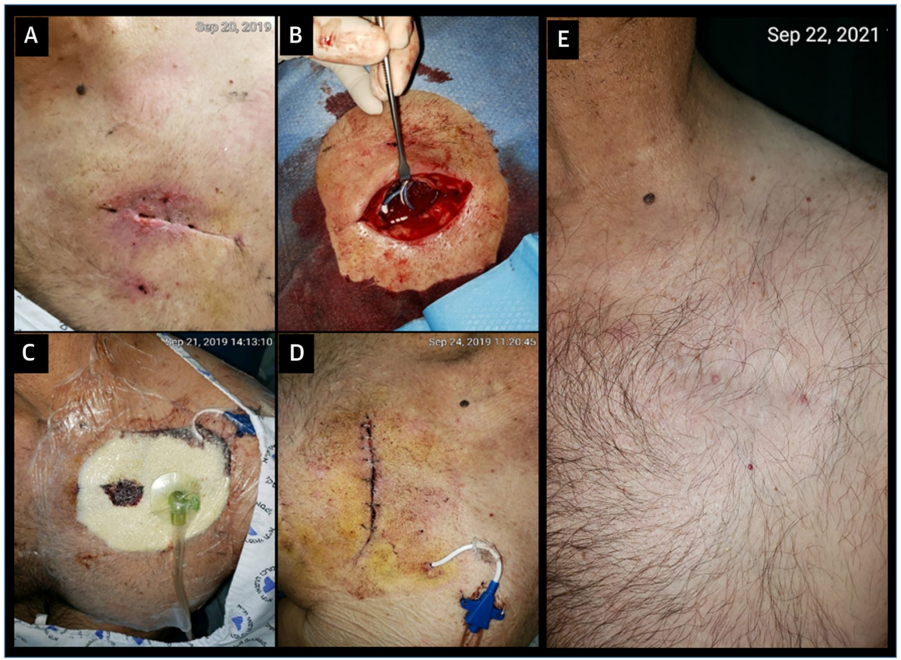
Table 10: Recommendations for preventive strategies after device implantation and for new re-implantations including alternative novel devices

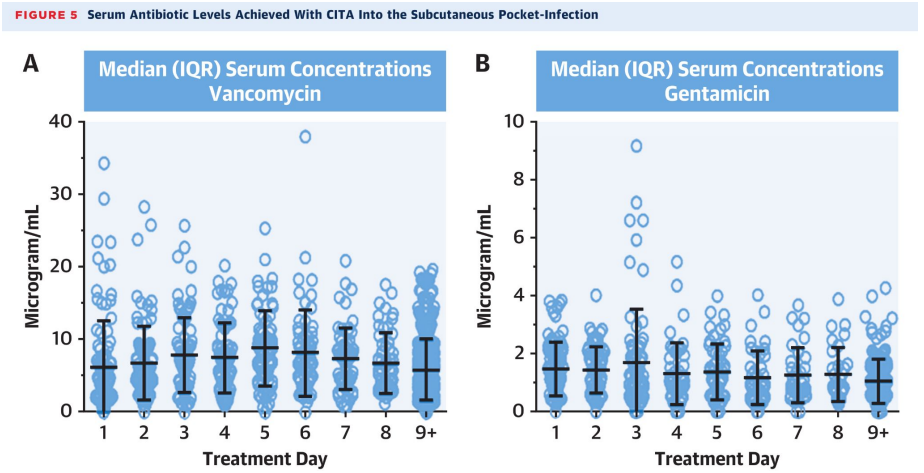
Consensus statement	Statement class	Scientific	References
Re-implantation should be delayed until signs and symptoms of local and systemic infection have resolved or postponed until blood cultures are negative for at least 72 h after the extraction if feasible (Table 10) [38, 123, 135].			
Temporary pacing in patients who are not pacemaker dependent		O	[28]
Replacement device implantation ipsilateral to the extraction site		E	[38]
Alternative novel devices as LPM and S-ICD may be considered in selected patients with high infective risk or in patients in whom these devices are considered better options after an CIED infection		O	[129–133]

CIED: cardiac implantable electronic device; E: expert opinion; LPM: leadless pacemaker; M: meta-analysis; O: observational studies; R: randomized trials; S-ICD: subcutaneous implantable cardiac defibrillator.

Blomström-Lundqvist C et al. Eur Heart J. 2020.

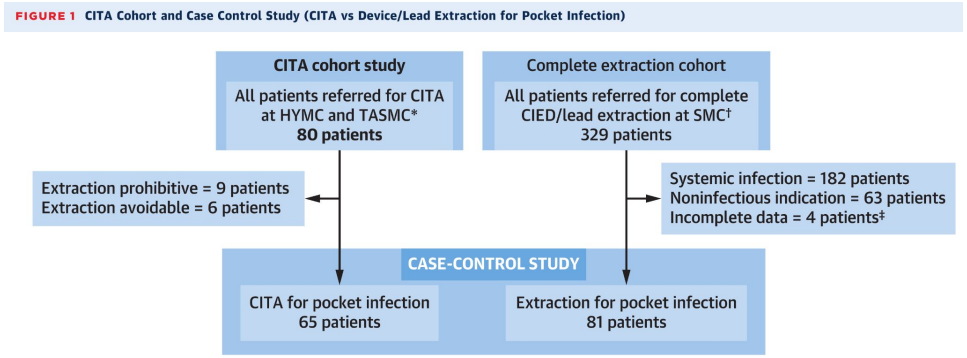
Regional Antibiotic Delivery for Implanted Cardiovascular Electronic Device Infections

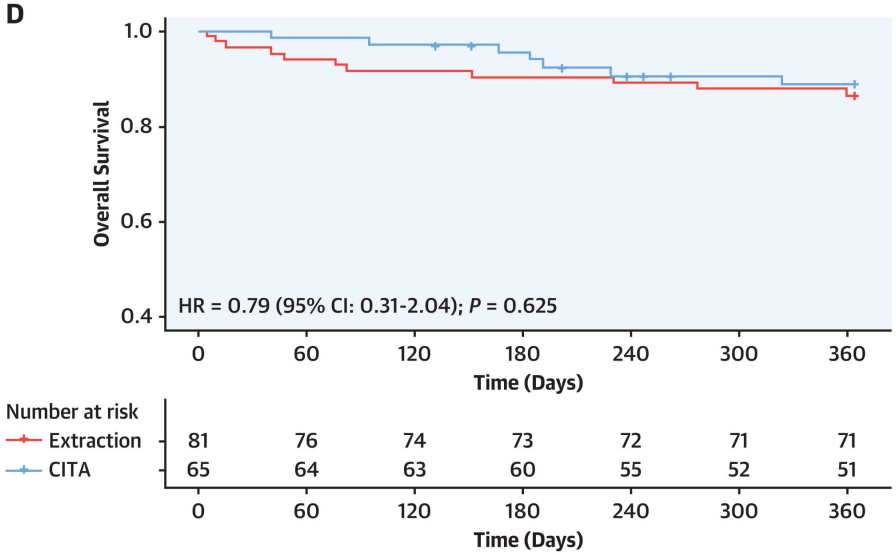




Topaz M et al. J Am Coll Cardiol. 2023.

Regional Antibiotic Delivery for Implanted Cardiovascular Electronic Device Infections

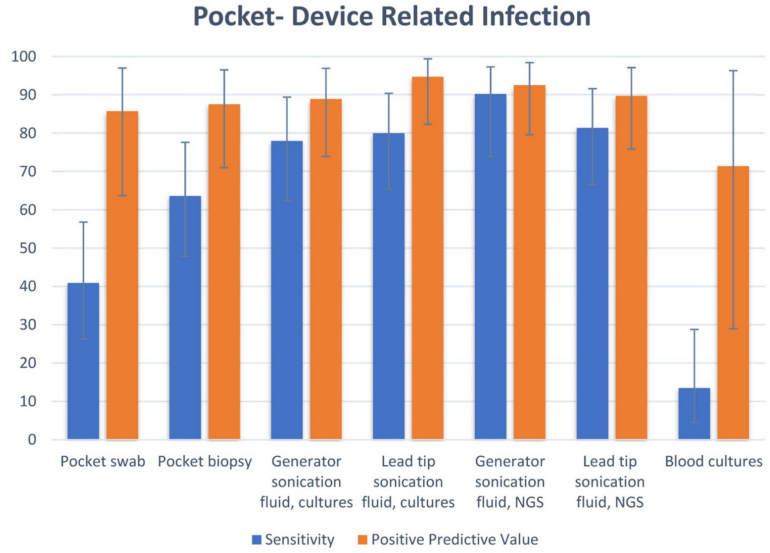


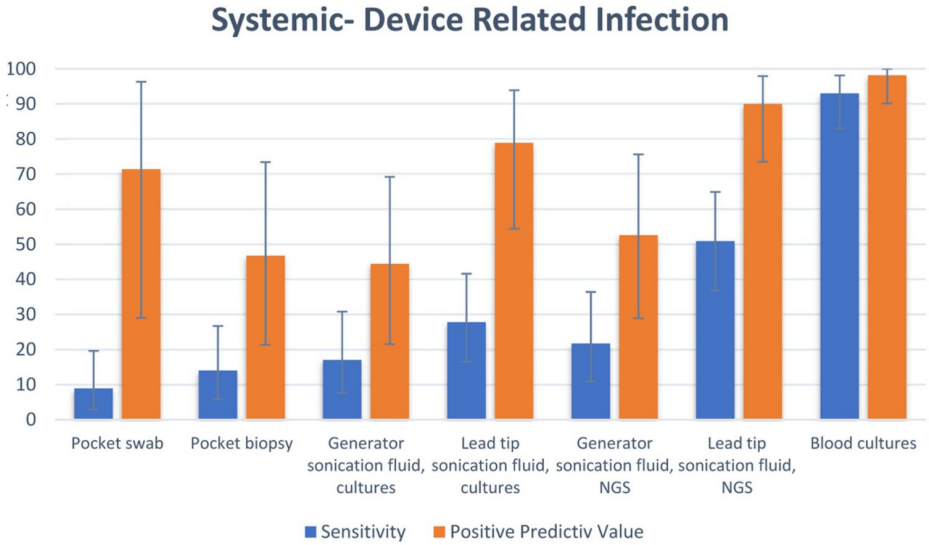


Topaz M et al. J Am Coll Cardiol. 2023.

Antibiotic timing

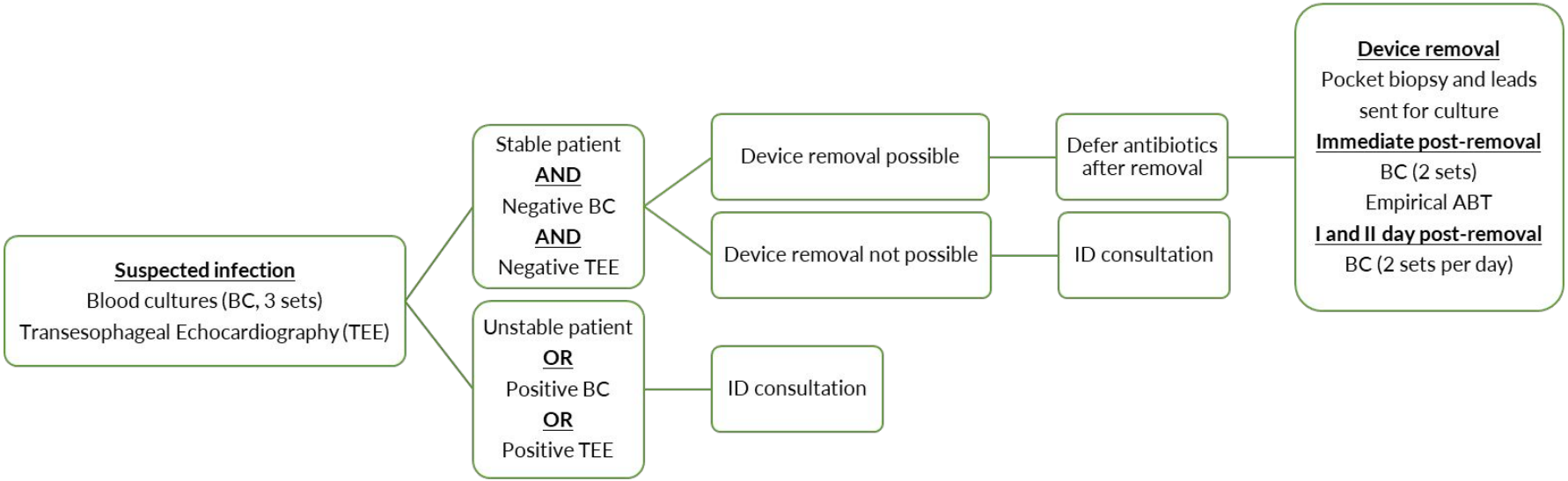
Microbiological diagnosis in cardiac implantable electronic device infections detected by sonication and next-generation sequencing





Olsen T et al. Heart Rhythm. 2022.

OSR Management



OSR Management

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

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Cardiac implantable electronic device infections: impact of initiation of antimicrobial treatment before or after device removal on microbiological yield

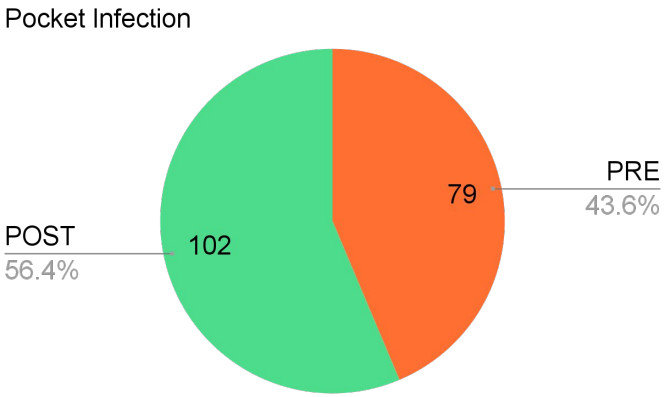
Dr. Giacomo Ponta, Dr. Martina Ranzenigo

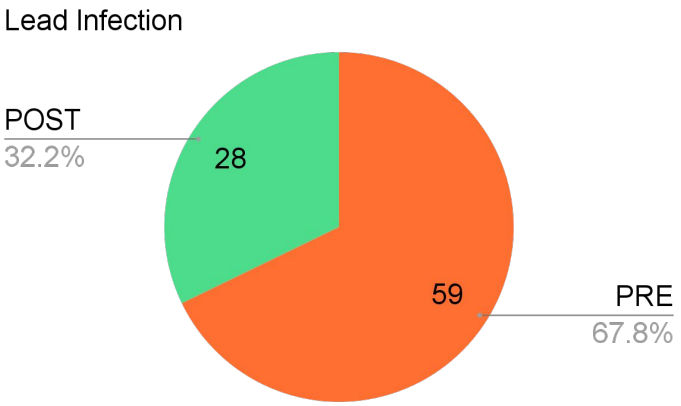
Patients' characteristics - I

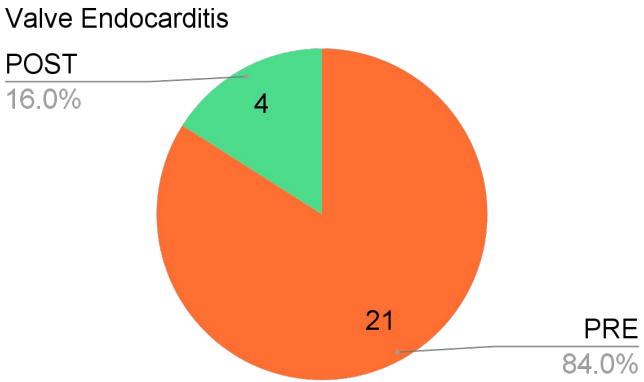
Variable	Overall (n=232)	Pre-removal antimicrobial treatment (PRE; n=116)	Post-removal antimicrobial treatment (POST; n=116)	P-value*
Age, years	72 (62-79)	72 (64-78)	73 (62-80)	0.283
Sex, male	194 (83.6%)	95 (81.9%)	99 (85.3%)	0.478
Charlson Comorbidity Index	4 (3-6)	4 (3-6)	4 (3-6)	0.878
Year of diagnosis				0.065
2011-2016	126 (54.3%)	70 (60.3%)	56 (48.3%)	
2017-2021	106 (45.7%)	46 (39.7%)	60 (51.7%)	
Underlying cardiac disease				0.506
DCM	83 (35.7%)	42 (18.1%)	41 (17.6%)	
ICM	53 (22.8%)	23 (9.9%)	30 (12.9%)	
AVB	43 (18.5%)	22 (9.4%)	21 (9.1%)	
SSS	34 (14.7%)	21 (9.1%)	13 (5.6%)	
Type of cardiac device				0.700
CRT	92 (39.6%)	46 (39.6%)	46 (39.6%)	
PM	69 (29.7)	37 (31.8%)	32 (27.5%)	
ICD	71 (30.6%)	33 (28.4%)	38 (22.7%)	
Time between implant and removal, months	79 (35-123)	80 (48-124)	74 (29-120)	0.268
Time between last revision/device upgrade and removal, days[a]	118 (61-208)	138 (63-192)	107 (59-247)	0.461

Ponta G & Ranzenigo M et al. Clin Microbiol Infect. 2023.

Patients' characteristics - II



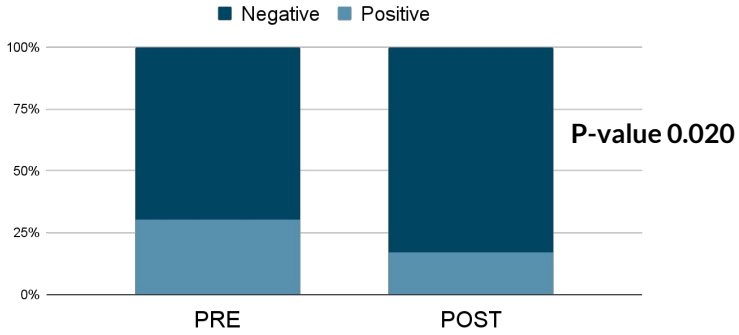




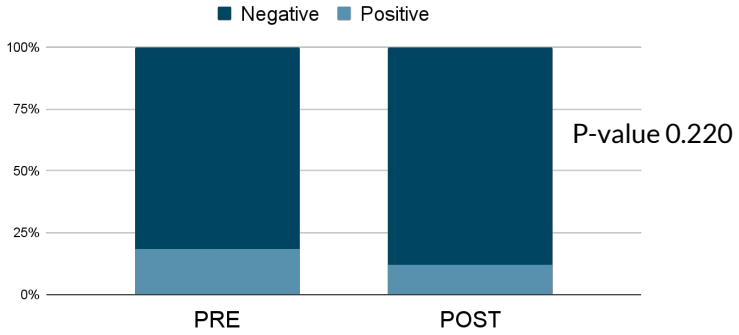
Ponta G & Ranzenigo M et al. Clin Microbiol Infect. 2023.

Results - Microbiological yield

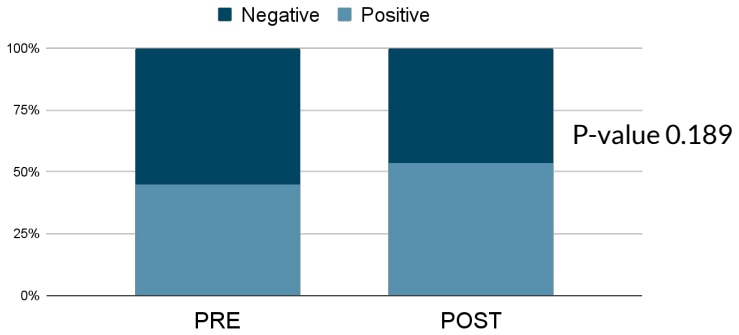
Pre-removal BC



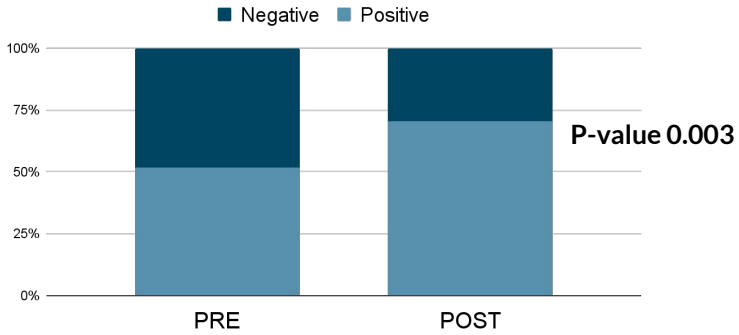
Immediate post-removal BC



Pocket biopsy culture

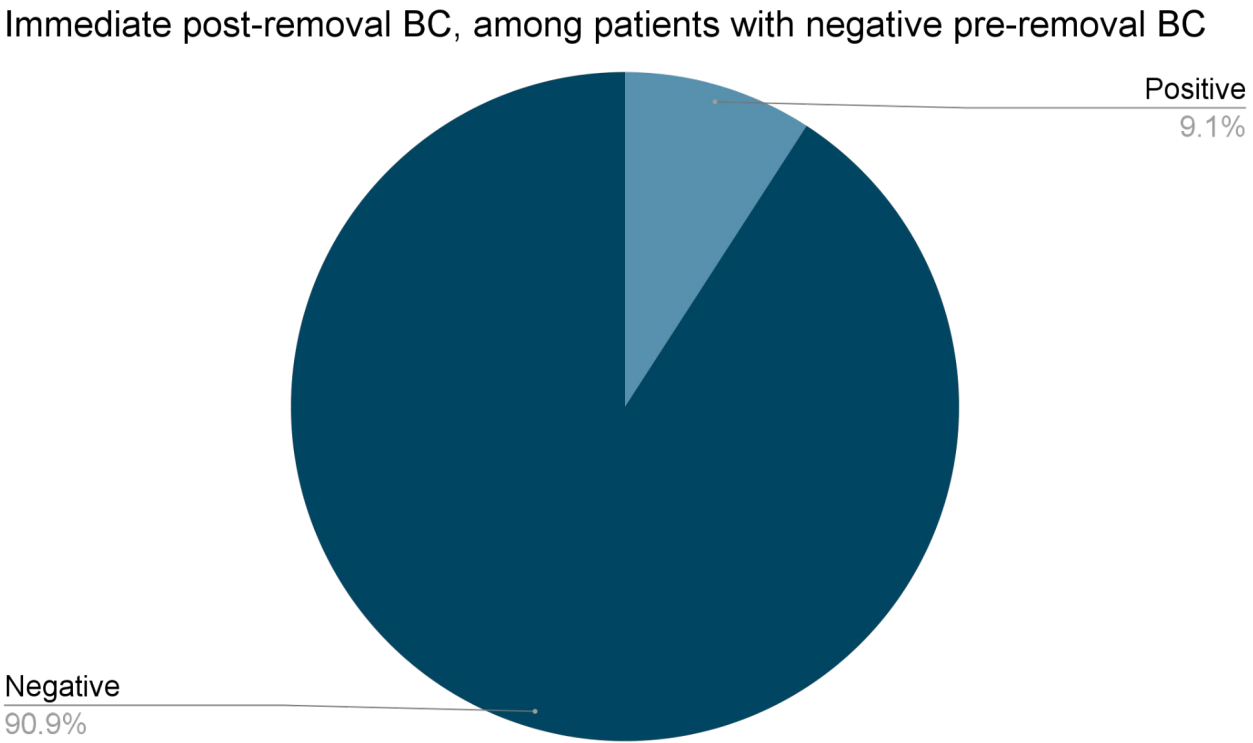


Lead culture



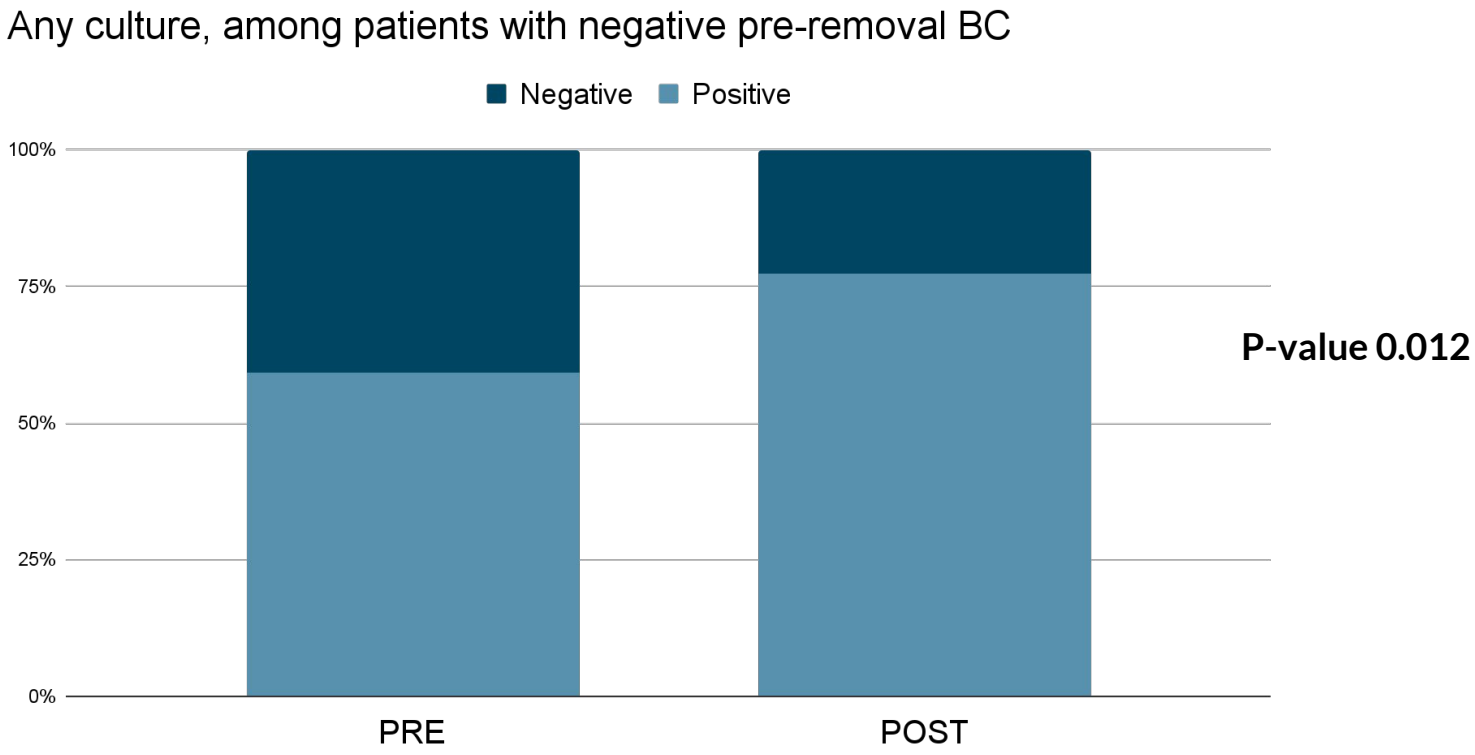
Ponta G & Ranzenigo M et al. Clin Microbiol Infect. 2023.

Results - Microbiological yield



Ponta G & Ranzenigo M et al. Clin Microbiol Infect. 2023.

Results - Microbiological yield



Ponta G & Ranzenigo M et al. Clin Microbiol Infect. 2023.

Results - Outcomes

Variable	Overall (n=232)	Pre-removal antimicrobial treatment (PRE; n=116)	Post-removal antimicrobial treatment (POST; n=116)	P-value*
Six-month recurrence	7/144 (4.8%)	5/69 (7.2%)	2/75 (2.6%)	0.374
Relapse	1 (14.2%)	1 (20%)	0 (0%)	
Reinfection, microbial isolate	3 (42.8%)	2 (40%)	1 (50%)	
Reinfection, no microbial isolate	3 (42.8%)	2 (40%)	1 (50%)	
Six-month mortality	8/131 (6.1%)	6/63 (9.5%)	2/68 (2.9%)	0.227

*By chi-square test

Ponta G & Ranzenigo M et al. Clin Microbiol Infect. 2023.

Conclusions

- Immediate post-removal blood cultures useful for increasing microbiological yield
- Higher microbiological yield with antimicrobial therapy start after CIED removal
    - Especially in patients with negative pre-removal blood cultures
- Comparable outcomes with deferred antimicrobial treatment

Ponta G & Ranzenigo M et al. Clin Microbiol Infect. 2023.

Oral and long-acting therapy

Oral therapy - Guidelines

For *isolated pocket infections* empirical i.v. therapy is recommended after blood cultures have been obtained (Table 9, Fig. 3). Definitive treatment should be given according to culture result with an appropriate antibiotic with a narrow spectrum, if possible a betalactam antibiotic. Combination therapy is not needed. A switch to oral treatment after device removal is reasonable since the remaining infection only involves skin and soft tissue, but evidence-based recommendations are lacking. In

For *pocket infection with positive blood culture but without vegetation on leads or valves*, the definite treatment follows recommendations given above but the systemic involvement makes a switch to an oral antibiotic regimen inappropriate (Table 9, Fig. 3). Shorter post-extraction treatment duration is considered possible by some experts [19].

Blomström-Lundqvist C et al. Eur Heart J. 2020.

Oral vs. IV Abx for Endocarditis

Author	Yr	N	Regimen (Oral vs. IV)	Success
Stamboulian	'91	30	Amox 1 gm qid vs. CTX—*Strep*	100% (15/15) v 100% (15/15)
Heldman	'96	93	Cipro + Rif vs. std IV—*Staph*	95% (18/19) v 88% (22/25)
Iversen/ Bungaard‡	'19	400	Std oral vs. std IV—GPC	74% (146/199) v 62% (125/201)
*Tissot-Dupont**	*'19*	*341*	*TMP-SMX+clinda vs. std IV--Staph*	*81% (138/171) v 70% (119/170)*
Totals (N=3 RCTs)		523		77% (179/233) v 70% (162/241)
(+ 1 quasi expt)*		*(864)*		*78% (317/404) v 68% (281/411)*

*Quasi-experimental, pre-post study. Italicized totals include the quasi-experimental data.
‡Iversen reported early follow up, Bungaard 3 year follow up from the same study.
Refs at https://www.bradspellberg.com/oral-antibiotics

Wald-Dickler N et al. Am J Med. 2022; https://www.bradspellberg.com/oral-antibiotics

Oral Is the New IV. Challenging Decades of Blood and Bone Infection Dogma: A Systematic Review

Study or Subgroup	Oral Events	Oral Total	IV Events	IV Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Stamboulian 1991	15	15	15	15	19.8%	0.00 [-0.12, 0.12]	1991
Heldman 1996	18	19	22	25	11.0%	0.07 [-0.09, 0.23]	1996
Iversen/Bungard 2019	146	199	125	201	34.5%	0.11 [0.02, 0.20]	2019
Tissot-Dupont 2019	138	171	119	170	34.6%	0.11 [0.02, 0.20]	2019
Total (95% CI)		**404**		**411**	**100.0%**	**0.08 [0.03, 0.14]**	
Total events	317		281				

Heterogeneity: Tau² = 0.00; Chi² = 3.05, df = 3 (P = 0.38); I² = 2%
Test for overall effect: Z = 3.01 (P = 0.003)

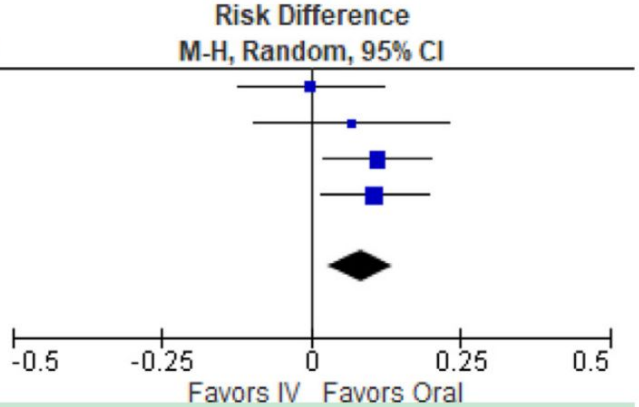
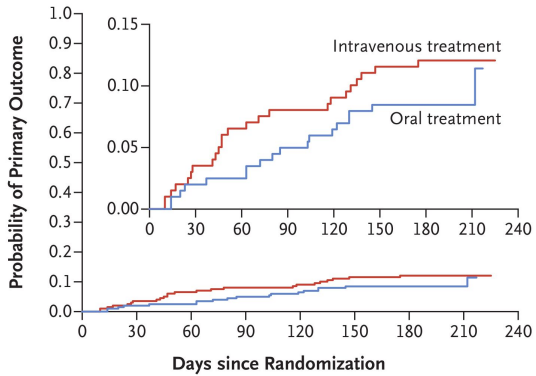


Figure 4 Meta-analysis forest plot of endocarditis treatment success. Oral therapy was significantly more effective.

Wald-Dickler N et al. Am J Med. 2022; https://www.bradspellberg.com/oral-antibiotics

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis



No. at Risk

Intravenous treatment	199	192	186	183	181	176	174	28	0
Oral treatment	201	197	196	191	188	184	183	36	0

Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.

The primary composite outcome was all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from randomization until 6 months after antibiotic treatment was completed. The oral treatment group shifted from intravenously administered antibiotics to orally administered antibiotics at a median of 17 days after the start of treatment. The inset shows the same data on an enlarged y axis.

Iversen K et al. N Engl J Med. 2019.

Five-Year Outcomes of the Partial Oral Treatment of Endocarditis (POET) Trial

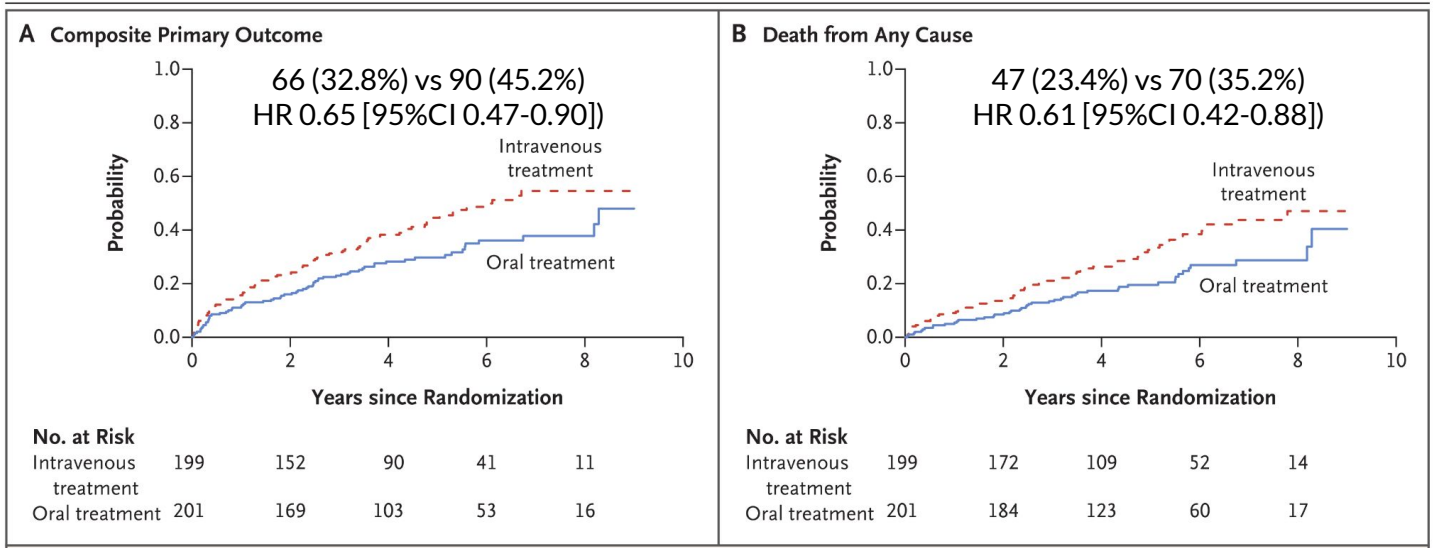


Figure 1. Cumulative Incidence of Events.

Shown are plots of the cumulative incidence of events from randomization to a median follow-up of 5.4 years. The patients assigned to the intravenous treatment group received intravenous antibiotic therapy for the entire treatment period, and the patients assigned to receive step-down treatment shifted from intravenous antibiotics to oral antibiotics after clinical stabilization was reached. The composite primary outcome consisted of death from any cause, unplanned cardiac surgery, embolic events, and relapse of a blood culture result positive for the primary pathogen.

Pries-Heje MM et al. N Engl J Med. 2022.

Guidelines for Diagnosis and Management of Infective Endocarditis in Adults
A WikiGuidelines Group Consensus Statement

Table 3. Summary of Oral Transitional Antibiotics Used in Published Clinical Studies[a]

Drug	Organism	Dose	References
Amoxicillin	• Sensitive streptococci (with or without combination treatment) • Enterococci (only in combination with rifampin or linezolid)	1 g 4 times daily	Iversen et al,[55] 2019; Stamboulian et al,[61] 1991
Dicloxacillin	Sensitive staphylococci (data from RCT only in combination with rifampin)	1 g 4 times daily	Iversen et al, 2019[55]
Levofloxacin[b]	Sensitive staphylococci (only in combination with rifampin)	750 mg once daily	Iversen et al,[55] 2019; Heldman et al,[62] 1996
Moxifloxacin	Sensitive streptococci, enterococci, or staphylococci (only in combination with amoxicillin, rifampin, or linezolid)	400 mg once daily	Iversen et al,[55] 2019
TMP-SMX	Sensitive staphylococci	960 mg or 4800 mg daily in divided doses	Tissot-Dupont et al,[46] 2019; Freling et al,[47] 2023
Linezolid	Sensitive gram-positive cocci (alone or in combination with rifampin, moxifloxacin, or amoxicillin)[c]	600 mg twice daily	Iversen et al,[55] 2019; Tascini et al,[68] 2011; Falagas et al,[69] 2006; Colli et al,[70] 2007; Muñoz et al,[71] 2007; Freling S et al,[47] 2023
Rifampin	Only as adjunctive agent (as previously described)	600 mg once or twice daily	Iversen et al,[55] 2019; Heldman et al,[62] 1996; Acocella G,[72] 1983; Freling et al,[47] 2023

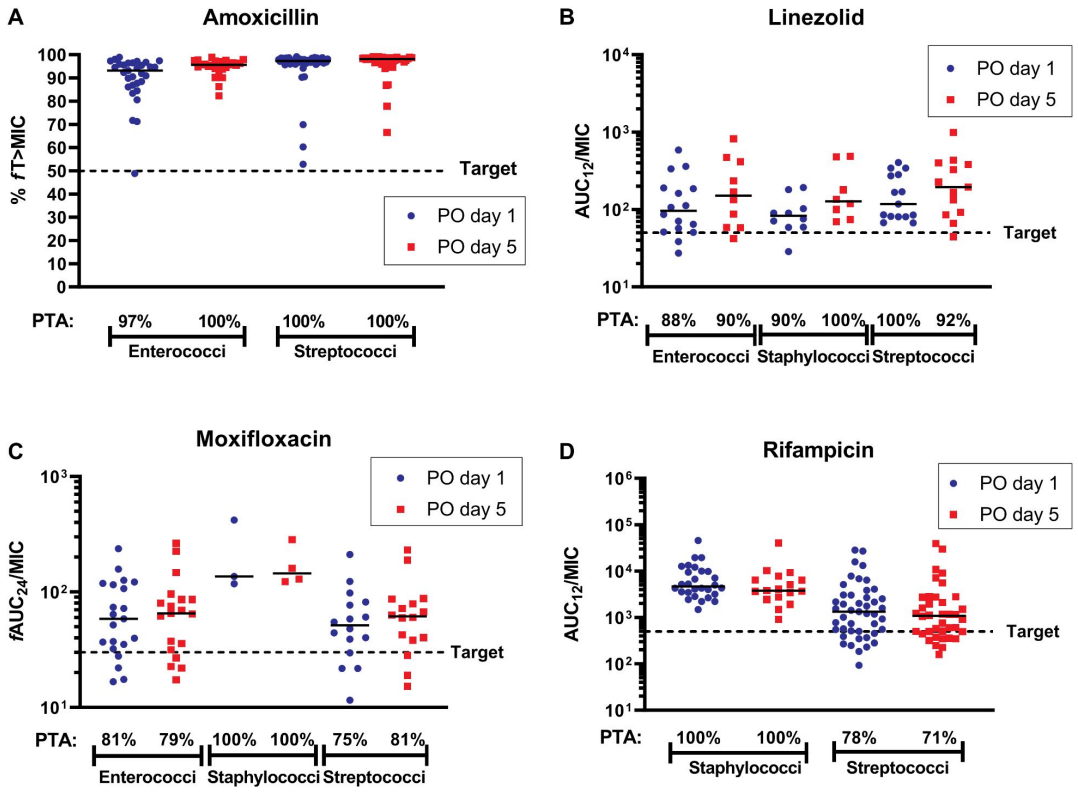
Antibiotic blood levels

Table 1. Peak Blood Levels vs MICs Achieved by Antibiotics Used to Treat Infective Endocarditis in Published Studies

Oral drug	Peak blood level, μg/mL[a]	MIC_{90}, μg/mL[b]	Peak blood level to MIC_{90} ratio
Antibiotics with peak blood level to MIC_{90} ratio ≤1			
Tetracycline, 250 mg	1	≥4	0.125
Erythromycin, 500 mg	0.5	≥4	0.125
Sulfanilamide, 4000 mg[5-9]	50	50-70	0.8
Antibiotics with peak blood level to MIC_{90} ratio >1			
Penicillin V, 500 mg, for *Streptococcus* spp	5	1	5
Amoxicillin, 1000 mg, for *Streptococcus* spp	10	1	10
Levofloxacin, 750 mg, for *Staphylococcus* spp	9	4	2.25
Moxifloxacin, 400 mg, for *Staphylococcus* or *Streptococcus* spp			
Staphylococcus aureus	4	4	1
Streptococcus spp	4	0.25	16
Rifampin, 600 mg, for gram-positive cocci	7	1	7
TMP-SMX, 320 mg/1600 mg, for *Staphylococcus* spp	100	4.75	22
Linezolid, 600 mg, for gram-positive cocci	15	2	7.5
Clindamycin, 600 mg, for *Staphylococcus* spp	10	2	5

Spellberg B et al. JAMA Intern Med. 2020.

Attainment of Target Antibiotic Levels by Oral Treatment of Left-sided Infective Endocarditis: A POET Substudy



Bock M et al. Clin Infect Dis. 2023.

Dalbavancin as Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the General Hospital of Vienna

Table 1. Duration of Dalbavancin Therapy Stratified by Type of Infective Endocarditis, Pathogen, Duration of Therapy Before Dalbavancin, Reason for Change to Dalbavancin Therapy, Weekly Regimen, Adverse Effects, and Outcome of Dalbavancin Therapy

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
	21	Native valve	*S. sanguinis*	Vancomycin (1), daptomycin (1)	OPAT	No	No	Once
	22	CDE	*S. epidermidis*	No	OPAT	No	No	Once
	23	CDE	*S. aureus*	Flucloxacillin (1)	OPAT	Resistance	No	Once
	24	Native valve	*S. aureus*	Ceftriaxone (1), daptomycin (1)	OPAT	No	No	Twice
	25	Prosthetic valve	*S. aureus*	Flucloxacillin and rifampicin (1)	OPAT	No	No	Twice
	26	Prosthetic valve	*S. sanguinis*	Penicillin G (1)	OPAT	No	No	Twice
	27	Native valve IE	*Staphylococcus caprae*	Cefazoline (1)	OPAT	No	No	Twice

Abbreviations: CDE, cardiac device–related endocarditis; IE, infective endocarditis; OPAT, outpatient parenteral antimicrobial therapy; RCI, reversible creatinine increase.

[a]In combination with rifampicin.

Tobudic S et al. Clin Infect Dis. 2018.

Dalbavancin as Primary and Sequential Treatment for Gram-Positive Infective Endocarditis: 2-Year Experience at the General Hospital of Vienna

Table 1. Duration of Dalbavancin Therapy Stratified by Type of Infective Endocarditis, Pathogen, Duration of Therapy Before Dalbavancin, Reason for Change to Dalbavancin Therapy, Weekly Regimen, Adverse Effects, and Outcome of Dalbavancin Therapy

Duration of Dalbavancin	Patient			Therapy Before Dalbavancin	Reason for Change to	Failure of Dalbavancin	Adverse	Regimen (Once or
	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
	21	Native valve	*S. sanguinis*	Vancomycin (1), daptomycin (1)	OPAT	No	No	Once
	22	CDE	*S. epidermidis*	No	OPAT	No	No	Once
	23	CDE	*S. aureus*	Flucloxacillin (1)	OPAT	Resistance	No	Once
	24	Native valve	*S. aureus*	Ceftriaxone (1), daptomycin (1)	OPAT	No	No	Twice
	25	Prosthetic valve	*S. aureus*	Flucloxacillin and rifampicin (1)	OPAT	No	No	Twice
	26	Prosthetic valve	*S. sanguinis*	Penicillin G (1)	OPAT	No	No	Twice
	27	Native valve IE	*Staphylococcus caprae*	Cefazoline (1)	OPAT	No	No	Twice

Abbreviations: CDE, cardiac device–related endocarditis; IE, infective endocarditis; OPAT, outpatient parenteral antimicrobial therapy; RCI, reversible creatinine increase.

[a]In combination with rifampicin.

In 1 patient with a CDE due to a methicillin-susceptible *S. aureus* who received only incomplete surgical source control, dalbavancin therapy was discontinued owing to microbiological and clinical failure.

Tobudic S et al. Clin Infect Dis. 2018.

Long-acting and drug resistance

Emergence of dalbavancin non-susceptible, vancomycin-intermediate *Staphylococcus aureus* (VISA) after treatment of MRSA central line-associated bloodstream infection with a dalbavancin- and vancomycin-containing regimen

Dalbavancin exposure *in vitro* selects for dalbavancin-non-susceptible and vancomycin-intermediate strains of methicillin-resistant *Staphylococcus aureus*☆

Emerging resistance in *Staphylococcus epidermidis* during dalbavancin exposure: a case report and *in vitro* analysis of isolates from prosthetic joint infections

Emergence of a dalbavancin induced glycopeptide/lipoglycopeptide non-susceptible *Staphylococcus aureus* during treatment of a cardiac device-related endocarditis

Emergence of Dalbavancin, Vancomycin, and Daptomycin Nonsusceptible *Staphylococcus aureus* in a Patient Treated With Dalbavancin: Case Report and Isolate Characterization

Werth BJ et al. Clin Microbiol Infect. 2021; Werth BJ et al. Clin Microbiol Infect. 2018; Al Janabi J et al. J Antimicrob Chemother. 2023; Kussmann M et al. Emerg Microbes Infect. 2018; Zhang R et al. Clin Infect Dis. 2022.

Conclusions

Conclusions

- Gram-positive pathogens account for the majority of the isolates
- Device removal is essential
- In selected patients empirical treatment may be deferred until after device removal to improve microbiological yield
- Partial oral therapy is safe and effective
- Long-term suppression should be considered in patients with retained devices

Thanks!

Any questions?

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Barriers

to management of CIED infections

- Underdiagnosis
- Delayed referral
- Low rate of extraction
- Persistent belief in antibiotics alone
- Perception that extraction is dangerous

Consequences

- 7-fold increase in 30-day mortality

With antimicrobial therapy alone vs. extraction

Key strategies

to ensure timely management of CIED infections

Educate doctors

- ↑ Awareness of signs and symptoms
- ↑ Use of blood cultures and cardiac imaging (TTE/TEE)
- ↑ Referral for early extraction (<3 days of diagnosis)

Educate patients

- ↑ Awareness
- Seek urgent medical care

Establish multidisciplinary teams

Cardiologists, ID specialists, thoracic surgeons

Regional networks/pathways

To extraction centres

Atar D et al. Eur Heart J. 2023.