

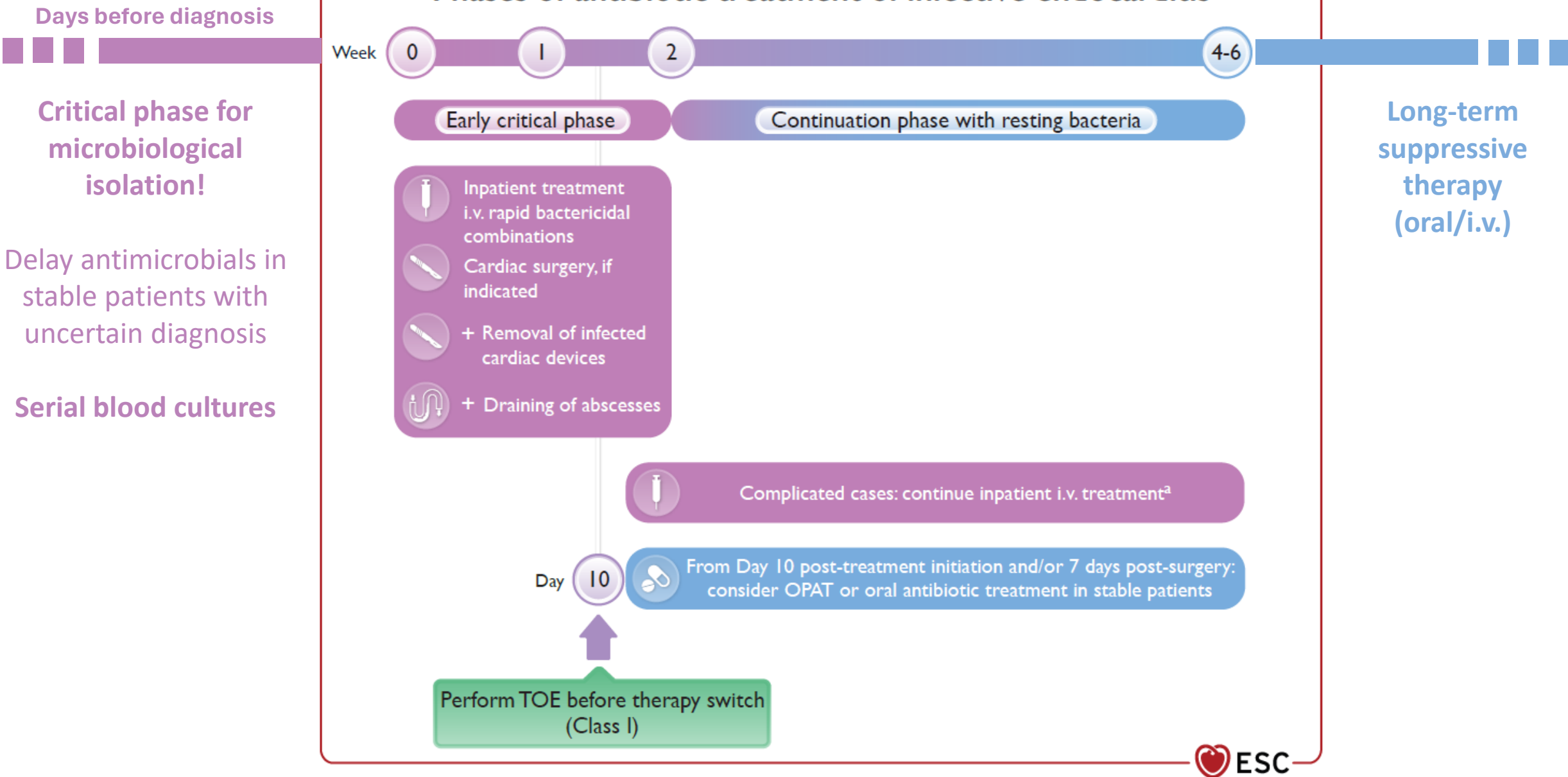
USO RAZIONALE DEGLI ANTIBIOTICI NELL'ERA DELLE RESISTENZE BATTERICHE

17 MAGGIO
2024
Sala Congressi
Ospedale Di Sarno

Trattamento delle endocarditi infettive native e protesiche

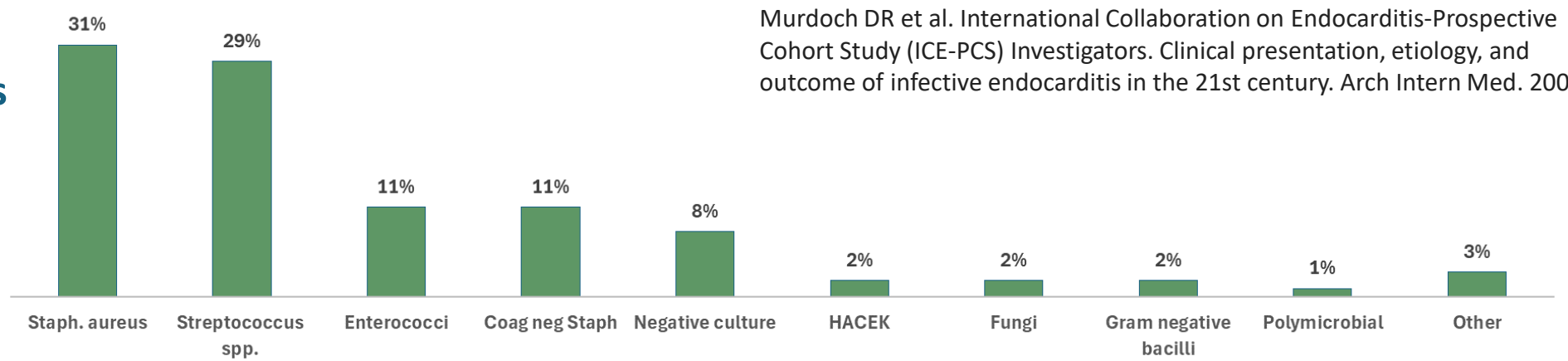
Lorenzo Bertolino

Phases of antibiotic treatment of infective endocarditis



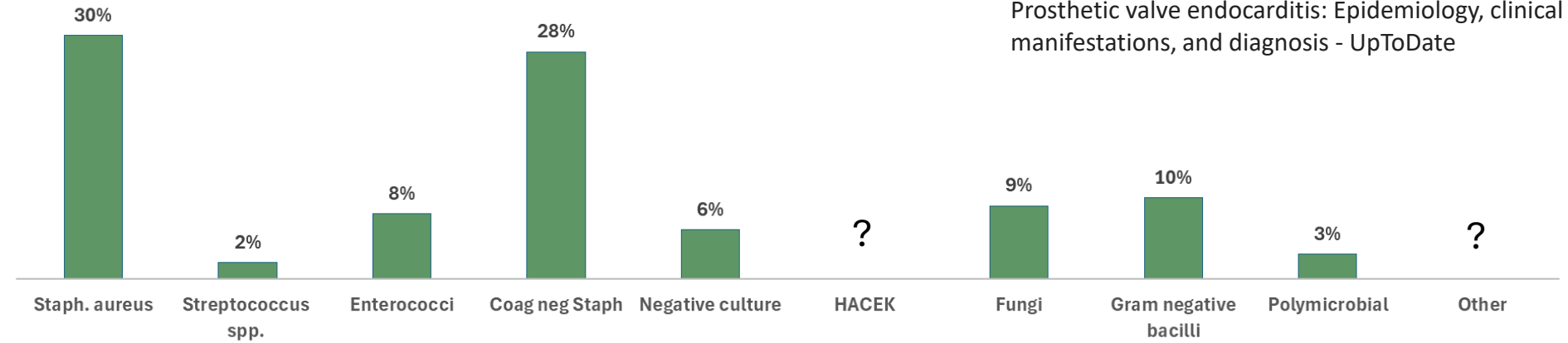
Native valve Endocarditis

- 1. Community-acquired
- 2. Younger patients
- 3. PWID
- 4. Low comorbidity rate



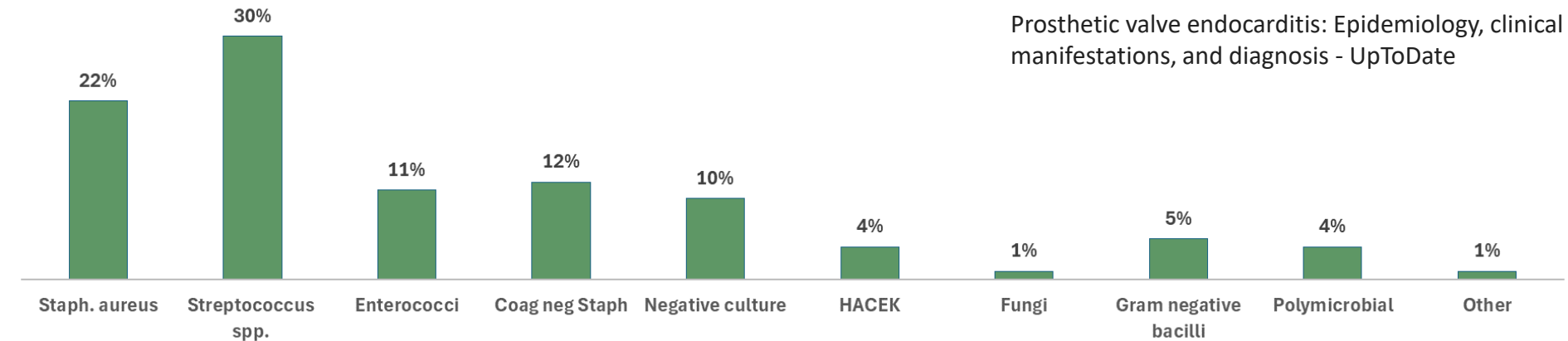
Murdoch DR et al. International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century. Arch Intern Med. 2009

Early PVE (< 12 months)



Prosthetic valve endocarditis: Epidemiology, clinical manifestations, and diagnosis - UpToDate

Late PVE (> 12 months)



Prosthetic valve endocarditis: Epidemiology, clinical manifestations, and diagnosis - UpToDate

Infective Endocarditis After Transcatheter versus Surgical Aortic Valve Replacement








Panagides et al., 2023 | *Clinical Infectious Diseases*

BACKGROUND: Scarce data are available comparing infective endocarditis following SAVR and TAVR.

PARTICIPANTS: Data were collected from two international cohorts : "The infective Endocarditis after TAVR" and the "International Collaboration on Endocarditis" registries

METHODS
A 1:1 paired matching approach was used to compare clinical characteristics and outcomes of TAVR and SAVR patients.

- 1688 patients included**
- ✓ 602 (35.7%) surgical bioprostheses
 - 666 (39.5%) mechanical prostheses
 - 70 (4.2%) homograft
 - ✓ 350 (20.7%) TAVR

-  Vegetations
-  New moderate or severe aortic regurgitation
-  Perivalvular extension
-  *Staphylococcus aureus*
-  Enterococci
-  Cardiac surgery
-  1-year mortality

	Bioprosthetic SAVR (N=200)	TAVR (N=200)	p-value
Vegetations	62.5%	82%	p<0.001
New moderate or severe aortic regurgitation	43.4%	13.5%	p<0.001
Perivalvular extension	47.9%	27%	p<0.001
<i>Staphylococcus aureus</i>	13.4%	22%	p=0.033
Enterococci	21.2%	22.9%	p=0.695
Cardiac surgery	44.4%	27.3%	p<0.001
1-year mortality	46.5%	44.8%	p=0.697

CONCLUSION: Clinical presentation, type of causative microorganism and treatment differed between patients with an IE located on SB compared to TAVR. Despite these differences, both groups exhibited very high and similar mortality rates at 1-year follow-up.

Empiric antimicrobial treatment according to ESC 2023 guidelines

In patients with community-acquired NVE or late PVE (≥ 12 months post-surgery), ampicillin in combination with ceftriaxone or with (flu)cloxacillin and gentamicin should be considered using the following doses:²⁵⁵

Adult antibiotic dosage and route

Ampicillin	12 g/day i.v. in 4–6 doses
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses
Gentamicin ^d	3 mg/kg/day i.v. or i.m. in 1 dose

Paediatric antibiotic dosage and route

Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses
Ceftriaxone	100 mg/kg i.v. or i.m. in 1 dose
(Flu)cloxacillin	200–300 mg/kg/day i.v. in 4–6 equally divided doses
Gentamicin ^d	3 mg/kg/day i.v. or i.m. in 3 equally divided doses

IIa

C

In patients with early PVE (<12 months post-surgery) or nosocomial and non-nosocomial healthcare-associated IE, vancomycin or daptomycin combined with gentamicin and rifampin may be considered using the following doses:³⁹⁵

Adult antibiotic dosage and route

Vancomycin ^e	30 mg/kg/day i.v. in 2 doses
Daptomycin	10 mg/kg/day i.v. in 1 dose
Gentamicin ^d	3 mg/kg/day i.v. or i.m. in 1 dose
Rifampin	900–1200 mg i.v. or orally in 2 or 3 doses

Paediatric antibiotic dosage and route

Vancomycin ^e	40 mg/kg/day i.v. in 2–3 equally divided doses
Gentamicin ^d	3 mg/kg/day i.v. or i.m. in 3 equally divided doses
Rifampin	20 mg/kg/day i.v. or orally in 3 equally divided doses

IIb

C

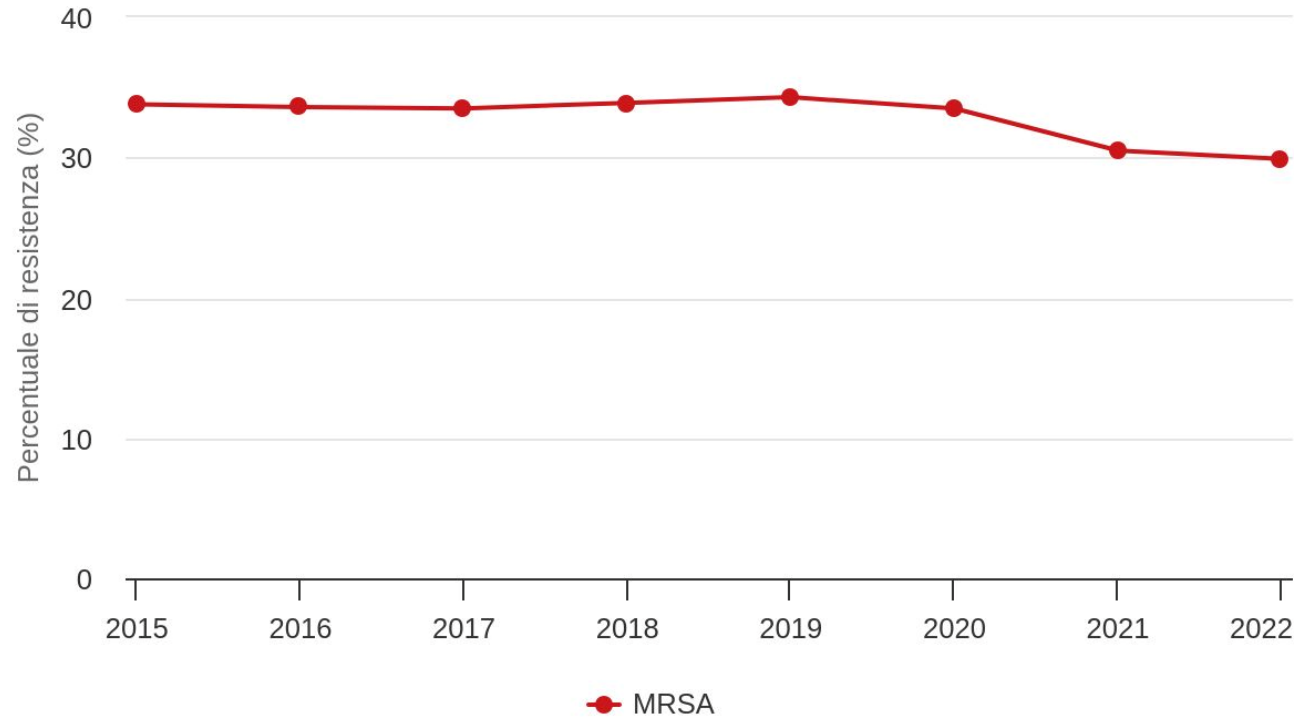


Local epidemiology

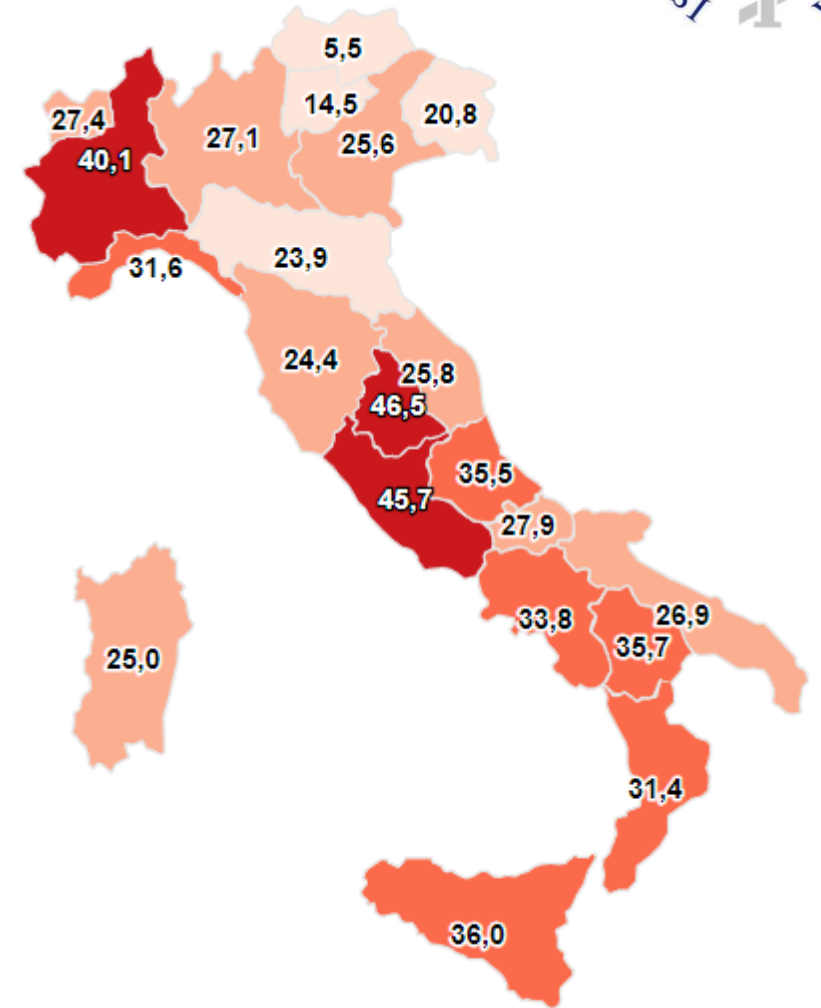


Resistenza alla meticillina, Italia 2015-2022

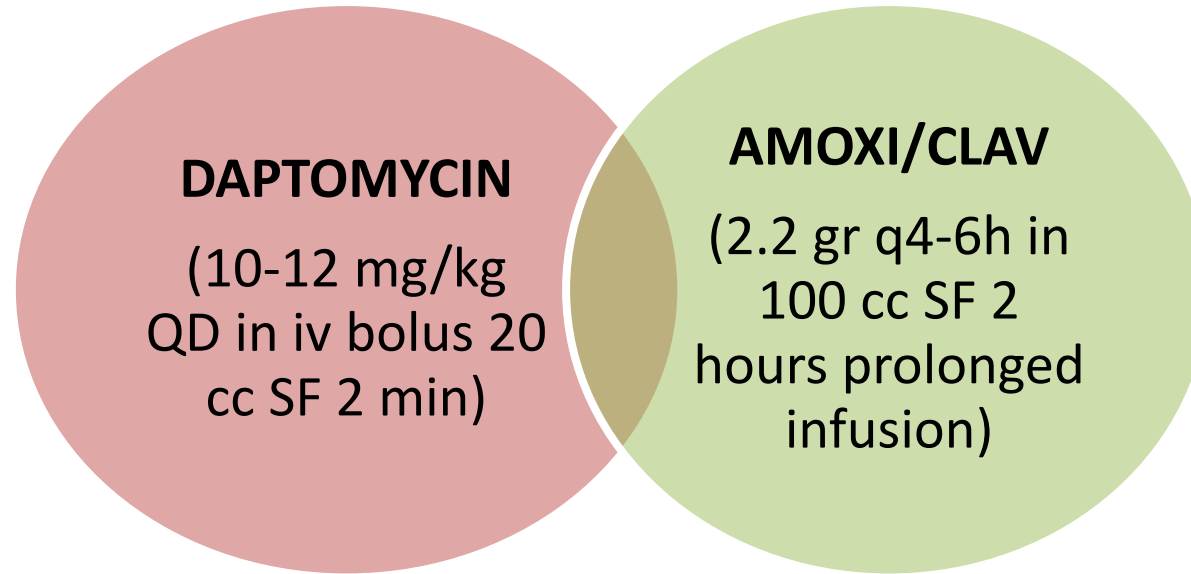
Staphylococcus aureus



AR-ISS



Empiric antimicrobial treatment for IE



Staphylococcus spp. (MR/MS) – Enterococcus spp. – Streptococcus spp.

- . Biofilm active
- . Bactericidal
- . High blood stream concentration

- . Sinergic additive effect (SEE-SAW)
- . Low risk of nephrotox

The bug → *Staphylococcus spp.*

(*S. aureus*, *S. epidermidis*, *S. hominis*, *S. lugdunensis*, *S. haemolyticus* etc.)



Methicillin-susceptible



Methicillin-resistant

NVE

4-6 weeks

Cefazolin

**2 gr q8h extended
iv infusion**

PVE



At least 6 weeks

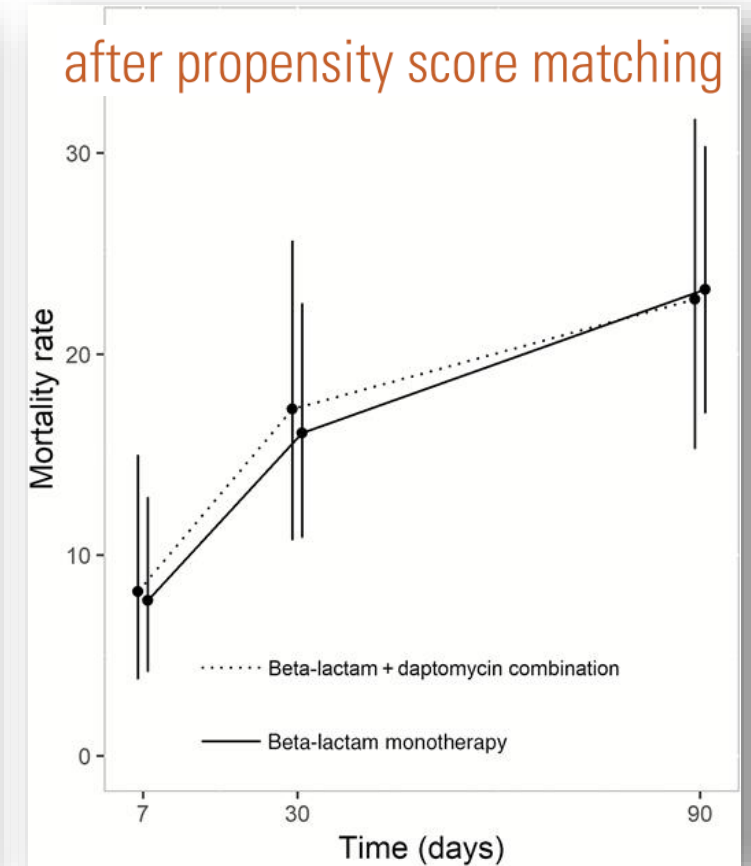
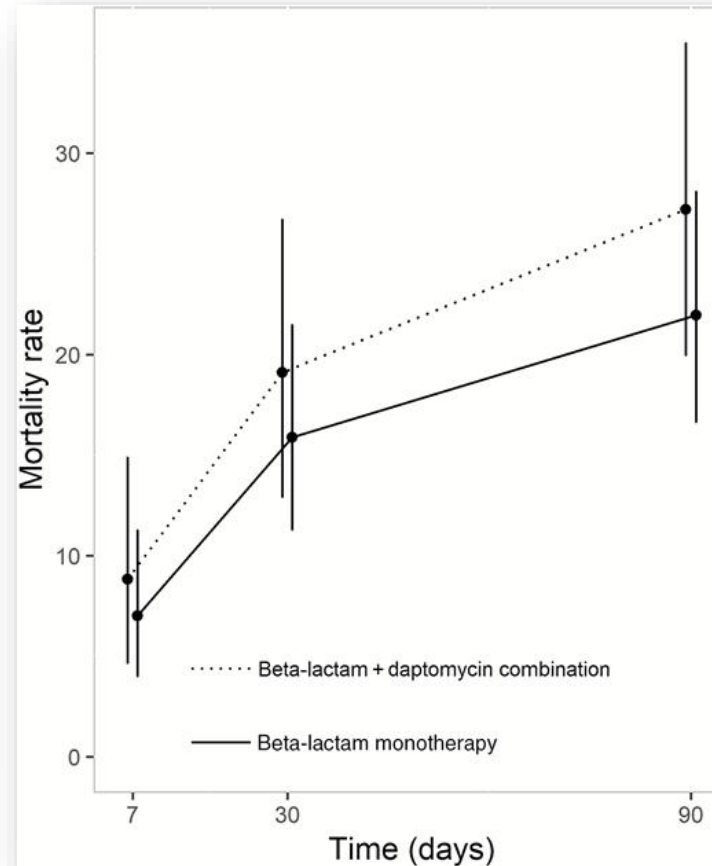
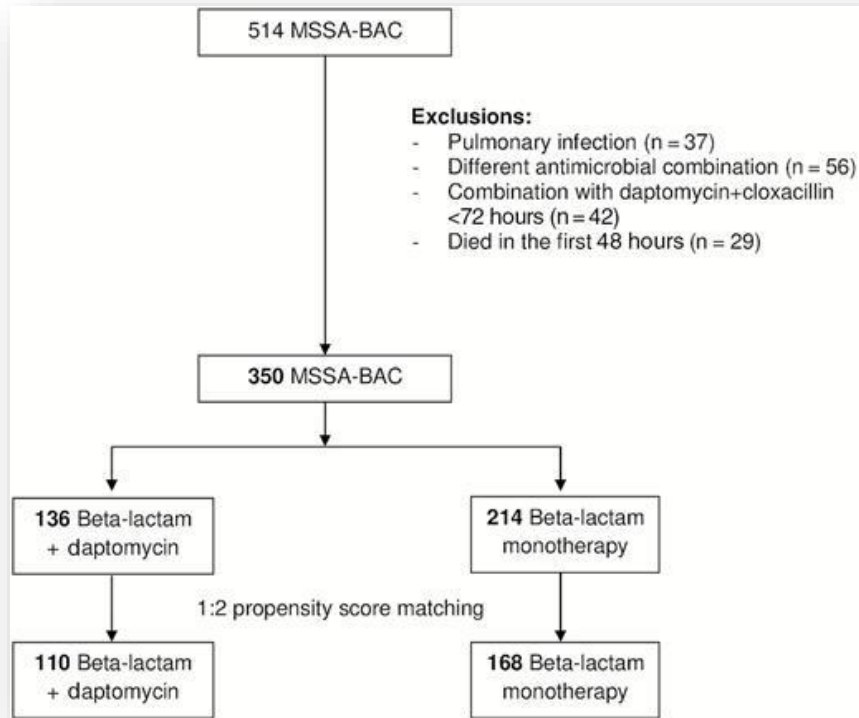
Combination therapy??

**Gentamicin or
Rifampin??**

**Beta-lactam allergy or in
patients with concomitant
vertebral bone infection:
Daptomycin + Fosfomycin**


Impact of β -Lactam and Daptomycin Combination Therapy on Clinical Outcomes in Methicillin-susceptible *Staphylococcus aureus* Bacteremia: A Propensity Score-matched Analysis

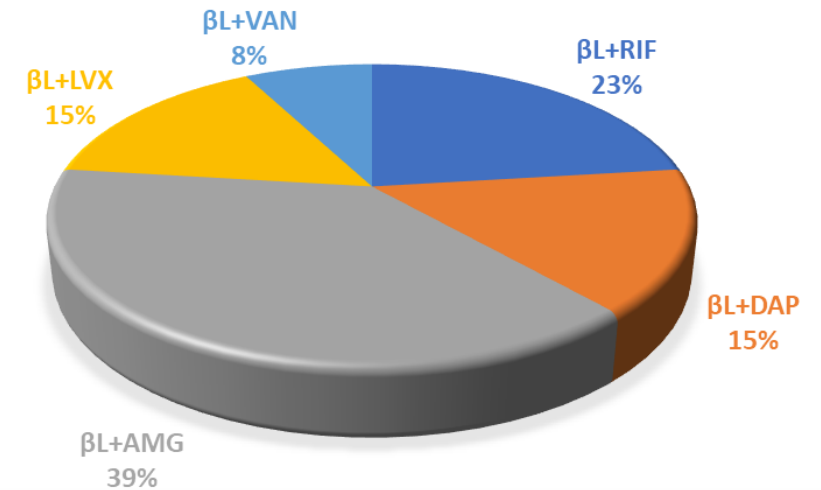
Sara Grillo,^{1,2} Guillermo Cuervo,^{1,2,3} Jordi Carratalà,^{1,2,3,4} Immaculada Grau,^{1,2,4,5} Natàlia Pallarès,^{6,7} Cristian Tebé,^{6,8} Lluïsa Guillem Tió,¹ Oscar Murillo,^{1,2,3,4} Carmen Ardanuy,^{2,4,5,9} M. Angeles Domínguez,^{2,3,4,9} Evelyn Shaw,^{1,2,3} Carlota Gudiol,^{1,2,3,4} and Miquel Pujol^{1,2,3}



Combination therapy for MS Staph aureus bacteremia

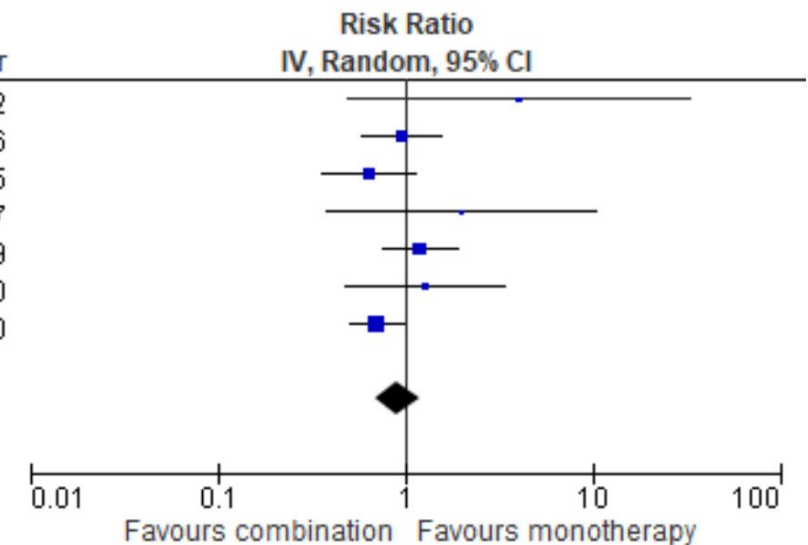
The Effectiveness of Combination Therapy for Treating Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Systematic Literature Review and a Meta-Analysis

Sara Grillo ^{1,†}, Mireia Puig-Asensio ^{1,2,3,*,†} , Marin L. Schweizer ^{3,4}, Guillermo Cuervo ^{1,2}, Isabel Oriol ⁵, Miquel Pujol ^{1,2} and Jordi Carratalà ^{1,2,6}



30-day mortality

Study or Subgroup	Combination therapy		Monotherapy		Weight	Risk Ratio IV, Random, 95% CI	Year
	Events	Total	Events	Total			
Korzeniowski 1982	5	43	1	35	1.7%	4.07 [0.50, 33.24]	1982
Ruotsalainen 2006	26	191	27	190	19.8%	0.96 [0.58, 1.58]	2006
Forsblosom 2015	28	261	16	96	16.6%	0.64 [0.36, 1.14]	2015
Park 2017	4	46	2	46	2.6%	2.00 [0.39, 10.39]	2017
Grillo 2019	26	136	34	214	21.8%	1.20 [0.76, 1.91]	2019
Cheng 2020	8	53	6	51	6.8%	1.28 [0.48, 3.44]	2020
Rieg 2020	50	313	59	262	30.7%	0.71 [0.51, 1.00]	2020
Total (95% CI)		1043		894	100.0%	0.92 [0.70, 1.20]	
Total events	147		145				
Heterogeneity: Tau ² = 0.03; Chi ² = 8.14, df = 6 (P = 0.23); I ² = 26%							
Test for overall effect: Z = 0.63 (P = 0.53)							



The bug → *Staphylococcus spp.*

(*S. aureus*, *S. epidermidis*, *S. hominis*, *S. lugdunensis*, *S. haemolyticus* etc.)



Methicillin-susceptible



Methicillin-resistant

NVE
4-6 weeks

PVE 
At least 6 weeks

NVE
4-6 weeks

PVE 
At least 6 weeks

Cefazolin
2 gr q8h extended
iv infusion

Combination therapy??

Daptomycin 10 mg/kg in
20 cc SF i.v. bolus 2 min
or Vancomycin 30 mg/kg
i.v. in 2-3 doses

Combination therapy??

Gentamicin and/or
rifampin according to
ESC guidelines

**Beta-lactam allergy or in
patients with concomitant
vertebral bone infection:**
Daptomycin + Fosfomycin

Combination therapy for MRSA bacteremia

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β -Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia
A Randomized Clinical Trial

Steven Y. C. Tong, MBBS, PhD; David C. Lye, MBBS; Dafna Yahav, MD; Archana Sud, MD; J. Owen Robinson, MD; Jane Nelson, BN; Sophia Archuleta, MD;

Table 3. Primary and Secondary Outcomes

Outcomes	No./Total No. (%)		Risk Difference, % (95% CI)	P Value
	Combination Therapy	Standard Therapy		
Primary Outcome^{a,b}				
Primary analysis population	59/170 (35)	68/175 (39)	-4.2 (-14.3 to 6.0)	.42
Per protocol	47/144 (33)	68/175 (39)	-6.2 (-16.7 to 4.3)	.25
Secondary Outcomes^c				
All-cause mortality^d				
Day 14	13/170 (8)	13/174 (7)	0.2 (-5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (-3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (-3.7 to 12.7)	.28
Persistent bacteremia^e				
Day 2	50/167 (30)	61/173 (35)	-5.3 (-15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	-8.9 (-16.6 to -1.2)	.02
Microbiological relapse ^a	14/169 (8)	18/175 (10)	-2.0 (-8.1 to 4.1)	.52
Microbiological treatment failure ^a	16/170 (9)	17/175 (10)	-0.3 (-6.5 to 5.9)	.92
Acute kidney injury ^f	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

The bug → *Streptococcus spp*

(Oral streptococci, *S. gallolyticus*)



MIC Pen G < 0.12

NVE
4 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die

NVE
2 weeks

+ Gentamicin 3 mg/kg QD

PVE
6 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die

Beta-lactam allergy:

Teicoplanin or
Vancomycin



MIC Pen G 0.12-0.5 or > 0.5
Gemella, Granulicatella, Abiotrophia

NVE
4 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die
+ Gentamicin 3 mg/kg QD
For 2 weeks

PVE
6 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die
+ Gentamicin 3 mg/kg QD
For 2 weeks

The bug → *Enterococcus spp*

(*E. faecalis* / *E. faecium*)



Amp-S
HLGR neg

NVE or PVE
6 weeks

Ampicillin 12 gr/die
plus
Ceftriaxone 2 gr q12h
or
+ Gentamicin 3 mg/kg QD



Amp-R
HLGR neg

NVE or PVE
6 weeks

Teicoplanin 12 mg/kg QD (LD)
+ Gentamicin 3 mg/kg QD



Amp-S
HLGR positive

NVE or PVE
6 weeks

Ampicillin 12 gr/die
plus
Ceftriaxone 2 gr q12h

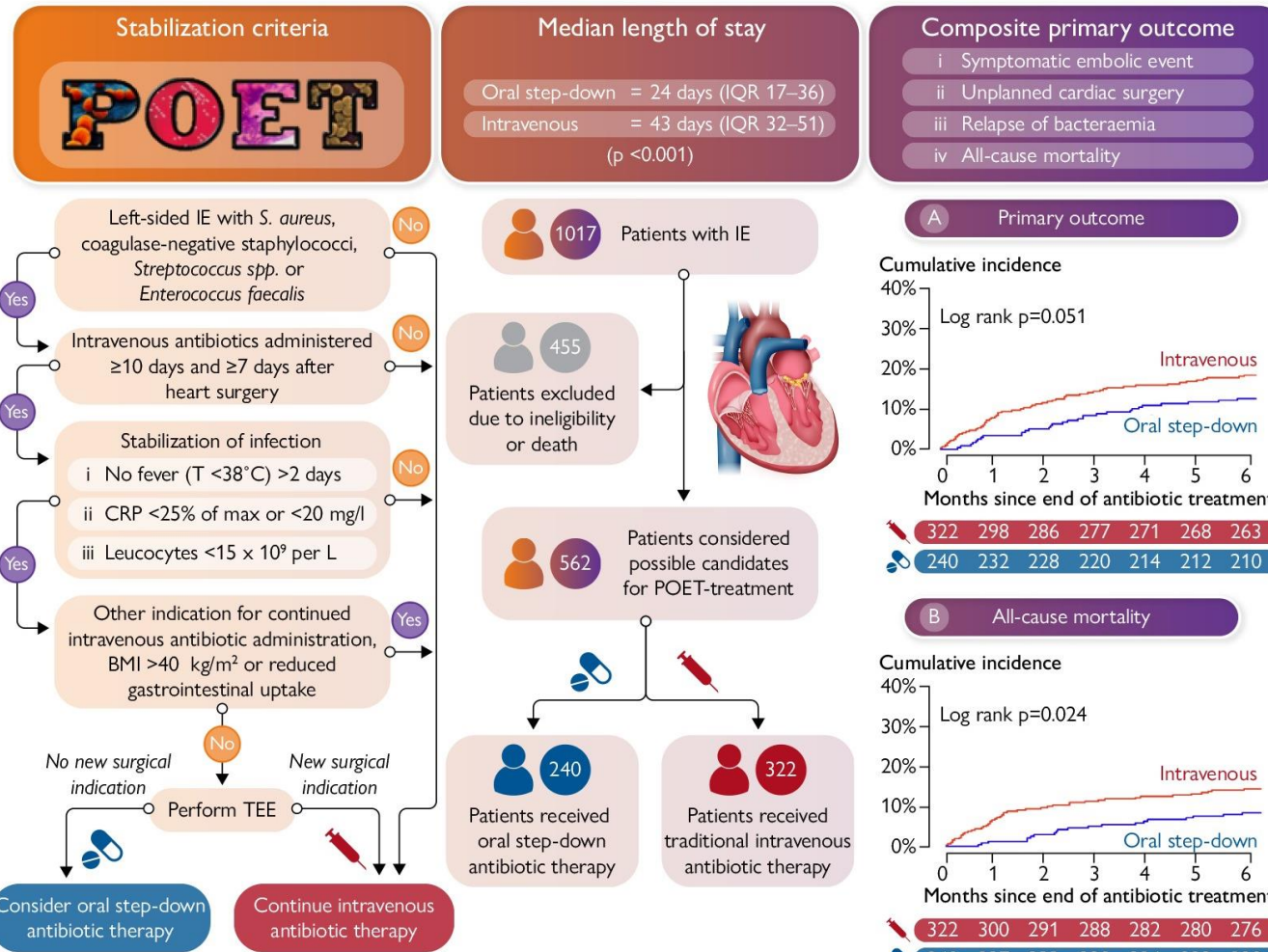


Amp-R
HLGR positive

NVE or PVE
6 weeks

Teicoplanin 12 mg/kg QD (LD)

Partial Oral Endocarditis Treatment – The Danish POETry Study



Outpatient Parenteral Antibiotic Treatment vs Hospitalization for Infective Endocarditis: Validation of the OPAT-GAMES Criteria

Juan M. Pericàs,^{1,2,a} Jaume Llopis,^{1,3,a} Patricia Muñoz,^{4,c} Víctor González-Ramallo,⁴ M. Eugenia García-Leoni,⁴ Aristides de Alarcón,⁵ Rafael Luque,⁵ M. Carmen Fariñas,⁵ Miguel A. Goenaga,⁷ Marta Hernández-Meneses,¹ David Nicolás,¹ Antonio Ramos-Martínez,⁸ M. Angeles Rodríguez-Esteban,⁹ Aroa Villoslada-Gelabert,¹⁰ and José M. Miró,^{1,11} on behalf of the GAMES Investigators^b

Exclusion criteria:

1. Patients with Child B or C liver cirrhosis

2. Severe central nervous system emboli

Multiple (>3), large (>2 cm), hemorrhagic, or with fixed neurologic deficits

3. Not drained large spleen or renal abscess

4. Vertebral abscesses requiring neurosurgery

5. Periannular complications or other severe conditions requiring surgery when this is contraindicated^b

Perivalvular abscess, fistula, perforation, pseudoaneurysm, severe pericardial effusion with signs of cardiac tamponade, etc.

6. Severe postsurgical complications

Ischemic stroke, brain hemorrhage, worsening of prior stroke/bleeding, hemodynamic collapse, surgical wound bleeding requiring new surgery, infection of the surgical wound (mediastinitis/osteomyelitis), ventilator-associated pneumonia, acute kidney failure requiring dialysis, cardiac blockade requiring pacemaker, critically ill-associated polyneuropathy

7. Highly difficult-to-treat microorganisms

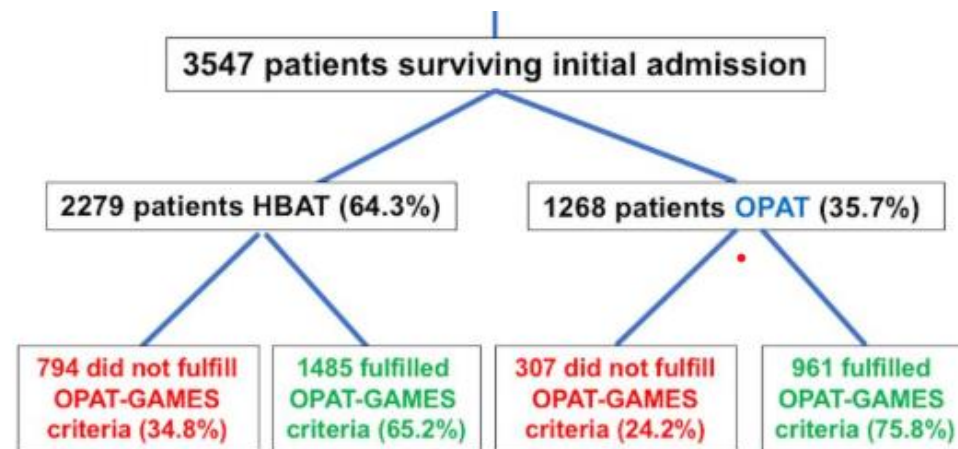
Those requiring intravenous antibiotic combinations that cannot be administered by means of OPAT or that require strict monitoring of drug levels either in blood or in other fluids owing to their potential toxicity or narrow therapeutic index (eg, methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci also resistant to alternative drugs such as daptomycin and linezolid, multidrug or extensively drug-resistant gram-negative rods, highly penicillin-resistant viridans group streptococci, fungi other than *Candida* spp.)

8. Active intravenous drug users

Outpatient parenteral antibiotic treatment is not recommended in patients with IE caused by highly difficult-to-treat microorganisms,^c liver cirrhosis (Child-Pugh B or C), severe cerebral nervous system emboli, untreated large extracardiac abscesses, heart valve complications, or other severe conditions requiring surgery, severe post-surgical complications, and PWID-related IE.

III

C



Outcomes	HBAT (n = 1116)	OPAT (n = 558)	
Readmissions	156 (14.0)	86 (15.4)	.438
1-y mortality	92 (8.2)	45 (8.1)	.899
IE-related	33 (3.0)	15 (2.7)	.752
Non-IE related	59 (5.3)	30 (5.4)	.939
Recurrences	22 (2.0)	14 (2.6)	.475
Relapses	13 (1.2)	7 (1.3)	.875
Reinfections	9 (0.8)	7 (1.3)	.409

Main benefits of oral step-down therapy

1. RCT showing no signs of increasing treatment failure in oral step-down
2. Shorter length of stay in-hospital of 2-3 weeks

Compared to OPAT:

1. Up to 12% of OPAT develop IV-line related complications
2. Lower COST of around 3000 € /patient

**Long-Acting
lipoglycopeptides**



ESC

European Society
of Cardiology

European Heart Journal (2023) 44, 3948–4042
<https://doi.org/10.1093/eurheartj/ehad193>

ESC GUIDELINES

2023 ESC Guidelines for the management of endocarditis

Surgical indications for LS-IE



Heart failure

Cardiogenic shock or
pulmonary oedema



Uncontrolled Infection

Local complications



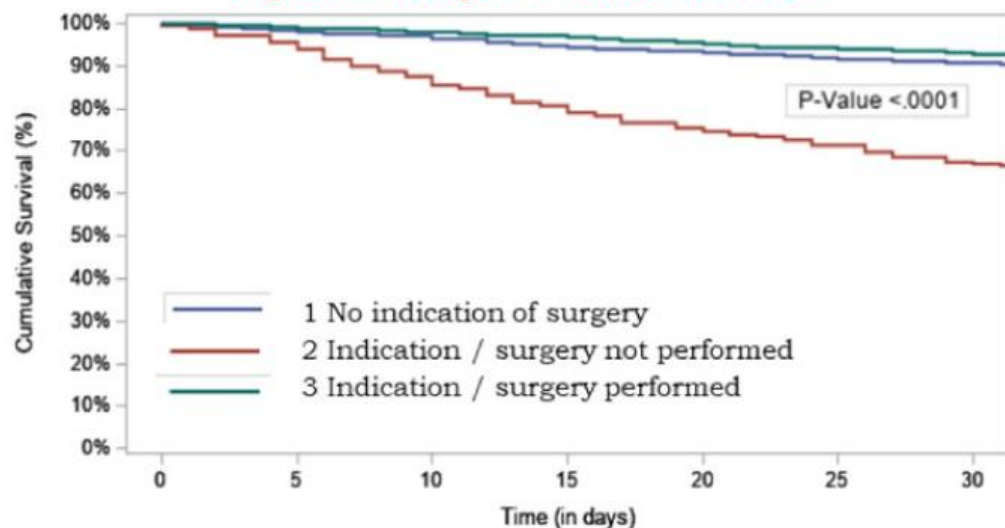
High risk of embolism

Vegetation above 10
mm or embolic event
despite appropriate ATB

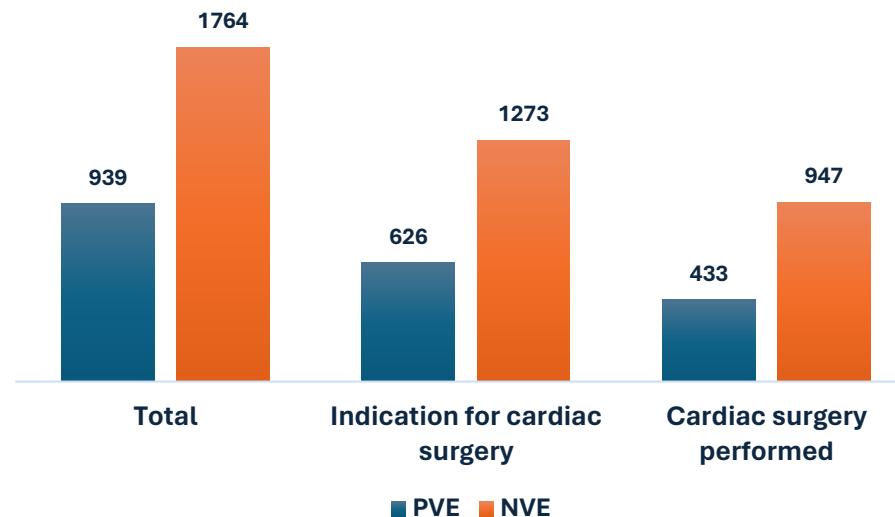
Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study

In-hospital mortality in EURO-ENDO

adjusted Kaplan-Meier curves



Highest one-month mortality in patients with failure to undertake surgery despite a guideline recommended indication



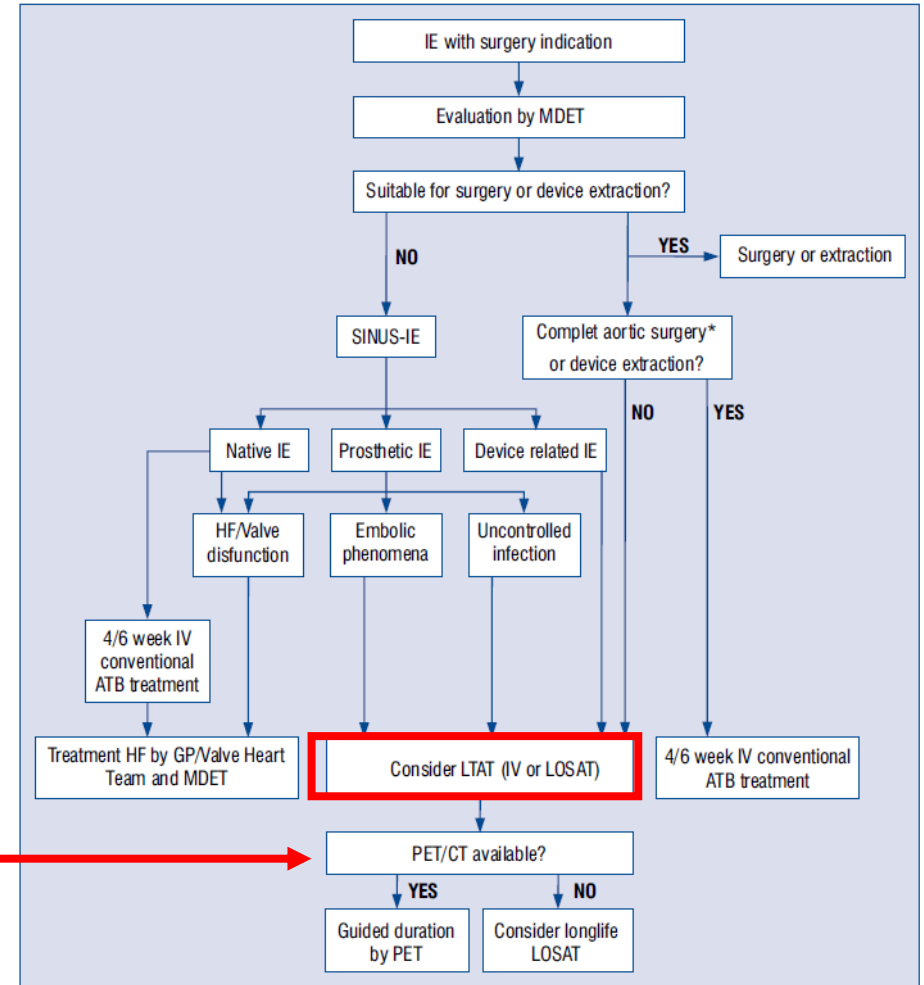
In PVE, 193 (31%) patients are not operated despite surgical indication

Main reason for surgery not performed is extremely high surgical risk (65%)

Long-term antibiotic therapy in patients with surgery-indicated not undergoing surgery infective endocarditis

Parameters	Overall (n = 32)
Age [years]	72 ± 17
Male sex	25 (78.1)
Healthcare-associated IE	17 (53.1)
Type of infection	
Prosthetic valve IE	21 (65.6)
Early/late PVE	8/13
Intracardiac device-related IE	7 (21.9)
Native IE	4 (12.5)
Clinical history-comorbidities	
Previous cardiac surgery	19 (59.4)
Previous IE	14 (43.8)
Chronic renal failure	14 (43.8)
Hemodialysis	3 (9.4)
Diabetes mellitus	9 (28.1)
COPD	5 (15.6)
Severe liver disease	4 (12.5)
Cancer	4 (12.5)
HIV	1 (3.1)
Charlson comorbidity index, median (IQR)	5 (3–7)

Indication for surgery	
Hemodynamic	1 (3.1)
<u>Uncontrolled infection</u>	24 (75)
Local complication	18
Embolic	1 (3.1)
Device infection	6 (18.8)
EuroSCORE I (%), median (IQR)	32 (17-46)
EuroSCORE II (%), median (IQR)	9.1 (6.7-14)
Reasons for no surgery	
<u>Unaffordable surgical risk</u>	24 (75)
Patient refusal	2 (6.3)
Intra-surgery clinical complication*	1 (3.1)
Surgeon refusal (technical risk)	5 (15.6)
Outcome	
0 to 60-day mortality	1 (3.1)
Cumulative 3-year mortality	12 (37)
Related to IE	4 (12.5)
Relapses	4 (12.5)



Take home points

- 1. Delay antimicrobials in stable patients with uncertain diagnosis**
- 2. Apply guidelines to local epidemiology**
- 3. Early step-down oral therapy is safe and effective in selected cases**
- 4. What to do in poor surgical candidates with PVE?**
- 5. Consider LTAT but be aware of drug-drug interaction or adverse event in elder comorbid patients**

USO RAZIONALE DEGLI ANTIBIOTICI NELL'ERA DELLE RESISTENZE BATTERICHE

17 MAGGIO
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Sala Congressi
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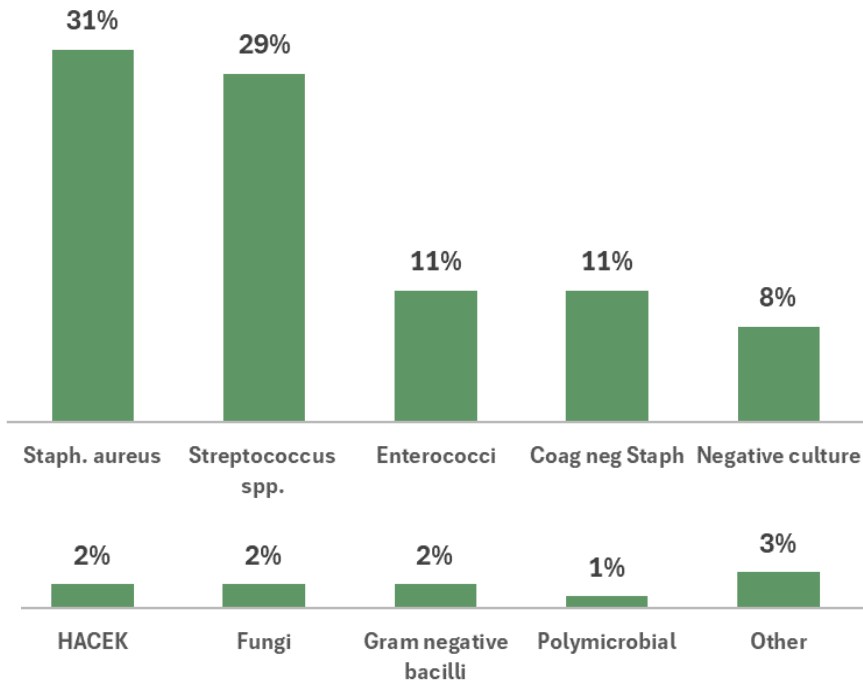
Grazie per l'attenzione

OUTLINE

- 1. General concepts and epidemiology**
- 2. Empirical and targeted antimicrobial treatment**
- 3. POET and OPAT**
- 4. Surgical treatment**
- 5. Long-term suppressive antimicrobial treatment**

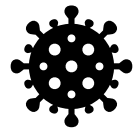
Native valve Endocarditis:

- 1.Community-acquired
- 2.Younger patients
- 3.PWID
- 4.Low comorbidity rate



Prosthetic valve Endocarditis

Organism	PVE after surgical valve replacement ^[1-5]			PVE after TAVR ^[6,7]
	Number of cases (%)			Number of cases (%)
	<2 months postoperatively	2 to 12 months postoperatively	>12 months postoperatively	
Streptococci*	6 (2)	6 (13)	84 (30)	46 (17)
Pneumococci	-	-	<1%	-
Enterococci	20 (8)	5 (11)	31 (11)	68 (25)
<i>Staphylococcus aureus</i>	75 (30)	6 (13)	62 (22)	65 (24)
Coagulase-negative staphylococci	69 (28)	17 (36)	34 (12)	57 (12)
HACEK group [†]	-	-	11 (4)	-
Gram-negative bacilli	26 (10)	2 (4)	13 (5)	3 (1)
Fungi (<i>Candida</i> species)	22 (9)	4 (8)	3 (1)	3 (1)
Polymicrobial/miscellaneous	7 (3)	4 (8)	12 (4)	24 (9)
Diphtheroids	9 (4)	-	5 (2)	-
Culture negative	16 (6)	3 (6)	27 (10)	14 (5)
Total number of cases	n = 250 cases	n = 47 cases	n = 282 cases	n = 275



The bug → Staph. aureus or CoNS - MS



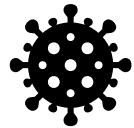
NVE

Cefazolin 2 gr q8h extended iv infusion for 4 weeks (valid option in penicillin allergic patients) – No combination with aminoglycoside



PVE

Consider combination of cefazolin with rifampin 300 mg q8h or aminoglycoside 3 mg/kg once daily (few data supporting those combinations)



The bug → Staph. aureus or CoNS - MR



NVE

Daptomycin 10 mg/kg in 20 cc SF i.v. bolus 2 min **or Vancomycin** 30 mg/kg i.v. in 2-3 doses for 4-6 weeks



PVE

Consider combination of daptomycin with rifampin 300 mg q8h or aminoglycoside 3 mg/kg once daily (few data supporting those combinations)



The bug → *Streptococcus spp*

(Oral streptococci, *S. gallolyticus*)



MIC Pen G < 0.12



MIC Pen G 0.12-0.5 or > 0.5
Gemella, Granulicatella, Abiotrophia

NVE
4 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die

NVE
4 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die
+ Gentamicin 3 mg/kg QD
For 2 weeks

NVE
2 weeks

+ Gentamicin 3 mg/kg QD

PVE
6 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die

PVE
6 weeks

Ceftriaxone 2 gr/die or
Amoxicillin/Ampicillin 12 gr/die
+ Gentamicin 3 mg/kg QD
For 2 weeks

Beta-lactam allergy:

Teicoplanin or
Vancomycin

The bug → *Enterococcus spp*

(*E. faecalis* / *E. faecium*)



Amp-S
HLGR neg

NVE or PVE
6 weeks

Ampicillin 12 gr/die
plus
Ceftriaxone 2 gr q12h
or
+ Gentamicin 3 mg/kg QD



Amp-R
HLGR neg

NVE or PVE
6 weeks

Teicoplanin 12 mg/kg QD (LD)
+ Gentamicin 3 mg/kg QD



Amp-S
HLGR positive

NVE or PVE
6 weeks

Ampicillin 12 gr/die
plus
Ceftriaxone 2 gr q12h



Amp-R
HLGR positive

NVE or PVE
6 weeks

Teicoplanin 12 mg/kg QD (LD)