



Infectious Disease Practice

Efficacy and safety of antistaphylococcal penicillin or cephazolin-based combinations versus monotherapy for methicillin-susceptible *Staphylococcus aureus* infective endocarditis: A propensity score analysis of nationwide prospective cohort



Jorge Calderón-Parra^{a,b,*}, Sara Grillo^c, Patricia Muñoz^{d,e}, Marina Machado-Vilchez^{d,e}, Antonia Delgado-Montero^{f,g}, Arístides De Alarcón-González^{h,i,j}, Manuel Poyato-Borrego^{h,i,j}, MA Goenaga-Sánchez^k, M. Carmen Fariñas-Alvarez^{l,m}, José M. Miró^{n,o}, Luis Eduardo López-Cortés^{p,q}, Raquel Rodríguez-García^r, José A. Oteo^{s,t}, Antonio Martínez-Ramos^{a,b,u}, on behalf of the Spanish Collaboration on Endocarditis (GAMES)

^a Infectious Diseases Unit, Internal Medicine Department, University Hospital Puerta de Hierro, Majadahonda, Madrid, Spain

^b Research Institute Puerta de Hierro-Segovia de Arana (IDIPHS), Majadahonda, Spain

^c Infectious Diseases Unit, Hospital Santa Creu and Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

^d Infectious Diseases Department, University Hospital Gregorio Marañón, Madrid, Spain

^e Health research institute Gregorio Marañón, CIBER respiratory diseases-CIBERES (CB06/06/0058), Faculty of Medicine, Complutense University of Madrid, Spain

^f Cardiology Department, University Hospital Gregorio Marañón, Madrid, Spain

^g CIBER cardiovascular diseases-CIBERCV, Spain

^h Clinical Infectious Diseases, Microbiology and Parasitology Unit, University Hospital Virgen del Rocío, Sevilla, Spain

ⁱ CIBER infectious diseases-CIBERINFEC, Health Institute Carlos III, Madrid, Spain

^j Biomedicine Institute of Sevilla (IBiS), Spain

^k Infectious Diseases Department, University Hospital of Donosti, ISS Bodonostia, San Sebastian, Spain

^l Infectious Diseases Department, University Hospital Marqués de Valdecilla, Santander, Spain

^m CIBER infectious diseases – CIBERINF(CB21/13/00068), Health institute Carlos III, Madrid, Spain

ⁿ Infectious Diseases Department, Hospital Clinic, University of Barcelona, Barcelona, Spain

^o CIBERINFEC Research institute Carlos III, Madrid, Spain

^p Clinical Infectious Diseases and Microbiology Department, University Hospital Virgen Macarena, Sevilla, Spain

^q Biomedicine Institute of Sevilla (IBiS), Department of Medicine, University of Sevilla/CSIC, CIBERINFEC, Sevilla, Spain

^r Intensive Medicine Department, University Hospital Central de Asturias, Oviedo, Spain

^s Infectious Diseases Department, University Hospital San Pedro, Logroño, Spain

^t Biomedicine Investigation Center of La Rioja (CIBIR), Logroño, Spain

^u Department of Medicine, University Autonoma of Madrid, Madrid, Spain

ARTICLE INFO

Article history:

Accepted 12 November 2024

Available online 17 November 2024

Keywords:

Infective endocarditis
Staphylococcus aureus
Combination therapy
Prognosis
Mortality

SUMMARY

Objectives: We aimed to evaluate the usefulness of antistaphylococcal penicillin (ASP) or cephazolin-based combinations versus monotherapy in patients with native-valve infective endocarditis (IE) caused by methicillin-susceptible *Staphylococcus aureus* (MSSA).

Methods: Post-hoc analysis of a multicentre prospective cohort. We include patients from 2008 to 2022 with definite native-valve, left-side IE due to MSSA treated primarily with ASP/cephazolin. Patients were categorized according to whether they initially received monotherapy or combination therapy for more than 72 h. A propensity score-matched cohort was planned.

Results: Out of 420 included cases, 94 (22.4%) received monotherapy and 326 (77.6%) combination. Median combination duration was 14 days (interquartile range 10–20).

Sixty-eight combination cases were matched with 68 monotherapy controls. Baseline characteristics were well balanced. There were no differences in in-hospital or one-year mortality between groups (OR

* Correspondence to: Infectious Diseases Unit, Department of Internal Medicine, University Hospital Puerta de Hierro, C/ Manuel de Falla 1, 28222 Majadahonda, Spain.
E-mail address: jorge050390@gmail.com (J. Calderón-Parra).

0.85, 95%CI 0.33–2.18 and HR 0.68, 95%CI 0.35–1.31, respectively). Endocarditis relapses and persistent bacteraemia rates were similar (0% vs 1.5%, $p = 1.000$; and 19.1% vs 13.2%, $p = 0.352$, respectively). Drug-related adverse events were more frequent in the combination group (15.0% vs 1.1%, $p < 0.001$).

Conclusions: Antibiotic combinations for patients with native valve left-sided MSSA endocarditis did not improve patient's outcomes. Drug-related adverse events were more frequent in combination patients.

© 2024 The Author(s). Published by Elsevier Ltd on behalf of The British Infection Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Infective endocarditis (IE) is a serious infections, with an increasing incidence in recent years, and associated with great morbidity and mortality.¹ Although in the past *Streptococcus spp.* was the most frequent cause of EI, nowadays *Staphylococcus spp.*, and especially methicillin-susceptible *Staphylococcus aureus* (MSSA) is the most frequent microorganism involved in this infection.^{2,3} Moreover, it is associated with worse outcomes than other aetiologies.^{2,3} Hence, evaluation of the best treatment approach is urgently needed.

Currently, there is controversy about the usefulness of antibiotic combination best for improving outcomes of patients with MSSA IE.^{4,5} Some experts propose that this infections requires an synergic and bactericidal combination therapy with an antistaphylococcal penicillin (ASP) or cephazolin plus a non-beta-lactam antibiotic (most commonly vancomycin, daptomycin, rifampin or an aminoglycoside).^{5,6} This approach is based on a consistent in-vitro synergic effect found between these combinations and the more frequent and faster focus sterilization found in in-vivo animal models.^{7,8}

Clinically, combination therapy has been previously evaluated in MSSA and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia, demonstrating a reduction in bacteraemia duration.^{9–11} Yet, these trials have failed to show better patient-center outcomes when compared to ASP or cephazolin monotherapy.¹²

Nevertheless, the aforementioned studies have not specifically evaluated patients with left-sided IE. Patients with this condition were excluded or, at best, represented less than 10% of patients.¹¹ In valvular vegetations, there is a particularly high-inoculum of MSSA bacteria that is not found in other settings and can potentially influence a worse prognosis.^{13,14} Thus, experts have hypothesized that, while combination therapy is not beneficial in most MSSA bacteraemia cases, reducing hastily this inoculum with combinations could be specifically beneficial for IE patients.^{7,15,16} This hypothetic benefit would be of utmost importance during the first days-weeks of therapy, when the inoculum in vegetation is still high.

However, to our knowledge, there is no current good-quality available evidence evaluating the clinical impact of combination therapy in patients with left-side IE. This is due both to the complexity of conducting clinical trials in endocarditis and the important bias that observational cohorts suffers from, including selection bias.¹⁷ Nevertheless, there are now statistical tools to try to overcome these bias, being propensity-score matching one of the most useful in this regard.^{18,19}

Accordingly, our main purpose was to evaluate, by means of a propensity-score based analysis, the efficacy and safety of ASP/cephazolin based combination treatment versus monotherapy in patients with left-sided native valve caused by MSSA.

Patients and methods

Between January 2008 and December 2022, consecutive patients with definite or possible IE according to Duke's modified criteria were prospectively included in the Spanish Collaboration on

Endocarditis registry (GAMES for its Spanish abbreviation). This registry is maintained by 34 Spanish hospitals. Cohort registration was approved by regional and local ethics committees, and all patients signed informed consent.

At each center, a multidisciplinary team completes an anonymized and standardized form with the IE episode and a follow-up form after one year of the episode. Demographic, clinical, microbiological, echocardiographic, and prognostic sections are recorded. These standardized forms include information regarding the antibiotics treatments received, considering specific antibiotics prescribed, antibiotic-related adverse reaction, dates of prescription and cessation, and reason of cessation.

Patients

For this study, patients with definite IE caused by MSSA were included. We exclude patients with intracardiac and intravascular prosthesis or devices (either arterial graft or stent, prosthetic valve and cardiac implantable electronic device), patients with extravascular prosthetic infections, patients without left-side valve involvement and patients deceased during the first 48 h (in order to avoid survivor bias). Patients in whom ASP or cephazolin were not initiated in the first 5 days and maintained at least 50% of the total treatment or until oral stepdown were also excluded.

Patients were categorized according to the antibiotic scheme used in two mutually exclusive groups; 1- Monotherapy group: patients treated with ASP or cephazolin in monotherapy or with combination treatment less than 48 h. 2- Combination group: patients treated with ASP or cephazolin in combination with other antibiotic class, initiated during the first 5 days and continued for at least 72 h.

Definitions

IE was defined using the 2023 European Cardiac Society modified Duke criteria.²⁰ Microbiological diagnosis was determined by blood or valve culture. Hospital-acquired, non-hospital healthcare-related, and community-acquired IE, definitions from previous studies were followed.²¹ Chronic renal failure was defined as a previous serum creatinine greater than 1.4 mg/dL. Worsening or new onset renal impairment was defined as worsening at least 25% of creatinine clearance, as measured by Cockcroft-Gault equation. All necessary variables were collected to calculate the Charlson Comorbidity Index.²² Persistent bacteraemia was defined as positive blood cultures more than seven days after effective antibiotic therapy. Relapses were defined as a new episode of IE caused by the same microorganism during the first year of follow-up. Surgical indications followed the latest European guidelines²⁰ and, for this study, cardiac surgery was defined as an open surgery involving left-sided cardiac valves. The specific surgical technique was at discretion of attending cardiothoracic surgeon. A direct identification was made of patients who had surgical indication but were not operated. IE-related mortality was dead associated with IE or its complications according to case-by-case assessment by local investigators.

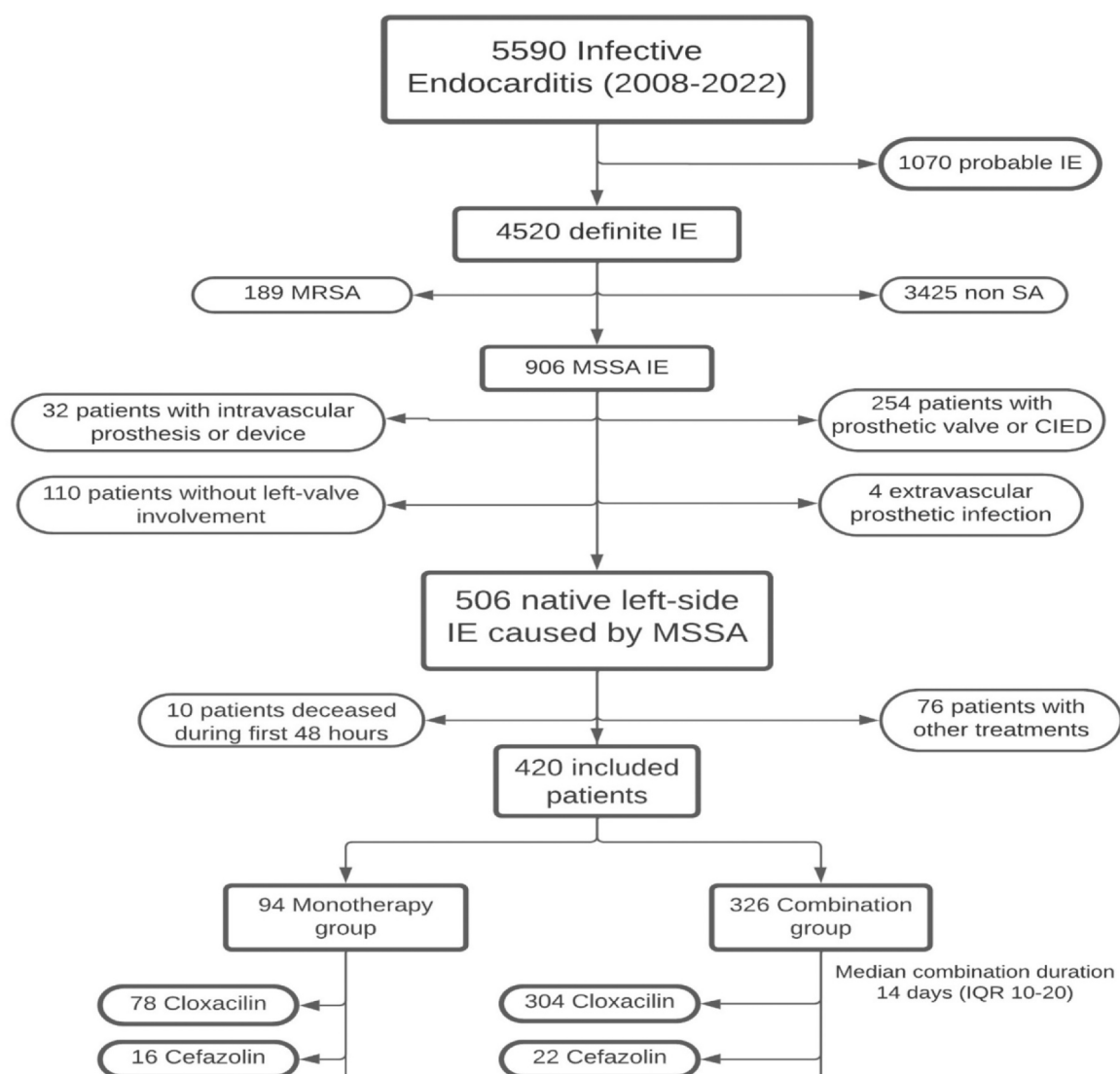


Fig. 1. Patient's flowchart. IE: infective endocarditis. SA: *Staphylococcus aureus*. MRSA: Methicillin-resistant *Staphylococcus aureus*. MSSA: Methicillin-susceptible *Staphylococcus aureus*. CIED: Cardiac implantable electronic device. IQR: Interquartile range.

Endpoints

The primary endpoint was all-cause in-hospital mortality. Secondary efficacy endpoints include one-year mortality, IE-related mortality, persistent bacteraemia and IE relapses. Safety endpoints included drug-related adverse events, adverse events leading to antibiotic discontinuation, and specific drug-related events, both in the total cohort and in the PSM cohort.

Statistical analysis

Qualitative variables are expressed as absolute numbers and percentages. Quantitative variables are expressed as median and interquartile range (IQR).

A propensity score (PS) was preplanned using variables previously related to IE mortality and that could potentially influence the selection of the treatment regimen. We include as covariables in the PS age,^{23–25} sex,²⁶ Charlson index,^{2,3,24} nosocomial IE,^{27–29} intracardiac complications,^{2,3,25} osteoarticular involvement,^{30,31} central nervous system (CNS) involvement,^{32–34} septic shock^{2,32} and cardiac surgery.^{35,36} To generate the PSM cohort, a 1:1 matching based on the PS was made, using the “nearest-neighbor” strategy, without replacement, and with a fixed 0.01 calliper.^{18,37,38}

For univariate analyses, categorical variables were compared using Chi2 or Fisher test when necessary, and quantitative variables were compared using Mann-Whitney's U.

For the multivariate analysis for the in-hospital mortality, those variables with $p < 0.20$ in univariate analysis and that were considered clinically significant were included in a multivariate logistic regression model. Adjusted *odds ratios* (OR) and its 95% confident intervals (95% CI) are provided.

For the multivariate analysis for one-year mortality, the effect of the combination treatment was assessed by means of a multivariate regression Cox analysis including those variables with $p < 0.20$ in univariate analysis and that were considered clinically significant. Survival curves were obtained, and adjusted *hazards ratios* (HR) and its (95% CI) are provided.

Bilateral p -value below 0.05 was considered significant. All statistical analyses were performed with SPSS version 25 software (SPSS INC., Chicago, Illinois, USA).

Results

Out of a total of 5590 infective endocarditis in the cohort, we included 420 left-side native valve IE caused by MSSA. Fig. 1 represents

Table 1

Univariate analysis comparing patients with beta-lactam monotherapy versus combination therapy. CNS: Central nervous system.

Variable	Monotherapy (n = 94)	Combination (n = 326)	p
Age (years)	67 (53–76)	65 (51–75)	0.321
Sex (man)	62.7% (59)	57.3% (187)	0.349
COMORBIDITIES			
Charlson comorbidity index	4 (3–7)	4 (2–7)	0.658
Chronic pulmonary disease	9.5% (9)	14.4% (47)	0.224
Ischemic heart disease	22.3% (21)	20.5% (67)	0.707
Chronic cardiac failure	27.6% (26)	21.1% (69)	0.185
Diabetes mellitus	28.7% (27)	31.6% (103)	0.596
Previous stroke	8.5% (8)	9.8% (32)	0.803
Chronic renal failure	27.7% (26)	32.2% (105)	0.402
Active neoplasm	18.0% (17)	13.5% (44)	0.266
Liver cirrhosis	12.7% (12)	11.6% (38)	0.770
Natural valve disease	37.2% (35)	35.0% (114)	0.462
LOCATION OF ENDOCARDITIS ^a			
Aortic valve	41.5% (39)	36.5% (119)	0.379
Mitral valve	68.1% (64)	71.8% (234)	0.487
Right-sided valves	1.1% (1)	4.0% (13)	0.208
Mural endocarditis	0	2.5% (8)	0.208
ADQUISITION OF INFECTION			
Community	55.3% (52)	63.8% (208)	0.136
Nosocomial	36.2% (34)	26.4% (86)	0.064
Non-hospital healthcare-acquired	8.5% (8)	9.8% (32)	0.704
PRIMARY FOCUS OF INFECTION			
Vascular	37.2% (35)	27.9% (91)	0.082
Cutaneous	16.0% (15)	16.0% (52)	0.999
Other	7.4% (7)	11.0% (36)	0.439
Unknown	39.4% (37)	45.1% (147)	0.324
CLINICAL COURSE			
Intracardiac complication	38.3% (36)	37.7% (123)	0.893
<i>Perforation</i>	24.5% (23)	24.8% (81)	0.900
<i>Paravalvular abscess</i>	18.1% (17)	17.8% (58)	0.990
<i>Pseudoaneurysm</i>	2.1% (2)	5.8% (19)	0.147
<i>Cardiac fistula</i>	4.2% (4)	1.5% (1)	0.108
Acute cardiac failure	46.8% (44)	44.7% (146)	0.728
Acute renal failure	40.4% (38)	45.4% (148)	0.392
Embolization	29.8% (28)	32.8% (107)	0.370
CNS involvement	35.1% (33)	35.2% (115)	0.976
Persistent bacteremia	15.9% (15)	17.8% (58)	0.679
Septic shock	18.0% (17)	24.5% (80)	0.191
Osteoarticular involvement	11.7% (11)	17.2% (56)	0.201
MANAGEMENT AND OUTCOME			
Cloxacillin (vs cephazolin)	83.0% (78)	93.3% (304)	0.002
Surgical indication	40.4% (38)	50.9% (166)	0.079
Cardiac surgery performed	28.7% (27)	42.6% (139)	0.015
Surgery indicated not performed	11.7% (11)	8.3% (27)	0.187
In-hospital mortality	34.0% (32)	35.9% (117)	0.742
One-year mortality	45.7% (43)	38.0% (124)	0.179
Endocarditis relapse	1.1% (1)	1.8% (6)	0.511

^a The same patient could have multiple affected valves.

the patient's flowchart. Of the patients included, 94 patients (22.4%) received monotherapy with either ASP or cephazolin, and 326 (77.6%) received combination therapy. The most frequent companion antibiotic were aminoglycosides (126, 93 of them gentamycin), daptomycin (107), rifampicin (53) and vancomycin.³⁴ Median duration of antibiotic combination treatment was 14 days (IQR 10–20).

Comparison of patients with monotherapy and combination treatment

Table 1 compares characteristic of patients receiving monotherapy and combination treatment. There were no differences in age (median 67 years (IQR 53–76) vs 65 (IQR 51–75), $p = 0.321$), sex

Table 2

Univariate analysis comparing patients with beta-lactam monotherapy versus combination therapy in the propensity-score matched cohort.

Variable	Combination (n = 68)	Monotherapy (n = 68)	p
Age (years)	66 (45–75)	67 (53–77)	0.259
Sex (man)	70.6% (48)	70.6% (48)	1.000
COMORBIDITIES			
Charlson comorbidity index	4 (2–7)	4 (3–7)	0.627
Chronic pulmonary disease	20.5% (14)	7.3% (5)	0.026
Ischemic heart disease	27.9% (19)	20.6% (14)	0.397
Chronic cardiac failure	19.1% (13)	22.1% (15)	0.671
Diabetes mellitus	30.8% (21)	26.4% (18)	0.569
Previous stroke	14.7% (10)	7.4% (5)	0.171
Chronic renal failure	36.8% (25)	32.4% (22)	0.589
Active neoplasm	13.2% (9)	19.1% (13)	0.352
Liver cirrhosis	10.3% (7)	10.3% (7)	1.000
Natural valve disease	36.8% (25)	39.7% (27)	0.724
LOCATION OF ENDOCARDITIS ^a			
Aortic valve	39.7% (27)	42.6% (29)	0.727
Mitral valve	63.2% (43)	69.1% (47)	0.468
Right-sided valves	4.4% (3)	1.5% (1)	0.310
Mural endocarditis	2.9% (2)	0	0.382
ADQUISITION OF INFECTION			
Community	51.5% (35)	51.5% (35)	1.000
Nosocomial	36.8% (25)	36.8% (25)	1.000
Non-hospital healthcare-acquired	11.7% (8)	11.7% (8)	1.000
PRIMARY FOCUS OF INFECTION			
Vascular	38.2% (26)	41.2% (28)	0.726
Cutaneous	12.8% (8)	16.2% (11)	0.458
Other	13.2% (9)	5.9% (4)	0.244
Unknown	36.7% (25)	36.7% (25)	1.000
CLINICAL COURSE			
Intracardiac complication	32.4% (22)	32.4% (22)	1.000
<i>Perforation</i>	20.5% (14)	22.0% (15)	0.834
<i>Paravalvular abscess</i>	13.2% (9)	16.2% (11)	0.889
<i>Pseudoaneurysm</i>	4.4% (3)	2.9% (2)	0.901
<i>Cardiac fistula</i>	0	2.9% (2)	0.492
Acute cardiac failure	38.2% (26)	42.9% (29)	0.600
Acute renal failure	32.3% (22)	33.8% (23)	0.855
Embolization	26.5% (18)	27.9% (19)	0.586
CNS involvement	10.3% (7)	10.7% (7)	1.000
Persistent bacteremia	19.1% (13)	13.2% (9)	0.352
Septic shock	7.4% (5)	7.4% (5)	1.000
Osteoarticular involvement	5.9% (4)	5.9% (4)	1.000
MANAGEMENT AND OUTCOME			
Cloxacillin (vs cephazolin)	95.6% (65)	80.9% (55)	0.008
Surgical indication	54.4% (37)	44.1% (30)	0.230
Cardiac surgery performed	27.9% (19)	27.9% (19)	1.000
Surgery indicated not performed	27.9% (19)	17.6% (12)	0.152
In-hospital mortality	29.4% (20)	26.4% (18)	0.702
One-year mortality	29.4% (20)	38.2% (26)	0.277
IE-related mortality	29.4% (20)	27.9% (19)	0.850
Endocarditis relapse	0	1.5% (1)	1.000

Variables included in the PS: age > 75 years, sex, Charlson > 3, nosocomial acquisition, intracardiac complication, bone involvement, septic shock, cardiac surgery performed, CNS involvement. CNS: Central nervous system.

^a The same patient could have multiple affected valves.

(male 62.7% vs 57.3%, $p = 0.349$) or comorbidity (median Charlson index 4 points (IQR 3–7) vs 4 (IQR 2–7), $p = 0.658$). Patients with ASP/Cephazolin monotherapy had more frequent nosocomial-acquired IE (36.2% vs 26.4%, $p = 0.064$) and a vascular focus of infection (37.2% vs 27.9%, $p = 0.082$). There were no differences in clinical presentation between groups. Combination therapy group received cloxacillin more frequently as the backbone beta-lactam (93.3% vs 83.0%, $p = 0.002$), and cardiac surgery was performed more frequently (42.6% vs 28.7%, $p = 0.015$).

Table 3

Multivariate analysis for in-hospital mortality and one-year mortality in the propensity score-matched cohort. In-hospital mortality model was performed via a single-step logistic regression model. Odds ratio (OR) and 95% confidence interval are provided. One-year mortality model was performed via Cox regression model. Hazard ratio (HR) and 95% confidence interval are provided.

Variable	OR/HR	95% Confident interval	p
In-hospital mortality (Odds ratio)			
Combination therapy	0.85	0.33–2.18	0.732
Chronic pulmonary disease	0.53	0.13–2.19	0.380
Previous stroke	2.68	0.68–10.51	0.157
Surgery indicated not performed	7.65	2.74–21.36	<0.001
Cloxacillin (versus cephazolin)	1.27	0.22–7.44	0.789
One-year mortality (Hazard ratio)			
Combination therapy	0.68	0.35–1.31	0.248
Chronic pulmonary disease	0.48	0.16–1.41	0.182
Previous stroke	1.84	0.73–4.65	0.199
Surgery indicated not performed	3.95	1.97–7.91	<0.001
Cloxacillin (versus cephazolin)	0.87	0.30–2.56	0.803

Crude in-hospital mortality, one-year mortality, IE relapses and persistent bacteraemia were similar between the two groups (34.0% vs 35.9%, $p = 0.742$; 45.7% vs 38.0%, $p = 0.179$; 1.1% vs 1.8%, $p = 0.511$; and 15.9% vs 17.8%, $p = 0.679$, respectively).

Propensity score-matched cohort

Sixty-eight cases receiving combination therapy and 68 controls receiving monotherapy. Table 2 shows the comparison on both groups in the PSM cohort. All baseline variables were well-balanced between combination patients and monotherapy, except from chronic pulmonary disease (20.5% vs 7.3%, $p = 0.023$). Patients on combination received more frequently cloxacillin than those in monotherapy (95.6% vs 80.9%, $p = 0.008$). There were no other differences between groups.

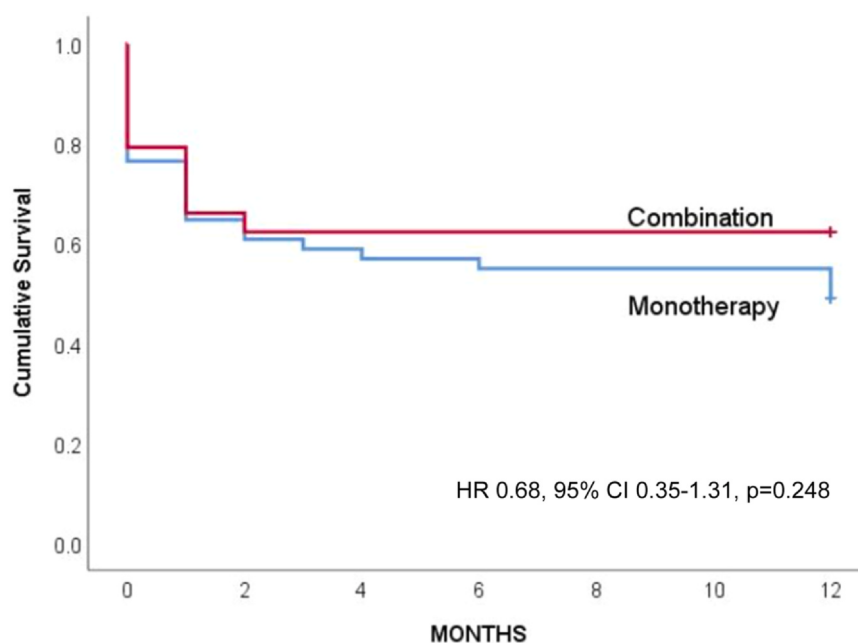


Fig. 2. Survival curve for one-year mortality in the propensity score-matched cohort. Variables included in the multivariate Cox regression model: combination therapy, chronic pulmonary disease, previous stroke, surgery indicated not performed and cloxacillin (versus cephazolin).

Primary and secondary efficacy endpoints

Table 3 shows the multivariate analysis for the primary endpoint in the PS cohort. After adjustment for covariables, there were no differences in in-hospital mortality between patients treated with monotherapy versus combination treatment in the PSM cohort (OR 0.85, 95% CI 0.33–2.18, $p = 0.732$). Additionally, there were no differences in one-year mortality between both groups (HR 0.68, 95% CI 0.35–1.31, $p = 0.248$, Fig. 2). As shown in Table 2, IE-related mortality was similar between both groups (29.4% vs 27.9%, $p = 0.850$), as well as endocarditis relapse (0% vs 1.5%, $p = 1.000$) and persistent bacteraemia (19.1% vs 13.2%, $p = 0.352$).

In the general cohort, multivariate analysis yielded similar results (supplementary table S1 and supplementary Fig. S1).

Additionally, in-hospital mortality was not different between ASP/cephazolin monotherapy (34.0%) versus combination with neither specific antibiotic (aminoglycoside 33.3%, $p = 0.912$; vancomycin 44.4%, $p = 0.271$; daptomycin 30.8%, $p = 0.628$; and rifampin 30.2%, $p = 0.632$).

Safety endpoints

Table 4 summarizes adverse reactions both in the general cohort and in the PSM cohort. Adverse reaction leading to withdrawal of antibiotic was numerically more frequent in the combination group versus monotherapy (3.4% vs 0%), although the difference did not reach statistical significance ($p = 0.077$). Presence of any drug-related adverse reaction was more frequent in combination group in both cohorts (15.0% vs 1.1%, $p < 0.001$). Specifically, drug-related acute renal failure was more frequent in combination group (6.1% vs 1.1%, $p = 0.046$).

Discussion

In our work, we aimed to assess the efficacy and safety of ASP or cephazolin-based combination therapy for native valve left-side IE caused by MSSA, in comparison to ASP or cephazolin monotherapy. Our main result is that combination therapy was not associated with

Table 4

Adverse reactions registered in patients with monotherapy and in those with combination therapy, both in the general cohort and in the propensity-matched cohort.

Total cohort			
Variable	Combination (n = 326)	Monotherapy (n = 94)	p
Antibiotic withdrawal because of adverse reaction	3.4% (12)	0	0.077
Any drug-related adverse reaction	15.0% (49)	1.1% (1)	< 0.001
Specific drug-related adverse reaction			
<u>Acute renal failure</u>	6.1% (20)	1.1% (1)	0.046
<u>Cutaneous rash/allergic reaction</u>	2.1% (7)	0	0.357
<u>Hematologic disorder</u>	2.1% (7)	0	0.357
<u>Ionic disorder</u>	1.5% (5)	0	0.591
<u>Hepatic enzyme elevation</u>	0.6% (2)	0	1.000
<u>Digestive intolerance</u>	0.6% (2)	0	1.000
<u>Fever</u>	0.6% (2)	0	1.000
<u>Other</u>	1.2% (4)	0	0.579
Propensity score-matched cohort			
Variable	Combination (n = 68)	Monotherapy (n = 68)	p
Antibiotic withdrawal because of adverse reaction	4.4% (3)	0	0.244
Any drug-related adverse reaction	14.7% (10)	1.5% (1)	0.009
Specific drug-related adverse reaction			
<u>Acute renal failure</u>	5.9% (4)	1.5% (1)	0.171
<u>Cutaneous rash/allergic reaction</u>	1.5% (1)	0	1.000
<u>Hematologic disorder</u>	3.0% (2)	0	0.496
<u>Ionic disorder</u>	0	0	-
<u>Hepatic enzyme elevation</u>	1.5% (1)	0	1.000
<u>Digestive intolerance</u>	0	0	-
<u>Fever</u>	3.0% (2)	0	0.496
<u>Other</u>	0	0	-

lower rates of in-hospital mortality, one-mortality, IE relapses or persistent bacteraemia. Moreover, it was associated with more frequent adverse reactions, especially acute renal injury. Therefore, when treated with ASP or cephazolin, we would not routinely recommend combination antibiotics for patients with native valve left-sided IE caused by MSSA.

Our data sums to the body of evidence suggesting lack of clinical efficacy of combination treatment for MSSA serious infections.¹¹ Our results are in line with previous clinical trials performed in MSSA bacteraemia that showed that different ASP/cephazolin based combinations were not associated with better outcomes, including aminoglycoside,^{39,40} daptomycin,^{9,41} vancomycin,⁹ and rifampin combination.⁴² Recently, a study evaluating combination with fosfomycin have also failed to show clinical improvement.⁴³ In general, these studies have only shown a slightly reduction bacteraemia duration, without affecting more important clinical outcomes.⁴⁴ Frequently, combination arms presented more frequent adverse reactions. The most notably exception is the use of rifampin for biofilm-associated infections (i.e., prosthetic arthritis or prosthetic endocarditis), which has showed to reduce relapses.^{11,42,45}

However, most of the mentioned evidence comes from MSSA bacteraemia or right-sided IE, without evaluating specifically left-sided IE. Left-sided IE could pose a special situation in which a very high-inoculum intravascular focus is present, and the search of a synergic combination could be relevant.¹³ In this regard, recent surveys have shown that many infectious diseases experts would choose a combination regimen when managing a patient with native valve left-sided IE.^{27,46,47} Of note, in our study, more than three quarters of the patients did receive combination therapy despite guidelines recommendations in favor of monotherapy. Accordingly, it is of vital importance to assess the clinical utility and safety of this approach.

To our knowledge, this is the first multicentre cohort study evaluating combination therapy specifically for MSSA IE. A previous uncentre retrospective study of IE conclude that gentamicin combination reduced time to defervescence but did not impact clinical outcomes.²⁸ Our data also shows a lack of clinical benefits in terms

of in-hospital mortality, one-year mortality, IE relapses and, even, in persistent bacteraemia (seven days). Moreover, patients receiving combination treatments had more frequent antibiotic-related adverse reactions, including more frequently acute renal injury related to treatment. These findings align with data derived from most of the aforementioned *Staphylococcus aureus* bacteraemia studies. The lack of clinical efficacy of combination synergic agents could be possibly related to the high and quick bactericidal effect of the backbone betalactam used in MSSA infections.^{29,48-50} Thus, our results should not be translated into situations where ASP or cephalosporins are not used as the backbone antibiotic (patients with betalactam anaphylaxis or MRSA infections), where the role of a bactericidal synergic combination could be useful. Therefore, we recommend that native-valve left-sided MSSA endocarditis should be generally managed with ASP/cephazolin monotherapy.

Notably, in our study almost half of the patients received cardiac surgery, and only 10% of patients had a surgical indication but did not receive cardiac surgery. This intervention is of vital importance in the management of IE caused by any microorganism, as shown in our results: surgery indicated and not performed had a strong association with in-hospital mortality. It has also been clearly shown in several previous studies that patients with surgery indication without receiving intervention had the poorest prognosis.^{2,3,35,36,51} It seems clear that pursuing the early performance of the cardiac surgery when indicated has more influence in the patients prognosis than the seek for synergic in-vitro antibiotic combinations. In this context, the frequent removal of the high-inoculum intravascular focus in our patients could have prevent us from finding efficacy in the combination treatment. However, after adjusting for cardiac surgery in the propensity score and for surgery indicated but not performed in the multivariate analysis, the use of combination resulted in no benefit.

Our work has certain limitations that must be mentioned. Most significantly, our study is based on an observational cohort, with the limitation inherit to this design, especially selection bias. However, we mitigated selection bias by means a robust statistical analysis including a propensity score matching approach. Secondly, as the

cohort was not specifically design to evaluate treatment effects, certain variables important to treatment selection and/or outcomes could not be gathered, i.e., positivity of first control blood cultures (first 48–72 h). Nevertheless, by including patients with combination as the initial treatment approach strategy we avoided comparing patients with monotherapy versus combination due to treatment failure. Thirdly, although our study is a national work including both referral and local centers, the external validity of our conclusions to other countries (especially, low-income countries) could be limited. Lastly, our main analysis included all combination treatments options. Further studies should evaluate other specific antibiotic, i.e., daptomycin-based combinations.

In conclusion, in our propensity score-matched prospective multicentre cohort, treatment of left-sided native IE caused by MSSA with combination antibiotics did not improve patients outcomes in comparison with monotherapy and was related to more frequent drug-related adverse events. Therefore, when treated with ASP or cephazolin, combination antibiotics should not be routinely recommended for this population. Further studies are needed evaluating the efficacy and safety of specific antibiotic combinations.

Ethical approval statement

Ethical approval was not required.

Role of funding source

No funding was received for this article.

Patients consent statement

The patient's written consent was obtained.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106352.

References

- Calderón-Parra J, Gutiérrez-Villanueva A, Yagüe-Diego I, Cobo M, Domínguez F, Forteza A, et al. Trends in epidemiology, surgical management, and prognosis of infective endocarditis during the XXI century in Spain: a population-based nationwide study. *J Infect Public Health* 2024 May 1;17(5):881–8.. [cited 2024 Apr 24]. <https://www.sciencedirect.com/science/article/pii/S1876034124000716>.
- Muñoz P, Kestler M, De Alarcón A, Miro JM, Bermejo J, Rodríguez-Abella H, et al. Current epidemiology and outcome of infective endocarditis: a multicenter, prospective, cohort study. *Medicine* 2015 Oct;94(43):e1816.
- Ambrosioni J, Hernández-Meneses M, Durante-Mangoni E, Tattevin P, Olaison L, Freiburger T, et al. Epidemiological changes and improvement in outcomes of infective endocarditis in Europe in the twenty-first century: an International Collaboration on Endocarditis (ICE) Prospective Cohort Study (2000–2012). *Infect Dis Ther* 2023 Apr;12(4):1083–101.
- Gudiol F, Aguado JM, Almirante B, Bouza E, Cercenado E, Domínguez MÁ, et al. Diagnosis and treatment of bacteremia and endocarditis due to *Staphylococcus aureus*. A clinical guideline from the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). *Enferm Infecc Microbiol Clin* 2015 Nov;33(9):625.e1–625.e23.
- Mensa José, Soriano Alex, Llinares Pedro, Barberán José, Montejo Miguel, Salavert Miguel, et al. Guía de tratamiento antimicrobiano de la infección por *Staphylococcus aureus*. *Rev Esp Quimioter* 2013;26(1):1–84.
- Castañeda X, García-De-la-Mària C, Gasch O, Pericàs JM, Soy D, Cañas-Pacheco MA, et al. Effectiveness of vancomycin plus cloxacillin compared with vancomycin, cloxacillin and daptomycin single therapies in the treatment of methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* in a rabbit model of experimental endocarditis. *J Antimicrob Chemother* 2021 May 12;76(6):1539–46.
- García-de-la-Mària C, Gasch O, García-González J, Soy D, Shaw E, Ambrosioni J, et al. The combination of daptomycin and fosfomycin has synergistic, potent, and rapid bactericidal activity against methicillin-resistant *Staphylococcus aureus* in a rabbit model of experimental endocarditis. *Antimicrob Agents Chemother* 2018 Jun;62(6):e02633–17.
- del Río A, García-de-la-Mària C, Entenza JM, Gasch O, Armero Y, Soy D, et al. Fosfomycin plus β -Lactams as synergistic bactericidal combinations for experimental endocarditis due to methicillin-resistant and glycopeptide-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2016 Jan;60(1):478–86.
- Tong SYC, Lye DC, Yahav D, Sud A, Robinson JO, Nelson J, et al. 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. *JAMA* 2020 Feb 11;323(6):527–37.
- Pujol M, Miró JM, Shaw E, Aguado JM, San-Juan R, Puig-Asensio M, et al. Daptomycin plus fosfomycin versus daptomycin alone for methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis: a randomized clinical trial. *Clin Infect Dis* 2021 May 4;72(9):1517–25.
- Grillo S, Puig-Asensio M, Schweizer ML, Cuervo G, Oriol I, Pujol M, et al. The effectiveness of combination therapy for treating methicillin-susceptible *Staphylococcus aureus* bacteremia: a systematic literature review and a meta-analysis. *Microorganisms* 2022 Apr 20;10(5):848.
- García de la Mària C, Cañas MA, Fernández-Pittol M, Dahl A, García-González J, Hernández-Meneses M, et al. Emerging issues on *Staphylococcus aureus* endocarditis and the role in therapy of daptomycin plus fosfomycin. *Expert Rev Anti Infect Ther* 2023 Mar;21(3):281–93.
- Nannini EC, Singh KV, Arias CA, Murray BE. In vivo effects of cefazolin, daptomycin, and nafcillin in experimental endocarditis with a methicillin-susceptible *Staphylococcus aureus* strain showing an inoculum effect against cefazolin. *Antimicrob Agents Chemother* 2013 Sep;57(9):4276–81.
- Schwartz FA, Nielsen L, Struve Andersen J, Bock M, Christophersen L, Sunnerhagen T, et al. Dynamics of a *Staphylococcus aureus* infective endocarditis simulation model. *APMIS* 2022 Aug;130(8):515–23.
- Wang A, Gaca JG, Chu VH. Management considerations in infective endocarditis: a review. *JAMA* 2018 Jul 3;320(1):72–83.
- Lemonovich TL, Haynes K, Lautenbach E, Amorosa VK. Combination therapy with an aminoglycoside for *Staphylococcus aureus* endocarditis and/or persistent bacteremia is associated with a decreased rate of recurrent bacteremia: a cohort study. *Infection* 2011 Dec;39(6):549–54.
- Mohyuddin GR, Prasad V. Detecting selection bias in observational studies—when interventions work too fast. *JAMA Intern Med* 2023 Sep 1;183(9):897–8.
- Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015 Dec 10;34(28):3661–79.. [cited 2021 Dec 21]. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4626409/>.
- Benedetto U, Head SJ, Angelini GD, Blackstone EH. Statistical primer: propensity score matching and its alternatives. *Eur J Cardiothorac Surg* 2018 Jun 1;53(6):1112–7.. [cited 2022 Feb 8]. <https://academic.oup.com/ejcts/article/53/6/1112/4978231>.
- Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al. 2023 ESC Guidelines for the management of endocarditis. *Eur Heart J* 2023 Oct 14;44(39):3948–4042.
- Yang F, Zhang B, Yu J, Shao L, Zhou P, Zhu L, et al. Epidemiology and the prognosis of healthcare-associated infective endocarditis in China: the significance of non-nosocomial acquisition. *Emerg Microbes Infect* 2015 Jul;4(7):e38.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987 Jan;40(5):373–83.. [cited 2022 Mar 5]. <https://linkinghub.elsevier.com/retrieve/pii/0021968187901718>.
- Diego-Yagüe I, Ramos-Martínez A, Muñoz P, Martínez-Sellés M, Machado M, de Alarcón A, et al. Clinical features and prognosis of prosthetic valve endocarditis due to *Staphylococcus aureus*. *Eur J Clin Microbiol Infect Dis* 2024 Oct;43(10):1989–2000.
- Armiñanzas C, Fariñas-Alvarez C, Zarauza J, Muñoz P, González Ramallo V, Martínez Sellés M, et al. Role of age and comorbidities in mortality of patients with infective endocarditis. *Eur J Intern Med* 2019 Jun;64:63–71.
- Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med* 2009 Mar 9;169(5):463–73.
- Varela Barca L, Vidal-Bonnet L, Fariñas MC, Muñoz P, Valerio Minero M, de Alarcón A, et al. Analysis of sex differences in the clinical presentation, management and prognosis of infective endocarditis in Spain. *Heart* 2021 Nov;107(21):1717–24.
- Alonso-Menchén D, Bouza E, Valerio M, de Alarcón A, Gutiérrez-Carretero E, Miró JM, et al. Non-nosocomial healthcare-associated infective endocarditis: a distinct entity? Data from the GAMES Series (2008–2021). *Open Forum Infect Dis* 2023 Aug 9;10(8):ofad393.. [cited 2024 Oct 10]. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10411035/>.

28. Giannitsioti E, Skiadas I, Antoniadou A, Tsiodras S, Kanavos K, Triantafyllidi H, et al. Nosocomial vs. community-acquired infective endocarditis in Greece: changing epidemiological profile and mortality risk. *Clin Microbiol Infect Dis* 2007 Aug;13(8):763–9.
29. Ortega-Loubon C, Muñoz-Moreno MF, Andrés-García I, Álvarez FJ, Gómez-Sánchez E, Bustamante-Munguira J, et al. Nosocomial vs. community-acquired infective endocarditis in Spain: location, trends, clinical presentation, etiology, and survival in the 21st Century. *J Clin Med* 2019 Oct 22;8(10):E1755.
30. Lieber SB, Tishler O, Nasrullah K, Fowler ML, Shmerling RH, Paz Z. Clinical features of patients with septic arthritis and echocardiographic findings of infective endocarditis. *Infection* 2019 Oct;47(5):771–9.
31. Lamas C, Bóia M, Eykyn SJ. Osteoarticular infections complicating infective endocarditis: a study of 30 cases between 1969 and 2002 in a tertiary referral centre. *Scand J Infect Dis* 2006 Jan 1;38(6–7):433–40. <https://doi.org/10.1080/003655405000546308>
32. Herrera-Hidalgo L, Muñoz P, Álvarez-Uría, Alonso-Menchén D A, Luque-Marquez R, Gutiérrez-Carretero E, et al. Contemporary use of cefazolin for MSSA infective endocarditis: analysis of a national prospective cohort. *Int J Infect Dis* 2023 Dec 1;137:134–43.. [cited 2024 Oct 10]. ([https://www.ijidonline.com/article/S1201-9712\(23\)00756-7/fulltext](https://www.ijidonline.com/article/S1201-9712(23)00756-7/fulltext)).
33. Park LP, Chu VH, Peterson G, Skoutelis A, Lejko-Zupa T, Bouza E, et al. Validated risk score for predicting 6-month mortality in infective endocarditis. *J Am Heart Assoc* 2016 Apr 18;5(4):e003016.
34. Miro JM, Anguera I, Cabell CH, Chen AY, Stafford JA, Corey GR, et al. Staphylococcus aureus native valve infective endocarditis: report of 566 episodes from the International Collaboration on Endocarditis Merged Database. *Clin Infect Dis* 2005 Aug 15;41(4):507–14.
35. Ramos-Martínez A, Calderón-Parra J, Miró JM, Muñoz P, Rodríguez-Abella H, Valerio M, et al. Effect of the type of surgical indication on mortality in patients with infective endocarditis who are rejected for surgical intervention. *Int J Cardiol* 2019 May 1;282:24–30.
36. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med* 2012 Jun 28;366(26):2466–73.
37. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med* 2010 Sep 10;29(20):2137–48.. [cited 2024 Oct 8]. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3068290/>).
38. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J* 2009 Feb;51(1):171–84.
39. Ribera E, Gómez-Jiménez J, Cortes E, del Valle O, Planes A, Gonzalez-Alujas T, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided Staphylococcus aureus endocarditis. A randomized, controlled trial. *Ann Intern Med* 1996 Dec 15;125(12):969–74.
40. Ramos-Martínez A, Muñoz Serrano A, de Alarcón González A, Muñoz P, Fernández-Cruz A, Valerio M, et al. Gentamicin may have no effect on mortality of staphylococcal prosthetic valve endocarditis. *J Infect Chemother* 2018 Jul;24(7):555–62.
41. Grillo S, Cuervo G, Carratalà J, Grau I, Pallarès N, Tebé C, et al. Impact of β -lactam and daptomycin combination therapy on clinical outcomes in methicillin-susceptible Staphylococcus aureus bacteremia: a propensity score-matched analysis. *Clin Infect Dis* 2019 Oct 15;69(9):1480–8.
42. Dotel R, Gl G, Sn H, Js D, Mvn O. Effectiveness of adjunctive rifampicin for treatment of Staphylococcus aureus bacteraemia: a systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2023 Mar 10;78(10). [cited 2024 Oct 15]. (<https://pubmed.ncbi.nlm.nih.gov/37583062/>).
43. Grillo S, Pujol M, Miró JM, López-Contreras J, Euba G, Gasch O, et al. Cloxacillin plus fosfomycin versus cloxacillin alone for methicillin-susceptible Staphylococcus aureus bacteremia: a randomized trial. *Nat Med* 2023 Oct;29(10):2518–25.
44. Cosgrove SE, Vigliani GA, Fowler VG, Abrutyn E, Corey GR, Levine DP, et al. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis* 2009 Mar 15;48(6):713–21.
45. Ri. Available from: eg S, Joost I, Weiß V, Peyerl-Hoffmann G, Schneider C, Hellmich M, et al. Combination antimicrobial therapy in patients with Staphylococcus aureus bacteraemia-a post hoc analysis in 964 prospectively evaluated patients. *Clin Microbiol Infect Dis* 2017 Jun;23(6):406.e1–8.
46. Buis DTP, Prins JM, Betica-Radic L, de Boer MGJ, Ekkelenkamp M, Kofteridis D, et al. Current clinical practice in antibiotic treatment of Staphylococcus aureus bacteraemia: results from a survey in five European countries. *J Antimicrob Chemother* 2022 Sep 30;77(10):2827–34.
47. Tong SYC, Campbell A, Bowen AC, Davis JS. A Survey of Infectious Diseases and Microbiology Clinicians in Australia and New Zealand about the management of Staphylococcus aureus bacteremia. *Clin Infect Dis* 2019 Oct 30;69(10):1835–6.. [cited 2022 Aug 10]. (<https://academic.oup.com/cid/article/69/10/1835/5429542>).
48. Hughes DW, Frei CR, Maxwell PR, Green K, Patterson JE, Crawford GE, et al. Continuous versus intermittent infusion of oxacillin for treatment of infective endocarditis caused by methicillin-susceptible Staphylococcus aureus. *Antimicrob Agents Chemother* 2009 May;53(5):2014–9.
49. Pasticci MB, Moretti A, Stagni G, Ravasio V, Soavi L, Raglio A, et al. Bactericidal activity of oxacillin and glycopeptides against Staphylococcus aureus in patients with endocarditis: looking for a relationship between tolerance and outcome. *Ann Clin Microbiol Antimicrob* 2011 Jun 9;10:26.
50. Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, et al. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. *Clin Microbiol Infect Dis* 2018 Feb;24(2):125–32.
51. Liang F, Song B, Liu R, Yang L, Tang H, Li Y. Optimal timing for early surgery in infective endocarditis: a meta-analysis. *Inter Cardiovasc Thorac Surg* 2016 Mar;22(3):336–45.