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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

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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

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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.

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 upmost 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 guidelines[20] 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 cardiosurgeon. 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.

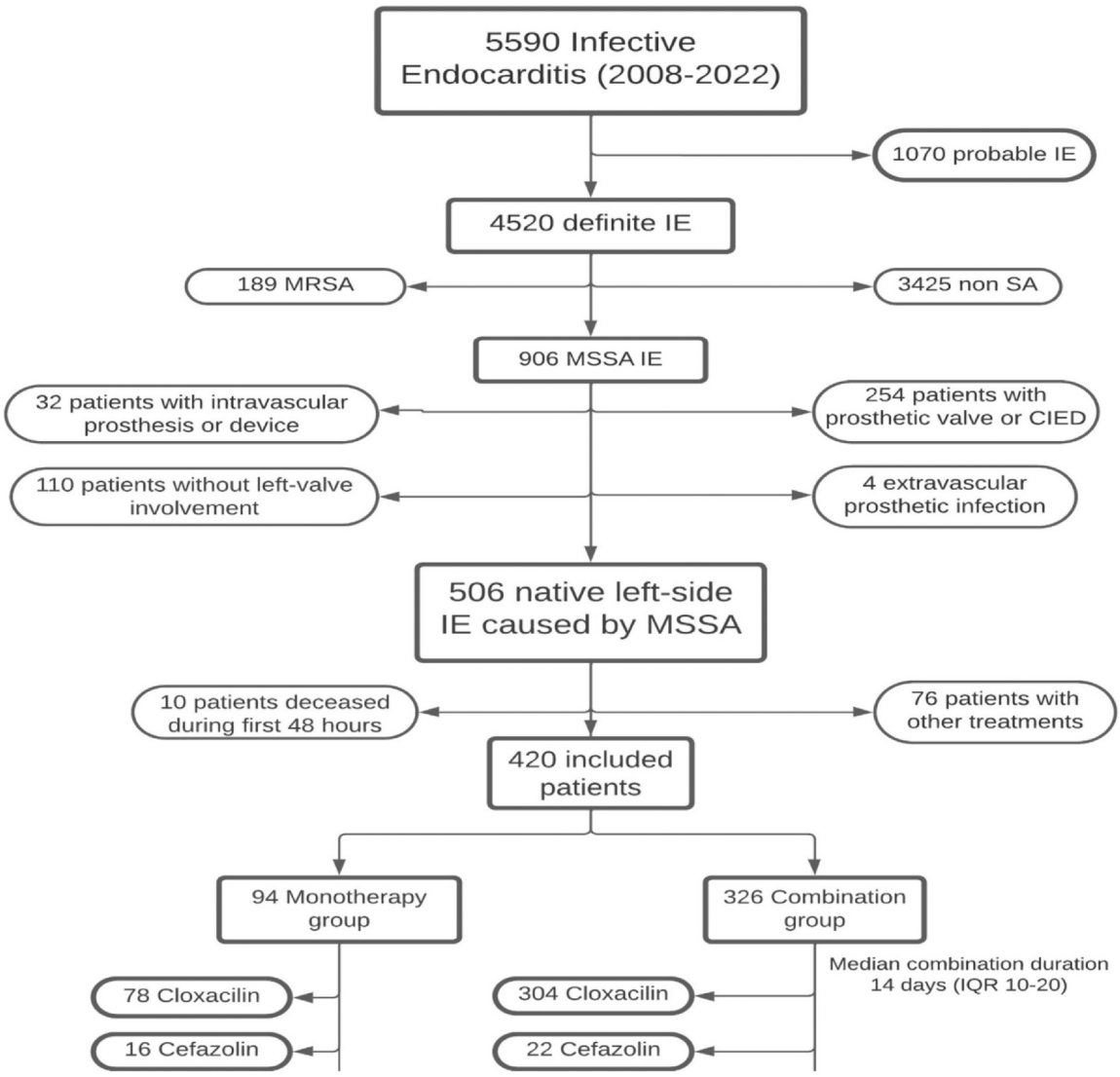

Fig. 1. Patient's flowchart. IE: infective endocarditis. SA: *Staphylococcus aureus*. MRSA: Methicillin-resistant *Staphylococcus aureus*. MSSA: Methicillin-susceptible *Staphylococcus aureus*. CIED: Cardiac implantable electronic device. IQR: Interquartile range.

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
Perforation	24.5% (23)	24.8% (81)	0.900
Paravalvular abscess	18.1% (17)	17.8% (58)	0.990
Pseudoaneurysm	2.1% (2)	5.8% (19)	0.147
Cardiac fistula	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.

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
Perforation	20.5% (14)	22.0% (15)	0.834
Paravalvular abscess	13.2% (9)	16.2% (11)	0.889
Pseudoaneurysm	4.4% (3)	2.9% (2)	0.901
Cardiac fistula	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 involment, septic shock, cardiac surgery performed, CNS involvment. CNS: Central nervous system.
[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 (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, EI 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.

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 statistically 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

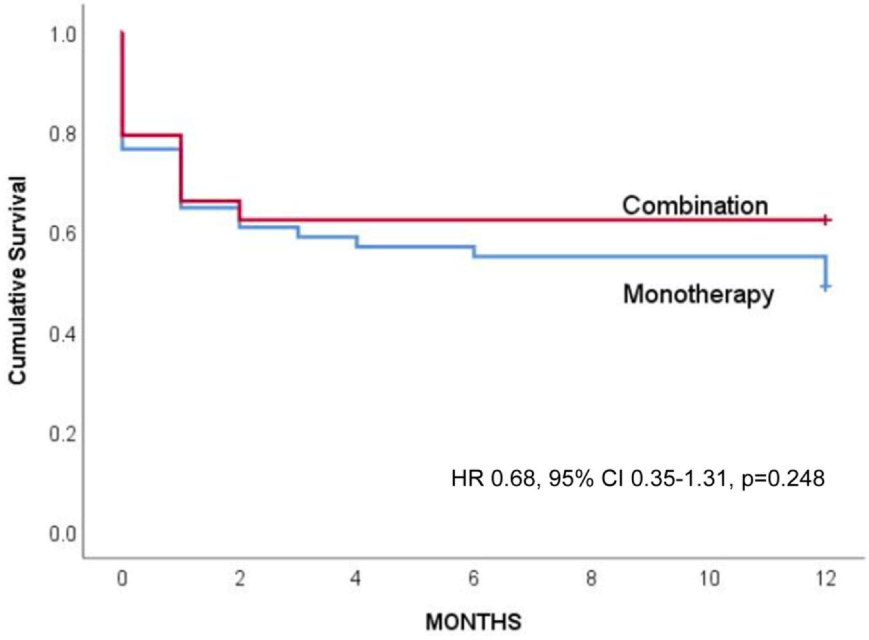

Fig. 2. Survival curve for one-year mortality in the propensity score-matched cohort. Variables included in the multivariate Cox regression model: combination therapy, chronic pulmonary disease, previous stroke, surgery indicated not performed and cloxacillin (versus cephazolin).

Table 4
Adverse reactions registered in patients with monoteraphy 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	0077
Any drug-related adverse reaction	15.0% (49)	1,1% (1)	< 0001
Specific drug-related adverse reaction			
Acute renal failure	6.1% (20)	1.1% (1)	0.046
Cutaneous rash/allergic reaction	2.1% (7)	0	0.357
Hematologic disorder	2.1% (7)	0	0.357
Ionic disorder	1.5% (5)	0	0.591
Hepatic enzyme elevation	0.6% (2)	0	1.000
Digestive intolerance	0.6% (2)	0	1.000
Fever	0.6% (2)	0	1.000
Other	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)	0009
Specific drug-related adverse reaction			
Acute renal failure	5.9% (4)	1.5% (1)	0.171
Cutaneous rash/allergic reaction	1.5% (1)	0	1.000
Hematologic disorder	3.0% (2)	0	0.496
Ionic disorder	0	0	-
Hepatic enzyme elevation	1.5% (1)	0	1.000
Digestive intolerance	0	0	-
Fever	3.0% (2)	0	0.496
Other	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 than 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 aformentioned *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 cephazolin 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.

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