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Contemporary use of cefazolin for MSSA infective endocarditis: analysis of a national prospective cohort

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ABSTRACT

Objectives: This study aimed to assess the real use of cefazolin for methicillin-susceptible *Staphylococcus aureus* (MSSA) infective endocarditis (IE) in the Spanish National Endocarditis Database (GAMES) and to compare it with antistaphylococcal penicillin (ASP).

Methods: Prospective cohort study with retrospective analysis of a cohort of MSSA IE treated with cloxacillin and/or cefazolin. Outcomes assessed were relapse; intra-hospital, overall, and endocarditis-related mortality; and adverse events. Risk of renal toxicity with each treatment was evaluated separately.

Results: We included 631 IE episodes caused by MSSA treated with cloxacillin and/or cefazolin. Antibiotic treatment was cloxacillin, cefazolin, or both in 537 (85%), 57 (9%), and 37 (6%) episodes, respectively. Patients treated with cefazolin had significantly higher rates of comorbidities (median Charlson Index 7, $P < 0.01$) and previous renal failure (57.9%, $P < 0.01$). Patients treated with cloxacillin presented higher rates of septic shock (25%, $P = 0.033$) and new-onset or worsening renal failure (47.3%, $P = 0.024$) with significantly higher rates of in-hospital mortality (38.5%, $P = 0.017$). One-year IE-related mortality and

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rate of relapses were similar between treatment groups. None of the treatments were identified as risk or protective factors.

Conclusion: Our results suggest that cefazolin is a valuable option for the treatment of MSSA IE, without differences in 1-year mortality or relapses compared with cloxacillin, and might be considered equally effective.

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Introduction

Infective endocarditis (IE) is a life-threatening infectious disease characterized by its high morbimortality [1,2]. Today, *Staphylococcus aureus* is the most common cause of IE in developed countries [3,4] with a growing incidence in the last decades due to its relationship with health-care contact [1,3]. Particularly, *S. aureus* IE has been associated with immunosuppression, prosthetic cardiac devices, hemodialysis, and other invasive procedures [3,4], as well as an aggressive presentation and poor prognosis [5].

Antistaphylococcal penicillin (ASP) is the recommended treatment for methicillin-susceptible *S. aureus* (MSSA) infections [1,2]. However, these drugs require multiple administrations per day and are a common cause of adverse events such as nephrotoxicity, hepatotoxicity, phlebitis, hypersensitivity reactions, and treatment discontinuation due to these side effects [6]. Hence, cefazolin has been proposed as an alternative treatment for MSSA infections and, when compared with ASPs, similar efficacy and fewer adverse events were reported [6–10].

In infections with high bacterial loads, such as IE, the use of cefazolin remains controversial because prior anecdotic reports [11–13] of treatment failures with cefazolin attributed to an inoculum effect (CzIE). This reduced efficacy of the drug in the presence of high bacterial burdens is thought to be due to the increased production of a certain type of staphylococcal β -lactamase (cephalosporinase) that efficiently hydrolyzes cefazolin, but without activity against ASPs. The clinical impact of the inoculum effect is uncertain and only a few studies supported that it could influence clinical outcomes in real practice [14–17]. Despite this, cefazolin is recommended only as an alternative therapy for MSSA IE, especially for penicillin-allergic patients with nonanaphylactic reactions [1,2]. However, in recent years, there has been growing evidence of cefazolin as a first-line treatment for MSSA IE with similar efficacy results as ASPs and a better safety profile [18–21].

The present study was conducted to corroborate the similar efficiency of ASPs and cefazolin for the treatment of MSSA IE in a long-term cohort. This study aims to assess the real use of cefazolin in MSSA IE in the Spanish National Endocarditis Database (GAMES) which includes more than 5000 prospectively collected episodes and compares with those treated with ASPs.

Materials and methods

Study design and data collection

Prospective observational cohort study with retrospective analysis of the Spanish Collaboration on Endocarditis—Grupo de Apoyo al Manejo de la Endocarditis infecciosa en España (GAMES) cohort. This cohort included IE consecutive cases from 39 Spanish hospitals between 2008 and 2020. Prospective collection of data variables through a specific central registration depository, multidisciplinary teams, and definitions are described elsewhere [22].

Population

All consecutive patients with definite or possible IE, according to the modified Duke criteria [22], were prospectively included in the GAMES registry. Patients with culture-confirmed MSSA IE treated with cloxacillin (available ASP in Spain) or cefazolin was selected. Switching between both treatments was permitted and recorded. Dosing regimens were cloxacillin 2 grams each 4 hours and cefazolin 2 grams each 8 hours, except for renal impairment adjustments. Patients with infections associated with pacemakers (PM) or intracardiac implantable defibrillators (ICD) were included. Patients were classified into three groups according to the predominant antibiotic treatment: i) cefazolin group (cefazolin treatment covered >75% of the treatment length); ii) cloxacillin group (cloxacillin treatment covered >75% of the treatment length); iii) mixed group (treatment which included cefazolin and cloxacillin sequentially, but less than <75% of the treatment length were covered with any of them). Patients treated with other antibiotic regimens were excluded.

End points

Primary outcomes assessed were intra-hospital mortality defined as death from any cause during hospitalization and up to 1 month after discharge. Secondary outcomes assessed were: i) relapse, defined as positive blood cultures caused by the same microorganism as the initial episode during the first 6 months of follow-up; ii) overall mortality during 1-year follow-up, defined as death from any cause; iii) endocarditis-related mortality during 1-year follow-up, defined as death derived from the infection or its sequelae; and iv) adverse events related with antimicrobial treatment. To evaluate the clinical factors associated with worse prognosis a composite end point was defined as relapse or death from any cause during follow-up. All cases were followed for 1 year.

Definitions

Persistent bacteremia was defined as positive blood cultures after 7 days of effective antibiotic therapy; acute renal failure was defined as a worsening equal or higher than 25% of serum creatinine or glomerular clearance occurring within a lapse of 72 hours; site of acquisition of IE was defined following International Collaboration on Endocarditis recommendation [4,22]; Charlson Comorbidity Index was employed as a method of categorizing comorbidities of the patients [22].

Renal toxicity

To evaluate the association of renal toxicity with antibiotic treatment, patients were grouped into two cohorts (cloxacillin-5 days vs cefazolin-5days) regarding the initial treatment (at least the first 5 days of treatment) [23]. Patients who initially received less than 5 days of treatment with the same antibiotic were excluded. Among these groups, we compared known risk factors for

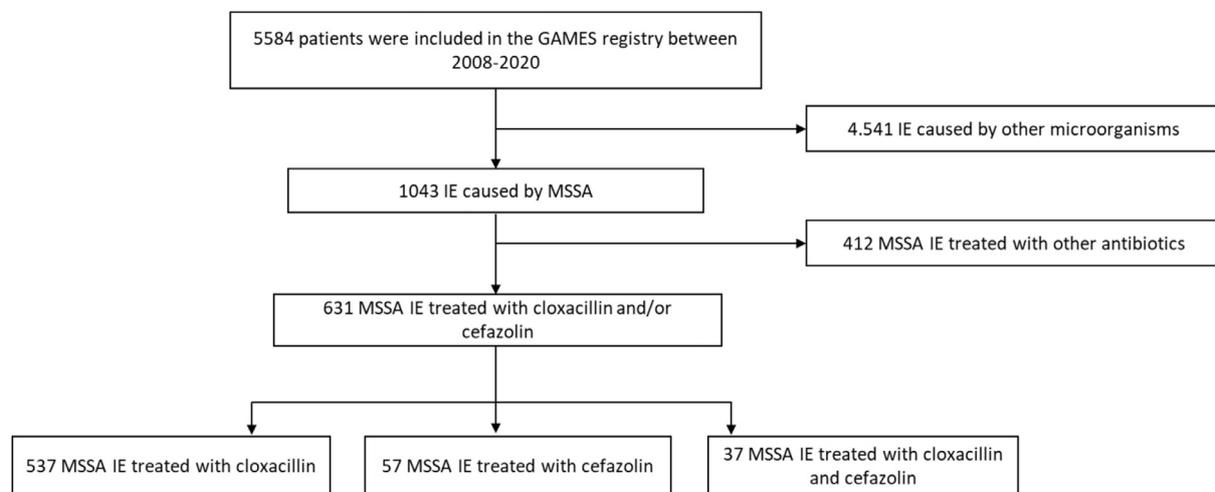


Figure 1. Patient flowchart.

GAMES, Spanish National Endocarditis Database; IE, infective endocarditis; MSSA, methicillin-susceptible *Staphylococcus aureus*.

renal failure (previous renal failure, age > 70 years, septic shock, and heart failure) and the frequency of new renal failure or worsening of renal function.

Statistical analysis

Categorical variables were summarized as percentages. Continuous variables were summarized as median and interquartile range (IQR). Quantitative variables were compared using Mann-Whitney test and categorical variables were compared using the chi-square test or Fisher exact *t* test. Stepwise logistic regression analyses were performed including variables present at admission with a *P*-value <0.1 in the univariate analysis, but also taking into account the clinical significance of each variable and the number of patients that reported the studied event. A two-sided *P* <0.05 was considered statistically significant. The statistical analysis was performed using SPSS version 28.0 (SPSS Inc, Chicago, IL, USA) and R 3.6.1 software (<https://www.r-project.org/>).

Ethics

This study complies with the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of the participating centers. Written informed consent was obtained from all patients.

Results

During the study period, 5584 episodes were included in the GAMES registry. Among them, 631 IE episodes were caused by MSSA treated with cloxacillin and/or cefazolin. The principal antibiotic treatment was cloxacillin, cefazolin, or both in 537 (85%), 57 (9%), and 37 (6%) episodes, respectively (Figure 1). Patients and IE characteristics are shown in Table 1. The group treated with cefazolin had significantly higher rates of comorbidities, with a significantly higher median Charlson score than those treated with cloxacillin or both treatments (median Charlson score 7 [4–9], 5 [3–7] and 5 [3–7], respectively). Diabetes mellitus, peripheral arterial disease, previous renal failure and chronic hemodialysis were all significantly more frequent in this group, with the tricuspid valve significantly more frequently involved and higher rate of multivalve affection (although, this latter characteristic did not reach statistical significance). Conversely, the mitral valve was more commonly affected in patients treated with cloxacillin

and in the mixed group. The proportion of healthcare-associated IE was significantly higher in those patients treated with cefazolin (mainly patients with chronic HD), whereas community-acquired IE was significantly more frequent in both cloxacillin and mixed groups.

Clinical manifestations and outcomes

Patients treated with cloxacillin had significantly higher rates of septic shock and new-onset or worsening renal failure (Table 2). Cardiac surgery was significantly less indicated in those patients treated with cefazolin and, remarkably, patients in the mixed group underwent cardiac surgery significantly less frequently, despite the indication. With regard to patients with infections associated with PM/ICD, removal of the device was less frequent in patients treated with cefazolin (extraction rate was 80%, 44.4%, and 83.3% in the cloxacillin, cefazolin, and mixed group, respectively, *P* = 0.021). Length of antibiotic treatment and length of stay were similar in all treatment groups. In the mixed group, the median length of treatment with cefazolin and cloxacillin was 15.5 (10–21) and 16 (11–24.5) days, respectively. In-hospital and 1-year mortality was significantly higher in those patients treated with cloxacillin. The difference in 1-year IE-related mortality between patients treated with cloxacillin and cefazolin did not reach statistical significance, despite a trend toward higher mortality in the cloxacillin group. Rate of relapses was similar in all groups.

Regarding treatment toxicity, patients treated with both antibiotics presented significantly higher rates of side effects, all related to cloxacillin treatment. Only one patient suffered nephrotoxicity attributed to cefazolin treatment. Side effects associated with cloxacillin treatment (in cloxacillin and mixed group) were major hypokalemia (*n* = 5), hematologic toxicity (*n* = 4), phlebitis (*n* = 3), vasculitis (*n* = 2), and others (*n* = 6).

Risk factor for mortality or relapse

Charlson score, new-onset or worsening heart failure, new-onset or worsening renal failure, septic shock, and cardiac surgery indication were associated with higher risk of 1-year mortality or relapse in the multivariate model. Prosthetic valve IE and central nervous system emboli showed a trend toward worse prognosis; however, did not reach statistical significance (Table 3). None of the antibiotic treatments were identified as risk or protective factors.

Table 1
Baseline and infection characteristics.

Baseline characteristics (%)	Treatment group			P
	Cloxacillin (537)	Cefazolin (57)	Mixed (37)	
Age (median [IQR])	67 (53–75)	67 (47–81)	67 (53–77)	0,717
Male gender	344 (64,1)	34 (59,6)	27 (73,0)	0,415
Charlson index (median [IQR])	5 (3–7)	7 (4–9)	5 (3–7)	0,001 ^{a,c}
Comorbidities				
Chronic lung disease	80 (14,8)	9 (15,7)	7 (18,9)	0,509
Coronary disease	140 (26,0)	12 (21,0)	11 (29,7)	0,606
Congestive heart failure	168 (31,2)	22 (38,5)	11 (29,7)	0,379
Diabetes	159 (29,6)	26 (45,6)	13 (35,1)	0,013 ^a
VIH	20 (3,7)	4 (7,0)	0	0,230
Injection drug user	31 (5,7)	6 (10,5)	2 (5,4)	0,385
Peripheral arterial disease	57 (10,6)	11 (19,2)	9 (24,3)	0,011 ^{a,b}
Cerebrovascular disease	54 (10,0)	5 (8,8)	6 (16,2)	0,273
Neoplasia	67 (12,4)	8 (14,0)	4 (10,8)	0,898
Previous renal failure	157 (29,2)	33 (57,9)	13 (35,1)	<0,01 ^{a,c}
Chronic hemodialysis	29 (5,4)	21 (36,8)	6 (16,2)	<0,01 ^{a,b,c}
Chronic liver disease	60 (11,1)	9 (15,7)	7 (18,9)	0,234
Congenital heart disease	27 (5,0)	2 (3,5)	0	0,613
Natural valve disease	200 (37,2)	18 (31,6)	16 (43,2)	0,477
Infection characteristics (%)				
EI location				
Aortic	185 (34,5)	19 (33,3)	14 (37,8)	0,897
Mitral	287 (53,4)	22 (38,6)	17 (45,9)	0,033 ^a
Tricuspid	51 (9,5)	11 (19,3)	2 (5,4)	0,021 ^a
Pulmonary	14 (2,6)	2 (3,5)	0	0,551
ICD/PM	60 (11,2)	9 (15,8)	6 (16,2)	0,416
Others ^d	4 (0,7)	4 (7,0)	2 (5,4)	<0,01 ^a
Multiple locations	66 (12,3)	12 (21,1)	4 (10,8)	0,160
Unknown	7 (1,3)	1 (1,8)	0	0,745
Type of endocarditis				
Native IE	389 (72,4)	41 (71,9)	25 (67,6)	0,815
Prosthetic IE	105 (19,6)	6 (10,5)	6 (16,2)	0,232
Acquisition of the infection				
Community-acquired	326 (60,7)	18 (31,6)	19 (51,4)	<0,01 ^a
Nosocomial acquisition	168 (31,3)	19 (33,3)	12 (32,4)	0,944
Healthcare-associated infection	43 (8,0)	20 (35,1)	6 (16,2)	<0,01 ^{a,c}
Presence of vegetation	409 (76,2)	45 (78,9)	31 (83,8)	0,526

IE, infective endocarditis; ICD/PM, intracardiac implantable defibrillators/pacemakers.

^a Differences between cloxacillin and cefazolin group.

^b Differences between cloxacillin and mixed group.

^c Differences between cefazolin and mixed group.

^d IE location classified as “others: in the cloxacillin group were located at left ventricular outflow tract, tendinous chords, right auricle, and interventricular septum; in the cefazolin group were located at tendinous chords, right auricle, and two permanent catheters; and in the mixed group were located at right auricle and superior cava vein.

Renal toxicity

Among patients included in the study, 611 were included in the nephrotoxicity subanalysis; 555 and 56 patients were treated with cloxacillin or cefazolin, respectively, during at least the first 5 days (Table 4). Previous renal failure was significantly more frequent in patients treated initially with cefazolin, and consequently, initial creatinine was higher in this group of patients. In contrast, significantly higher rates of new-onset renal failure were presented in patients initially treated with cloxacillin. In patients initially treated with cefazolin the new-onset renal failure happened mainly within the first week of treatment (4 (1–13) days), while in those patients initially treated with cloxacillin that was generally diagnosed after 2 weeks of treatment (15 (4–27) days). Septic shock was more frequent in the cloxacillin-5 days group; however, it did not reach statistical significance.

Profile and evolution of cefazolin treatment for MSSA endocarditis

MSSA IE treatment with cefazolin has evolved over the years. During the first period of the GAMES registry (2008–2013), cefazolin was anecdotal and its principal use was as continuation treatment after cloxacillin initial therapy. During the second period (2014–2020), cefazolin selection as initial or continuation treat-

ment significantly increased (Supplementary material F1). Total and MSSA IE cases in 2020 were biased by underdiagnosed and under-notification due to SARS-COV-2 pandemic. Most patients included in the cloxacillin group and mixed group received cefazolin as a continuation treatment. In contrast, in the majority of patients included in the cefazolin group, this drug remained the only antimicrobial until the end of the treatment (Supplementary material F2).

Discussion

Cloxacillin is the preferred treatment for MSSA EI in international guidelines [1,2]. However, its toxic effects and frequency of administration have prompted the seeking of alternative treatments that circumvent these limitations while maintaining the efficacy demonstrated by ASPs. The current investigation demonstrates the efficacy of cefazolin in comparison with ASP in a large national cohort of consecutive MSSA EI for more than 10 years. In our study, we did not observe differences in 1-year survival rate or relapse rate between patients treated with cloxacillin and cefazolin, but in-hospital mortality was significantly higher in those patients treated with cloxacillin.

However, some clinicians are reluctant to use cefazolin to treat serious MSSA infections because there is a concern about the CzIE

Table 2
Clinical presentation and outcomes.

Clinical presentation (%)	Treatment group			
	Cloxacillin (537)	Cefazolin (57)	Mixed (37)	p
Clinical complications	158 (29,4)	15 (26,3)	13 (35,1)	0,554
Leaflet perforation/rupture	79 (14,7)	7 (12,2)	6 (16,2)	0,620
Pseudoaneurysm	23 (4,3)	0	1 (2,7)	0,642
Perivalvular abscess	81 (15,1)	10 (17,5)	8 (21,6)	0,443
Intracardiac fistula	7 (1,3)	1 (1,7)	0	0,779
Vascular phenomena	103 (19,2)	10 (17,5)	8 (21,6)	0,887
New-onset murmur	173 (32,2)	18 (31,6)	10 (27,0)	0,806
New-onset or worsening heart failure	255 (41,9)	19 (33,3)	13 (35,1)	0,354
Persistent bacteremia ^d	75 (13,96)	9 (15,78)	4 (10,8)	0,495
Central nervous system emboli	161 (30,0)	12 (21,1)	8 (21,6)	0,227
Other major emboli	168 (31,8)	14 (24,6)	10 (27,0)	0,551
New-onset or worsening renal failure	254 (47,3)	18 (31,6)	13 (35,1)	0,024 ^a
Septic shock	134 (25,0)	7 (12,3)	5 (13,5)	0,033 ^a
Sepsis	185 (34,5)	19 (33,3)	11 (29,7)	0,836
Cardiac surgery indicated	358 (66,7)	28 (49,1)	27 (73,0)	0,002 ^{a,c}
Performed (% of indicated)	208 (38,7)	15 (26,3)	21 (56,8)	0,003 ^{b,c}
Length of stay (median [IQR]), days	35 (23-52)	31 (19-54)	47 (28-55)	0,084
Inclusion in OPAT	387 (7,0)	6 (10,5)	3 (8,1)	0,344
Length of antibiotic treatment (median [IQR]), days	32 (22-44)	35 (24-44)	34 (27-42)	0,707
With the antibiotic corresponding to the treatment group	31 (21-43)	34 (24-43)	-	0,543
Clinical outcomes (%)				
In-hospital mortality	207 (38,5)	13 (22,8)	7 (18,9)	0,017 ^{a,b}
1-year mortality	229 (42,6)	19 (33,3)	9 (24,3)	0,029 ^b
1-year IE-related mortality	8 (36,3)	1 (16,6)	0	0,360
Relapses ^e	11 (3,6)	1 (2,6)	1 (3,6)	0,782
Native valve	3	1	1	
Prosthetic valve	5	0	0	
ICD/PM	3	0	0	
Side effects	10 (1,9)	1 (1,8)	10 (27,0)	<0,01 ^{b,c}
Cloxacillin associated	10	0	10	
Cefazolin associated	0	1	0	

OPAT, outpatient parenteral antimicrobial treatment; IE, infective endocarditis; ICD/PM, intracardiac implantable defibrillators/pacemakers.

^a Differences between cloxacillin and cefazolin groups.

^b Differences between cloxacillin and mixed groups.

^c Differences between cefazolin and mixed groups.

^d Associated with the antibiotic treatment group.

^e Calculated using survivors as a denominator. Denominators for each group were as follows: “Cloxacillin” 537-229 = 308; “Cefazolin” 57-19 = 38; and “Mixed” 37-9 = 28.

Table 3
Logistic regression analysis of risk factors for mortality or relapse of MSSA endocarditis.

Relapse or death	Univariate analysis			Multivariate analysis							
	No	Yes	p	OR (CI95%)	p	0	1	2	3	4	5
Age (median (IQR))	63 (49 - 74)	70 (60 - 78)	<0,01	-	-						
Native IE	266 (73,7)	189 (70,0)	0,307	-	-						
Prosthetic IE	54 (15,0)	63 (23,3)	0,007	1,59 (0,98-2,56)	0,059						
Charlson index (median (IQR))	4 (2 - 6)	6 (4 - 8)	<0,01	1,26 (1,16-1,36)	<0,01						
Cardiac complications*	108 (29,9)	78 (28,9)	0,906	-	-						
New-onset or worsening heart failure	99 (27,4)	158 (58,3)	<0,01	2,87 (1,95-4,23)	<0,01						
Central nervous system emboli	86 (23,8)	95 (35,2)	0,002	1,48 (0,98-2,23)	0,06						
New-onset or worsening renal failure	126 (34,9)	159 (58,9)	<0,01	1,71 (1,164-2,523)	<0,01						
Septic shock	49 (13,6)	97 (35,9)	<0,01	2,16 (1,36-3,42)	<0,01						
Cardiac surgery indicated	206 (57,1)	207 (76,7)	<0,01	3,23 (2,12-4,92)	<0,01						
Cardiac surgery indicated not performed	55 (15,2)	121 (44,8)	<0,01	-	-						
Cardiac surgery indicated and performed	157 (43,5)	87 (32,2)	0,004	-	-						
Cloxacillin group	297 (82,9)	240 (88,9)	0,021	-	-						
Cefazolin group	37 (10,2)	20 (7,4)	0,218	-	-						
Mixed group	27 (7,5)	10 (3,7)	0,046	-	-						

*Leaflet perforation/rupture, pseudoaneurysm, perivalvular abscess, or intracardiac fistula. IE, infective endocarditis.

that is present in some MSSA isolates which exhibit significant increases (>4 fold) in their minimal inhibitory concentrations (MIC) at high bacterial inoculums levels (5×10^7 CFU/ml) that may be present in certain infections, such as endocarditis. This effect is the consequence of the production of beta-lactamase A which is encoded by the *blaZ* gene [16,24–26]. However, not all isolates producing type A beta-lactamase exhibit this phenomenon and the

level of beta-lactamase production has been shown to influence the inoculum effect by differential expression of the *blaZ* gene and/or its dosage [27]. Indeed, although CziE is reported in a wide range (23–65%) of MSSA isolates with geographical variations [24–26], a pronounced effect (MIC >16 mg/dl) that can overcome the effect of high doses (6–8 g) of cefazolin is observed in a lesser degree (0–15%) [14–17]. Hence, the real importance of this effect

Table 4
Renal toxicity association.

Risk factors for nephrotoxicity	Cloxacillin-5days (555)	Cefazolin-5days (56)	p
Age >70 years	237 (42,7)	24 (42,9)	0,982
Previous renal failure	164 (29,5)	32 (57,1)	<0,01
Initial creatinine (median [IQR]), mg/dl	1,00 (0,80-1,40)	1,30 (0,90-3,30)	0,009
Maximum creatinine (median [IQR]), mg/dl	2,40 (1,87-3,56)	3,57 (1,83-5,42)	0,157
New-onset or worsening renal failure	257 (46,3)	18 (32,1)	0,042
Worsening renal failure	97 (17,5)	12 (21,4)	0,462
Days until worsening (median [IQR])	12 (2-25)	13 (1-17)	0,757
New-onset renal failure	160 (28,8)	6 (10,7)	0,004
Days until new-onset (median [IQR])	15 (4-27)	4 (1-13)	0,077
Heart failure at diagnosis (median [IQR])	60 (50-65)	60 (50-65)	0,861
Septic shock	127 (22,9)	7 (12,5)	0,074

will depend on the percentage of high-producing isolates. It must also be remarked that therapeutic failures in severe infections produced by *S. aureus* have been observed with any antimicrobial and that other factors have been invoked [28]. In our study, the presence and influence of CzIE were not systematically investigated, and only seven episodes treated with cefazolin and worse evolution (persistent bacteremia) were examined, with a negative result.

Certain cefazolin therapeutic failures have been attributed to this *in vitro* phenomenon, however, very few reports have observed a worse outcome in patients treated with cefazolin compared with ASPs. It should be noted that the infection, management, and treatment regimen were heterogeneous in those studies, as well as clinical results [14–17]. The only study that observed increased mortality was reported by Miller et al [16], in a sample of 77 patients from three Argentinian hospitals with MSSA bacteremia (15 of them defined as complicated bacteremia). Isolates with CzIE were related in a multivariate analysis (risk ratio, 2.65; 95% confidence interval: 1.10-6.42; $P = 0.023$) with higher 30-day mortality. However, duration of bacteremia and microbiological clearance were not provided, patients treated with other antimicrobials (e.g. vancomycin) were included, and combination therapy was allowed (only 51 patients were treated exclusively with cefazolin) and furthermore, the dosing of antimicrobial agents was not collected specifically. Hence, conclusions must be considered with caution. The discordance between the hypothetical worse outcome with cefazolin and the good clinical results with this drug, even in patients with allegedly high inoculum can be due to various reasons: In many patients, cefazolin is used as second-line therapy after the use of ASPs for several days, leading to a reduced inoculum when cefazolin is started, as we observed in the mixed group of our study. Furthermore, due to the concern about CzIE, ASPs are more often prescribed than cefazolin in patients with MSSA IE and poor clinical condition mainly in intensive care units, favoring the better results of the cefazolin group prescribed in less severely ill patients.

Information regarding efficacy and safety of cefazolin for the treatment of MSSA IE is scarce and might be biased by treatment selection and sequential treatments. However, this fact has been overcome by the studies that have analyzed patients treated exclusively with cefazolin [18,19] and by two recent studies in which MSSA IE was treated exclusively treated with cefazolin during a long period in which a shortage of ASPs occurred in France [20,21]. In the 91 patients included in both studies, the 90-day mortality rate was similar between treatment groups (cefazolin and ASP) and one study [20] showed a higher need for treatment discontinuation due to adverse events in the ASP group, that is in accordance with our results. In our study, we also did not observe differences in 1-year mortality and relapses between cefazolin and cloxacillin groups, although in-hospital mortality was significantly higher in the cloxacillin group. That might be explained by a more aggressive IE presentation in the ASP group compared with the cefazolin,

which was indicated by a higher rate of septic shock (25% vs 12.3%), surgery indication (66.7% vs 49.1%) and new-onset or worsening renal failure (47.3% vs 31.6%) presented in these patients, all of them well-known worse prognostic factors. On the other hand, patients in the cefazolin group had more comorbidities and worse previous renal function and were probably treated with cefazolin for its lesser toxicity and safety administration in patients undergoing hemodialysis.

Among β -lactam antibiotics, ASPs are worse tolerated than cefazolin, and antibiotic discontinuation due to adverse events is more frequent [6]. In the present study side effects rates were similar between treatment groups, however, 95% of the reported adverse events (20/21) were associated with cloxacillin treatment. Despite that fact, cloxacillin toxicity in our study was lower than data previously reported. Also, it was noted that no nephrotoxicity was reported with cloxacillin, despite new-onset or worsening renal failure being present in 47% of patients treated with cloxacillin, which might or might not be associated with treatment choice. To deeply analyze the causes of nephrotoxicity in our cohort a subanalysis was conducted. Regardless of better initial renal condition, patients initially treated with cloxacillin exhibited higher rates of new-onset renal failure. Even more, in those patients initially treated with cloxacillin new-onset renal failure occurred after 2 weeks of treatment (15 [4–27] days), which is unlikely to be caused by an initial aggressive presentation, such as septic shock and is probably associated to the drug administered. In contrast, in those patients initially treated with cefazolin new-onset renal failure happened mainly within the first week of treatment (4 [1–13] days). This finding suggests that renal toxicity is more likely to be associated with cloxacillin treatment than with worse clinical presentation of IE.

Benefits of cefazolin treatment included safety administration in patients undergoing hemodialysis [29], reduced sodium contribution in patients with cardiac failure, reduced number of daily administrations, and consequently fewer catheter manipulations and concomitant complications. Also, its chemical stability in a wide range of concentrations allows its use in the outpatient parenteral antimicrobial therapy setting using elastomeric or electronic pumps with good clinical results [30]. For all these reasons it is not surprising, therefore, that its use grew steadily over time in this national cohort.

Finally, our study has several limitations. Firstly, the design of our study has intrinsic limitations product of the impossibility of controlling unknown confounders and, therefore, findings should be considered with caution. For example, in this study patients in the ASPs group were sicker, favoring the better results of the cefazolin group. This indication bias is frequent in studies comparing these two treatments [17,18] and can be partially reduced using matched propensity scores. However, the reduced number of patients treated with cefazolin and the diverse factors that can affect the final outcome in the *S. aureus* IE did not permit a sensitiv-

ity analysis. Secondly, the sample size of this study is limited and might have been underpowered to detect differences in outcomes, particularly because of the small number of patients treated with cefazolin. Due to the low number of relapses, detecting differences between groups would have required a much greater sample size. However, our study represents a national cohort with patients included over more than 10 years, which allowed us to detect risk factors for mortality and relapses already identified in the literature. Third, the rate of patients treated with other antibiotics was unexpected. However, it might be explained because during this long-term study diagnostic techniques and medical approaches have evolved at different speeds among the hospitals included. Due to the severity of this infection, broad-spectrum coverage might have been used until a certain diagnosis was reached, which might have been delayed until optimal diagnosis techniques were available. Lastly, adverse events might be misreported in our cohort, nevertheless, a subanalysis of the nephrotoxicity was conducted, showing the higher toxicity of cloxacillin.

In conclusion, the results of this study suggest that cefazolin is a valuable option for the treatment of MSSA IE. We did not find differences in one-year mortality or relapses compared with cloxacillin and therefore it might be considered equally effective as an ASP treatment. However, observational studies have inherent biases and do not provide the same level of evidence as randomized clinical trials, which are rare and difficult to conduct in IE, due to the small number of involved and the multiple factors that can affect the final outcome. Then, further investigations to corroborate those findings are warranted. Until then, the role of cefazolin should be revised.

Declarations of Competing Interest

The authors have no competing interests to declare.

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Author contributions

All of the authors listed meet the International Committee of Medical Journal Editors authorship criteria—that is, they substantially contributed to the conception and design, acquisition of data, drafting of the article, critical revision, and final approval of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2023.10.019](https://doi.org/10.1016/j.ijid.2023.10.019).

APPENDIX

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