Open Forum Infectious Diseases

MAJOR ARTICLE

Outcomes and Risk Factors of Septic Shock in Patients With Infective Endocarditis: A Prospective Cohort Study

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Background. Little is known about the characteristics and impact of septic shock (SS) on the outcomes of infective endocarditis (IE). We aimed to investigate the characteristics and outcomes of patients with IE presenting with SS and to compare them to those of IE patients with sepsis (Se) and those with neither Se nor SS (no-Se-SS).

Methods. This is a prospective cohort study of 4864 IE patients from 35 Spanish centers (2008 to 2018). Logistic regression analyses were performed to identify risk factors for SS and mortality.

Results. Septic shock and Se presented in 597 (12.3%) and 559 (11.5%) patients, respectively. Patients with SS were younger and presented significantly higher rates of diabetes, chronic renal and liver disease, transplantation, nosocomial acquisition, *Staphylococcus aureus*, IE complications, and in-hospital mortality (62.5%, 37.7% for Se and 18.2% for no-Se-SS, $P < .001$). *Staphylococcus aureus* (odds ratio [OR], 1.94; 95% confidence interval [CI], 1.34–2.81; $P < .001$), Gram negative (OR, 2.21; 95% CI, 1.25–3.91; $P = .006$), nosocomial acquisition (OR, 1.44; 95% CI, 1.07–1.94; $P = .015$), persistent bacteremia (OR, 1.82; 95% CI, 1.24–2.68; $P = .002$), acute renal failure (OR, 3.02; 95% CI, 2.28–4.01; $P < .001$), central nervous system emboli (OR, 1.48; 95% CI, 1.08–2.01; $P = .013$), and larger vegetation size (OR, 1.01; 95% CI, 1.00–1.02; $P. = 020$) were associated with a higher risk of developing SS. Charlson score, heart failure, persistent bacteremia, acute renal failure, mechanical ventilation, worsening of liver disease, *S aureus*, and receiving aminoglycosides within the first 24 hours were associated with higher in-hospital mortality, whereas male sex, native valve IE, and cardiac surgery were associated with lower mortality.

Conclusions. Septic shock is frequent and entails dismal prognosis. Early identification of patients at risk of developing SS and early assessment for cardiac surgery appear as key factors to improve outcomes.

Keywords. cardiac surgery; infective endocarditis; sepsis; septic shock; *Staphylococcus aureus*.

Infective endocarditis (IE) is a serious disease with increasing incidence in Western countries, presenting a high overall mortality (approximately 25%–30%) despite the improvements in cardiac surgery, antibiotic treatment, and diagnostic techniques of recent decades [1–3]. It is likely that the 2 ways to address this are to strengthen prevention measures and to rapidly identify and control risk factors of poor prognosis in patients with IE.

Septic shock (SS) is one of the risk factors for mortality in IE that entails poorer prognosis. Septic shock is also increasingly detected worldwide [4, 5]. Although the existing literature shows that IE-associated mortality skyrockets when SS develops, there are some factors conferring a higher risk of developing SS, such as *Staphylococcus aureus* or diabetes mellitus [6, 7]; multiorgan failure entails dismal prognosis [8, 9], and cardiac surgery might play a key role in improving the prognosis [8–10]. Nonetheless, there are major gaps that still need to be addressed, such as the exact prevalence of SS and sepsis (Se) in IE or the impact of cardiac surgery and its timing on survival.

We aimed to investigate the main characteristics of IE presenting with SS and Se in a large Spanish multicenter cohort,

Received 10 January 2021; editorial decision 8 March 2021; accepted 23 March 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab119

to compare them to those of patients without SS and/or Se, and to analyze risk factors for the development of SS as well as risk factors for mortality among patients with SS.

METHODS

Design

This is a multicenter prospective observational study that includes 35 Spanish centers between January 2008 and December 2018.

Patients

This study comprised adult individuals with IE diagnosed according to the modified Duke criteria [11] and receiving full treatment. Patients were allocated to one of the following categories depending on whether they presented Se or SS at any time during the IE episode: no Se/SS (no Se-SS), Se, and SS.

Definitions

The characteristics of the GAMES (Grupos de Apoyo para el Manejo de la Endocarditis en ESpaña) cohort, collection of data variables through a specific central registration depository (CRD), and general definitions are described elsewhere [12, 13]. Sepsis and septic shock developing once patients were admitted to the hospital and occurring before cardiac surgery were prospectively collected in the GAMES CRD by physicians in charge of the Endocarditis Team in each collaborating center according to definitions by international consensus in place [14]. The definition of sepsis was systemic inflammatory response syndrome due to infection with tissue hypoperfusion or organ dysfunction that responded to adequate fluid resuscitation, whereas septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation [14]. When a patient had both the boxes for sepsis and septic shock marked as "yes" in the CRD, he or she was assigned to the septic shock category.

Cardiac surgery was considered (1) emergent when performed on the same day as the surgery indication and (2) urgent when taking place during the following 24 hours. Persistent bacteremia was defined as persistence of positive blood cultures after 7 days of appropriate antibiotic treatment initiation. The length of antibiotic treatment was calculated both for all patients and only for those patients surviving the initial IE admission. Patients receiving either 3 mg/kg per day gentamicin or ≥1000 mg/day amikacin as either empirical or directed antibiotic treatment for IE during the first 24 hours were considered to have received an early high dose of aminoglycosides, which are frequently used as combination therapy in Se/SS according to guidelines [15].

Outcomes

Outcomes were as follows: development of septic shock during the index IE episode; in-hospital and 1-year mortality (death due to any causes during the initial admission and 365 days from the date of admission, respectively); and relapses (new episode of IE caused by the same microorganism within 6 months of the initial episode).

Patient Consent Statement

The design of the work has been approved by local ethical committees of sites participating in the GAMES cohort.

Statistical Analysis

Categorical variables were summarized as percentages, and continuous variables were summarized as means and standard deviations. Categorical variables were compared using the χ^2 test (or Fisher's exact test, where applicable). Continuous variables were compared using the Kruskal-Wallis test. Multivariable logistic regression analysis was utilized to investigate risk factors for the development of septic shock and hospital and 1-year mortality. Variables with $P < .20$ in the univariate analysis were included in the models (see selected variables in Supplementary Material A). The goodness of fit of the final multivariate model was assessed again by the Hosmer-Lemeshow test. Analysis of covariance using the Pearson correlation test or Spearman's rho was carried out to explore the relationship between sepsis/septic shock and IE caused by *S aureus*, and Kaplan-Meier survival curve free of mortality at 1 year was generated with log-rank test analysis and considering censored episodes according to the time measured for each endpoint. A 2-sided $P < .05$ was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL).

RESULTS

From 2008 to 2018, 597 patients developed SS (12.3%) and 559 patients developed Se (11.5%) during the IE episode of the 4864 patients included in the GAMES cohort during this period.

Patients with SS were significantly younger than those in the no-Se-SS group (Table 1). Patients both from the SS and Se group had significantly higher frequencies of several comorbidities, remarkably more chronic liver and kidney disease, than those of the no-Se-SS group. Native valve IE was significantly more common among patients with SS and Se, whereas CIED involvement was more frequent in no-Se-SS patients. The mitral valve was more frequently involved in the SS and the Se groups than in the no-Se-SS group. Community acquisition of the infection was significantly less frequent, whereas nosocomial acquisition was more common among patients with SS. *Staphylococcus aureus* as causative agent of IE was significantly more common in the SS and Se groups, whereas streptococci were overall less frequent. Coagulase-negative staphylococci were overall significantly less frequently the causative microorganisms of IE in the SS group. Culture-negative IE was significantly

Table 1. Comparison of Epidemiological and Etiological Characteristics and Type of Endocarditis Among Infective Endocarditis Episodes From the GAMES Cohort (2008–2018) According to the Presence of Sepsis and Septic Shock

Variables	No Sepsis-No Septic Shock (N = 3708)	Sepsis (N = 559)	Septic Shock (N = 597)	*P*
Median age, years (IQR)	69 (57–77)	68 (56–78)	66 (55–76)	.042[a]
Male sex (%)	2530 (68.2)	348 (62.2)	391 (65.4)	.277
Comorbidities				
Diabetes mellitus	1035 (27.9)	166 (29.7)	194 (32.5)	.024[a]
Chronic lung disease	685 (18.4)	124 (22.1)	114 (19.0)	.042[a]
Ischemic cardiomyopathy	1017 (27.4)	145 (25.9)	161 (26.9)	.492
Congestive heart failure	1240 (33.4)	199 (35.9)	219 (36.6)	.131
Moderate/severe liver disease	132 (3.5)	31 (5.5)	38 (6.3)	.030[a]
Moderate/severe chronic renal failure	500 (13.4)	116 (20.7)	126 (21.1)	<.001[a]
Hemodialysis	148 (3.9)	37 (6.6)	45 (7.5)	<.001[a]
Neoplasm	563 (15.1)	94 (16.8)	101 (16.9)	.304
Transplantation	66 (1.8)	8 (1.4)	25 (4.2)	.003[a]
Immunosuppressant therapy	202 (5.4)	34 (6.0)	40 (6.7)	.608
IV drug use	80 (2.1)	18 (3.2)	14 (2.3)	.418
HIV	60 (1.6)	15 (2.6)	12 (2.0)	.141
Previous IE	295 (8.0)	37 (6.6)	39 (6.5)	.303
Congenital cardiac abnormality	249 (6.7)	32 (5.7)	26 (4.3)	.035[a]
Natural valve disease	1653 (44.5)	287 (51.3)	248 (41.5)	.003[a]
Median age-adjusted Charlson score (IQR)	5 (3–7)	5 (3–7)	5 (3–7)	.200
Type of Endocarditis				
Native	2204 (59.4)	360 (64.4)	391 (65.5)	.028[a]
Prosthetic	1153 (31.1)	178 (29.8)	166 (29.7)	.690
CIED[b]	410 (11.1)	49 (8.8)	41 (6.9)	.002[a]
Valve involvement[c]				
Aortic	1934 (52.2)	233 (41.7)	299 (50.1)	<.001[a]
Mitral	1498 (40.4)	273 (48.8)	286 (47.9)	<.001[a]
Tricuspid	183 (4.9)	45 (8.1)	39 (6.5)	.003[a]
Pulmonary	40 (1.1)	20 (3.6)	12 (2.0)	<.001[a]
Diagnosis of Endocarditis According to Modified Duke Criteria				
Definite	2886 (77.8)	497 (88.9)	512 (85.7)	<.001[a]
Possible	822 (22.1)	62 (11.0)	85 (14.2)	<.001[a]
IE Acquisition				
Community	2253 (60.7)	343 (61.3)	317 (53.1)	.005[a]
Healthcare Associated				
-Nosocomial	1023 (27.5)	159 (28.4)	225 (37.6)	<.001[a]
-Non-nosocomial healthcare associated	310 (8.3)	45 (8.0)	40 (6.7)	.197
Unknown	122 (3.2)	12 (2.1)	15 (2.5)	.397
Causative Microorganisms				
Staphylococcus aureus	625 (16.9)	215 (38.5)	255 (42.7)	<.001[a]
Streptococci	1057 (28.5)	94 (16.8)	91 (15.2)	<.001[a]
Viridans group	417 (11.2)	24 (4.3)	24 (4.0)	<.001[a]
Group B (Streptococcus *agalactiae* and Streptococcus *dysgalactiae*)	81 (2.2)	18 (3.2)	22 (3.7)	.009[a]
Streptococcus *pneumoniae*	29 (0.8)	10 (1.8)	5 (0.8)	.063
Streptococcus *pyogenes*	7 (0.2)	1 (0.2)	2 (0.3)	.757
Bovis group streptococci	272 (7.3)	19 (3.4)	15 (2.5)	.008[a]
Other	251 (6.7)	22 (3.9)	23 (3.8)	.013[a]
Coagulase-negative staphylococci	673 (18.1)	101 (18.1)	79 (13.2)	.028[a]
Staphylococcus lugdunensis	27 (0.7)	12 (2.1)	6 (1.0)	.002[a]
Staphylococcus capitis	29 (0.8)	1 (0.2)	3 (0.5)	.230
Other	617 (16.6)	88 (15.7)	70 (11.7)	.002[a]
Enterococci	580 (15.6)	51 (9.1)	51 (8.5)	.001[a]
Enterococcus *faecalis*	535 (14.4)	47 (8.4)	43 (7.2)	.001[a]
Enterococcus *faecium*	35 (0.9)	4 (0.7)	7 (0.1)	.725
Other	10 (0.2)	0	1 (0.1)	.982
Gram negative	145 (3.9)	27 (4.8)	34 (5.7)	.101

Table 1. Continued

Variables	No Sepsis-No Septic Shock (N = 3708)	Sepsis (N = 559)	Septic Shock (N = 597)	*P*
Fungi	62 (1.7)	19 (3.4)	15 (2.5)	.008[a]
Candida spp	54 (1.5)	17 (3.0)	14 (2.3)	.010[a]
Other	8 (0.2)	2 (0.4)	1 (0.2)	.764
Other	861 (23.2)	240 (42.9)	276 (46.2)	<.001[a]
No etiological diagnosis	330 (8.9)	27 (4.8)	51 (8.5)	.002[a]

Abbreviations: CIED, cardiac implanted electronic device; HIV, human immunodeficiency syndrome; IE, infective endocarditis; IQR, interquartile range; IV, intravenous; MRSA, methicillin-resistant Staphylococcus *aureus*; MSSA, methicillin-susceptible *S aureus*.

[a]Statistically significant difference between columns 1 and 2, 2 and 3, and 1 and 3, respectively.

[b]Only episodes in which only CIED are affected are included in this group. Episodes have been classified as native or prosthetic valve where a concomitant valve involvement exists.

[c]The sum does not equal 100% because episodes with multivalve involvement are also counted.

less frequent in the Se group. Enterococci, particularly Enterococcus *faecalis*, caused IE less frequently in both the SS and the Se groups. An analysis of covariance showed a significant positive correlation between both SS and Se and *S aureus* etiology (Supplementary Material B). Patients with SS with IE caused by *S aureus* presented higher rates of mitral and pulmonic valve involvement, definite IE, nosocomial acquisition, persistent bacteremia, central nervous system (CNS) emboli, pulmonary emboli, surgical risk scores, and in-hospital and 1-year mortality than patients with SS and IE not caused by *S aureus*, whereas the latter had higher rates of aortic valve involvement, moderate-severe aortic regurgitation, intracardiac complications, and cardiac surgery, both emergent and elective (Supplementary Table 1).

Patients with SS and Se presented significantly more clinical and echocardiographic complications than patients within the no-Se-SS group overall (Table 2). In some cases, the complications were significantly higher also in the SS compared to the Se group, eg, new onset or worsening heart failure (which also positively correlated to the existence of prior chronic heart failure as shown in Supplementary Material B), use of intra-aortic balloon or ventricular-assist devices, mechanical ventilation, and acute renal failure. The median length of antibiotic treatment was shorter overall in SS but longer compared to no-Se-SS when survivors to the IE episode were analyzed. No significant differences between groups were found regarding the overall rates of cardiac surgery during the initial admission. Emergent surgery was significantly more frequent in patients with SS than in the other 2 groups. In-hospital and 1-year mortality were significantly higher in the SS group than in the other 2 groups, whereas deaths occurring after discharge were significantly less frequent in the SS group (Supplemental Table 2) than in the Se and no-Se-SS groups. Relapses were significantly higher in the no-Se-SS group.

In the multivariable model of risk factors associated with the development of SS (Table 3), *S aureus*, Gram-negative rods, nosocomial acquisition, persistent bacteremia, acute renal failure, CNS emboli, and vegetation size were associated with a higher risk of developing SS, whereas viridans group streptococci and bovis group streptococci were associated to lower risk.

Female sex, age-adjusted Charlson score, new onset of heart failure, persistent bacteremia, acute renal failure, mechanical ventilation, worsening of prior liver disease, *S aureus*, and administration of aminoglycosides during the first 24 hours were associated to higher in-hospital mortality, whereas (1) native valve IE and (2) cardiac surgery were associated with lower risk of death (Table 4). With regards to 1-year mortality, risk factors were older age, age-adjusted Charlson score, new onset heart failure, acute renal failure, mechanical ventilation, worsening of prior liver disease, and administration of aminoglycosides during the first 24 hours. Factors associated with lower risk of 1-year mortality were the same as those for in-hospital mortality, namely, male sex, native valve IE, and cardiac surgery.

Survival was significantly lower over time up to 1 year after admission for SS compared to the other 2 groups and for Se compared to those patients without either Se or SS (Figure 1).

DISCUSSION

The major findings of our study encompass a relatively high frequency of SS among patients with IE, approximately two thirds of whom died; SS affects patients with certain distinct baseline conditions and increased risk being associated to the etiology (*S aureus*, Gram negative), nosocomial acquisition, large vegetation size, and the development of complications (persistent bacteremia, acute renal failure, and CNS emboli), and therefore early identification of patients at higher risk is possible; and lastly, cardiac surgery was performed in 43% of patients with SS, mostly as emergent surgery, and was associated with lower mortality.

Staphylococcus aureus was the main causative agent among patients with IE presenting SS, which is consistent with the findings in the Olmos et al [6] study. Approximately 4 of 10 cases of IE presenting with SS were acquired nosocomially, which should raise a flag for improving prevention measures given the high associated mortality. Special attention should be placed on avoiding catheter-related bacteremia and early prosthetic valve IE.

Septic shock was associated with several complications of IE such as multiorgan involvement (ie, renal, liver and respiratory

Table 2. Comparison of Clinical and Therapeutic Characteristics and Outcomes Among Infective Endocarditis Episodes From the GAMES Cohort (2008–2018) According to the Presence of Sepsis and Septic Shock

Variables	No Sepsis-No Septic Shock (N = 3708)	Sepsis (N = 559)	Septic Shock (N = 597)	*P*
Clinical Complications of Endocarditis				
New onset or worsening heart failure	1254 (33.8)	284 (50.8)	366 (61.3)	<.001[a]
Persistent bacteremia	372 (10.0)	91 (16.3)	98 (16.4)	<.001[a]
Central nervous system emboli	613 (16.5)	153 (27.3)	195 (32.6)	<0.001[a]
Other major emboli	684 (18.4)	167 (29.8)	156 (26.1)	<.001[a]
Pulmonary emboli	148 (3.9)	48 (8.5)	44 (7.3)	<.001[a]
Vertebral osteomyelitis	121 (3.2)	21 (3.7)	16 (2.6)	.530
Nonvertebral osteomyelitis	53 (1.4)	14 (2.5)	14 (2.3)	.133
Renal abscess	43 (1.1)	15 (2.6)	15 (2.5)	.006[a]
Splenic abscess	115 (3.1)	30 (5.3)	38 (6.3)	.008[a]
Other Complications				
Heart conduction abnormality (atrial fibrillation or block)	306 (8.2)	71 (12.7)	80 (13.4)	.007[a]
Ventricular tachycardia or fibrillation or reverted cardiac sudden death	64 (1.7)	14 (2.5)	32 (5.3)	.019[a]
Acute renal failure	1038 (27.9)	279 (49.9)	375 (62.8)	<.001[a]
Intra-aortic balloon or ventricular assist devices	26 (0.7)	14 (2.5)	24 (4.0)	<.001[a]
Mechanical ventilation	199 (5.3)	85 (15.2)	295 (49.1)	<.001[a]
Unstable angina	39 (1.0)	26 (4.6)	10 (1.6)	<.001[a]
Worsening of prior liver disease	62 (1.6)	10 (1.8)	35 (5.8)	.006[a]
Echocardiographic Findings				
TEE performed	2949 (79.5)	420 (75.1)	457 (76.5)	.020[a]
Median ejection fraction (%, IQR)	60 (55–65)	60 (55–65)	60 (50–65)	.730
Median vegetation size (mm, IQR)	10 (7–16)	12 (8–18)	12 (8–19)	<.001[a]
Moderate-severe aortic regurgitation	1102 (29.7)	130 (23.2)	168 (28.1)	.002[a]
Moderate-severe mitral regurgitation	1218 (32.8)	231 (41.3)	213 (35.6)	.001[a]
Perivalvular abscess	501 (13.5)	139 (24.9)	121 (20.3)	<.001[a]
Intracardiac fistula	92 (2.4)	7 (1.2)	16 (2.6)	.126
Pseudoaneurysm	222 (5.9)	35 (6.2)	29 (4.8)	.317
Leaflet perforation/rupture	463 (12.4)	107 (19.1)	97 (16.2)	<.001[a]
Treatment Characteristics				
Median Length of Antibiotic Treatment, Days (IQR)				
• Overall	40 (28–45)	35 (23–44)	27 (11–43)	<.001[a]
• Among survivors of initial episode	42 (30–47)	42 (32–49)	43 (33–54)	<.001[a]
Received high-dose aminoglycosides within the first 24 hours	303 (8.2)	34 (6.1)	55 (9.2)	.059
Cardiac Surgery				
During admission	1728 (46.6)	255 (45.6)	254 (42.6)	.179
• Emergent	73 (1.9)	22 (3.9)	62 (10.3)	<.001[a]
• Urgent	386 (10.4)	67 (11.9)	83 (13.9)	.013[a]
• Elective	1269 (34.2)	166 (29.7)	109 (18.2)	<.001[a]
After discharge	161 (4.3)	18 (3.2)	11 (1.8)	.008[a]
• Within 3 months after discharge	70 (43.4)	6 (33.3)	4 (36.3)	.565
• 3–12 months	71 (44.0)	9 (50.0)	7 (63.6)	.344
• >12 months	14 (8.9)	2 (11.1)	0	.696
• Unknown	6 (3.7)	1 (5.5)	0	.793
Surgical Risk Among Patients Receiving Cardiac Surgery				
EuroScore, median (IQR)	9 (6–12)	9 (7–13)	12 (9–15)	<.001[a]
LogEuroScore, median (IQR)	15 (6–32)	17 (7–37)	32 (12–54)	<.001[a]
Patients with surgery indication in whom hemodynamic instability was a criterion to rule out surgery (1030/4864, 21.1%)	643 43 (6.6)[b]	168 30 (17.5)	219 104 (47.4)	<.001[a]
Outcomes				
In-hospital mortality	676 (18.2)	211 (37.7)	372 (62.3)	<.001[a]
One-year mortality	919 (24.7)	45 (45.7)	18 (65.3)	.001[a]
Relapses	62 (1.6)	4 (0.7)	3 (0.5)	.046[a]

Abbreviations: IQR, interquartile range; IV, intravenous; TEE, transesophageal echocardiography.

[a]Statistically significant difference between columns 1 and 2, 2 and 3, and 1 and 3, respectively.

[b]Hemodynamic instability was a factor that combined with the following in these 43 patients: stroke (14%), technical complexity (14%), poor prognosis regardless of cardiac surgery (90%), surgeon refuses (28%), death before surgery (23%), and advanced liver disease (14%).

Table 3. Multivariate Analysis of Risk Factors to Develop Septic Shock[a] Among Patients With Infective Endocarditis (N = 4864)

		95% CI		
Variables	OR	Lower	Upper	*P*
Nosocomial acquisition of IE	1.445	1.075	1.943	.015
Staphylococcus aureus	1.941	1.342	2.808	<.001
Gram negative	2.213	1.252	3.914	.006
Bovis group streptococci	.290	.088	.960	.043
Viridans group	.471	.232	.954	.037
Persistent bacteremia	1.820	1.237	2.677	.002
CNS emboli	1.475	1.084	2.008	.013
Acute renal failure	3.021	2.275	4.013	<.001
Vegetation size	1.014	1.002	1.026	.020

Abbreviations: CI, confidence interval; CNS, central nervous system; IE, infective endocarditis; OR, odds ratio.

[a]Before surgery in operated patients.

failure), emboli, and abscesses. It is interesting to note that it was also associated with a worsening of previous congestive heart failure and with new onset heart failure, although SS patients less frequently presented severe valve regurgitation. Given that mortality associated with SS was found to be much higher than that with Se, the conclusion from the clinical standpoint is to address sepsis promptly and correctly in its early phase according to the guidelines in place [15] to contain the inflammatory cascade that leads to Se and SS and ultimately to multiorgan failure and death. Nonetheless, the management of sepsis through the

Table 4. Multivariate Analysis of Risk Factors For In-Hospital Mortality and 1-Year Mortality Among Patients With Infective Endocarditis And Septic Shock (N = 597)

	In-Hospital Mortality				1-Year Mortality			
		95% CI				95% CI		
Variables	OR	Lower	Upper	*P*	OR	Lower	Upper	*P*
Male Sex	.643	.415	.998	.049	.632	.404	.989	.044
Age	1.011	.996	1.027	.153	1.018	1.002	1.034	.030
Age-adjusted Charlson score	1.162	1.063	1.270	.001	1.140	1.042	1.248	.004
Native	.558	.351	.885	.013	.537	.335	.862	.010
Aortic	.821	.504	1.337	.427	.732	.443	1.207	.221
Leaflet perforation/rupture	.810	.459	1.428	.466	.845	.473	1.508	.568
Perivalvular abscess	1.124	.654	1.932	.672	.979	.563	1.700	.939
Intracardiac fistula	2.247	.606	8.330	.226	1.981	.534	7.346	.307
Moderate-severe mitral regurgitation	1.462	.925	2.310	.104	1.460	.913	2.335	.114
Moderate-severe aortic regurgitation	1.440	.843	2.459	.182	1.706	.982	2.965	.058
New onset or worsening heart failure	1.982	1.300	3.021	.001	1.994	1.296	3.067	.002
Persistent bacteremia	1.815	1.018	3.236	.043	1.764	.974	3.194	.061
CNS emboli	1.121	.720	1.745	.613	1.055	.672	1.657	.816
Other major emboli	.612	.372	1.008	.054	.714	.429	1.188	.195
Heart conduction abnormality	1.415	.751	2.664	.283	1.404	.728	2.708	.312
Acute renal failure	2.011	1.317	3.069	.001	1.892	1.232	2.906	.004
Ventricular tachycardia or fibrillation	1.379	.478	3.979	.552	1.615	.517	5.039	.409
Mechanical ventilation	2.361	1.548	3.602	<.001	2.251	1.461	3.469	<.001
Intra-aortic balloon or ventricular-assist devices	4.848	1.456	16.138	.010	4.314	1.288	14.448	.018
Unstable angina	1.097	.240	5.011	.905	1.755	.317	9.708	.519
Worsening of prior liver disease	2.743	1.072	7.018	.035	4.771	1.596	14.264	.005
Renal abscess	1.445	.321	6.502	.632	1.327	.286	6.153	.718
Splenic abscess	.960	.346	2.664	.937	.860	.295	2.505	.782
Staphylococcus aureus	1.666	1.090	2.546	.018	1.479	.961	2.276	.076
Nosocomial acquisition of IE	.963	.625	1.481	.862	1.067	.687	1.658	.772
Cardiac surgery	.417	.268	.649	<.001	.383	.244	.601	<.001
Aminoglycosides first 24 hours	2.691	1.291	5.607	.008	2.636	1.237	5.617	.012

Abbreviations: CI, confidence interval; CNS, central nervous system; IE, infective endocarditis; OR, odds ratio.

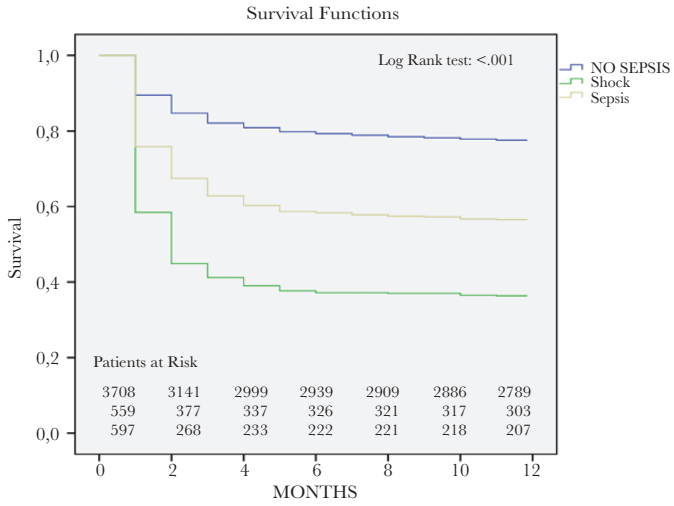

Figure 1. Kaplan-Meier survival curves at 1 year.

use of abundant intravenous fluids besides the administration of antibiotics might be challenging due to the risk of fluid overload and secondary development of heart failure.

Furthermore, and closely related to the previous point, patients at a higher risk of developing SS should be rapidly identified. According to our results, factors such as transplantation, chronic liver disease, aortic valve involvement, potential nosocomial acquisition, and causative agents (*S aureus* and Gram negative bacilli) might help raise awareness in the early approach to the patients, whereas other predictors such as persistent bacteremia, CNS emboli, a large vegetation size, or acute renal failure are probably detected too late to improve the prognosis in most cases.

The rapid identification of patients and their transfer to reference centers for cardiac surgery when necessary, and the establishment of endocarditis teams in both reference tertiary centers and second-level hospitals are of special relevance, because cardiac surgery appears to be effective in improving the overall prognosis of patients with IE and SS. It is well known that multiorgan failure and septic shock are major reasons for cardiac surgeons to refuse surgery, because both have a large impact in the calculation of surgical risk irrespective of the risk score used [16]. However, 42.6% of patients with SS in our cohort received cardiac surgery during their admission, more than half of whom were operated on within 48 hours. The rapid decision making and readiness for cardiac surgery in IE, and the surgical expertise in such a relatively complex and infrequent entity such as IE, largely relies on the existence of a highly cohesive group of health professionals [17–19]. Also, it should be noted that surgery in IE is not limited to valvular surgery but also encompasses the removal of the source infection from other locations such as the spleen or the spine, which is directly related to the risk of persistent bacteremia. Therefore, alignment with other surgical teams is also crucial.

Concerning follow-up and medium term prognosis, survivors of IE presenting with SS showed lower mortality rates from discharge up to 1 year. The observed lower rate of relapse is probably related to the lower number of patients at risk due to the high in-hospital mortality. Hence, there were no findings in our study suggesting that patients surviving an episode of IE with SS should be followed-up differently than other patients.

Our study has some limitations. The definition of "severe sepsis" and "sepsis" changed during the study period [14, 20], and this might have affected how treating physicians collected this information. However, the definition in the GAMES CRD did not change, and in all cases this did not affect how information on SS was gathered. Some relevant information such as the exact resuscitation measures applied was not collected. Another gap in data is the severity scores used in the clinical approach to Se and SS such as Sequential Organ Failure Assessment (SOFA). Moreover, a bias of reference is likely to influence our results, because the bulk of data from patients with SS comes from reference centers for cardiac surgery.

CONCLUSIONS

In conclusion, SS is a relatively common complication of IE. Younger ages, high rates of diabetes mellitus, transplantation, chronic renal and liver disease, aortic involvement, nosocomial acquisition, and *S aureus* etiology are foremost features of patients with IE developing SS. Septic shock is also associated with many complications related to IE and a very high mortality. Noticeably, cardiac surgery was associated with improved outcomes. Patients with risk factors for developing SS should be rapidly identified and monitored and considered for transfer to reference centers. Moreover, signs of sepsis in IE should be detected and managed accordingly to avoid progression to SS. If

hemodynamics degenerate or the IE is diagnosed already with SS in course, early surgery should be considered.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We dedicate this article to Dr. Juan Gálvez-Acebal (Seville), who played a key role in launching the Grupos de Apoyo para el Manejo de la Endocarditis en ESpaña (GAMES) project and died recently. In addition, we thank Iván Adán for his task as data coordinator of the GAMES cohort and for his statistical support. The list of GAMES investigators is available in the Supplementary Material.

Author contributions. All the authors listed in the contributors' affiliations meet the ICMJE Authorship Criteria, that is, they substantially contributed to conception and design, acquisition of data, drafting of the article, critical revision, and final approval of the manuscript.

Financial support. This work was funded by the Ministerio de Sanidad y Consumo of Spain (FIS NCT00871104, Instituto de Salud Carlos III), and the Institut d'Investigacions Biomèdiques Pi i Sunyer provided a personal 80:20 research grant (to J. M. M.) during 2017–2021.

Potential conflicts of interest. J. M. M. has received consulting honoraria and/or research grants from Angelini, Bristol-Myers Squibb, Contrafect, Genentech, Gilead Sciences, MSD, Medtronic, Novartis, Pfizer, and ViiV. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. Lancet **2012**; 379:965–75.
2. Hoen B, Duval X. Clinical practice. Infective endocarditis. N Engl J Med **2013**; 368:1425–33.
3. Wang A, Gaca JG, Chu VH. Management considerations in infective endocarditis: a review. JAMA **2018**; 320:72–83.
4. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med **2013**; 369:840–51.
5. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet **2020**; 395:200–11.
6. Olmos C, Vilacosta I, Fernández C, et al. Contemporary epidemiology and prognosis of septic shock in infective endocarditis. Eur Heart J **2013**; 34:1999–2006.
7. Leroy O, Georges H, Devos P, et al. Infective endocarditis requiring ICU admission: epidemiology and prognosis. Ann Intensive Care **2015**; 5:45.
8. Mirabel M, Sonneville R, Hajage D, et al.; ENDOREA Study Group. Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis. Eur Heart J **2014**; 35:1195–204.
9. Krajinovic V, Ivancic S, Gezman P, Barsic B. Association between cardiac surgery and mortality among patients with infective endocarditis complicated by sepsis and septic shock. Shock **2018**; 49:536–42.
10. Gelsomino S, Maessen JG, van der Veen F, et al. Emergency surgery for native mitral valve endocarditis: the impact of septic and cardiogenic shock. Ann Thorac Surg **2012**; 93:1469–76.
11. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–8.
12. Mateos Gaitán R, Boix-Palop L, Muñoz García P, et al. Infective endocarditis in patients with cardiac implantable electronic devices: a nationwide study. Europace **2020**; 22:1062–70.
13. Pericàs JM, Llopis J, Muñoz P, et al.; GAMES Investigators. A contemporary picture of enterococcal endocarditis. J Am Coll Cardiol **2020**; 75:482–94.
14. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (sepsis-3). JAMA **2016**; 315:801–10.
15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International Guidelines for management of sepsis and septic shock: 2016. Crit Care Med **2017**; 45:486–552.
16. Pericàs JM, Quintana E, Miró JM. Bugs at the operating theatre in infective endocarditis: one step forward, still a long way to go. J Thorac Dis **2019**; 11:E182–91.
17. Chambers J, Sandoe J, Ray S, et al. The infective endocarditis team: recommendations from an international working group. Heart **2014**; 100:524–7.
18. Ruch Y, Mazzucotelli JP, Lefebvre F, et al. Impact of setting up an "Endocarditis Team" on the management of infective endocarditis. Open Forum Infect Dis **2019**; 6:ofz308.
19. Davierwala PM, Marin-Cuartas M, Misfeld M, Borger MA. The value of an "Endocarditis Team". Ann Cardiothorac Surg **2019**; 8:621–9.
20. Levy MM, Fink MP, Marshall JC, et al; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med **2003**; 29:530–8.