Outcomes and risk factors of septic shock in patients with infective endocarditis: a prospective cohort study

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**Key points:** Septic shock and sepsis presented respectively in 12.3% and 11.5% patients with endocarditis. Septic shock is associated to very high mortality rates. Cardiac surgery is associated to lower mortality in patients with septic shock.
Abstract

**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:** Prospective cohort study of 4,864 IE patients from 35 Spanish centers (2008 to 2018). Logistic regression analyses were performed to identify risk factors for SS and mortality.

**Results:** SS and Se presented respectively in 597 (12.3%) and 559 (11.5%) patients. Patients with SS were younger and presented significantly higher rates of diabetes, chronic renal and liver disease, transplantation, nosocomial acquisition, *S.aureus*, IE complications, and in-hospital mortality (62.5%, 37.7% for Se and 18.2% for no-Se-SS, p<.001). *S.aureus* (OR 1.94, 95%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), CNS 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 24h were associated with higher in-hospital mortality, whereas male sex, native valve IE and cardiac surgery were associated with lower mortality.
Conclusions: SS 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: Infective endocarditis, sepsis, septic shock, *Staphylococcus aureus*, cardiac surgery.
Introduction

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]. Likely, the two 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. SS 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 *S. aureus* or diabetes mellitus [6,7]; multi-organ 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, 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 amongst patients with SS.

Methods

*Design:* Multicenter prospective observational study including 35 Spanish centers between January 2008 and December 2018.

*Patients:* 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 or not they presented sepsis or septic shock at any time during the IE episode: no sepsis/septic shock (no Se-SS), sepsis (Se), and septic shock (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 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 central registration depository (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 emergent when performed on the same day as the surgery indication, and 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/day gentamicin or ≥1000 mg/day amikacin as either empirical or directed antibiotic treatment for IE during the first 24h 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: Development of septic shock during the index IE episode; in-hospital and one-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 as means and standard deviations. Categorical variables were compared using the chi-square 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 one-year mortality. Variables with P<0.20 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, Kaplan-Meier survival curve free of mortality at one year was generated with log-rank test analysis and considering censored episodes according to the time measured for each endpoint. A two-sided P<0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc. Chicago. Illinois. USA).
Results

From 2008 to 2018, 597 patients developed SS (12.3%) and 559 patients developed Se (11.5%) during the IE episode of the 4,864 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 amongst patients with SS and Se while 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 while nosocomial acquisition was more common amongst patients with SS. *S. 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 less frequent in the Se group. Enterococci, particularly *E. 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 emboli, pulmonary emboli, surgical risk scores, in-hospital and one-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, e.g., 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 two groups. In-hospital and one-year mortality were significantly higher in the SS group than in the other two 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 24h were associated to higher in-hospital mortality, whereas native valve IE, and cardiac surgery were associated to lower risk of death (Table 4). With regards to one-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 24h. Factors associated with lower risk of 1-year mortality were the same than for in-hospital mortality, namely male sex, native valve IE, and cardiac surgery.

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

Discussion

Major findings of our study encompass a relatively high frequency of SS among patients with IE, almost 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.

S. aureus was the main causative agent among patients with IE presenting SS, which is consistent with the findings in Olmos et al study [6]. Almost four out of ten 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.

SS was associated to a number of complications of IE such as multi-organ involvement (i.e, renal, liver and respiratory failure), emboli, and abscesses. Interestingly, it was also associated to a worsening of previous congestive heart failure and to new onset heart failure although SS patients less frequently presented severe valve regurgitation. Given mortality associated to SS was found to be much higher than that to 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] in order to contain the inflammatory cascade that leads to Se and SS and ultimately to multi-organ failure and death. Nonetheless, the management of sepsis through the 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, 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 detected probably 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, since cardiac surgery appears to be effective in improving the overall prognosis of patients with IE and SS. It is well known that multi-organ failure and septic shock are major reasons for cardiac surgeons to refuse surgery, as 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 who were operated within 48h. The rapid decision-making and readiness for cardiac surgery in IE, and the surgical expertise in such a relatively complex and infrequent entity as IE, largely relies on the existence of a highly cohesive group of health professionals [17-19]. It is worth reminding that surgery might not be uniquely targeted to heart valves, but also to control the focus of infection from other sources such as splenic, spinal or renal abscesses is also extremely important and relates to persistent
bacteremia being a risk factor for mortality. 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 one 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 any 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 SOFA. Moreover, a bias of reference is likely to influence our results, since the bulk of data from patients with SS comes from reference centers for cardiac surgery.

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. SS is also associated to 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.
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Figure Legends

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

|                                | No sepsis-no septic shock (N= 3,708) | Sepsis (N=559) | Septic shock (N=597) | P       |
|--------------------------------|--------------------------------------|----------------|----------------------|---------|
| Median age, years (IQR)        | 69 (57 – 77)                         | 68 (56 – 78)   | 66 (55 – 76)         | .042    |
| 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    |
| Chronic lung disease           | 685 (18.4)                           | 124 (22.1)     | 114 (19.0)           | .042    |
| 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    |
| Moderate/severe chronic renal failure | 500 (13.4)          | 116 (20.7)     | 126 (21.1)           | <.001   |
| Hemodialysis                   | 148 (3.9)                            | 37 (6.6)       | 45 (7.5)             | <.001   |
| Neoplasm                       | 563 (15.1)                           | 94 (16.8)      | 101 (16.9)           | .304    |
| Transplantation                | 66 (1.8)                             | 8 (1.4)        | 25 (4.2)             | .003    |
| 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    |
| Natural valve disease          | 1653 (44.5)                          | 287 (51.3)     | 248 (41.5)           | .003    |
| Median age-adjusted Charlson   | 5 (3 – 7)                            | 5 (3 – 7)      | 5 (3 – 7)            | .200    |
|                          | Definite | Possible | Unknown |
|--------------------------|----------|----------|---------|
| **Type of endocarditis** |          |          |         |
| Native                   | 2204 (59.4) | 360 (64.4) | 391 (65.5) | .028<sup>a</sup> |
| Prosthetic               | 1153 (31.1) | 178 (29.8) | 166 (29.7) | .690 |
| CIED*                    | 410 (11.1) | 49 (8.8)  | 41 (6.9)  | .002<sup>c</sup> |
| **Valve involvement**    |          |          |         |
| Aortic                   | 1934 (52.2) | 233 (41.7) | 299 (50.1) | <.001<sup>a,b</sup> |
| Mitral                   | 1498 (40.4) | 273 (48.8) | 286 (47.9) | <.001<sup>a,c</sup> |
| Tricuspid                | 183 (4.9)  | 45 (8.1)  | 39 (6.5)  | .003<sup>a</sup> |
| Pulmonary                | 40 (1.1)   | 20 (3.6)  | 12 (2.0)  | <.001<sup>a</sup> |
| **Diagnosis of endocarditis according to modified Duke criteria** | | | |
| Definite                 | 2886 (77.8) | 497 (88.9) | 512 (85.7) | <.001<sup>a,c</sup> |
| Possible                 | 822 (22.1) | 62 (11.0) | 85 (14.2) | <.001<sup>a,c</sup> |
| **IE acquisition**       |          |          |         |
| Community                | 2253 (60.7) | 343 (61.3) | 317 (53.1) | .005<sup>b,c</sup> |
| Health-care associated   |          |          |         |
|  - Nosocomial            | 1023 (27.5) | 159 (28.4) | 225 (37.6) | <.001<sup>b,c</sup> |
|  - Non-nosocomial health-care associated | 310 (8.3) | 45 (8.0) | 40 (6.7) | .197 |
| Unknown                  | 122 (3.2) | 12 (2.1) | 15 (2.5) | .397 |
| **Causative microorganisms** | | | |
| S. aureus                | 625 (16.9) | 215 (38.5) | 255 (42.7) | <.001<sup>a,c</sup> |
| Streptococci             | 1057 (28.5) | 94 (16.8) | 91 (15.2) | <.001<sup>a,c</sup> |
| Viridans group           | 417 (11.2) | 24 (4.3) | 24 (4.0) | <.001<sup>a,c</sup> |
| Group B (S. agalactiae and | | | | |
| Organism                        | Count (Frequency) | Count (Frequency) | Count (Frequency) | p-value |
|--------------------------------|------------------|------------------|------------------|---------|
| S. dysgalactiae                | 81 (2.2)         | 18 (3.2)         | 22 (3.7)         | .009^a  |
| S. pneumoniae                  | 29 (0.8)         | 10 (1.8)         | 5 (0.8)          | .063    |
| S. 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,c|
| Other                          | 251 (6.7)        | 22 (3.9)         | 23 (3.8)         | .013^a,c|
| Coagulase-negative staphylococci | 673 (18.1)     | 101 (18.1)       | 79 (13.2)        | .028^b,c|
| S. lugdunensis                 | 27 (0.7)         | 12 (2.1)         | 6 (1.0)          | .002^a  |
| S. capitis                     | 29 (0.8)         | 1 (0.2)          | 3 (0.5)          | .230    |
| Other                          | 617 (16.6)       | 88 (15.7)        | 70 (11.7)        | .002^c  |
| Enterococci                    | 580 (15.6)       | 51 (9.1)         | 51 (8.5)         | .001^a,c|
| E. faecalis                    | 535 (14.4)       | 47 (8.4)         | 43 (7.2)         | .001^a,c|
| E. 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    |
| Fungi                          | 62 (1.7)         | 19 (3.4)         | 15 (2.5)         | .008^a  |
| Candida spp                    | 54 (1.5)         | 17 (3.0)         | 14 (2.3)         | .010^b  |
| Other                          | 8 (0.2)          | 2 (0.4)          | 1 (0.2)          | .764    |
| Other                          | 861 (23.2)       | 240 (42.9)       | 276 (46.2)       | <.001^a,c|
| No etiological diagnosis      | 330 (8.9)        | 27 (4.8)         | 51 (8.5)         | .002^a,b|

^a, b, c Statistically significant difference between columns 1&2, 2&3, and 1&3, respectively.

HIV: Human immunodeficiency syndrome; IQR: Interquartile range; MSSA: methicillin-susceptible S. aureus; MRSA: methicillin-resistant S. aureus; PCM/DF: pacemakers/defibrillators

*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.

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

| Clinical complications of endocarditis | No sepsis-no septic shock (N=3,708) | Sepsis (N=559) | Septic shock (N=597) | P |
|----------------------------------------|-------------------------------------|----------------|---------------------|---|
| New onset or worsening heart failure   | 1254 (33.8)                        | 284 (50.8)     | 366 (61.3)          | <.001<sup>a,b,c</sup> |
| Persistent bacteremia                  | 372 (10.0)                         | 91 (16.3)      | 98 (16.4)           | <.001<sup>a,c</sup>  |
| Central nervous system emboli          | 613 (16.5)                         | 153 (27.3)     | 195 (32.6)          | <0.001<sup>a,c</sup> |
| Other major emboli                    | 684 (18.4)                         | 167 (29.8)     | 156 (26.1)          | <.001<sup>a,c</sup>  |
| Pulmonary emboli                      | 148 (3.9)                          | 48 (8.5)       | 44 (7.3)            | <.001<sup>a,c</sup>  |
| Vertebral osteomyelitis               | 121 (3.2)                          | 21 (3.7)       | 16 (2.6)            | .530 |
| Non-vertebral osteomyelitis           | 53 (1.4)                           | 14 (2.5)       | 14 (2.3)            | .133 |
| Renal abscess                         | 43 (1.1)                           | 15 (2.6)       | 15 (2.5)            | .006<sup>a,c</sup>   |
| Splenic abscess                       | 115 (3.1)                          | 30 (5.3)       | 38 (6.3)            | .008<sup>a,c</sup>   |
| Other complications                   |                                    |                |                     |                |
| Heart conduction abnormality (atrial fibrillation or block) | 306 (8.2) | 71 (12.7) | 80 (13.4) | .007<sup>a,c</sup> |
| Ventricular tachycardia or fibrillation or reverted cardiac sudden death | 64 (1.7) | 14 (2.5) | 32 (5.3) | .019<sup>b,c</sup> |
| Acute renal failure                   | 1038 (27.9)                        | 279 (49.9)     | 375 (62.8)          | <.001<sup>a,b,c</sup> |
| Intra-aortic balloon or ventricular assist devices | 26 (0.7) | 14 (2.5) | 24 (4.0) | <.001<sup>a,b,c</sup> |
| Mechanical ventilation               | 199 (5.3)                          | 85 (15.2)      | 295 (49.1)          | <.001<sup>a,b,c</sup> |
| Unstable angina                       | 39 (1.0)                           | 26 (4.6)       | 10 (1.6)            | <.001<sup>a,b</sup>  |
| Category                                      | Group 1 | Group 2 | Group 3 | p-value |
|----------------------------------------------|---------|---------|---------|---------|
| Worsening of prior liver disease             | 62 (1.6)| 10 (1.8)| 35 (5.8)| .006<sup>b,c</sup> |
| Echocardiographic findings                   |         |         |         |         |
| TEE performed                                | 2949 (79.5)| 420 (75.1)| 457 (76.5)| .020<sup>a</sup> |
| Median ejection fraction (%)                 | 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<sup>a,c</sup> |
| Moderate-severe aortic regurgitation         | 1102 (29.7)| 130 (23.2)| 168 (28.1)| .002<sup>a</sup> |
| Moderate-severe mitral regurgitation         | 1218 (32.8)| 231 (41.3)| 213 (35.6)| .001<sup>a,b</sup> |
| Perivalvular abscess                         | 501 (13.5)| 139 (24.9)| 121 (20.3)| <.001<sup>a,c</sup> |
| 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<sup>a,c</sup> |
| Treatment characteristics                    |         |         |         |         |
| Median length of antibiotic treatment, days (IQR) | | | | |
| Overall                                      | 40 (28 – 45)| 35 (23 – 44)| 27 (11 – 43)| <.001<sup>a,b,c</sup> |
| Among survivors of initial episode           | 42 (30 – 47)| 42 (32 – 49)| 43 (33 – 54)| <.001<sup>c</sup> |
| Received high-dose aminoglycosides within the first 24h | 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<sup>a,b,c</sup> |
| Urgent                                       | 386 (10.4)| 67 (11.9)| 83 (13.9)| .013<sup>c</sup> |
| Elective                                     | 1269 (34.2)| 166 (29.7)| 109 (18.2)| <.001<sup>b,c</sup> |
After discharge | 161 (4.3) | 18 (3.2) | 11 (1.8) | .008c
---|---|---|---|---
  • 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) | LogEuroScore, median (IQR) |
|---|---|---|
| | 9 (6 – 12) | 9 (7 – 13) | 12 (9 – 15) | <.001b,c |
| | 15 (6 – 32) | 17 (7 – 37) | 32 (12 – 54) | <.001b,c |

Patients with surgery indication in whom hemodynamic instability was a criterion to rule out surgery (1,030/4,864, 21.1%)

| | 643 | 168 | 219 |
|---|---|---|---|
| | 43 (6.6)* | 30 (17.5) | 104 (47.4) | <.001a,b,c |

Outcomes

| | In-hospital mortality | One-year mortality | Relapses |
|---|---|---|---|
| | 676 (18.2) | 211 (37.7) | 372 (62.3) | <.001a,b,c |
| | 919 (24.7) | 45 (45.7) | 18 (65.3) | <.001a,b,c |
| | 62 (1.6) | 4 (0.7) | 3 (0.5) | .046c |

*a, b, c Statistically significant difference between columns 1&2, 2&3, and 1&3, respectively.

* 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* among patients with infective endocarditis (N=4,864).

| Risk Factor                          | OR    | 95% CI   | p    |
|--------------------------------------|-------|----------|------|
|                                      | Lower | Upper    |      |
| Nosocomial acquisition of IE         | 1.445 | 1.075    | 1.943| .015 |
| S. 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 |

* Before surgery in operated patients
Table 4. Multivariate analysis of risk factors for in-hospital mortality and one-year mortality amongst patients with infective endocarditis and septic shock (N=597).

|                       | In-hospital mortality | One-year mortality |
|-----------------------|-----------------------|--------------------|
|                       | OR        | 95%CI       | p   | OR        | 95%CI       | p   |
|                       | Lower      | Upper      |     | Lower      | Upper      |     |
| Male Sex              | .643       | .415       | .998 | .632       | .404       | .989 |
| Age                   | 1.011      | .996       | 1.027 | 1.018      | 1.002      | 1.034 |
| Age-adjusted Charlson score | 1.162   | 1.063      | 1.270 | 1.140      | 1.042      | 1.248 |
| Native                | .558       | .351       | .885 | .537       | .335       | .862 |
| Aortic                | .821       | .504       | 1.337 | .732       | .443       | 1.207 |
| Leaflet perforation/rupture | .810  | .459       | 1.428 | .845       | .473       | 1.508 |
| Perivalvular abscess  | 1.124      | .654       | 1.932 | .979       | .563       | 1.700 |
| Intracardiac fistula  | 2.247      | .606       | 8.330 | 1.981      | .534       | 7.346 |


| Condition                                      | RR   | 95% CI  | Adjusted RR | 95% CI  | Unadjusted RR | 95% CI  |
|-----------------------------------------------|------|---------|-------------|---------|---------------|---------|
| Moderate-severe mitral regurgitation           | 1.46 | .92     | 2.31        | .10     | 1.46          | .91     |
| Moderate-severe aortic regurgitation           | 1.44 | .84     | 2.46        | .18     | 1.71          | .92     |
| New onset or worsening heart failure           | 1.98 | 1.30    | 3.02        | .00     | 1.99          | 1.29     |
| Persistent bacteremia                          | 1.82 | 1.02    | 3.24        | .04     | 1.76          | .97     |
| CNS emboli                                     | 1.12 | .72     | 1.75        | .61     | 1.06          | .67     |
| Other major emboli                             | .61  | .37     | 1.01        | .05     | .71           | .43     |
| Heart conduction abnormality                   | 1.45 | .75     | 2.66        | .28     | 1.40          | .72     |
| Acute renal failure                            | 2.01 | 1.31    | 3.07        | .00     | 1.89          | 1.23     |
| Ventricular tachycardia or fibrillation        | 1.38 | .48     | 3.98        | .55     | 1.61          | .52     |
| Mechanical ventilation                         | 2.36 | 1.55    | 3.60        | <.00    | 2.25          | 1.46     |
| Intra-aortic balloon or ventricular-assist devices | 4.84 | 1.46    | 16.14       | <.00    | 4.31          | 1.28     |
| Unstable angina                                | 1.09 | .24     | 5.01        | .90     | 1.75          | .31     |
| Worsening of prior liver disease               | 2.74 | 1.07    | 7.02        | .03     | 4.77          | 1.59     |
| Renal abscess                                  | 1.45 | .32     | 6.50        | .63     | 1.32          | .28     |
| Splenic abscess                                | .96  | .35     | 2.66        | .93     | .86           | .29     |

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|                      |      |      |      |      |      |      |
|----------------------|------|------|------|------|------|------|
| **S. aureus**         | 1.666| 1.090| 2.546| .018 | 1.479| .961 |
| Nosocomial acquisition of IE | .963 | .625 | 1.481| .862 | 1.067| .687 |
| Cardiac surgery       | .417 | .268 | .649 | <.001| .383 | .244 |
| Aminoglycosides first 24h | 2.691| 1.291| 5.607| .008 | 2.636| 1.237|
|                      |      |      |      |      |      |      |
