Contemporary epidemiology and prognosis of septic shock in infective endocarditis†

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Aims

The prognosis of patients with infective endocarditis (IE) remains poor despite the great advances in the last decades. One of the factors closely related to mortality is the development of septic shock (SS). The aim of our study was to describe the profile of patients with IE complicated with SS, and to identify prognostic factors of new-onset SS during hospitalization.

Methods and results

We conducted a prospective study including 894 episodes of IE diagnosed at three tertiary centres. A backward logistic regression analysis was undertaken to determine prognostic factors associated with SS development. Multivariable analysis identified the following as predictive of SS development: diabetes mellitus [odds ratio (OR) 2.06; confidence interval (CI) 1.16–3.68], Staphylococcus aureus infection (OR: 2.97; CI: 1.72–5.15), acute renal insufficiency (OR: 3.22; CI: 1.28–8.07), supraventricular tachycardia (OR: 3.29; CI: 1.14–9.44), vegetation size ≥15 mm (OR: 1.21; CI: 0.65–2.25), and signs of persistent infection (OR: 9.8; CI: 5.48–17.52). Risk of SS development could be stratified when combining the first five variables: one variable present: 3.8% (CI: 2–7%); two variables present: 6.3% (CI: 3.2–12.1%); three variables present: 14.6% (CI: 6.8–27.6%); four variables present: 29.1% (CI: 11.7–56.1%); and five variables present: 45.4% (95% CI: 17.5–76.6%). When adding signs of persistent infection, the risk dramatically increased, reaching 85.7% (95% CI: 61.2–95.9%) of risk.

Conclusions

In patients with IE, the presence of diabetes, acute renal insufficiency, Staphylococcus aureus infection, supraventricular tachycardia, vegetation size ≥15 mm, and signs of persistent infection are associated with the development of SS.

Introducción

Despite the great advances in the last decades, mortality in infective endocarditis (IE) remains exceedingly high.1–3 Different investigations have pointed out risk factors associated with poor prognosis and higher mortality.1,2,4–16 One of the factors more tightly related to mortality in IE is the development of septic shock (SS).8–14,17 Regrettably, risk factors for the development of SS among patients with IE have not previously been defined. In addition, it is well known that the epidemiological profile of IE has changed over the last few years, with newer predisposing factors, increased use of invasive procedures at risk for bacteraemia, increased patients’ age, and a slightly different microbiological profile. All of them might influence in some way on the development of SS.

The aim of our study was to analyse the actual epidemiology, microbiologic profile, echocardiographic characteristics, and clinical outcome of the episodes of IE complicated with SS. Quick identification of patients at highest risk of SS might offer the opportunity to change the course of the disease and improve patients’ prognosis. Therefore, we also wanted to identify prognostic factors associated with SS development during hospitalization, so we analysed separately the group of patients that did not have SS at admission.

†There is no relationship with industry.

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Methods

Patient population

This study was conducted at three tertiary care centres with surgical facilities, which have been working together on IE with the use of standardized protocols, uniform data collection, and identical diagnostic and therapeutic criteria from the beginning of the study. From 1996 to 2010, 894 consecutive episodes of IE were prospectively recruited on an ongoing multipurpose database. This registry has been approved by the local ethical committee. For purposes of analysis and comparison, we distinguished three groups: Group I (n = 156), episodes who had SS at anytime during the clinical course of the disease, Group II (n = 738) gathered all the episodes who did not, and Group III (n = 104) included patients who develop SS during hospitalization, i.e. in this latter group, 52 episodes with SS that was already present at admission were excluded. This third group was made in order to identify predictors of new-onset SS, avoiding possible confounding factors that could be present if only patients with SS at anytime had been analysed.

To ensure consecutive enrolment, all patients who underwent echocardiography to rule out IE were clinically followed until a diagnosis was established. Patients with a final diagnosis of IE were included in the study. Only definite and possible cases of IE were included. Duke criteria were applied until 2002, and modified Duke criteria thereafter.18

All patients underwent a detailed clinical history, standard physical examination, electrocardiography, blood analysis, urinalysis, a set of three blood cultures at admission, and three additional blood cultures 48–72 h later, and transthoracic (TTE) and transoesophageal echocardiography (TOE). If blood cultures were negative after 72 h, specific serological tests were done for Chlamydia, Brucella, Q fever, Legionella, and Mycoplasma. Empiric antibiotic therapy was started after blood cultures were taken, and specific antibiotic treatment was initiated once the results of blood cultures were available.

Definition of terms

Nosocomial and community-acquired IE were defined according to the literature.16 Early prosthetic valve IE was defined as occurring within the first year after surgery, and late prosthetic valve IE beyond 1 year.19 Acute onset IE was applied when the time between the appearance of symptoms and hospital admission was <15 days.20 Chronic anaemia was defined as a haemoglobin concentration <9 g/dL; renal insufficiency was established when the serum creatinine concentration was >2 mg/dL. Supraventricular tachycardia was registered as universally defined. Those patients with sinus tachycardia or other type of arrhythmias were not included under this category.

Persistent signs of infection were defined as persistent bacteremia or fever after 7 days of appropriate antibiotic treatment, once other possible foci of infection had been ruled out.16 Septic shock was defined as the presence of an acute circulatory failure in sepsis, characterized by persistent arterial hypotension (systolic pressure <90 mmHg) despite adequate volume resuscitation.21

The diagnosis of systemic embolism was based on clinical signs and/or data derived from imaging procedures. Heart failure was diagnosed on the basis of guidelines criteria.22

Vegetations were measured in various planes and the greatest diameter was recorded for subsequent analysis. In the case of multiple vegetations, the largest was measured. Perivalvular complications have been defined in detail elsewhere.23,24 Severely depressed left ventricular function was defined as an ejection fraction <30%.25

Empiric antibiotic regimens were chosen for culture-negative cases according to established guidelines16,26 or the reference literature on this matter (before 2005).

Surgery was defined as early if done before the antibiotic regimen was completed, and was performed when any of the following occurred: heart failure refractory to medical treatment, recurrent embolism with persistent vegetations in the echocardiogram, persistent signs of infection, and fungal endocarditis. The initial presence of perivalvular complications in patients with a favourable clinical course was not an indication for early surgery, although the enlargement of pseudoaneurysms and abscesses or the progression to a fistula were considered indications. When a patient meeting surgical criteria did not undergo surgery, the reason was either because of patient rejection, unacceptably high-surgical risk or when the patient was too frail.

Statistical analysis

Continuous variables are reported as a mean value and standard deviation. In dichotomic variables, the groups were compared by a two-tailed Student’s t-test or Mann–Whitney U-test when necessary. In the case of multiple categories, the ANOVA or Kruskal–Wallis test were used. Categorical variables are expressed as a frequency and a percentage, and were compared with the χ² test and Fisher’s exact test when appropriate. Influence of different variables in the development of SS was first tested in a univariable analysis (Pearson χ² test or ANOVA). Two multivariable logistic regression analysis were performed by means of a backward logistic method, the first one considering the prevalence of SS as the dependent variable, and the second one considering development or not of SS as the dependent variable. No significant multicollinearity (assessed using variance inflation factors) was detected in the models. The Hosmer–Lemeshow goodness-of-fit test was also performed.

To create figure 1, factors that were found to bear prognostic importance in the multivariate analysis were combined to stratify the predicted risk of developing SS. This risk was obtained by the calculation of the probability of each patient from adjusted model coefficients. The weighted averages of the probabilities, and their confidence intervals (CI) (calculated by bootstrapping), adjusted by the model for the number of factors present were represented in the figure.

The adjusted odds ratios (ORs) with 95% CIs for each variable have been calculated. All tests were two-sided and differences were considered statistically significant at P-values <0.05. Statistical analysis was performed with PASW Statistics V 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Univariable analysis in patients who had septic shock at anytime during the clinical course of the infection

Epidemiological and clinical characteristics

The mean age of our patient population (n = 894) was 61 ± 16 years, 580 (64.8%) were men, 26.28% of the episodes were nosocomial, and 324 patients (36.2% of the episodes) were referred from another hospital; 156 patients (17.4%) had SS at any time, and 104 patients (11.6%) had new-onset SS during hospitalization. The median time at which new-onset SS occurred was 2 weeks.

Demographic characteristics, previous cardiopathy, comorbidities, possible portal of entry, and clinical presentation comparisons between patients who had SS and those who did not are summarized in Table 1.
Age and gender distribution were similar in both groups. A trend towards greater incidence of nosocomial infection was detected in Group I. Concerning comorbidity, diabetes mellitus, chronic renal failure, cancer, and chronic obstructive pulmonary disease were more common in Group I. Intravenous drug users were also more frequent in this group. With respect to possible portals of entry, previous use of intravascular catheters was detected more commonly among episodes from Group I, whereas dental procedures were more frequent in Group II.

As regard to symptomatology, an acute onset of symptoms was more common in Group I. At admission, dyspnoea, presence of pulmonary infiltrates, acute abdominal syndrome, acute renal failure, confusional syndrome, and coma appeared more frequently in patients with present SS (Table 1).

The presence of supraventricular tachycardia at admission was more common in episodes from Group I. Among radiological findings, it is worth to mention that pulmonary congestion signs and septic emboli were more frequently present in Group I (Table 1).

**Microbiological profile**

*Staphylococcus aureus* and Gram-negative bacilli were more frequently isolated in Group I, whereas *Streptococcus viridans* and coagulase-negative staphylococci were more commonly found in Group II (Table 2).

**Echocardiographic findings**

Echocardiographic data are shown in Table 3. Vegetations, as well as periannular abscesses, were more frequently detected in Group I. Vegetations were also larger in this group. Severely depressed left ventricular function was more common among episodes from Group I. No differences were found in the infection location or the type of valve affected (native vs. prosthetic).

**In-hospital evolution**

During hospitalization, development of heart failure, acute renal failure, and liver and limb emboli were more common in patients with SS. In addition, these patients underwent surgery less frequently. Overall, 114 of 156 (73.1%) patients with SS died. Death was much less common in Group II (Table 4). Among patients with SS, those who underwent surgery (n = 70) had lower mortality than those who received medical treatment alone (n = 86): (64.3 vs. 80.2%; P = 0.026); 84.8% of patients with SS were operated on during the SS, whereas 15.2% underwent surgery after good haemodynamic recovery. The median time at which surgery was performed was 13 days (5–24 days).

**Multivariable analysis in patients who had septic shock at anytime during the clinical course of the infection**

We performed a multivariable analysis in order to determine the variables that were independently associated with the presence of SS at anytime during the clinical course of the disease. We included in the model the variables that were considered clinically relevant and those that were significant in the univariable analysis (age, diabetes, chronic renal failure, cancer, acute onset of symptoms, nosocomial acquisition, supraventricular tachycardia, *S. aureus*, vegetation detection, vegetation size, periannular complications, heart failure, acute renal failure, stroke, hepato-splenic embolism, signs of persistent infection). Independent prognostic factors of SS are shown in Table 5.

A multivariable analysis of in-hospital mortality was also performed (Table 6), including SS and variables that we had found to influence it in the univariable analysis.

**Univariable analysis in patients with new-onset septic shock during hospitalization**

To approach to this second part of the study, and as stated in methods, episodes with SS at admission were excluded, and those who develop SS during hospitalization (Group III), were compared with the episodes from Group II. Data comparing these groups are available in Supplementary material online, Tables S1–S4.

**Multivariable analysis in patients with new-onset septic shock during hospitalization**

To determine the variables that were independently associated with the development of SS during hospitalization a multivariable logistic regression analysis was performed. As in the case of SS at anytime, we included in the model the variables that were considered clinically relevant and were significant in the univariable analysis. Significance of the Hosmer–Lemeshow goodness-of-fit test of the model was P = 0.903. No multicollinearity was detected. According to an incidence of new-onset SS of 11.6% in our patient population, the model has a sensitivity of 82% and a specificity of 71%.
| Table 1  | Demographic and clinical characteristics, electrocardiographic, and radiological findings at admission in 894 episodes of infective endocarditis |
|-----------------------------------------------|-------------------------------------------------|----------------|
|                                                | SS at anytime Group I (n = 156) | Without SS Group II (n = 738) | P-value |
| Age (years)                                    | 61 (± 16)                                  | 61 (± 16)                        | 0.768   |
| Male gender                                    | 97 (62.2)                                  | 483 (65.4)                       | 0.437   |
| Referred                                       | 61 (39.6)                                  | 263 (35.8)                       | 0.376   |
| Nosocomial acquisition                         | 50 (32.3)                                  | 185 (25.3)                       | 0.055   |
| Previous cardiopathy                          | 83 (53.9)                                  | 506 (68.9)                       | <0.001  |
| Rheumatic                                      | 13 (9.6)                                   | 46 (7)                           | 0.285   |
| Prosthesis                                     | 43 (31.9)                                  | 250 (37.9)                       | 0.182   |
| Degenerative                                   | 15 (11.1)                                  | 68 (10.3)                        | 0.784   |
| Previous endocarditis                         | 0 (0)                                      | 17 (2.6)                         | 0.093   |

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<thead>
<tr>
<th>Possible portal of entry</th>
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<tr>
<td>Dental procedures</td>
<td>1 (0.6)</td>
<td>59 (8)</td>
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<tr>
<td>Intravascular catheter</td>
<td>24 (15.4)</td>
<td>68 (9.2)</td>
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<tr>
<td>Genitourinary procedures</td>
<td>3 (1.9)</td>
<td>23 (3.1)</td>
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<tr>
<td>Gastrointestinal procedures</td>
<td>4 (2.6)</td>
<td>19 (2.6)</td>
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<thead>
<tr>
<th>Comorbidity</th>
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<tr>
<td>Intravenous drug users</td>
<td>19 (12.2)</td>
<td>44 (6)</td>
</tr>
<tr>
<td>HIV</td>
<td>9 (5.8)</td>
<td>37 (5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>46 (29.5)</td>
<td>130 (17.6)</td>
</tr>
<tr>
<td>Chronic anaemia</td>
<td>32 (20.5)</td>
<td>131 (17.8)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>24 (15.4)</td>
<td>68 (9.3)</td>
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<tr>
<td>Immunodepression</td>
<td>18 (11.5)</td>
<td>67 (9.1)</td>
</tr>
<tr>
<td>Malignant neoplasia</td>
<td>24 (15.4)</td>
<td>61 (8.3)</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>19 (12.2)</td>
<td>52 (7.1)</td>
</tr>
<tr>
<td>Dermopathy</td>
<td>1 (0.6)</td>
<td>17 (2.3)</td>
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<tr>
<th>Clinical manifestations</th>
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<tbody>
<tr>
<td>Acute onset (&lt;15 days)</td>
<td>98 (63.2)</td>
<td>327 (44.8)</td>
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<tr>
<td>Heart failure</td>
<td>64 (41.6)</td>
<td>260 (35.3)</td>
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<tr>
<td>Fever</td>
<td>119 (76.3)</td>
<td>528 (71.8)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>83 (53.2)</td>
<td>298 (40.6)</td>
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<tr>
<td>Pulmonary emboli</td>
<td>12 (7.7)</td>
<td>32 (4.3)</td>
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<tr>
<td>Pulmonary infiltrates</td>
<td>34 (21.8)</td>
<td>86 (11.7)</td>
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<tr>
<td>Acute renal failure</td>
<td>52 (33.3)</td>
<td>81 (11)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (16.7)</td>
<td>74 (10)</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>5 (3.2)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Skin findings</td>
<td>15 (9.6)</td>
<td>74 (10)</td>
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<tr>
<td>Splenomegaly</td>
<td>14 (9)</td>
<td>65 (8.9)</td>
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<tr>
<td>Coma</td>
<td>12 (7.7)</td>
<td>11 (1.5)</td>
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<tr>
<td>Confusional syndrome</td>
<td>38 (24.4)</td>
<td>67 (9.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>18 (11.6)</td>
<td>98 (13.3)</td>
</tr>
<tr>
<td>Arthritis/spondylodiscitis</td>
<td>21 (13.5)</td>
<td>114 (15.5)</td>
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<th>Electrocardiographic findings</th>
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<tr>
<td>First degree AV block</td>
<td>6 (4)</td>
<td>43 (5.9)</td>
</tr>
<tr>
<td>Second and third degree AV block</td>
<td>2 (1.3)</td>
<td>21 (2.9)</td>
</tr>
<tr>
<td>Right bundle-branch block</td>
<td>5 (3.3)</td>
<td>13 (1.8)</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>7 (4.6)</td>
<td>17 (2.3)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2 (1.3)</td>
<td>4 (0.5)</td>
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Continued
Independent prognostic factors of new-onset SS are shown in Table 7.

Finally, the factors that were found to bear prognostic importance in the multivariable analysis were combined to stratify the predicted risk. The weighted average of the probabilities and the bootstrapped CIs are presented.

First, the number of factors present at admission was analysed (diabetes mellitus, S. aureus, acute renal insufficiency, supraventricular tachycardia, and vegetation size ≥15 mm). If one of these factors was present, the model predicted risk of developing SS was 3.8% (95% CI: 2.7–7%). When two of the factors were present, the risk increased to 6.3% (95% CI: 3.2–12.1%).

Risk was 14.6% (95% CI: 6.8–27.6%) in patients with three factors, 29.1% (95% CI: 17.5–56.1%) with four factors, and it increased to 45.4% (95% CI: 17.5–76.6%) when five factors were present.

When adding signs of persistent infection to the presence of the factors mentioned before, the predicted risk dramatically doubled independently of the number of variables present, reaching 85.7% (95% CI: 61.2–95.9%) when the five were present (Figure 1).

Discussion

Despite major advances in the diagnosis, antibiotic therapy, and surgical treatment of IE, this disease continues to be associated with a high mortality rate. Septic shock is one of the factors associated with worse prognosis. However, none study has investigated in-depth the factors that may be related with the development of this severe complication. In the herein study, we have analysed the epidemiology, clinical characteristics, microbiological profile, echocardiographic findings, and in-hospital evolution of a large series of patients with SS. These data were compared with those of patients who did not present SS. To the best of our knowledge, this study is the first trying to identify predictors of new-onset SS during hospitalization. Our work is also unique for the following reasons: it is a prospective, multicentre study, all patients underwent TOE, and uniform data collection, includes a very high number of patients, and diagnostic and therapeutic criteria have been used since the beginning of the study.

The results obtained with both analysis (SS at anytime, and new-onset SS during hospitalization), are similar, and therefore most points may be discussed interchangeably.

Regarding to comorbidity conditions, diabetes mellitus and cancer were more commonly present in patients with SS. Previous studies on septic patients have documented that the pre-existing diagnosis of diabetes, and cancer, are independent predictors of SS. Likewise, Chirillo et al., recently found that the cause of death among diabetic patients with IE was mostly related to infection. Individuals with diabetes mellitus have a greater frequency and severity of infections. In fact, in addition
### Table 3  Echocardiographic findings

<table>
<thead>
<tr>
<th></th>
<th>SS at anytime</th>
<th>Without SS</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Group I (n = 156)</td>
<td>Group II (n = 738)</td>
<td></td>
</tr>
<tr>
<td>Prosthetic involvement</td>
<td>46 (29.5)</td>
<td>262 (35.5)</td>
<td>0.151</td>
</tr>
<tr>
<td>Right-sided endocarditis</td>
<td>26 (16.7)</td>
<td>117 (15.9)</td>
<td>0.891</td>
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<tr>
<td><strong>Location of the infection</strong></td>
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<tr>
<td>Aortic native valve</td>
<td>31 (23)</td>
<td>171 (26.1)</td>
<td>0.440</td>
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<tr>
<td>Mitral native valve</td>
<td>44 (32.6)</td>
<td>152 (23.2)</td>
<td>0.022</td>
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<tr>
<td>Tricuspid native valve</td>
<td>12 (8.9)</td>
<td>32 (4.9)</td>
<td>0.065</td>
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<td>Aortic mechanical prosthesis</td>
<td>8 (5.9)</td>
<td>71 (10.9)</td>
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<td>Mitral mechanical prosthesis</td>
<td>18 (13.3)</td>
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<td>1 (0.7)</td>
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<td>Aortic bioprosthesis</td>
<td>11 (8.1)</td>
<td>33 (5)</td>
<td>0.153</td>
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<tr>
<td>Mitral bioprosthesis</td>
<td>1 (0.7)</td>
<td>7 (1.1)</td>
<td>&gt;0.999</td>
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<tr>
<td>Tricuspid bioprosthesis</td>
<td>2 (1.5)</td>
<td>2 (0.3)</td>
<td>0.138</td>
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<tr>
<td>Implantable electronic devices</td>
<td>6 (4.4)</td>
<td>45 (6.9)</td>
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<td>Vegetations</td>
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<tr>
<td>Detection by echocardiography</td>
<td>141 (90.4)</td>
<td>588 (79.7)</td>
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<td>Size ≥ 10 mm</td>
<td>66 (57.4)</td>
<td>280 (44.7)</td>
<td>0.012</td>
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<td>Size ≥ 15 mm</td>
<td>46 (29.5)</td>
<td>170 (23)</td>
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<td>Moderate-severe valve failure</td>
<td>98 (62.8)</td>
<td>469 (63.6)</td>
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<td>Periannular complications</td>
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<td>Abscess</td>
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<td>126 (17.1)</td>
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<td>Pseudoaneurysm</td>
<td>21 (13.5)</td>
<td>111 (15)</td>
<td>0.613</td>
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<td>Fistula</td>
<td>6 (3.8)</td>
<td>26 (3.5)</td>
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<tr>
<td>Severe systolic dysfunction</td>
<td>8 (6.6)</td>
<td>9 (1.7)</td>
<td>0.011</td>
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Values are n (%). Bold values are significant.

### Table 4  Clinical events during in-hospital evolution in 894 episodes of infective endocarditis

<table>
<thead>
<tr>
<th></th>
<th>SS at anytime</th>
<th>Without SS</th>
<th>P-value</th>
</tr>
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<tr>
<td></td>
<td>Group I (n = 156)</td>
<td>Group II (n = 738)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>109 (69.9)</td>
<td>367 (49.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>CNS embolism</td>
<td>31 (19.9)</td>
<td>127 (17.2)</td>
<td>0.428</td>
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<td>Spleen embolism</td>
<td>18 (11.5)</td>
<td>52 (7)</td>
<td>0.058</td>
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<tr>
<td>Liver embolism</td>
<td>3 (1.9)</td>
<td>2 (0.3)</td>
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<td>Kidney embolism</td>
<td>5 (3.2)</td>
<td>11 (1.5)</td>
<td>0.175</td>
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<td>Limb embolism</td>
<td>19 (12.2)</td>
<td>54 (7.3)</td>
<td>0.044</td>
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<td>Other embolisms</td>
<td>35 (22.4)</td>
<td>133 (18)</td>
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<tr>
<td>Acute renal insufficiency</td>
<td>47 (30.1)</td>
<td>125 (16.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AV block</td>
<td>8 (5.1)</td>
<td>57 (7.7)</td>
<td>0.275</td>
</tr>
<tr>
<td>Persistent infection</td>
<td>118 (75.6)</td>
<td>201 (27.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>70 (44.9)</td>
<td>427 (57.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Death</td>
<td>114 (73.1)</td>
<td>132 (17.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CNS, central nervous system; AV block, atrioventricular block.
Values are n (%). Bold values are significant.
to cardiovascular disease, infection is one of the leading causes of death in hospitalized patients with diabetes. The reasons for this include abnormalities in cell-mediated immunity and phagocyte function, diminished vascularization, as well as an increased rate of colonization of S. aureus. Increased susceptibility to nosocomial bacterial infections in patients who are experiencing a critical illness like cancer is also well known.35

As expected, S. aureus infections were independently associated with SS. This virulent microorganism has been associated with poor prognosis and a high likelihood of SS of any origin.36,37 Moreover, many investigations have demonstrated the association of S. aureus infection with an unfavourable clinical course, higher rates of persistent infection, and higher mortality in IE.3,4,6–11,13,37–39 In this series, patients with SS had more frequently an acute clinical onset and a more aggressive clinical course of the disease (confusional syndrome, acute abdominal syndrome, heart failure), most probably related to virulent causative microorganisms such as S. aureus, and Gram-negative bacilli.

Acute renal failure is known to be a systemic manifestation of IE severity.20 In our series, acute renal failure at admission was associated with SS. In other studies, acute renal insufficiency was also related to the development of SS of any origin.60 The presence of supraventricular tachycardia was more frequent in patients with SS. In severe sepsis, tachycardia increases the cardiac output and the blood flow to tissues as a host defence mechanism against infection. In IE, tachycardia may also occur as a result of severe valvular failure, sepsis-induced myocardial depression, myocarditis, or severe anaemia. Nonetheless, the onset of new supraventricular arrhythmias in patients with infection appears to be a manifestation of multiple system organ failure as it is closely associated with severe sepsis.45–47

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Prognostic implications of the vegetation size at admission are still a matter of controversy. In this and other studies,46 the size of vegetation at admission measured by TOE was independently associated with development of SS. Valvular vegetation is a sign of local infection. How local infection leads to multi-organ dysfunction and hypotension is uncertain. Our hypothesis is that uncontrolled local infection eventuates in bacteraemia. Thereafter, circulating bacteria or their products, stimulate inflammatory reactions within the vasculature and other tissues, leading to organ dysfunction and hypotension. Contrary to this hypothesis, other authors suggest that circulating bacteria do not directly trigger SS.49 In fact, the risk for developing severe sepsis and SS has not correlated directly with the density of isolated bacteria in the patients’ blood.50 In our series the fraction of patients who had positive culture was not greater among those with SS. Bacterial toxins or other systemic or local inflammatory mediators might trigger SS.

In our study, when analysing patients’ outcome, subjects with SS underwent surgery much less frequently and had a higher mortality than those without. In addition, patients with SS who underwent surgery had a mortality rate lower than that of those who received medical therapy alone. These facts suggest that prognosis might depend largely on the amenability to treat the local process. Nonetheless, it is not fully established if surgery improves prognosis in these patients, since surgery under these circumstances is associated with high mortality rates.

Three aims are the cornerstone of therapy in patients with IE and SS: rapid administration of iv high-dose adequate antibiotics, generous use of fluid supply and vasopressors to reverse hypotension and tissue hypoperfusion (sepsis-induced renal insufficiency is usually reversible), and prompt removal of the infected tissue (valves, abscesses, infected devices, and other distant infectious metastatic lesions). Some authors have suggested that despite

Table 5 Independent predictors of septic shock development at anytime

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1.63</td>
<td>0.95–2.81</td>
<td>0.073</td>
</tr>
<tr>
<td>S. aureus</td>
<td>3.50</td>
<td>2.13–5.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute renal insufficiency</td>
<td>3.67</td>
<td>1.67–8.08</td>
<td>0.001</td>
</tr>
<tr>
<td>Vegetation size ≥ 15 mm</td>
<td>2.43</td>
<td>1.35–4.38</td>
<td>0.003</td>
</tr>
<tr>
<td>Abscesses</td>
<td>1.79</td>
<td>1.04–3.08</td>
<td>0.034</td>
</tr>
<tr>
<td>Signs of persistent infection</td>
<td>10.98</td>
<td>6.51–18.51</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 6 Independent predictors of in-hospital mortality

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock at anytime</td>
<td>7.07</td>
<td>4.05–12.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.36</td>
<td>1.54–3.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Periannular complications</td>
<td>2.41</td>
<td>1.53–3.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Signs of persistent infection</td>
<td>1.87</td>
<td>1.19–2.94</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table 7 Independent predictors of new-onset septic shock during hospitalization

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>2.06</td>
<td>1.16–3.68</td>
<td>0.016</td>
</tr>
<tr>
<td>S. aureus</td>
<td>2.97</td>
<td>1.72–5.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute renal insufficiency</td>
<td>3.22</td>
<td>1.28–8.07</td>
<td>0.016</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>3.29</td>
<td>1.14–9.44</td>
<td>0.033</td>
</tr>
<tr>
<td>Vegetation size ≥ 15 mm</td>
<td>1.21</td>
<td>0.65–2.25</td>
<td>0.080</td>
</tr>
<tr>
<td>Signs of persistent infection</td>
<td>9.80</td>
<td>5.48–17.52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

...
removal of infection foci is a key element to control SS, it entails a high risk in patients with IE, and so justifies a conservative management. If we consider SS as a manifestation of persistent infection, urgent surgery is advised in this setting as this condition indicates failure of medical management and is associated with high mortality. Nevertheless, one may decide not to operate if severe comorbidity exists or the patient is in an extreme critical condition.

Findings of the present work might reinforce a strategy of early surgery in patients who have high risk for developing SS.

A large, randomized study, might clarify whether cardiac surgery would improve the grim prognosis of patients with IE and SS.

Limitations
This study has several limitations. It is part of a multiproposal prospective collection with a large number of cases, but it has potentially referral bias because all the participants are tertiary care centres.

Severe sepsis and SS may be confusing terms, and although the definition of SS was clearly stated in methods, a gradation of the severity of SS could have been useful for patients’ stratification risk. Circulating biological markers, such as plasma IL-6, IL-10, TNF, pro-calcitonin levels, and other parameters that might correlate with patients’ outcome, were not studied. Prognostic scores based on bedside evaluations, such as the APACHE II, and the sequential organ failure assessment, were not systematically performed.

Conclusions
We conclude that in patients with IE, the presence of diabetes, acute renal insufficiency, S. aureus infection, supraventricular tachycardia, vegetation size (≥15 mm), and signs of persistent infection are associated with the development of SS. Mortality in patients with IE and SS is much higher than in those without SS. Those patients with SS who did not undergo surgery had the poorest prognosis.

Supplementary material
Supplementary material is available at European Heart Journal online.

Conflict of interest: none declared.

References
the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388–2422.


