Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study†

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Aims The aim here is to analyse epidemiology, optimal treatment, and predictors of 6-month mortality in infective endocarditis (IE).

Methods and results A prospective observational cohort study included 193 patients with 203 episodes of definite IE by the modified Duke criteria. Thirty-four percent of episodes involved prosthetic valves. Thirty-three percent of episodes were nosocomial. Forty-three percent included staphylococci, 26% streptococci, and 17% enterococci. At least one complication occurred in 79% of the episodes and 63% had surgical intervention. Six-month mortality was 22%: 33% for staphylococci, 24% for enterococci, and 8% for streptococci. Seventy-four percent of patients with a contraindication to surgery died when compared with 7% with medical treatment without a contraindication and 16% with surgical treatment. In multivariable logistic regression, predictors of 6-month mortality were age (P = 0.03), the causative microorganism (P = 0.04), and treatment group (P < 0.001).

Conclusion Compared with older series, we observed more prosthetic valve IE, nosocomial IE, and surgery. Staphylococcus aureus and Enterococcus faecalis were predominant microorganisms. Age, staphylococci, and a contraindication to surgery predicted 6-month mortality. Nearly half of deaths had a contraindication to surgery. Six-month mortality did not differ significantly between patients who received surgical treatment as against those who received medical treatment without a contraindication to surgery.

KEYWORDS
Endocarditis; Microbiology; Duke criteria; Cardiac surgery; Outcome

Introduction

The incidence of infective endocarditis (IE) is rising. Several authors suggest that epidemiological features of IE may have changed during the last decades because of an increase in degenerative valvular disease in the elderly, placement of prosthetic valves, and exposure to invasive procedures and nosocomial bacteremia.1–4 In some series, Staphylococcus aureus has emerged as the most common cause of IE and rates of Streptococcus viridans seem to decrease.3,5,6 Despite progress in diagnostic and therapeutic accuracy, almost half of IE episodes have at least one complication.6,7 Although lower mortality rates have been observed over the last 3 decades, overall mortality remains as high as 20–25%.6

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Clinical research
Valvular heart disease
Infective endocarditis

Data collection
All data were prospectively collected in a database following a predefined protocol designed by W.E. Peetemans, P. Herijgers, and M.-C. Herregods. The protocol included registration of epidemiological and microbiological features, echocardiography data, diagnosis of definite IE according to the modified Duke criteria, treatment strategy according to the American Heart Association guidelines with predefined indications for surgical intervention, and 6-month follow-up. All data were independently reviewed by three experts.

(i) Epidemiological features included age, sex, predisposing heart disease, and risk factors.
(ii) Microbiological features included blood cultures, serology, valve- or tissue cultures, and microscopy. For episodes with blood cultures that remained negative, specific analyses were performed, including additional sets of blood cultures on enriched media and serological tests for C. burnetti, Brucella spp., Mycoplasma pneumoniae, Chlamydia spp., Aspergillus spp., and Bartonella spp.
(iii) Diagnostic tools included transthoracic and transoesophageal echocardiography (TEE). Measurements of vegetation length were performed in various planes. In the presence of multiple vegetations, the largest length was used for analysis. In three patients, echocardiography results were not completely available because they underwent cardiac surgery immediately after admission because of severe, life-threatening shock.
(iv) Effective treatment groups included medical and surgical treatment. Indications for surgery were severe valvular dysfunction with heart failure, severe valvular dysfunction without heart failure, abscess or perivalvular extension, failure of conservative medical treatment, large vegetations with high risk of embolization, or (recurrent) embolization during antibiotic treatment and pacemaker infection. Contraindications to surgery included major cerebrovascular events with haemorrhagic aspect on CT scan, history of multiple or technically difficult surgical procedures, high operative risk because of cardiopulmonary status, and a poor prognosis for other comorbid conditions.
(v) Course, complications before admission, during hospitalization, and up to 6-month follow-up. Septic embolism at fundoscopic examination was not counted in the group of embolization. At 4 and 8 weeks follow-up, a transthoracic echocardiography and an outpatient visit were scheduled and reported to our centre if done by a referring cardiologist. At 6-month follow-up, an outpatient visit and TEE were provided with registration of heart failure, sequelae of embolization and metastatic infection, and echocardiography features. Out of 203 episodes, only three were missed at late follow-up: one was a political refugee and two patients moved to another city without leaving contact data.

Definitions
Prosthetic valve endocarditis (PVE) was classified as early or late, depending on when infection was diagnosed: early PVE within 12 months after surgery and late PVE after 12 months.

Nosocomial IE was defined as an infection occurring >72 h after admission to the hospital or IE acquired in association with a significant invasive procedure performed during a recent hospitalization ≤8 weeks before the onset of symptoms.

Persistent infection was defined as a repeat episode of IE caused by the same microorganism developing <1 year after the first episode.

Endpoint
This prospective observational cohort study aimed to perform a descriptive analysis of a contemporary patient population and to define optimal effective treatment groups and identify predictors of 6-month mortality in patients with IE.

Statistical analysis
Continuous data were presented as medians and interquartile ranges (IQR), unless stated otherwise. In bivariable and multivariable analyses about 6-month mortality rate, only first episodes were included. Continuous variables were compared with the Mann–Whitney U test and categorical variables with the chi² test or Fisher’s exact test. In order to assess linearity, the quadratic age effect has been introduced in the model, and it was not found statistically significant. The patient variables that were analysed in the bivariable analysis included age, gender, nidus of infection (prosthetic, native, other), referral, nosocomial or community origin, causative microorganism, embolism, heart failure, and treatment group (surgical therapy, medical therapy due to and without a contraindication to surgery). Variables that tended to be significantly associated with death in the bivariable analysis were included in the multivariable logistic regression analysis. Multivariable logistic regression analysis was performed to identify independent prognostic factors for death. Variables introduced in the multivariable model included age, gender, the nidus of infection, the causative microorganism, and treatment group. The significance level used in bivariable analysis was P < 0.1 and in multivariable analysis P < 0.05. All the reported P-values were two-sided.

Six-month survival according to treatment group (Figure 1) was estimated by the Kaplan–Meier method, using the Bonferroni correction. Statistical analysis was performed with the SPSS software package (version 10.0, Chicago, IL, USA).

Results
Epidemiology
Overall, 193 patients suffered from 203 IE episodes, with a male/female ratio of 3/2. The median age was 67 years (IQR 54–73). In the study, 55% (n = 112) of episodes were referred from another hospital, 33% (n = 67) were nosocomial IE, 34% (n = 70) of episodes involved prosthetic valves, and 26% (n = 18) were of early and 74% (n = 52) of late post-operative onset. Of the prosthetic valves, 59% were mechanical, 36% bioprosthetic, 3% homografts, and 7% valve reconstructions. Fifteen percent (n = 30) of episodes presented with two infected valvular sites. (Table 1).

The median time between onset of symptoms and diagnosis of IE was 8 days (IQR 3–15). Diagnostic delays were due to the atypical presentation of IE and the presence of long-lasting fever associated with other symptoms such as cough, diarrhoea, or urinary tract symptoms. Other diagnostic delays were due to difficult to culture or identify microorganisms (e.g. C. burnetti), the fact that patients with low-grade fever or weight loss waited long before visiting a physician, and the suboptimal performance of an initial TTE that may have overlooked small vegetations before diagnosis was established by TEE.
The most frequent predisposing acquired cardiac condition for native valve endocarditis (NVE) was degenerative valvular disease in 55% (71/129) of episodes. Mitral valve prolapse was present in 9% (n = 19) of patients, and 12% (n = 24) had prior IE. The most frequent predisposing congenital cardiac condition was a bicuspid aortic valve in 5% (n = 11) of patients. In 16% (n = 32), no predisposing heart disease was discernible. Twenty-seven patients (13%) were immune-suppressed, five (2%) were haemodialysis patients, 13 (6%) had cancer, 19 (9%) had chronic obstructive pulmonary disease, 24 (12%) had diabetes mellitus, and three (1%) had liver cirrhosis. Two patients had illegal substance abuse.

### Microbiology

The predominant causative microorganisms were staphylococci, isolated in 43% (n = 87) of episodes: *S. aureus* (n = 62, 31%), coagulase-negative staphylococci (CoNS, n = 23, 11%), and two *Staphylococcus lugdunensis*. Twenty-four percent (15/62) were methicillin-resistant *S. aureus* (MRSA). Streptococci (n = 52, 26%) were *S. viridans* (n = 25, 12%), *Streptococcus bovis* (n = 16, 8%), and others. Enterococci (n = 34, 17%) were *Enterococcus faecalis* (n = 30, 15%), *Enterococcus faecium* (n = 3, 2%), and one *Enterococcus durans*. Both in community-acquired and nosocomial IE, *S. aureus* was the most frequent causative agent (Table 2). *S. viridans* IE was mainly community-acquired, whereas enterococcal IE was nearly equally distributed between community and nosocomial origin. Fifty percent (n = 5) of nosocomial enterococcal endocarditis was due to urinary or gastrointestinal tract procedures. In NVE, *S. aureus* was the prevailing organism, followed by *S. viridans, E. faecalis*, and *S. bovis*. *S. bovis* was associated with intestinal adenoma or carcinoma in 63% (n = 10) of episodes. In PVE, *S. aureus, CoNS, and E. faecalis* were the prevailing organisms. All episodes of *S. viridans* PVE were of late onset. Culture-negative endocarditis (CNE) was registered in 11% (n = 23). In 66% of episodes with negative blood cultures, antibiotic therapy had been administered before blood cultures were taken. In only a small proportion (4%), IE was culture-negative without previous antibiotic administration.

### Echocardiography data

Echocardiography examinations in our hospital were available in 200 episodes (99%). The great majority (92%) underwent TEE, and 8% had only a transsthoracic echocardiography due to urgent cardiac surgery or IE detected peroperatively. In episodes with vegetation size ≥10 mm, 34% had embolism vs. 17% in episodes with vegetation size <10 mm (P = 0.004). The mitral valve was associated with embolization in 24% and the aortic valve in 20% (P = 0.52).

Overall, 25 of 200 episodes (13%) had abscess on echocardiography. Pre-operatively performed echocardiography (n = 124) detected abscess in 19 episodes (15%).

Six patients with a contraindication to surgery had abscess on initial TEE. Newly developed severe regurgitation was detected in 95 episodes (48%).

### Treatment

Combined medical and surgical treatment was performed in 63% (n = 127) of episodes. Fifteen percent (n = 31) of episodes had a contraindication to surgery, and 79% (n = 88)
of the referred IE episodes needed surgical intervention. The rate of surgery for NVE was 71% (n = 92) and for PVE 41% (n = 29, P < 0.001).

Table 3 summarizes the primary indications and contraindications to surgery. Surgical intervention was mainly indicated because of congestive heart failure. Patients with this indication had NYHA class III or IV and severe valvular regurgitation greater than or equal to 3/4. Peroperatively, abscess was detected in 38% (n = 48) of episodes. Nearly half (14/29) of undetected abscesses was localized on the posterior mitral annulus. The median time from diagnosis to surgical intervention was 6 days. Early (= within 7 days) surgical intervention was performed in 67 episodes (53%), and 31 episodes were operated within the first 24 h after diagnosis. Episodes due to CoNS and S. aureus were found to be operated earlier than those due to enterococci, S. bovis, and S. viridans (median 2.5, 3.5, 6.0, 19.5, and 27 days, respectively).

**Course and complications**

From admission up to 6-month follow-up, at least one complication was observed in 79% (n = 161) of episodes. Overall, congestive heart failure (n = 155) was the most
frequent complication followed by embolism \( (n = 57) \). The distribution of cerebral vs. peripheral embolism was 40/17, and 7\% \( (n = 4) \) of embolic events were both cerebral and peripheral. Two of 10 episodes with pacemaker IE had pulmonary embolism. Eighteen percent \( (10/57) \) of embolic events occurred after initiation of antibiotic therapy. Table 4 shows the distribution of complications.

During a follow-up period of 6 months, 11 episodes (7\%) presented with at least one complication: one embolic event, one metastatic infection, three surgical re-interventions for valvular disease, one permanent pacemaker, and five congestive heart failure.

Six patients (3\%) had persistent infection; two patients had CNE in the second episode, and one patient had CNE in the first episode and CoNS in the second.

### Outcome

The 6-month mortality rate was 22\% \( (n = 42) \). Nineteen patients (31\%) with PVE expired, and this was non-significantly higher than 22 patients with NVE (18\%, \( P = 0.09 \)). Sixteen patients (27\%) with nosocomial IE died, and this was non-significantly higher than 26 patients with community-acquired IE (19\%, \( P = 0.23 \)). Twenty patients (74\%) with a contraindication to surgery died, and this was significantly higher than three deaths (7\%) with medical treatment without a contraindication to surgery and than 19 deaths (16\%) with combined surgical–medical treatment \( (P < 0.001) \). (Figure 1).

The 6-month mortality rate was associated with the causative microorganism \( (P = 0.01) \): the highest mortality rate was observed for staphylococci (33\%, \( n = 26 \)) [\( S. aureus 32\% (n = 19) \) and CoNS 35\% \( (n = 7) \)]. The mortality rate of MRSA was 47\% \( (n = 7) \). The mortality rate in patients with enterococci was 24\% \( (n = 8) \) and streptococci 8\% \( (n = 4) \). One with \( S. bovis \) and two with \( S. agalactiae \) died due to cardiac inoperability and one with \( S. viridans \) died due to electromechanical dissociation post-operatively. Two patients with CNE, one with HACEK IE, and one with Pseudomonas aeruginosa IE expired. Figure 2 shows the outcome according to the causative microorganisms and the nature of the affected valve.

### Predictors of 6-month mortality

The patient variables that were analysed included age, gender, nidus of infection (prosthetic, native, other), referral, nosocomial or community origin, causative microorganism, embolism, heart failure, and effective treatment group (surgical, medical with and without a contraindication to surgery). In bivariable analyses, factors associated with 6-month mortality were age \( (P < 0.001) \), female gender \( (P = 0.04) \), causative microorganism \( (P = 0.009) \), nidus of infection \( (P = 0.09) \), and treatment group \( (P < 0.001) \). More specifically, staphylococci, PVE, and a contraindication to surgery carried a worse outcome (Table 5). Six-month mortality was non-significantly higher in patients with embolism \( (P = 0.1) \). Multivariable logistic regression revealed that age \( (OR, 1.1; 95\% CI, 1–1.1; P = 0.03) \), the causative microorganism \( (P = 0.04) \), and treatment group \( (P < 0.001) \) were independently associated with 6-month mortality.

### Table 4 Complications of IE before admission and during hospitalization

<table>
<thead>
<tr>
<th>Complication</th>
<th>Before admission</th>
<th>During hospitalization</th>
<th>Total (% of all IE episodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical therapy</td>
<td>Surgical and medical therapy</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>70</td>
<td>12</td>
<td>61</td>
</tr>
<tr>
<td>Embolization</td>
<td>47</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Metastatic infection</td>
<td>13</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Septic shock</td>
<td>14</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Cardiovascular collapse</td>
<td>4</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Mycotic aneurysm</td>
<td>4</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Pacemaker removal</td>
<td>–</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Surgical re-intervention</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Redo valve surgery</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Other^</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sternotis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

^Including one resection of pseudo-aneurysm and three episodes with thoracotomy because of haemothorax.
mortality (predictive accuracy of the model was 85%). Particularly, staphylococcal and enterococcal IE had a worse prognosis compared with streptococcal IE; 6-month mortality in patients with combined surgical–medical treatment vs. exclusively medical therapy in patients without a contraindication to surgery was not statistically significantly different ($P = 0.14$).

**Discussion**

This prospective observational cohort study revealed changing trends in epidemiology, aetiology, microbiology, treatment, and outcome of IE in the new millennium.

This study of 203 IE episodes found an increasing number of IE patients with higher age associated with degenerative valvular disease. Owing to the older patient population and greater availability of cardiac surgery, the rate of PVE is increasing compared with older series. The proportion of nosocomial IE (33%) was high in our study compared with previous series (7–29%) and may be due to a high rate of prior hospitalization and invasive procedures. The relative incidence of cardiac disorders predisposing to IE has changed, shifting from rheumatic heart disease in younger patients to degenerative valvular disease in the elderly. Risk factors for IE were recognizable in many episodes but those that may have been prevented by antibiotic prophylaxis represented only 25% of all IE episodes. The prevalence of episodes without clear underlying heart disease predisposing to IE was low (16%) compared with 29–47% in other series. Staphylococci, in particular *S. aureus*, and *E. faecalis* were the most frequent causative microorganisms. *S. aureus* predominated in community-acquired and nosocomial IE as well as in NVE and PVE. Recent series also found *S. aureus* as the main microorganism; however, in previous decennia and also in a few recent studies, *S. viridans* was still the prevailing aetiological agent. *E. faecalis* was the second most frequent microorganism in this study. Enterococcal IE is emerging, probably due to increased exposure to invasive urinary and gastrointestinal tract procedures. Nosocomial enterococcaemia is currently a minor criterion in the modified Duke criteria. In our series, enterococci were nearly equally distributed between community and nosocomial origin, suggesting thatnosocomial enterococcaemia may be added to community-acquired enterococcaemia and become a major criterion as proposed before for *S. aureus*. The incidence of *S. viridans* IE seems to decrease. On the contrary, *S. bovis* IE becomes more prevalent, probably related to an older population associated with intestinal adenoma or carcinoma (63% in our series), and this finding supports the recommendation to perform a colonoscopy.

Pacemaker IE was caused entirely by staphylococci, except for one CNE. This finding is in agreement with another pacemaker IE series. We reported 11% of episodes having CNE and these were in 66% due to prior antibiotics. Previous series have reported frequencies of CNE of 9–25%. In only 4%, IE was culture-negative without previous antibiotic administration, and this is in line with earlier data (5–7%).

Diagnostic delay between onset of symptoms and diagnosis was 8 days and could decrease by higher clinical suspicion of IE in patients with persistent fever, prosthetic valve, previous hospital procedures, or surgery and by early initial performance of TEE instead of TTE.

At least one complication was present in 79%. This high number of complications may be due the high rates of staphylococcal IE, PVE, and nosocomial IE. Another reason is that severely ill IE episodes were transferred to our hospital. Furthermore, this study prospectively recorded all events from admission up to 6-month follow-up.

### Table 5 Bivariable association between patient characteristics and 6-month mortality

<table>
<thead>
<tr>
<th></th>
<th>Total $n = 193$ (%)</th>
<th>Survived $n = 151$ (%)</th>
<th>Died $n = 42$ (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>$63 \pm 1.1$</td>
<td>$61 \pm 1.3$</td>
<td>$71 \pm 1.4$</td>
<td>0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>118 (61)</td>
<td>98 (65)</td>
<td>20 (48)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nidus of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native valve</td>
<td>123 (64)</td>
<td>101 (67)</td>
<td>22 (52)</td>
<td></td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>61 (32)</td>
<td>42 (28)</td>
<td>19 (45)</td>
<td></td>
</tr>
<tr>
<td>Other localization</td>
<td>9 (5)</td>
<td>8 (5)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Transferred patient</td>
<td>109 (56)</td>
<td>86 (57)</td>
<td>23 (55)</td>
<td>0.8</td>
</tr>
<tr>
<td>Nosocomial IE</td>
<td>59 (31)</td>
<td>43 (28)</td>
<td>16 (38)</td>
<td>0.2</td>
</tr>
<tr>
<td>Causative microorganism</td>
<td></td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>80 (41)</td>
<td>54 (36)</td>
<td>26 (62)</td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>52 (27)</td>
<td>48 (32)</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>Enterococci</td>
<td>33 (17)</td>
<td>25 (17)</td>
<td>8 (19)</td>
<td></td>
</tr>
<tr>
<td>Culture-negative</td>
<td>21 (11)</td>
<td>19 (13)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7 (4)</td>
<td>5 (3)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Embolism</td>
<td>50 (26)</td>
<td>35 (23)</td>
<td>15 (36)</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>93 (48)</td>
<td>72 (48)</td>
<td>21 (50)</td>
<td>0.8</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical without contraindication</td>
<td>44 (23)</td>
<td>41 (27)</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>Medical due to contraindication</td>
<td>27 (10)</td>
<td>7 (5)</td>
<td>20 (48)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>122 (63)</td>
<td>103 (68)</td>
<td>19 (45)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SEM of number.
TEE was performed in 92% of episodes and remains the diagnostic test of choice. There was a significant association between embolism and vegetation size ≥10 mm. Echocardiography detected abscess in only 40% of surgically treated patients with abscess, which suggests a major preoperative underestimation of the severity of cardiac involvement. Nearly half of undetected abscesses were localized on the posterior mitral annulus. Further study is required to investigate in which cases and circumstances abscesses are missed.

Notable was the high rate of surgical intervention (63%) in this series. A high number of PVE and S. aureus IE may be the major reasons for this finding. The high rate of surgery in patients with NVE may be due to the referral patient population. The percentage of surgical intervention in previous series varied from 18 to 54%, and our results reflect the tendency of clinicians to proceed to surgery more often than before. Furthermore, surgery is often performed early in the course of the disease, as in our series. The favourable outcome of valve surgery for IE in previous series has contributed considerably to this evolving trend. The 16% mortality rate in patients with combined surgical–medical therapy was comparable with data from the literature and was lower than in medically treated patients (32%). This finding is consistent with previously published series. However, 6-month mortality in the medically treated group was very high because this group included a large number of patients with a contraindication to cardiac surgery. Of the patients in the medically treated group who died, 87% had a contraindication to surgery. Almost half of deaths (20/42) included patients with a contraindication to surgery. Only three patients (7%) in the medically treated group without a contraindication expired. A limitation of previous retrospective studies is that most severely ill patients who were not considered good candidates for surgery remained in the medical group, evidently distorting the results. We found that the outcome in surgically and medically treated patients without a contraindication to surgery was not statistically significantly different. Optimal timing and indication for surgery deserve further study.

Six-month mortality was non-significantly higher for PVE than for NVE and significantly higher for staphylococci than for other microorganisms, as found in other series. CoNS have been considered to be low-virulence pathogens, but recent studies, supported by the present study, have demonstrated that CoNS IE are associated with a high mortality rate.

Multivariable logistic regression revealed that age, the causative microorganism (staphylococci), and treatment group (a contraindication to surgery) were predictors of 6-month mortality. The high prevalence of S. aureus IE and its acute onset and poor prognosis stress the importance of an early diagnosis and treatment. Further improvement in the management of S. aureus IE is needed.

Despite diagnostic and therapeutic advances, mortality is still high in IE. A reason for this finding may be that an older patient population is associated with more PVE and nosocomial IE, which are both associated with higher mortality rates. The elderly have more comorbid conditions or a debilitated cardiopulmonary status with subsequently a higher risk for surgical intervention or contraindication to surgery. Another explanation is an increasing amount of microorganisms associated with a worse prognosis (staphylococci, enterococci) and a decreasing amount of microorganisms associated with a good prognosis (streptococci). Moreover, worldwide, there is an increasing amount of MRSA, associated with high mortality rates.

The main limitation of the study is the fact that it reports from a single tertiary care institution and referral centre that may have caused a selection bias towards more severe or complicated cases, resulting in limitations to the generalization of the results.

The management of IE remains challenging. The observed changes towards more S. aureus and enterococcal IE, PVE and nosocomial IE, which are all associated with a more severe prognosis, underscores the need for an integrated and multidisciplinary approach.

Nearly half of all deaths included patients with a contraindication to surgery, suggesting that contraindications must be thoroughly evaluated and every effort should be taken to prepare these patients for surgery.

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