Short communication

Infective endocarditis: Clinical presentation, etiology, and early predictors of in-hospital case fatality

Endocardites infectieuses : présentation clinique, diagnostic microbiologique et facteurs prédictifs de mortalité précoce

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Abstract

Objective. – We aimed to assess the clinical presentation, microbial etiology and outcome of patients presenting with infective endocarditis (IE).

Patients and methods. – We conducted a four-year retrospective study including all patients presenting with IE.

Results. – We included 121 patients in the study. The median age was 74.8 years. Most patients had native valve IE (57%). Staphylococcus aureus accounted for 24.8% of all IE. Surgery was indicated for 70 patients (57.9%) but actually performed in only 55 (44.7%). Factors associated with surgery were younger age (P = 0.002) and prosthetic valve IE (P = 0.001). Risk factors associated with in-hospital mortality were diabetes mellitus (OR = 3.17), chronic renal insufficiency (OR = 6.62), and surgical indication (OR = 3.49). Mortality of patients who underwent surgery was one sixth of that of patients with surgical indication who did not have the surgery (P < 0.001).

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Keywords: Infective endocarditis; Epidemiology

Résumé

Objectif. – Définir la présentation clinique, la microbiologie et le pronostic des patients atteints d’endocardite infectieuse (EI).

Patients et méthodes. – Étude rétrospective sur quatre ans incluant tous les cas d’EI.

Résultats. – Au total, 121 patients (âge médian de 74,8 ans) ont été inclus dans l’étude. Parmi eux, 57 % présentaient une EI sur valve native. Staphylococcus aureus représentait 24,8 % des microorganismes isolés. Une indication opératoire (IO) était présente chez 70 patients (57,9 %) mais réalisée que chez 55 (44,7 %). Les facteurs associés à la réalisation d’une chirurgie étaient le jeune âge des patients (p = 0,002) et la présence d’une prothèse valvulaire (p = 0,001). Le diabète (OR = 3,17), l’insuffisance rénale chronique (OR = 6,62) et l’IO (OR = 3,49) semblaient associés à la mortalité. La mortalité des patients avec une chirurgie cardiaque était six fois inférieure à celle des patients avec indication de chirurgie mais non réalisée (p < 0,001).

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Mots clés : Endocardite infectieuse ; Épidémiologie

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1. Background

Infective endocarditis (IE) is associated with high morbidity and mortality. The epidemiology of IE has changed since the first evaluation of 209 case patients by Sir William Osler in 1885 [1]. However, prevention strategies did not manage to reduce the incidence of this life-threatening disease currently reaching 33.8 case patients/million patient-years in France [2]. In-hospital case fatality for patients presenting with IE reaches 20% [3] with a one-year case fatality of 25% [4]. Although aggressive therapy has become essential to saving lives and eradicating infection in many patients, reported rates of surgery remain heterogeneous and the benefit of surgery on mortality is arguable. Nevertheless, recent study results support an early surgical management of patients presenting with complicated IE [5].

2. Methods

2.1. Study design

We performed a retrospective study in a 537-bed teaching hospital in Paris, France, from January 2009 to December 2013.

2.2. Patient selection

All patients aged 18 years or older presenting with IE, as defined by modified Duke criteria, were included in the study using data from the hospital record database [6]. All medical files were reviewed and classified according to Duke classification. Prosthetic valve endocarditis was considered early-onset if it occurred within a year from valve implantation and late-onset if it occurred thereafter. Data was retrospectively collected.

2.3. Definition

“Stroke” was defined as an acute neurological deficit of vascular etiology lasting >24 hours and was further characterized as ischemic or hemorrhagic using neuroimaging results.

Antimicrobial therapy initiation was defined as the first day of appropriate antibiotic therapy according to antimicrobial results.

Cardiac surgery during hospitalization was indicated on the basis of the 2009 European Society of Cardiology (ESC) guidelines [7] and the final decision was made in agreement with the cardiologists and cardiac surgeons. Time to surgery was defined as the interval between IE diagnosis and the date of surgery.

2.4. Statistical analysis

Continuous variables were reported as medians with 25th and 75th percentiles. Categorical variables were reported as frequencies and percentages of the specified group. Univariate comparisons were made using Chi² test or Kruskal Wallis test as appropriate. A difference was considered significant at a level of 5% (alpha risk). All analyses were performed using the Epi Info software, version 7.0 (CDC, Atlanta).

3. Results

3.1. Epidemiology

A total of 121 patients were included in the study: 87 presented with definite IE and 34 with possible IE according to modified Duke criteria [6]. The median age was 74.8 years (mean 71.1 years; IQR 62.3–81.2 years). Most patients (57%) had native valve IE. Predisposing conditions were common in patients presenting with IE. Patients characteristics are presented in Table 1. The most common underlying condition was diabetes mellitus (14.4%). Fever was only observed in 72.7% of patients.

The most common predisposing conditions were related to prior cardiac surgery (45.4%) for valve replacement (28%) or pacemaker (PM)/implantable cardioverter defibrillator (ICD) implantation (11.5%).

3.2. Microbiology

Blood cultures were performed for all patients to determine the disease-causing agent. A total of 15 patients (12.4%) had negative blood cultures. Among them eight had a molecular diagnosis performed by 16S rRNA gene PCR assay on valve: five were positive for Streptococcus mitis, Streptococcus gallolyticus, coagulase-negative Staphylococcus, and Pantoea agglomerans. Of those patients, 10 (66.7%) received
3.3. Surgical management of IE

Surgery was indicated for 70 patients (57.9%) but performed in only 55 (47.9%) (Table 2). Patients who underwent valve surgery were on average seven years younger (P=0.002) and were more likely to present with prosthetic valve and implantable cardiac electronic device-related IE (OR = 3.75, 95% CI = 1.65–8.52) than patients who did not have the surgery. Sex and staphylococcal infection were not statistically differently distributed in both groups. There was no difference in terms of in-hospital mortality between patients who benefited from a surgical management and patients who were only medically managed (14.5% and 18.1%, respectively, P = 0.592).

3.4. Complications

The overall in-hospital case fatality was 16.5% (20/121). Embolic events occurred in 51 of 121 patients (42.1%), mostly asymptomatic embolic events diagnosed on the basis of imaging results. The main sites of embolic infarction were the brain (n = 15, 29.4%) and spleen (n = 15, 29.4%). Other sites included the lungs (25.5%), kidneys (19.6%), and bones/vertebral disc (15.7%).

Factors associated with in-hospital mortality are presented in Table 3. Diabetes mellitus (OR = 3.17, 95% CI = 1.02–9.8), chronic renal insufficiency (OR = 6.62, 95% CI = 2.06–21.27), and indication for surgery according to ESC 2009 guidelines (OR = 3.48, 95% CI = 1.09–11.1) were significantly associated with poor outcome. A trend for staphylococcal infections was observed (OR = 2.39, 95% CI = 0.87–6.58). Factors such as valve status, systemic embolization, delay for negative blood culture, delay for surgery after diagnosis, and whether patients were treated in hospital with community-acquired and native

### Table 2
Factors associated with surgical management.

<table>
<thead>
<tr>
<th>Factors</th>
<th>No surgery, n = 66 (%)</th>
<th>Surgery, n = 55 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>74.4</td>
<td>67.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (36.4)</td>
<td>16 (29.1)</td>
<td>0.397</td>
</tr>
<tr>
<td>Male</td>
<td>42 (63.6)</td>
<td>39 (70.9)</td>
<td></td>
</tr>
<tr>
<td>Valve status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native valve</td>
<td>54 (81.8)</td>
<td>30 (54.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prosthetic valve/PM/ICD</td>
<td>12 (18.2)</td>
<td>25 (45.4)</td>
<td></td>
</tr>
<tr>
<td>Microbiology of IE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>18 (27.2)</td>
<td>12 (21.8)</td>
<td>0.489</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
<td>9 (13.6)</td>
<td>5 (9.1)</td>
<td>0.436</td>
</tr>
<tr>
<td>Streptococci spp</td>
<td>20 (30.3)</td>
<td>18 (32.7)</td>
<td>0.775</td>
</tr>
<tr>
<td>Enterococci spp</td>
<td>11 (16.7)</td>
<td>9 (16.4)</td>
<td>0.964</td>
</tr>
<tr>
<td>Other</td>
<td>8 (12.1)</td>
<td>11 (20)</td>
<td>0.236</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>12 (18.1)</td>
<td>8 (14.5)</td>
<td>0.592</td>
</tr>
</tbody>
</table>

PM: pacemaker; ICD: implantable cardioverter defibrillator.

### Table 3
Risk factors for in-hospital mortality; univariate analysis.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Survivors, n = 101</th>
<th>Non-survivors, n = 20</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>73.6</td>
<td>75.5</td>
<td>1.0</td>
</tr>
<tr>
<td>25th–75th percentile</td>
<td>61.6–81.8</td>
<td>65.3–78.8</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 (35.6)</td>
<td>4 (20)</td>
<td>0.113</td>
</tr>
<tr>
<td>Most common underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (11.9)</td>
<td>6 (30)</td>
<td>0.037</td>
</tr>
<tr>
<td>Moderate or severe renal diseases</td>
<td>38 (37.6)</td>
<td>16 (80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of IE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native valve</td>
<td>60 (59.4)</td>
<td>9 (45)</td>
<td>0.234</td>
</tr>
<tr>
<td>Prosthetic valve/PM/ICD</td>
<td>41 (40.6)</td>
<td>11 (55)</td>
<td></td>
</tr>
<tr>
<td>Site of the valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>37 (36.6)</td>
<td>7 (35)</td>
<td>0.890</td>
</tr>
<tr>
<td>Mitral</td>
<td>32 (31.7)</td>
<td>5 (25)</td>
<td>0.533</td>
</tr>
<tr>
<td>Right side</td>
<td>17 (16.8)</td>
<td>3 (15)</td>
<td>0.840</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (14.9)</td>
<td>5 (25)</td>
<td>0.264</td>
</tr>
<tr>
<td>Staphylococcus aureus infection</td>
<td>22 (21.8)</td>
<td>8 (40)</td>
<td>0.085</td>
</tr>
<tr>
<td>Streptococci spp infection</td>
<td>31 (30.7)</td>
<td>7 (35)</td>
<td>0.705</td>
</tr>
<tr>
<td>Systemic embolization</td>
<td>43 (42.6)</td>
<td>7 (35)</td>
<td>0.530</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td>54 (53.5)</td>
<td>16 (80)</td>
<td>0.03</td>
</tr>
<tr>
<td>Surgery actually performed</td>
<td>47 (46.5)</td>
<td>8 (40)</td>
<td>0.922</td>
</tr>
<tr>
<td>Delay for surgery after diagnosis (median, days)</td>
<td>7.7</td>
<td>10.5</td>
<td>0.263</td>
</tr>
<tr>
<td>Delay for negative blood culture (median, days)</td>
<td>4.5</td>
<td>3.5</td>
<td>0.414</td>
</tr>
</tbody>
</table>

PM: pacemaker; ICD: implantable cardioverter defibrillator.

IE is still a severe disease with high morbidity and mortality despite more than a century of advances in diagnosis and treatment. The results of our study revealed a change in IE patients’ characteristics. S. aureus is the most common cause of IE according to the international collaboration on endocarditis-prospective cohort study [8]. In our study HACEK (Haemophilus species, Actinobacillus actinoymetecomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) endocarditis was most frequently associated with the presence of mechanical valves/PM or ICD and those results are similar to Chambers’ [9]. We confirmed that the enterococcal IE group (16.5%) is the third most important group of IE after staphylococcal (36.4%) and streptococcal (31.4%) IEs. Our results also confirmed that community-acquired and native
valve-related IEs caused by *Enterococcus* spp are less frequently observed [10, 11].

4.1. Surgery

Complicated IE has become a surgical disease. A total of 55 of our patients (45.4%) underwent surgical therapy. It has been demonstrated that patients with indication for surgery who do not undergo surgery have a higher in-hospital case fatality (up to 80%) [12]. Surgery was indicated for 70 of our patients (57.8%) but only 55 (45.4%) actually underwent surgical therapy. The in-hospital mortality of patients presenting with IE for whom surgery was indicated and performed was one sixth of that of patients with surgical indication who did not undergo surgical therapy (14.5% vs 86.7%; *P*<0.001). The main factors associated with the performance of cardiac surgery were age and prosthetic valve/PM/ICD (patients who underwent surgery were younger (67.7 years vs 74.4 years; *P*=0.002) and were more likely to have had a prosthetic valve/PM/ICD-related IE).

4.2. Embolism

Two types of embolic events must be distinguished during infective endocarditis: (1) embolic events occurring before antibiotic therapy initiation [13] and (2) embolic events occurring during and after therapy which could be prevented by valve surgery [14].

In this study embolic events occurred in 42.1% of patients presenting with IE. This figure is similar to the ones observed in previous studies [15]. Unlike other studies [16, 17], we did not observe any significant difference in demographic characteristics, causative agent, and type of infective valve between the embolic and the non-embolic groups. The absence of difference may be due to a lack of statistical power and to the absence of echocardiographic data analysis. We did not observe any difference in terms of *S. aureus* infection between both groups but we observed an association between *S. aureus* infection and in-hospital mortality. In some studies, *S. aureus* infection was associated with both higher rates of complications and mortality in IE patients [17], whereas the authors of other studies did not find any association between embolism and the causative microorganism [18]. We evaluated the clinical impact of embolism. On the basis of previous studies, the group of patients presenting with embolism showed similar in-hospital mortality than patients without any embolism (17.1% vs 15.7%; *P*=0.694) [12].

4.3. In-hospital case fatality

In-hospital case fatality was similar to that reported in the literature [19]. We observed several factors associated with in-hospital mortality: chronic renal insufficiency, diabetes mellitus, and a trend for *S. aureus*-related IE. These factors have repeatedly been reported in previous studies [20].

Our study has several limitations. In spite of the retrospective nature of this study, some hospital stays for IE may not have been encoded with an IE-specific diagnostic code. Furthermore, we only studied in-hospital mortality. A six-month-mortality end point would have probably been more appropriate as the benefit of surgery can usually be observed at this point [20].

5. Conclusion

IE remains a severe and deadly disease despite recent advances in diagnosis and treatment. IE presentation is now more acute and is characterized by a high rate of *S. aureus* infection in patients with previous healthcare exposure. We also observed that surgery may play a crucial role in improving patients’ outcome. Nearly 50% of IE patients undergo surgery; early identification of surgical indications may therefore improve mortality.

Authors’ contribution

B.P. performed the statistical analysis and wrote the article. A.M., C.C., and J.C.N. contributed to writing the article. A.L. performed MICs. N.E.H., P.A., and R.C. contributed to developing the database. A.L.M. created the project and contributed to writing the article.

Disclosure of interest

The authors declare that they have no competing interest.

References
