Prevalence of infective endocarditis in patients with gram positive Cocci bacteraemia

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Methods

Introduction

Infective endocarditis (IE) is a serious complication of bacteremia and is most often caused by Gram positive cocci. Due to an unspecified presentation of symptoms, the diagnosis of IE might be delayed or even missed, which may worsen the course of the disease. We investigated the unspecific presentation of symptoms, the diagnosis of IE might be delayed due to an unspecified presentation of symptoms, the diagnosis of IE might be delayed or even missed, which may worsen the course of the disease. We investigated the prevalence of IE in patients where echocardiography was encouraged due to the presence of Gram positive Cocci bacteraemia.

Methods

The study included patients with Gram positive Cocci bacteraemia hospitalised at two Danish hospitals between March and December 2016. Information concerning echocardiography, demographics, and bacterial species was collected from the patients’ medical files. Patients without echocardiography were followed for six months to confirm or reject possible IE.

Results

Patients (n=585) hospitalised from March to December 2016 with Gram positive Cocci bacteraemia were included in the study. Patients without echocardiography performed during hospitalisation were followed through their patient files for six months. Patients were considered as not having IE if they were alive and not hospitalised within six months after the date of the positive blood culture. Patients, who did not have an echocardiography performed during hospitalisation were followed through their patient files for six months. Patients were considered as not having IE if they were alive and not hospitalised within six months after the date of the positive blood culture. Patients, who died without having an echocardiography performed, were categorised as “IE not excluded” unless the date of death was at least six months after inclusion in the study, in which case, patients were categorised as “IE excluded”. The study was performed in accordance with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (ntr. 2012-58-0004 (3-3013-1845/1)).

Statistical analysis

Binary data are shown as n (%) and continuous data as the mean with the associated standard deviation. Continuous variables were compared between two groups using the Student’s t-test and continuous data were compared between three groups using the ANOVA test. Binary variables were compared using the Chi-square test. The Kaplan-Meier survival curves were

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RESULTS

The study included 585 patients with Gram positive Coxiella burnetii pneumonia hospitalised at Herlev-Gentofte Hospital (n=379) and Nordsjællands Hospital (n=206). The study population was divided into patients who had a TOE and/or TTE performed (n=414) and patients who did not have a TOE and/or TTE performed (n=171); TOE was performed in 289 (49.4%) patients. Patients who underwent echocardiography were more likely to be male, had a significantly higher percentage of hypertension, diabetes mellitus, heart failure, valve prostheses, and rheumatologic disease compared with patients who did not undergo TOE/TTE (Table 1). Echocardiographic findings are presented in Table 2. Seventy-two (12.3%) patients were diagnosed with IE, 56 (9.6%) were categorised as IE not excluded, and 457 (78.1%) as IE excluded. Accordingly, the best estimate of the prevalence of IE in this study ranged from 12.3% to 21.9%. None of the patients who did not undergo echocardiography developed IE during the follow-up period (Figure 1).

Bacteria

The specific bacteria species are described in Table 3. A total of 389 patients (66.5%) had bacteriaemia of the most typical bacteria to cause IE, i.e., Staphylococcus aureus, non-haemolytic streptococci, Enterococcus faecalis, and coagulase-negative staphylococci. Of these bacteriaemia patients, 63 (16.2%) were diagnosed with IE, 30 (7.7%) were categorised as IE not excluded, and 296 (76.1%) did not have IE. Accordingly, the prevalence of IE among patients with infections of the most typical bacteria to cause IE ranged from 12.3% to 23.9%. Staphylococcus aureus, Enterococcus faecalis, and non-haemolytic streptococci accounted for the majority (80.5%) of IE cases (Table 4).

Clinical characteristics of IE patients

Patients with IE were primarily male and significantly older than patients in whom IE was excluded. A valve prosthesis, cardiac device, previous IE, dialysis, and rheumatologic disease occurred significantly more often among patients with IE compared with the other two groups. Furthermore, patients with IE had more frequently >50% positive blood cultures and a significantly longer duration of symptoms than patients with IE excluded and not excluded. The prevalence of cancer and nosocomial infection was lower in the group with IE compared with the other two patient groups (Table 2).

TABLE 1

Baseline characteristics of patients who had TTE/TOE

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Patients who underwent TTE/TOE (n=414)</th>
<th>Patients who did not undergo TTE/TOE (n=171)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years), (SD)</td>
<td>73.4 (14.5)</td>
<td>71.4 (18.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Female gender</td>
<td>159 (38.4)</td>
<td>91 (53.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>196 (47.3)</td>
<td>80 (46.8)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>238 (57.5)</td>
<td>78 (45.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>109 (26.3)</td>
<td>30 (17.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>COPD</td>
<td>61 (14.7)</td>
<td>19 (11.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Dialysis</td>
<td>34 (8.2)</td>
<td>7 (4.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cancer</td>
<td>94 (22.7)</td>
<td>49 (28.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Liver disease</td>
<td>21 (5.1)</td>
<td>15 (8.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Alcoholism*</td>
<td>73 (17.6)</td>
<td>21 (12.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Heart failure</td>
<td>56 (13.5)</td>
<td>12 (7.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart valve prosthesis</td>
<td>31 (7.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>CHD and valve disease without operation</td>
<td>28 (6.8)</td>
<td>7 (4.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiac device</td>
<td>30 (7.2)</td>
<td>6 (3.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous IE</td>
<td>9 (2.2)</td>
<td>3 (1.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Rheumatologic disease</td>
<td>71 (17.1)</td>
<td>18 (10.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Iatrogenic immunosuppression</td>
<td>80 (19.3)</td>
<td>35 (20.5)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Clinical characteristics of 585 patients included in the study and localisation of infective endocarditis. Data are given as n (%) unless otherwise noted. *Former or present alcoholism defined as severe overconsumption of alcohol based on patient files. **Defined as first positive blood culture in a patient >48 hours after admission. SD: Standard deviation. IE: Infective endocarditis. COPD: Chronic Obstructive Pulmonary Disease. CHD: Congenital Heart Disease.

Outcome

Surgical interventions were necessary in 15 (20.8%) patients with IE valve prosthesis implantation, n=12; pacemaker removal, n=3). The 30-day and 90-day mortality rates for IE patients vs. patients with IE excluded were 18.1% vs. 10.7% (p=0.11) and 30.6% vs. 15.3% (p=0.003), respectively. Kaplan-Meier survival curves are shown in Figure 2.

DISCUSSION

The most important findings in this study were that 12-22% of patients with Gram positive Coxiella burnetii had IE, and 16-24% of patients infected with common IE bacterial strains were diagnosed with IE. Staphylococcus aureus, Enterococcus faecalis, and non-haemolytic streptococci, were the most common bacterial strains to cause IE. The overall mortality among patients with IE was significantly higher than the mortality among patients without IE.
Previous studies focused on the prevalence of IE in patients with bacteremia from specific bacterial species. Vos et al. compared two matched groups of patients with Gram positive bacteremia. Patients in one group (study group) underwent echocardiography consecutively and patients in the control group underwent echocardiography occasionally. The study group had a higher prevalence of IE (19% vs. 7%), and the IE patients in this group had a lower mortality than IE patients in the control group, presumably due to the diagnosis and treatment of IE at an earlier stage [14]. This emphasizes the importance of conducting echocardiography early, preferably before clear clinical signs of IE present, which also supports our results. Vos et al. found a higher percentage of patients underwent echocardiographies than we did, and they only included patients with streptococci, enterococci, and Staphylococcus aureus bacteremia. Furthermore, the patients had to have one additional risk factor for IE to participate in the study. These factors could explain the higher prevalence of IE in their study vs. ours.

A 22-32% prevalence of IE was previously reported in patients with Staphylococcus aureus bacteremia [6-8]. In these studies, TTE and/or TOE were performed in all patients. In one of the studies, patients had to have more than one positive blood culture and suspected IE to fulfil the inclusion criteria and, furthermore, patients who only had a TTE performed without IE as the outcome were excluded [7]. As expected, these inclusion criteria led to a higher prevalence of IE in patients with Staphylococcus aureus bacteremia than in our study. To avoid selection bias by only including patients who underwent echocardiography and, thus, the cases most suspicious of having IE, we chose not to exclude the patients who did not undergo echocardiography. Instead, we followed these patients for a period of six months after inclusion in the study in an attempt to discover all cases of IE. None of these patients developed IE during follow-up. However, it is possible that some patients in this group might have had IE and were cured by regular antibiotic treatment, as previous studies have shown that a shorter treatment with antibiotics might be as potent as longer treatment [15].

The prevalence of IE among patients with Enterococcus faecalis bacteremia in this study (33%) was higher compared with other studies evaluating enterococal IE (42-29%) [9-12]. Our rate of examination by TTE and TOE was higher than other studies and may explain these results [9,12]. Also, one of the studies estimated the prevalence of enterococcal IE collectively, including patients only had one TTE/TOE performed, which might increase the risk of missing IE due to an initial negative examination, since it is recommended that some patients in this group might have had IE and were cured by regular antibiotic treatment, as previous studies have shown that a shorter treatment with antibiotics might be as potent as longer treatment [15].

Further limitations of this study include the small sample size and the lack of a control group. The study was performed at a single center, which may limit the generalizability of the results. In conclusion, the study suggests that an increased prevalence of IE in patients with Gram positive bacteremia is associated with a higher mortality, and the diagnosis and treatment of IE at an earlier stage can improve outcomes.

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to repeat TOE/TTE after five to seven days if IE is highly suspected [4]. On the other hand, the improved imaging quality of TOE may lead to false positive cases of IE, making the estimate too high. This problem was partly countered by means of the local IE teams, who ensured the diagnosis was based on more than just echocardiographic findings.

Some of the patients in the study died without having an echocardiography and had no autopsy; thus, it is unknown if they had IE or not. We categorised most of these patients as IE not excluded and consequently, the range of prevalence of IE became very wide. Patients without echocardiography and no hospitalisation within the follow-up period of six months were considered not to have IE. It is possible that a few patients had IE without hospitalisation during follow-up as some patients are not properly diagnosed and are cured by regular antibiotic treatment [15]. Hence the prevalence of IE from this study is likely minimal and could possibly be even higher.

Clinical implications

We hope that the findings of this study will lead to more echocardiographies when a blood culture detects Gram positive cocci bacteria. This is especially important in cases with Staphylococcus aureus, Enterococcus faecalis, and non-haemolytic streptococcal bacteremia.

CONCLUSION

In this study, there was a 12%-22% prevalence of IE in patients with Gram positive Cocci bacteria. When focussing on patients with bacteremia from the most typical bacteria to cause IE, the prevalence was 16-24%. These findings strongly support that routine echocardiography should be performed in this patient group. However, clinical evaluation is still important in the diagnosis of IE.

ACKNOWLEDGEMENTS

We thank the clinical microbiologists from the Department of Clinical Microbiology at Herlev-Gentofte Hospital for helping us identify patients with Gram positive bacteremia hospitalised in the included hospitals during the study period.

REFERENCES