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Investigation of blood culture-negative early prosthetic valve endocarditis reveals high prevalence of fungi

Franck Thuny,1,2 Pierre-Edouard Fournier,1,3 Jean-Paul Casalta,3 Frédérique Gouriet,1,3 Hubert Lepidi,1,3 Alberto Riberi,4 Frédéric Collart,6 Gilbert Habib,2 Didier Raoult1,3

ABSTRACT

Context Early prosthetic valve endocarditis is a deadly disease and blood cultures remain negative in 14–30% of cases.

Objectives To analyse the clinical and microbiological profile of patients with blood culture-negative (BCN) early prosthetic valve endocarditis (PVE) in order to define the most appropriate empiric treatment.

Design, Setting and Participants From June 2001 to February 2009, a prospective multimodal strategy incorporating serological, molecular and histopathological assays was performed in all the samples referred to the laboratory for a suspicion of blood culture-negative endocarditis (BCNE) from France and abroad (n=718). A total of 31 patients with BCN early PVE was identified. Their microbiological profile was compared with that of 22 patients with blood culture-positive (BCP) early PVE and 628 patients with community-acquired BCNE identified during the same period.

Results A pathogen was identified in 10 patients (32%) with BCN early PVE. Fungi were the most common pathogens identified, being found in 16% versus 4.5% in the case of BCP early PVE and 0.5% in community-acquired BCNE (p<0.001). The global microbiological profile of BCN early PVE differed strongly from that of BCP early PVE and community-acquired BCNE. A higher rate of microbiological diagnosis was obtained in patients who underwent surgery (9/21 (43%) vs 1/10 (10%), p<0.07) and an increased rate of recurrences was observed when a pathogen could not be identified (9/21 (43%) vs 1/10 (10%), p=0.07).

Conclusions BCN early PVE exhibits specific aetiologies as fungi are the most frequent pathogens identified. Therefore, fungi should be investigated particularly by molecular methods on surgical specimens and an antifungal drug might be added to the empiric treatment.

Prosthetic valve endocarditis (PVE) is a serious complication of heart valve replacement surgery occurring at a rate of 0.3–1% per patient-year1–5 and representing currently more than one fifth of all cases of infective endocarditis (IE).6 Infection of the prosthetic valve can be acquired in the operating theatre or during the immediate postoperative period through wound infections, intravascular catheter infections, urinary tract infection, or pneumonia.7 These cases of early postoperative endocarditis usually occur within the first year after valvular surgery, and staphylococci, Gram-negative bacilli, enterococci and fungi are the most frequently identified pathogens by blood cultures.5–8 However, recent series showed that blood cultures remain negative in 14–50% of cases,5 8–11 which may delay the diagnosis and increase morbidity and mortality. In these cases of blood culture-negative (BCN) early PVE, the international guidelines recommend an antimicrobial treatment covering pathogens usually identified by blood cultures, speculating that the same agents cause both BCN early PVE and blood culture-positive (BCP) early PVE.12 13 Those recommendations for antibiotic treatment are empirical and are not based on evidence. We have found previously that most of the aetiologies of blood culture-negative endocarditis (BCNE) are not those of blood culture-positive endocarditis.14

Therefore, taking advantage of our large database, we aimed to define the clinical and microbiological profile of BCN early PVE using a comprehensive strategy incorporating a battery of the most recent laboratory techniques14–16 at our reference centre, where samples from patients with BCNE are referred from many countries in the world. Then, we compared the microbiological profile of BCN early PVE with that of patients hospitalised at the cardiology and cardiac surgery departments of our institution for BCP early PVE and community-acquired BCNE from our entire database.

METHODS

Patients

From June 2001 to February 2009, all patients with a suspicion of BCNE for whom specimens were referred to our laboratory from France and abroad were eligible for study entry. A structured questionnaire was used to collect the following data: patient’s age, sex, comorbidity index17 signs and symptoms, duration of symptoms, history of antimicrobial therapy for the current illness that prompted the patient to seek medical attention, antecedent disease, predisposing factors for IE (including systemic disease, type of prosthetic valve, intravenous drug abuse and dental or surgical manipulation), echocardiographic data, treatment received during the course of hospitalisation and treatment. Finally, patients with a suspicion of BCN PVE in whom the following criteria were met were included in the present study: definite or possible IE according to modified Duke criteria,18 early PVE defined as PVE occurring within the first year after heart valve replacement surgery,8 12 13

For the comparison of the microbiological profiles we also analysed the causal pathogens of all the

See Editorial, p 733

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For the comparison of the microbiological profiles we also analysed the causal pathogens of all the
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episodes of possible or definite BCP early PVE diagnosed during the same period in the cardiology department of our institution and of possible or definite community-acquired BCNE referred to our laboratory.

The study was approved by the local ethics committee under reference 07-015. The study was also approved by the Commission Nationale Informatique et Libertés under reference 1223186.

Diagnostic procedures
The diagnostic strategy was standardised for of all suspicions of BCNE.14

Serology
Serology for Coxella burnetii, Bartonella quintana, Bartonella henselae and Legionella spp, Chlamydiae spp, Brucella melitensis, Mycoplasma pneumoniae and Aspergillus spp were systematically performed as previously described.19

Culture
Homogenised cardiac valve specimens suitable for culture, that is frozen at −80°C following surgery and sent in dry ice, and heparinised blood specimens processed in the same way, were inoculated onto human endothelial cells (ECV 304) grown in shell phials, as reported elsewhere.20 Three weeks after inoculation, bacteria detected by Gimenez and acridine orange staining, electron microscopy or immunofluorescence using the patient’s serum, were identified by amplification and sequencing of the 16S rRNA gene as previously described.15

Histopathology
Paraffin-embedded heart valves were examined with haematoxylin and eosin for histopathological features.21 To detect microorganisms within tissues Giemsa, Gram (Brown–Brenn and Brown–Hopps), periodic acid Schiff, Grocott–Gomori, Warthin–Starry, Gimenez and Ziehl–Nielsen stains were systematically performed, as described elsewhere.21 For patients for whom all other techniques remained negative, we performed auto-immunohistochemistry, as previously described.22

Molecular detection
Bacterial DNA was extracted from surgically excised tissues (periprosthetic tissues, vegetations), or EDTA blood when no valve was available, using the QIAmp Tissue kit (Qiagen, Hilden, Germany) as described by the manufacturer and PCR amplification, followed by sequencing of the 16S or 23S rRNA gene for bacteria and 18S for fungi.23 24

Outcome
All events occurring within the 6 months after the first day of hospitalisation were obtained by systematic consultations and physician contacts for the patients from Marseille, and by contacting the physician for the other centres. We recorded the deaths from any causes and IE recurrences defined as a new episode of possible or definite IE.

Statistical analysis
Categorical variables were expressed as numbers and percentages and were compared by using χ² of Fisher’s exact test (two-tailed). Continuous variables were expressed as median and interquartile range (IQR) and compared by using the Mann–Whitney test. For all tests, statistical significance was determined at the 0.05 level. All statistical analyses were performed using Statview 5.0.

RESULTS
Baseline characteristics
During the period of the study, specimens from 718 new patients from France or abroad were included in the total database. Using the Duke criteria, 42 patients were classified as excluded from the diagnosis of endocarditis. Among the remaining 676 patients with endocarditis, 17 (2.5%) were classified as non-infective endocarditis (marantic endocarditis in six, Libmann–Sacks endocarditis in four and Behçet disease in one) and were excluded. Finally, among the 659 patients with definite (n=452) or possible (n=207) BCNE, 51 were identified as having BCN early PVE (definite in 20, possible in 11), which occurred at a median time of 55 days (IQR 18.3–120) after heart valve surgery. Among the 11 patients with possible BCN early PVE, all had at least one major criterion and one minor criterion, and five underwent surgery (positive histology in four). The clinical features of all patients with BCN early PVE are summarised in table 1. Eighteen patients were hospitalised at our institution and 13 at different centres. The median age was 64 years (IQR 48.5–72.8), the majority of cases involved bioprosthetic valves (64.5%), and 16 patients (52%) had received previous antimicrobial treatment before the diagnosis. Among the 31 patients included, 21 patients (68%) underwent surgical treatment.

Microbiological profile
Our diagnostic procedures allowed aetiological diagnosis in 10 patients (52%). Fungi were the most common identified pathogens, with five cases (16%), none of them being immunocompromised. Streptococci were identified in three patients (10%), Lactobacillus spp in one patient (3%) and Legionella spp in one patient (3%). The results of the diagnostic tests are summarised in table 2. The microbiological profile of the patients with BCN early PVE differed greatly from that of patients with BCP early PVE and patients with community-acquired BCNE (table 3). Fungi were the aetiologic agent in 16% of the BCN early PVE, 4.5% of the BCP early PVE and 0.5% of the community-acquired BCNE (p<0.001).

Table 1 Clinical features of BCN early PVE

<table>
<thead>
<tr>
<th>Feature</th>
<th>BCN complete</th>
<th>BCN partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite infective endocarditis</td>
<td>20 (64.5%)</td>
<td>52 (48.5%)</td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>54 (48.5–72.8)</td>
<td>64 (48.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>22 (71%)</td>
<td>40 (73%)</td>
</tr>
<tr>
<td>Comorbidity index &gt;2</td>
<td>8 (28%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (6.5%)</td>
<td>3 (6.1%)</td>
</tr>
<tr>
<td>Intravenous drug user</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>1 (3%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Previous antimicrobial treatment</td>
<td>16 (52%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Fever</td>
<td>24 (77%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Immunological phenomena</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Type of prosthetic valve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioprosthetic</td>
<td>20 (64.5%)</td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td>12 (39%)</td>
<td></td>
</tr>
<tr>
<td>Homograft</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Vegetation</td>
<td>17 (55%)</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>11 (35.5%)</td>
<td></td>
</tr>
<tr>
<td>New prosthetic valve dehiscence</td>
<td>15 (48%)</td>
<td></td>
</tr>
<tr>
<td>Acute heart failure</td>
<td>12 (39%)</td>
<td></td>
</tr>
<tr>
<td>Total embolic events</td>
<td>10 (32%)</td>
<td></td>
</tr>
<tr>
<td>Embolic events under medical treatment</td>
<td>4 (13%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (29%)</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled infection under medical treatment</td>
<td>10 (32%)</td>
<td></td>
</tr>
</tbody>
</table>

*p: Persisting fever and/or positive blood cultures >7–10 days.

BCN, blood-culture negative; IQR, interquartile range; PVE, prosthetic valve endocarditis.
Table 3  Comparison of microbiological profile according to the type of infective endocarditis

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Diagnostic procedures</th>
<th>BCN early PVE n=31</th>
<th>BCP early PVE* n=22</th>
<th>Community-acquired BCNE* n=628</th>
<th>p Value †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Modified Duke</td>
<td>Serology (Definite), Culture (Possible)</td>
<td>PCR from blood, PCR from tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td>0 (0%)</td>
<td>12 (54.5%)</td>
<td>13 (2%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>3 (10%)</td>
<td>3 (14%)</td>
<td>28 (4.5%)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Enterococci</td>
<td>0 (0%)</td>
<td>3 (14%)</td>
<td>0 (0%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td>5 (18%)</td>
<td>1 (4.5%)</td>
<td>0 (0.5%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>229 (36.5%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Bartonella spp</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>86 (14%)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Legionella spp</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>1 (0.2%)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Tropheryma whippelii</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>12 (2%)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1 (3%)</td>
<td>3 (14%)</td>
<td>29 (5%)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>No diagnosis</td>
<td>21 (68%)</td>
<td>227 (36%)</td>
<td>227 (36%)</td>
<td>0.0004</td>
<td></td>
</tr>
</tbody>
</table>

*Data only from the Department of Cardiology (Timone Hospital, Marseille, France) during the same period.
†All the comparisons were made between the three groups but for the ‘no diagnosis’ variable in which only culture-negative (BCN) early prosthetic valve endocarditis (PVE) and community-acquired blood culture-negative endocarditis (BCNE) groups were compared.

BCP, blood culture-positive; NA, not available.

**DISCUSSION**

To the best of our knowledge, the present study is the first to analyse specifically the clinical and microbiological profile of patients with BCN early PVE. The extensive diagnostic strategy used in our laboratory allowed us to identify a causative pathogen in one-third of cases and demonstrated the high prevalence of fungi.

**Postoperative BCN: a diagnostic challenge**

Early PVE is a serious disease with a high rate of complications and mortality.7 8 In this acute and often destructive infection, the microbiological diagnosis is a critical step allowing the initiation of appropriate antimicrobial therapy against virulent and, sometimes, resistant pathogens. However, blood cultures remain negative in 14–30%,1–5 17 25 of cases often delaying the initiation of treatment, with a potential profound impact on clinical outcome.26 27 In a study of patients undergoing surgical treatment for IE, negative blood cultures were independently associated with an adverse outcome after surgery,28 29 Negative blood cultures are, therefore, of considerable concern in the management of these patients, and may result from inadequate microbiological techniques, infection with highly fastidious bacteria or non-bacterial pathogens, or the earlier administration of antimicrobial agents before blood cultures were obtained.12 The microbiological diagnosis of BCNE, especially after cardiac surgery, is thus a critical challenge.

**BCN early PVE: diagnostic methods**

To the best of our knowledge, no previous series have addressed specifically the issue of BCN early PVE, because its low frequency makes it difficult to identify a sufficient number of
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cases for study in any one medical centre during a short enough period to avoid the confounding effect of changes in management and diagnosis. Since the large series of 348 cases of BCNE that we published previously, our laboratory has received an increasing number of specimens from patients with BCNE, and we were able to analyse specifically a series of patients with BCN early PVE. We thus demonstrated that microbiological identification requires the use of alternative laboratory diagnostic methods, including systematic serological evaluation, pathological examination of valvular samples and molecular tools. Serology allowed us to identify IE related to Aspergillus spp in two cases and Legionella spp in another one, which are pathogens known to be mostly implicated in nosocomial and post-cardiac surgery IE. Besides, in the present work, PCR identified a pathogen frequently from valve samples and blood. We therefore believe that this method, by sequencing of the 16S or 23S rRNA gene for bacteria and 18S for fungi, should be used systematically in cases of BCN early PVE. In recent studies, PCR using universal primers for bacteria and fungi was demonstrated to be a highly valuable tool for valvular specimens, with the identification of streptococci and fastidious bacteria as the main agents. In the present work, of the 11 patients with possible IE, five underwent surgery. Among them, valve PCR identified a pathogen in two patients despite a negative valve culture, and then would have converted diagnoses to definite diagnoses if PCR had been included as a major Duke criterion. However, the inclusion of this method as a major criterion is still debated and, at this time, PCR should not supersede cultures.

Although the use of PCR from blood samples in the diagnosis of IE is more controversial, it allowed us to diagnose a fungal agent (Saccharomyces spp) in one case of possible endocarditis.

BCN early PVE: implications of the high prevalence of fungi

We found that aetiological agents of BCN early PVE were fastidious pathogens rather than usual bacteria. We were able to identify a pathogen in a third of cases. The microbiological spectrum was different from that of BCP early PVE and community-acquired BCNE, and fungi were the most frequent pathogens identified.

Fungi are the cause of 1–6% of all cases of IE and 10% of PVE. Advances in medical and surgical therapies, such as prosthetic valve replacement, have been suggested as being implicated in the increasing incidence of fungal IE. This emerging disease is associated with an unacceptably high mortality of approximately 50% related to the poor medical condition of patients and to a difficult diagnosis because of the low sensitivity of blood cultures. In the present study, we found a relatively high prevalence of those fungal pathogens in patients with BCNE who had had a recent valve replacement. These findings are crucial because they have two important implications. First, they raise the question of the role of cardiac surgery not only for the treatment of this kind of IE (‘therapeutic surgery’) but for the identification of fungi by culture and molecular techniques. Therefore, the trend towards a higher rate of microbiological identification in patients who have undergone surgical management might encourage us to indicate ‘diagnostic surgery’ to identify the cause of infection and then to start adequate antimicrobial therapy promptly. This surgical decision would be easier to make because the pathogens most frequently identified were fungi, which usually require ‘therapeutic surgery’. Therefore, the question of ‘diagnostic surgery’, in a patient with BCN early PVE associated with negative serologies and no standard indication for ‘therapeutic surgery’, needs to be addressed in future studies. Second, the identification of fungi as the most frequently found pathogens might have a potential impact on the choice of antimicrobial treatment in cases of early PVE with negative blood cultures. The selection of the most appropriate medical therapy in this situation remains difficult and empirical, because the most recent laboratory diagnostic techniques are not available in many centres. By now, the European (European Society of Cardiology) guidelines recommend a combination of vancomycin, gentamicin and rifampicin, and the American (American Heart Association) guidelines recommend the addition a fourth antibiotic, namely cefepime. However, these recommendations are deduced by analysis of the most common bacterial causes of IE identified by conventional cultures, namely staphylococci, Gram-negative bacilli and enterococci. Here we showed that pathogens found in BCN early PVE do not mirror those of BCP early PVE, and that the recommended empirical antimicrobial therapy would not be effective in half of our documented cases and 20% of the total number of cases. The frequency of fungi justifies the addition of a fungicidal therapy. Moreover, no staphylococci were identified. Therefore, we suggest that the recommended combination of vancomycin, gentamicin, rifampicin and cefepime might be initiated as the first-line empirical therapy while awaiting the results of blood cultures, and should be replaced by a combination including amphotericin B, ampicillin and rifampicin if they remain negative. The addition of an antifungal drug is also supported by the fact that fungi are the second most frequently identified causative pathogens in all early PVE. However, this suggestion needs to be confirmed by other studies.

Limitations

Despite its originality, this study has several limitations, including a referral bias and a relatively small sample size. The patients analysed in the present work were usually referred from other centres because their usual diagnostic strategy failed to identify a causative pathogen. Our series thus describes the profile of the most difficult to diagnose BCN early PVE rather than the usual form of the disease. Therefore, our results need to be confirmed by other research on the topic, including multi-centre data and non-selected surveys.

CONCLUSION

Aetiological pathogens found during BCN early PVE are commonly fastidious and fungi are the most frequent. They can be identified by using a battery of laboratory techniques, including serology, histopathology and molecular biology procedures. If these results are confirmed by other large series, BCN early PVE might require a modification of the recommended empirical antimicrobial therapy including the addition of an antifungal drug.

Competing interests None.

Ethics approval The study was approved by the local ethics committee under reference 07-015. The study was also approved by the Commission Nationale Informatique et Libertés under reference 1223186.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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