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Risk factors for early onset prosthetic valve endocarditis: a case–control study

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SUMMARY

Background: Early onset prosthetic valve endocarditis (EO-PVE) is an infrequent complication of cardiac valve surgery. It is considered a healthcare-associated infection due to contamination of the prosthesis during the implant or in the early postoperative period.
Aim: To evaluate which factors may be related to the acquisition of EO-PVE.
Methods: A nested case–control study was conducted from 2006 to 2016. Cases were patients who had definite prosthetic endocarditis by the modified Duke criteria up to 12 months of heart valve replacement. Cases and controls were matched by age, gender, date and type of surgery.
Findings: There were 26 cases and 78 controls, in 2496 valve surgeries. The median incidence of EO-PVE was 1.1%. Risk factors identified during surgery were: use of ≥2 cryoprecipitate units (odds ratio (OR): 5.95; 95% confidence interval (CI): 1.31–27.0) and ≥2 plasma units (OR: 2.73; 95% CI: 1.0–7.5). In the postoperative period, associated factors were bloodstream infection (OR: 14.00; CI: 1.49–131.77), pneumonia (4.38; 1.21–15.84), any infection (4.46; 1.63–12.21), central line for ≥2 weeks (5.33; 2.06–13.78), presence of dialysis catheter (3.22; 1.15–9.03), and new open chest surgery (3.89; 1.28–11.78). Mortality at 12 months was 34.6% in cases and 6.4% in controls (OR: 7.73; CI: 2.3–26.06).
Conclusion: Cases had more infections, invasive procedures and surgical re-interventions in the early postoperative period, which favoured contamination of the newly implanted prosthesis. A preventive approach, with reinforcement of infection control practices, may curb the incidence of this condition.

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Introduction

Cardiac valve replacement surgery plays an important part in the treatment of patients with valve disease. Approximately 280,000 prosthetic heart valves are implanted worldwide annually [1]. In Brazil, around 12,000 prosthetic heart valves are implanted by the public health system per year [2].

Several complications are described after heart valve replacement such as thrombosis, systemic embolization, haemolysis, structural valve deterioration and infective endocarditis [1]. Prosthetic valve endocarditis (PVE) is considered one of the most serious complications related to these procedures [3].

In heart valve surgery, several risk factors for the development of postoperative infections (mediastinitis, surgical site infection or endocarditis) have been described [4,5]. The most relevant ones related to the patient are obesity, smoking, hyperglycaemia and concomitant infection [4,5]. Those related to the surgical procedure are inadequate prophylactic antibiotic, asepsis failure, trichotomy technique, glycaemic control, tissue hypoxia, blood products use, cardiopulmonary bypass, aortic clamping time, total surgical time and surgeon experience [4–6]. These factors, however, are not necessarily related to the development of early onset-PVE (EO-PVE).

EO-PVE is an infrequent complication with incidence ranging from 1% to 6% [7–10]. It occurs up to 12 months after valve implantation and is considered a healthcare-associated infection due to contamination of the prosthesis during the implant surgery or in the early postoperative period [3,6,7,10–12]. In most series, the mortality associated with EO-PVE ranges from 15% to 80% [7,10,13,14].

In the last four decades, some authors have attempted to define the most important risk factors for the development of EO-PVE. However, these studies are difficult to compare, due to the methodological diversity between them, the changes in the definition of the time for EO-PVE (60 days–12 months), and the modifications in the criteria for the diagnosis of endocarditis [3,15,16]. Some risk factors appear more frequently, such as a recent episode of infectious endocarditis, advanced heart failure, postoperative bloodstream infection (BSI) and surgical wound complications [6,13,14,17–19].

The aim of this study was to analyse associated factors for EO-PVE acquisition in a cardiac surgical hospital.

Methods

Study design

This was a nested case–control study, conducted in Instituto Nacional de Cardiologia (INC), a referral centre for cardiac surgery in Rio de Janeiro, Brazil. INC is a public tertiary care surgical hospital that performs about 230 valve replacement surgeries annually. Data were extracted from medical records, from the infection control service database and from the case report forms of the International Collaboration on Endocarditis (ICE) cohort, of which INC has been a site member since 2006. All adult patients who had a prosthetic valve implant at INC from January 2006 to March 2016 were included. Exclusion criteria were heart valve replacement surgery in another institution, endovascular valve surgery, and death within 48 h of surgery. Cases were patients who developed EO-PVE within 12 months of the valve replacement and had definite infective endocarditis by the modified Duke criteria [16]. Controls were patients who had valve replacement surgery at INC and who did not develop prosthetic valve endocarditis (PVE) within 12 months of implant surgery (case:control ratio = 1:3).

Cases and controls were matched by gender, age at surgery (±10 years), date of implant surgery (±12 months), and site of valve implantation (e.g. a case that had mitral valve replacement was compared to a control who also had a mitral procedure).

The study variables were divided according to the timing of surgery as preoperative, perioperative, and postoperative. Preoperative variables were: educational level (years of study), body mass index, smoking and alcohol habits (both as a qualitative measure), New York Heart Association (NYHA) functional class, ejection fraction, and pulmonary artery systolic pressure (PASP), EuroScore I, diabetes, liver disease, chronic obstructive pulmonary disease, acquired immune deficiency syndrome, cardiovascular diseases, malignancies and chronic kidney disease were grouped and evaluated as the Charlson comorbidity score, and individually (Supplementary Table I), recent infection (30 days before surgery), recent use of antibiotics (90 days before surgery, except for rheumatic fever prophylaxis and oral procedure prophylaxis), presence of active infective endocarditis, history of rheumatic valve disease, and length of hospital stay (LOS) before surgery.

Perioperative variables: adequate antibiotic prophylaxis (according to the hospital protocols, Supplementary Table II), *Staphylococcus aureus* decolonization (chlorhexidine bath the night before or on the morning of the surgery, and nasal mupirocin twice daily for five days prior to surgery for all patients), elective or urgent surgery (urgent as procedure performed ≤48 h after the diagnosis of EO-PVE), placement and type of prosthesis (mechanical or biological), total surgical time, cardiopulmonary bypass and aortic clamp time, blood glucose level (highest value during surgery), and blood components used.

Postoperative variables: SOFA score (on intensive care unit admission), blood glucose (highest value in the first 24 h after surgery), duration of mechanical ventilation, total time of central venous catheter (CVC) use (if use was intermittent, time was added; if more than one central line was used, the one with the longest time *in situ* was considered), haemodialysis catheters (analysed apart from other CVCs), development of infections (pneumonia, BSI, mediastinitis, and urinary tract infection), need for new open chest surgery, total length of hospital stay, and death. Only episodes of BSI in which the micro-organism was different from that causing EO-PVE were considered. This was done because it was not possible to determine whether the diagnosed BSI was already a manifestation of the EO-PVE episode.

The minimum follow-up time for all variables analysed (including death and occurrence of endocarditis) was 12 months after valve replacement surgery for both groups.

Statistical analysis

The measure of association used was the odds ratio (OR) in univariate analysis. Categorical variables were expressed in frequencies (%) and compared with the χ^2-test or Fisher's exact test. Continuous variables were expressed as mean and standard deviation (SD) if the distribution was normal, or as median

Table I
Risk factors for EO-PVE in the preoperative period of 104 patients undergoing valve replacement surgery, Instituto Nacional de Cardiologia, Rio de Janeiro, 2006 to 2016

Variable	Cases ($n = 26$)	Controls ($n = 78$)	OR (95% CI)	*P*-value
Age (years), mean (SD)	46.5 (±16.5)	46.9 (±15.9)	–	0.902
Educational level, mean (SD)	8.6 (±3.1)	8.4 (±3.9)	–	0.558
NYHA, median (IQR)	3 (2–3)	3 (2–3)	–	0.673
EuroScore I, median (IQR)	3.7 (2.8–10)	4.7 (2.5–10)	–	0.665
Charlson score, median (IQR)	2 (1–3)	2 (1–3)	–	0.833
PASP (mmHg), median (IQR)	56.0 (45.0–68.0)	55.5 (35.7–70)	–	0.519
EF, median (IQR)	60 (55.5–70.5)	63 (56.2–72)	–	0.876
BMI, mean (SD)	23.7 (±5.66)	24.3 (±4.38)	–	0.624
Smoking	10 (41.7%)	23 (30.3%)	1.65 (0.64–4.25)	0.327
Alcohol use	13 (50.0%)	23 (30.3%)	1.2 (0.52–2.75)	0.987
Rheumatic valvulopathy[a]	15 (57.7%)	39 (56%)	1.05 (0.42–2.65)	0.999
Recent infection[b]	8 (30.8%)	15 (19.2%)	1.87 (0.68–5.10)	0.276
Previous use of antibiotics[c]	7 (26.9%)	16 (20.5%)	1.43 (0.5–4.0)	0.145
Active endocarditis[d]	6 (23.1%)	10 (12.8%)	2.04 (0.66–6.30)	0.221
Urgent surgery[e]	2 (7.7%)	9 (11.5%)	0.64 (0.13–3.17)	0.580

EO-PVE, early onset prosthetic valve endocarditis; SD, standard deviation; OR, odds ratio; CI, confidence interval; NYHA, New York Heart Association functional class; IQR, interquartile range; EF, ejection fraction of the left ventricle; PASP, pulmonary artery systolic pressure; BMI, body mass index.
[a] Previous rheumatic valve disease.
[b] 30 days before surgery.
[c] 90 days before surgery.
[d] Endocarditis as the reason for implant surgery.
[e] Urgent surgery: surgery performed within 72 h after the diagnosis of early onset prosthetic valve endocarditis.

and interquartile range (IQR), assuming a non-normal distribution. Student's *t*-test and Mann–Whitney *U*-tests were used to compare continuous variables, according to the normality of the data. $P < 0.05$ was considered statistically significant for all analyses. The statistical package R, version 3.1.0, was used for calculations and MedCalc statistical software for survival analyses (Kaplan–Meier curves and log-rank test for comparison). The sample size was estimated as 23 patients using an α-value of 0.05 and a β-value of 0.1 (for a power of 90%).

A logistic regression was performed in order to verify a possible group of variables that were associated with the main outcome. Variables with $P < 0.25$ were used to compose the model. The selection of variables of the model was done through the stepwise technique where variables with $P > 0.05$ were discarded.

Ethical considerations

The Institutional Review Board at INC approved this study (number 1,297,807). All patients signed a consent form before being enrolled in the ICE study.

Results

Between 2006 and 2016, there were 26 cases of EO-PVE in a total of 2496 valvular surgeries. The annual incidence ranged from 0.0% to 2.14% with a median of 1.1%. We included 78 patients as controls. The affected prostheses were biological in 14 (53.8%) cases and mechanical in 12 (46.2%) and no difference was identified regarding type of prostheses (Supplementary Table III). Only three cases had prior valve replacement. The procedures performed in the cases were aortic in 10 (38.5%), mitral in 10 (38.5%), mitro-aortic in five (19.2%), and mitro-tricuspid in one (3.8%). The main surgical indications were valve regurgitation in seven (26.9%), active endocarditis in six (23.2%) and valve stenosis in five (19.2%) cases.

The median time interval between valve replacement and the diagnosis of EO-PVE was 33 days (IQR: 19.25–118.75). Eighteen (69.3%) cases occurred up to three months and 22 (84.6%) cases occurred up to six months after the index surgery.

The most frequent causative micro-organisms isolated from blood cultures in our cohort were *S. epidermidis* 23.1% ($n = 6$), followed by *Enterococcus faecalis* 15.4% ($n = 5$), Gram-negative bacilli 15.4% ($n = 5$) and *Candida* spp. 11.5% ($n = 3$). There were no infections caused by *S. aureus* and 19.2% ($n = 5$) of blood cultures were negative. The microbiological description of our cohort is shown in detail in Supplementary Table IV.

Preoperative risk factors are presented in Table I and those related to the surgical procedure in Table II. Analysing separately the amount of each blood component transfused: there was a greater use of plasma and cryoprecipitate units for the cases, with an OR for plasma of 2.73 (95% CI: 1.0–7.5) and an OR of 5.95 (95% CI: 1.31–27) for cryoprecipitate.

The risk factors related to the postoperative period are presented in Table III.

The median (IQR) total time of hospitalization was 67.5 (36.7–85) vs 32 (24–44.7) days ($P < 0.001$) in cases and controls respectively. The median (IQR) time from admission to valve replacement surgery was 13.5 (7.5–21.2) and 15 (7.5–23) days in the cases and controls ($P = 0.721$), respectively.

Table II
Risk factors for EO-PVE related to the surgical procedure in 104 patients undergoing valve replacement, Instituto Nacional de Cardiologia, Rio de Janeiro, 2006 to 2016

Variable	Cases ($n = 26$)	Controls ($n = 78$)	OR (CI 95%)	*P*- value
Total surgical time (min), median (IQR)	297.5 (252.5–376.2)	268.5 (220–321)	–	0.189
CPB (min), median (IQR)	130 (97–189.2)	116 (98.5–158.7)	–	0.455
Cold ischaemia (min), median (IQR)	108 (77.5–156.7)	98 (82.2–141)	–	0.545
Blood glucose, mean (SD)	203.8 (±56.7)	214.9 (±62.4)	–	0.453
Decolonization[a]	14 (56.0%)	45 (58.4%)	0.86 (0.35–2.13)	0.817
Antibiotic prophylaxis	18 (81.8%)	51 (68.9%)	1.94 (0.59–6.40)	0.615
Any transfusion	14 (53.8%)	29 (37.2%)	1.97 (0.80–4.84)	0.169
Red blood cells	No transfusion	No transfusion	1.89 (0.72–4.95)	0.189
	14 (53.8%)	53 (67.9%)		
	≥2 units	≥2 units		
	10 (38.5%)	20 (25.6%)		
Platelets	No transfusion	No transfusion	2.22 (0.83–5.95)	0.106
	17 (65.4%)	63 (80.8%)		
	≥2 units	≥2 units		
	9 (34.6%)	15 (19.2%)		
Plasma	No transfusion	No transfusion	2.73 (1.0–7.50)	0.047
	16 (61.5%)	63 (80.8%)		
	≥2 units	≥2 units		
	9 (34.6%)	13 (16.7%)		
Cryoprecipitate	No transfusion	No transfusion	5.95 (1.31–27.0)	0.022
	21 (80.8%)	75 (96.2%)		
	≥2 units	≥2 units		
	5 (19.2%)	3 (3.8%)		

EO-PVE, early onset prosthetic valve endocarditis; SD, standard deviation; OR, odds ratio; CI, confidence interval; IQR, interquartile range; CPB, cardiopulmonary bypass.
Plasma and red blood cells do not sum 100% because some patients used <2 units.

The treatment modality for EO-PVE was clinical for 14 (53.8%) and surgical for 12 (46.2%). Mortality was 28.6% for patients who were treated conservatively and 50% for those who had new surgery ($P = 0.421$).

The postoperative 12-month mortality rate was significantly higher in cases (34.6% vs 6.41%; $P < 0.001$). The survival curves are presented in Figure 1.

In the multivariate analysis, BSI remained significantly associated with EO-PVE, with an OR of 76.10 (95% CI: 8.57–675; $P < 0.0001$) as did mortality, with an OR of 11 (95% CI: 2.77–43.9; $P < 0.001$).

Discussion

There are limited published data about EO-PVE and since the year 2000 only a few papers have reported specifically on risk factors related to EO-PVE [10,13,14]. Our results show that the incidence of EO-PVE in our centre is similar to that reported in other studies recently [7,13,14,19]. All our cases presented acutely, and slightly more than two-thirds within three months after valve replacement.

In the preoperative period, there was no difference regarding the severity of underlying disease in cases and controls. Both groups were similar regarding NYHA functional class, comorbidities (Charlson score) and surgical risk by EuroScore I. Some studies have found NYHA functional class as a risk factor for EO-PVE, one with OR of 12.3 for functional class III/IV and another for patients in class IV [14,19]. However, other authors did not demonstrate this difference [13,20]. In our study, the median functional class for both groups was III, evidence of patients with advanced cardiac dysfunction.

A frequently described risk factor is the presence of active infective endocarditis at the time of valve replacement surgery. There was no difference between cases and controls in our study, and in all our cases the micro-organism causing EO-PVE was different from the causative micro-organism of infective endocarditis that led to original valve replacement surgery. No published study after 2000 was able to demonstrate this variable as a risk factor [10,14,19]. In fact, only one study from 1994 shows an OR of 6.8 for active infective endocarditis at the time of valve replacement as a risk for EO-PVE [6].

Regarding *S. aureus* decolonization regime, which was standard, we found no statistical difference in decolonization rates between cases and controls; the recommendation to use decolonization in all patients is controversial although it is interesting to note that there were no cases of EO-PVE due to this micro-organism in our sample. The rate of mupirocin resistance *S. aureus* at our institution is <1%.

No other published series describes educational levels in patients with EO-PVE. In our study, although there was no difference between groups, educational levels were low, with <25% of the patients having completed high school. This demonstrates the low socioeconomic status of our cohort, which may be associated with the high frequency of rheumatic valve lesions in our patients.

The exclusion of patients who died up to 48 h after the index valve surgery should not interfere with the analysis of the risk

Table III
Risk factors for EO-PVE associated with the postoperative period in 104 patients undergoing valve replacement, Instituto Nacional de Cardiologia, Rio de Janeiro, 2006 to 2016

Variable	Cases ($n = 26$)	Controls ($n = 78$)	OR (95% CI)	*P*-value
Bloodstream infection	4 (15.4%)	1 (1.3%)	14.00 (1.49–131.77)	0.013
Pneumonia	6 (23.1%)	5 (6.4%)	4.38 (1.21–15.84)	0.027
Mediastinitis	3 (11.5%)	2 (2.6%)	4.96 (0.78–31.49)	0.098
Urinary tract infection	2 (7.7%)	2 (2.6%)	3.30 (0.44–24.78)	0.260
Other infections[a]	3 (11.5%)	7 (9%)	1.32 (0.32–5.54)	0.708
Any infection[b]	11 (42.3%)	11 (14.1%)	4.46 (1.63–12.21)	0.005
Blood glucose, mean (SD)	163.3 (±59.0)	158.9 (±30.6)	–	0.902
SOFA, median (IQR)	4 (1–4)	3 (1–5)	–	0.928
CVC LOS	≤2 weeks 10 (38.5) >2 weeks 16 (61.5)	≤2 weeks 60 (76.9) >2 weeks 18 (23.1)	5.33 (2.06–13.78)	<0.001
Haemodialysis catheter use	9 (34.6)	11 (14.1)	3.22 (1.15–9.03)	0.021
Haemodialysis catheter LOS	≤2 weeks 2 (22.2) >2 weeks 7 (77.8)	≤2 weeks 6 (54.5) >2 weeks 5 (45.5)	4.20 (0.59–30.0)	0.196
Mechanical ventilation (days), median (IQR)	4.0 (1–13.25)	1.0 (1.0–1.0)	–	<0.001
New surgery[c]	8 (30.8%)	8 (10.3%)	3.89 (1.28–11.78)	0.024

EO-PVE, early onset prosthetic valve endocarditis; OR, odds ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CVC, central venous catheter; SOFA, Sequential Organ Failure Assessment; LOS length of stay.
[a] Sinusitis, pseudomembranous colitis, cholecystitis, and tracheobronchitis.
[b] One episode per patient.
[c] New chest reopening.

factors. In this interval there would not be sufficient time for the occurrence of endocarditis in the newly implanted valve. These early deaths were essentially related to the surgical complexity and patient severity of illness, not to acquired infection.

The intraoperative variables cardiopulmonary bypass and aortic clamping times were slightly longer in the cases, but without statistical significance. Prolonged surgical time is recognized as a risk factor for infections in surgeries [5,21].

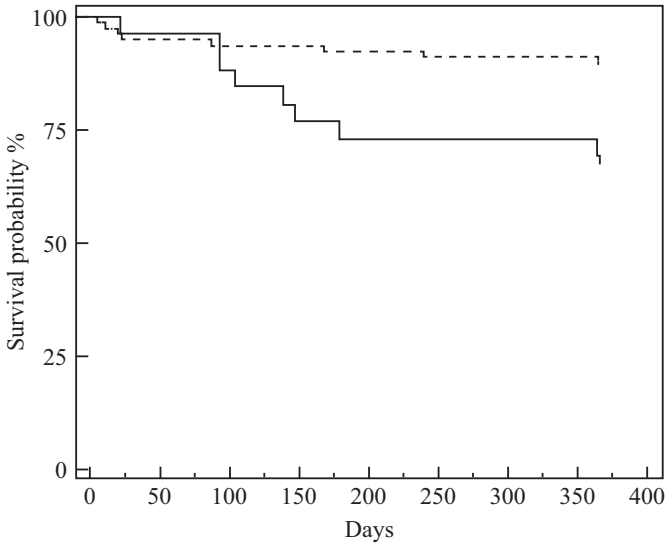

Figure 1. Probability of survival curves at 12 months of 104 patients undergoing valve replacement surgery, Instituto Nacional de Cardiologia, Rio de Janeiro, 2006 to 2016. $P < 0.001$. Solid line: cases; dashed line: controls.

The operative serum glucose levels were not significantly different between the two groups, but it is interesting to note that in both groups it was elevated (mean ≥ 200 mg/mL). This is another risk factor associated with surgical site infection, but it was not related to the development of EO-PVE [4,5].

Transfusion was not associated with a higher risk of EO-PVE, but when analysing individually the amount of each blood product administered, there was a significant difference with a greater use of cryoprecipitate in the cases and a tendency for a greater use of plasma. This may indicate technically more complicated surgeries with increased bleeding among these patients, which increased the risk of postoperative infection. A study in the USA of 15,592 cardiac surgeries (9965 valvular surgeries) showed that the increased use of red blood cells (RBCs), platelets and plasma was related to more sepsis and BSI. This same study also showed that the use of RBCs and platelets was related to deep sternal wound infection [22]. The need for a new sternotomy was greater in cases than in controls. In both groups the main reason for re-operation was bleeding. This information correlates with the finding in our study of greater use of plasma and cryoprecipitate during the index surgery and may indicate that the cases had more complicated surgeries and were, therefore, more prone to bleeding.

In our study, the presence of infection in the postoperative period was associated with an increased risk of EO-PVE. The most closely related infection was primary BSI; this is considered a causal factor of EO-PVE, together with the direct contamination of the prosthesis that may occur during the

surgical procedure [11,17,18,23—25]. Postoperative pneumonia was also related to an increased risk of EO-PVE, whereas mediastinitis, urinary tract infection and other infections, although more frequent in the cases, were not statistically different. Other authors have found the presence of surgical wound infection and fever in the postoperative period as a risk factor [6,13,19]. The latter, however, is a rather non-specific event, since fever is a common physiological response to surgical trauma.

Prolonged use of CVC was consistently more frequent in the cases. The presence of a haemodialysis catheter, irrespective of its LOS *in situ*, was also related to a higher occurrence of EO-PVE. These catheters may lead to BSI. The presence of multiple invasive vascular devices for a prolonged period of time may lead to a higher risk of BSI and consequently of PVE [13,18,23,24,26]. Other authors have attempted to correlate LOS of CVC with risk of EO-PVE; in their study, which compared cases and controls, there was a trend towards longer periods of catheter use in the cases [19].

Healthcare-associated infective endocarditis is a growing entity, and it can be hospital-associated or non-hospital-associated; in the latter, haemodialysis plays an important role [23,27]. Preventive strategies need to be adopted, and the catheter bundle measures have been published [28—31]. It includes the provision of care using a standard combination of interventions to prevent central-line-associated BSI, such as hand hygiene, use of maximum sterile barriers at line insertion, cleansing the insertion site with chlorhexidine, avoiding use of the femoral and jugular sites for line insertion, and the prompt removal of unnecessary catheters. BSI is the main predisposing factor for EO-PVE [12,18,23,25,27].

The longer duration of mechanical ventilation in cases was associated with an increased risk, similar to results of another study that showed a risk of EO-PVE attributed to ventilation for more than 48 h [6]. This may be related to a higher incidence of tracheobronchitis and pneumonia in the cases. As pneumonia may be a source of BSI, there are several preventive strategies regarding ventilator-associated pneumonia, the bundle for which includes elevation of head of bed (30°—45°), daily sedation interruption and assessment of readiness to extubate, use of subglottic secretion drainage, avoidance of scheduled ventilator circuit changes, and oral cavity hygiene with chlorhexidine [31,32].

The 30-day mortality between groups was similar, because the control patients died earlier with direct complications of the valvular surgery. The mortality in the cases only surpassed the controls after three months of the valve surgery. This is probably due to the incubation period of the EO-PVE-related micro-organisms. In our study, patients with EO-PVE were nearly eight times more likely to die compared to controls. This is similar to another international study, in which the OR for death in EO-PVE patients was 7.0 (95% CI: 1.02—47; $P = 0.047$) [33]. Although our study was not designed for this outcome, the mortality related to the EO-PVE treatment was not significantly different between the conservative and surgical approaches, and these results are similar to other published series [7,10].

Our study has some limitations: it is from a single centre, it is observational, and it is retrospective. The results obtained are not definitive and may not be extrapolated to other institutions. However, EO-PVE is a major infection and few centres have any expertise in it.

In conclusion, EO-PVE is a condition with a high mortality — sevenfold that of controls at one-year follow-up. Patients with EO-PVE had more infections, vascular invasion, mechanical ventilation and surgical re-interventions in the early postoperative period. Given the study design, it is not possible to make a causal inference of these factors with respect to EO-PVE. These variables may not be independent, but rather show a risk profile. Our data suggest that the cases evolve with more complications and interventions during the postoperative period, favouring the occurrence of BSI and other infections, consequently increasing the risk of contamination of the newly implanted prostheses. A preventive approach, with reinforcement of infection control practices in the early postoperative period, may curb the incidence of this serious condition.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jhin.2018.07.013.

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