Early-onset prosthetic valve endocarditis definition revisited: Prospective study and literature review

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**A B S T R A C T**

**Objective:** To determine the annual incidence of prosthetic valve endocarditis (PVE) and to evaluate its current classification based on the epidemiological distribution of agents identified and their sensitivity profiles.

**Methods:** Consecutive cases of PVE occurring within the first year of valve surgery during the period 1997–2014 were included in this prospective cohort study. Incidence, demographic, clinical, microbiological, and in-hospital mortality data of these PVE patients were recorded.

**Results:** One hundred and seventy-two cases of PVE were included, and the global annual incidence of PVE was 1.7%. Most PVE cases occurred within 120 days after surgery (76.7%). After this period, there was a reduction in resistant microorganisms (64.4% vs. 32.3%, respectively; \( p = 0.007 \)) and an increase in the incidence of Streptococcus spp (19% vs. 23.5%; \( p = 0.007 \)). A literature review revealed 646 cases of PVE with an identified etiology, of which 264 (41%) were caused by coagulase-negative staphylococci and 43 (7%) by Streptococcus spp. This is in agreement with the current study findings.

**Conclusions:** Most PVE cases occurred within 120 days after valve surgery, and the same etiological agents were identified in this period. The current cut-off level of 365 days for the classification of early-onset PVE should be revisited.

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**Introduction**

Prosthetic valve endocarditis (PVE) occurs in 3–6% of patients in the first 5 years after valve replacement (Lalani et al., 2013). The incidence is higher in the first year, ranging from 1.4% to 3.1% worldwide (Gordon et al., 2000; López et al., 2007). It is estimated that 600 to 1800 cases of early-onset PVE occur annually in the USA (Gordon et al., 2000). Despite advances in medical knowledge, infective endocarditis (IE) remains a potential life-threatening disease with mortality rates ranging from 23% to 48% (Calderwood et al., 1985).

PVE is often divided into early-onset and late-onset based on how long after valve replacement surgery the IE occurs. This classification is important because it differentiates between infections directly related to the surgical procedure and perioperative period (early-onset PVE) and infections with an etiology similar to native valve endocarditis, i.e., late-onset PVE. Thus, early-onset PVE behaves as a single clinical entity with an inherent etiology, empirical treatment, and prognosis (Gordon et al., 2000). However, controversy remains regarding the precise time after the procedure at which the etiology shifts from early-onset PVE to late-onset PVE. Determination of that moment is crucial, because it has significant implications in clinical practice, including the choice of therapy, the activation of hospital infection surveillance protocols,
and improving the patient prognosis. Most previous studies have defined early-onset PVE as a case that occurs within 1 year after valve replacement and late-onset PVE as a case that is diagnosed after this period (López et al., 2007).

Few studies have assessed early-onset PVE and the definition of its time window in detail (Gordon et al., 2000; López et al., 2007; Verkkala et al., 1987; Shafer and Hall, 1970; Killen et al., 1970; Ralph-Edwards et al., 1994; Lee et al., 2011; Chen et al., 1990; Heimberger and Duma, 1989; Musci et al., 2010; Sett et al., 1993; Auger et al., 1981; Thuny et al., 2000; Castillo et al., 2004; Grover et al., 1994; Anguera et al., 2006; Wang et al., 2007; Grubitzsch et al., 2014; Hill et al., 2008; Rivas et al., 2005; Nonaka et al., 2013). Therefore, the aims of the present study were to determine the annual incidence of PVE and to evaluate the classification of PVE within 1 year after surgery based on the epidemiological distribution of agents identified and their sensitivity profiles.

Methods

From February 1997 to February 2014, all consecutive PVE cases seen at the Heart Institute (InCor), University of São Paulo Medical School, Brazil were included in a prospective cohort. The Heart Institute is a tertiary cardiology care hospital with 500 beds that performs nearly 500 cardiac valve operations per year. The infection control team performs active surveillance in consecutive patients undergoing valve surgery during the first year after the procedure. All patients who met the inclusion criteria outlined below were enrolled. The incidence of PVE was obtained based on these patients.

The inclusion criteria were age >10 years, IE classified as ‘defined’ by the modified Duke criteria (Li et al., 2000), and diagnosis within 1 year after valve replacement. Patients who had undergone surgery at another hospital were excluded. The microorganisms were identified from blood cultures and cultures of excised valve tissue. The study received approval from the ethics committee of the study institution. Patients were followed until discharge, and demographic, clinical, echocardiographic, microbiological, and mortality data were obtained.

The following microorganisms were classified as ‘resistant’: methicillin-resistant coagulase-negative staphylococci, methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacilli, and ampicillin-resistant Enterococcus spp.

Statistical analysis

Categorical variables are presented as absolute counts and proportions; these were compared using Fisher’s exact test or the Chi-square test, as appropriate. Continuous variables are presented as the mean and standard deviation, or as the median and interquartile range (IQR); differences between groups were assessed using the t-test or the rank sum test, as appropriate. p-Values of <0.05 were considered significant. In the table with multiple agents presented below, the overall significance was compared using the Chi-square test. For agent-specific significance, the Hochberg post-hoc procedure was used. All statistical analyses were performed using Stata version 13.0 (StataCorp, USA).

Results

One hundred eighty-one cases of PVE were included. An outbreak of nine cases of PVE caused by Mycobacterium chelonae related to the prosthetic manufacturing process was identified during the study period (Strabelli et al., 2010). These cases were excluded from the analysis to not overvalue a specific etiology from an outbreak. Thus, 172 cases of PVE were studied; 104 (60%) were male, the median age was 53 years (range 10–83 years), and 161 (93%) had a biological valve prosthesis. One hundred two and two patients (59%) had a visible vegetation on echocardiography; the median size of these vegetations was 13.7 ± 8 mm. With regard to valve involvement, 91 patients (53%) had aortic valve vegetations, 91 (53%) had mitral valve vegetations, and 11 patients (6%) had involvement of more than one valve. Twenty-six patients (15%) had an embolic event, 125 (73%) underwent cardiac surgery, and 71 patients (41%) died.

The global annual incidence of PVE during the study period was 1.7% (highest 3.1% in 2003 and lowest 0.5% in 2009).

Etiology

The distribution of the cases in the first year after valve replacement is shown in Figure 1. The median time from valve surgery to the diagnosis of PVE was 52 days (IQR 22–107 days); 69.7% (120/172) of cases occurred very early after valve replacement surgery (90 days) and 76.7% (132/172) within 120 days. The microorganisms isolated were coagulase-negative staphylococci (CoNS; 45.3%), Staphylococcus aureus (15.6%), Enterococcus spp (14.1%), Gram-negative bacilli (10.6%), Streptococcus spp (7%), fungi (6.3%), and HACEK (Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus, Actinobacillus actinomy- cetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae; 0.7%). Culture-negative PVE occurred in 34 (19.8%) patients.

The highest decrease in incidence and considerable shift in etiology was observed 120 days after valve surgery (Table 1): after 120 days, a higher prevalence of Streptococcus spp and a lower prevalence of resistant microorganisms were found. All MRSA and 81.6% (40/49) of methicillin-resistant CoNS isolated in this study were found at <120 days after surgery. The microorganisms identified, as well as the usual bacterial resistance at the different time points after valve replacement are shown in the Supplementary Material.

Discussion

The annual incidence of PVE found in this study was 1.7%, similar to previous studies, which have reported an incidence ranging between 1.4% and 3.1% (Gordon et al., 2000). It was also found that most cases occurred within 120 days and that the etiology was similar in this period.

The decrease in PVE incidence observed from 1997 to 2014 probably reflects technical improvements and continuous efforts at infection control by surgical and intensive care teams. Despite this decrease, the incidence remains higher than expected. A study at the Cleveland Clinic from 1992 to 1997 also showed a decrease in incidence of PVE from 1.5 to 0.7 cases per 100 valve replacement surgeries (Gordon et al., 2000). The present study findings support
the need for continuous education of hospital staff to reduce nosocomial infection rates.

Infection surveillance in the first year after surgery showed that almost 70% of PVE cases occurred within 90 days of surgery and 77% occurred within 120 days. The results of the present study are similar to those reported by Lee et al. (2011): 46.4% of PVE cases were diagnosed in the first 2 months after valve replacement. The authors of another three studies that found the median time between valve surgery and PVE was 53 days (Thuny et al., 2010), 120 days (Gordon et al., 2000), and 129 days (López et al., 2007). These findings are consistent with the US Centers for Disease Control (CDC) recent modification of prosthetic infection surveillance. This directive changed the definition of a nosocomial infection from 1 year to 90 days after surgery (CDC/NHSN, 2017). Due to the high incidence of PVE in this period, patients who present to the Emergency Department with fever and/or acute valve dysfunction should be screened for IE with blood cultures and a transesophageal echocardiogram (Habib et al., 2016).

After 120 days, there was a decrease in PVE incidence but also a change in etiology, including an increase in Streptococcus spp and a decrease in methicillin-resistant staphylococcal and Gram-negative bacillus infections. Most CoNS, S. aureus, and Gram-negative bacillus infections occurred in the first 120 days after surgery; Streptococcus spp cases were concentrated in the second time period (>120 days). Thus, there was a shift in infection pattern 120 days after valve replacement. In the first 120 days, more microorganisms of a nosocomial origin were identified. These constituted most of the infections in the first year after valve replacement. While methicillin-resistant CoNS may occur after this period, the etiological pattern is similar to that of community-acquired IE.

A literature review evaluating the etiology of PVE within 1 year after valve replacement for the years 1970–2015 showed the following prevalence rates from the pooled data of 646 PVE episodes (Gordon et al., 2000; López et al., 2007; Verkka et al., 1987; Shafer and Hall, 1970; Killen et al., 1970; Ralph-Edwards et al., 1994; Lee et al., 2011; Chen et al., 1990; Heimberger and Duma, 1989; Musci et al., 2010; Sett et al., 1993; Auger et al., 1981; Thuny et al., 2010; Castillo et al., 2004; Grover et al., 1994; Anguera et al., 2006; Wang et al., 2007; Grubitzsch et al., 2014; Hill et al., 2008; Rivas et al., 2005; Nonaka et al., 2013): 41% CoNS, 24% S. aureus, 7% Enterococcus spp, 9% Gram-negative bacilli, 7% Streptococcus spp, and 6% fungi. Overall, the etiology of PVE in the present study was similar to these data. Data in the literature are limited in terms of the distribution of the etiology within the first year (Verkka et al., 1987; Shafer and Hall, 1970; Killen et al., 1970; Ralph-Edwards et al., 1994). Therefore, classifying all patients with PVE within the first year of valve surgery as having early-onset disease may not be appropriate.

The frequency of culture-negative disease varies across studies. In the present study cohort, 19.8% of cases were culture-negative; previous authors have reported frequencies ranging from 15% (Castillo et al., 2004) to 38.5% (Grubitzsch et al., 2014). Castillo et al. found that culture-negative cases were more frequent in the first year after valve surgery. These findings could be due to the previous use of antibiotics or, less frequently, to other etiologies not identified in standard blood cultures but found on pathology of the valve specimens, such as fungi (Thuny et al., 2010) or mycobacteria (Strabelli et al., 2010). Therefore, pathologists should systematically perform Ziehl–Neelsen and Grocott staining of excised valve specimens from patients with culture-negative PVE in the first year after operation.

**Empirical antibiotic treatment proposal**

Current guidelines recommend empirical treatment for early PVE (less than 1 year after valve surgery) and culture-negative cases with a combination of vancomycin, gentamicin, and rifampicin ± cefepime (level of evidence C) (Habib et al., 2016; Baddour et al., 2015). The present study findings concur with the recommendations for PVE occurring within the first 120 days after surgery. However, after this initial period it may be more appropriate to initially give the same empirical treatment as for late PVE (combination of penicillin, gentamicin, and oxacillin) because the incidence of resistant Staphylococcus and Gram-negative bacilli decreases considerably. Initial therapy with more potent antibiotics could be restricted to cases with negative blood cultures and no response to initial therapy, or those with severe sepsis at presentation. This approach could lead to higher antibiotic efficacy and less damage to the patient’s natural flora.

**Study limitations**

This study has some limitations. First, it was a single center study performed at a tertiary cardiac referral center involving patients with more severe disease. Second, only a small number of patients were included, and third, the study was performed at a single center.
cases occurred at > 120 days after valve replacement. However, PVE is an unusual condition.

**Clinical impact**

This study is the largest review of PVE and provides important information to improve patient care. Differences in PVE etiology within the first year after valve surgery should be considered in decisions regarding empirical antibiotic therapy.

**Conclusions**

Most PVE cases occurred within 120 days after valve surgery and the same etiological agents were identified during this period. The current cut-off level of 365 days for the classification of early-onset PVE should be revisited.

**Funding**

None.

**Conflict of interest**

None.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.ijijd.2017.09.004](http://dx.doi.org/10.1016/j.ijijd.2017.09.004).

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