Treatment Strategies and Risk of Recurrence in Patients With Heart Valve Prosthesis, *Staphylococcus aureus* Bacteremia, and Possible Endocarditis —A Retrospective Cohort Study

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Patients with heart valve prosthesis (HVP) and *Staphylococcus aureus* bacteremia (SAB) are at risk for endocarditis. In this retrospective, population-based cohort study of 134 patients with SAB and HVP, 97 patients (72%) were diagnosed with possible endocarditis. Despite that most patients with possible endocarditis received short antibiotic treatment, only 3 patients suffered recurrent SAB.

Keywords. heart valve prosthesis; prosthetic valve endocarditis; recurrence; *Staphylococcus aureus* bacteremia.

Staphylococcus aureus is the most common cause of infective endocarditis, and ∼10%–20% of *S. aureus* bacteremia (SAB) episodes become complicated by endocarditis [1]. It has been shown that heart valve prosthesis (HVP) is a significant risk factor for endocarditis in patients with SAB [1]. Prosthetic valve endocarditis (PVE) caused by *S. aureus* is a severe infection, with a 1-year mortality of up to 50% [2]. *S. aureus* PVE treatment includes a combination of intravenous antibiotics, and heart valve surgery is often performed [3]. The most recognized diagnostic criteria, the Duke criteria, depend on microbiological findings and echocardiographic examinations [4]. However, both transthoracic (TTE) and transesophageal echocardiography (TOE) have shown lower sensitivity in patients

with HVP, resulting in many patients with HVP and SAB receiving a diagnosis of possible PVE [5, 6]. As such, the European Society of Cardiology (ESC) modified the Duke criteria in 2015, incorporating new imaging modalities to increase accuracy [3].

When managing patients with SAB, it is important to identify cases with complications. Fowler et al. identified the presence of prosthetic material as a risk factor for complications resulting from SAB [7]. The Infectious Diseases Society of America's (IDSA's) guidelines for MRSA state that no prosthetic materials must be present in the intravascular space to meet criteria for uncomplicated SAB and that complicated SAB should be treated with at least 4 weeks of intravenous antibiotics [8]. In Sweden, there are no national guidelines for complicated SAB, resulting in diverging treatment of patients with HVP and SAB without a diagnosis of PVE. The aim of this population-based study was to examine investigations, treatments, and the possible connections with recurrence of SAB within 90 days in patients with SAB and HVP with possible endocarditis.

METHODS

This study was conducted in the region of Skåne in Southern Sweden (population of 1 391 000 as of 2020), with 10 hospitals contributing data. The Clinical Microbiology Laboratory, Region Skåne, Lund, serves the entire region. All episodes of SAB during 2015–2020 were identified from the laboratory database, and patients over 18 years of age with HVP were included. Patients with SAB from 2016 and 2017 have previously been described in a cohort study on time to blood culture positivity in relation to endocarditis [9]. Medical records were studied, and parameters were collected according to a preestablished protocol (Supplementary Table 1). Patients were studied for 1 year after their initial SAB episode. Continuous variables were expressed as medians with interquartile ranges, and the Mann-Whitney *U* test was used for comparison of such variables. The primary outcome was recurrence of SAB within 90 days.

Definitions

The ESC 2015 criteria for infective endocarditis were used, and patients with possible PVE were studied further [3]. Patients with rejected IE were those for whom the criteria for possible IE were not met. Treatment strategies were classified as "treated as PVE" or "not treated as PVE" according to the intended strategy by the treating physician. Patients not treated as PVE were divided into 3 groups depending on duration of intravenous antibiotic therapy: "<14 days," "14–27 days," and "≥28 days." Mode of acquisition was classified as community

acquired, health care associated, or nosocomial [10]. Comorbidity was evaluated according to the updated Charlson comorbidity index by Quan et al. [11], and sepsis was defined according to Sepsis-3 [12]. Origin of infection was defined as described by Berge et al. [13]. Recurrence was defined as a new episode of SAB within 90 days after completed antibiotic therapy with clinical recovery upon completion.

RESULTS

Between 2015 and 2020, 136 patients with HVP over 18 years of age developed SAB. Two patients were excluded due to inaccessible medical records, which left 134 patients. All but 1 patient had *S. aureus* isolates sensitive to methicillin. In total, 98 patients met clinical criteria for possible endocarditis, of whom 1 received a definite diagnosis of endocarditis upon surgery. The remaining 97 patients (73%) constituted the study cohort. Definite endocarditis was diagnosed in 32 patients (23%), and 5 patients (4%) had a rejected diagnosis. Of patients with possible PVE, 63 (65%) underwent TTE and 49 (51%) TOE, of whom none indicated endocarditis. Twenty-nine patients (30%) underwent further investigations to detect cardiac changes or embolization, none of which suggested PVE (Table 1).

Of patients with possible PVE, 26 (27%) died before completing the course of treatment. Of the remaining 71 patients, 9 (13%) received treatment for PVE, of whom 1 underwent surgical treatment without signs of endocarditis. Of patients with possible endocarditis, 62 (87%) were not treated for PVE, of whom 27 (44%) received <14 days of intravenous antibiotics, 32 (52%) received 14–27 days, and 3 (5%) received ≥28 days (Figure 1). The exact treatment durations are given in Supplementary Figure 1.

Three patients had recurrent SAB, diagnosed 5 days after completed therapy in 2 patients and 22 days after completed therapy in 1 patient. Details about the 3 patients with recurrent SAB are given in Supplementary Table 2. No significant differences were found between patients with recurrence vs no recurrence regarding duration of intravenous antibiotic (median, 15 days vs 15 days) or total duration of antibiotic therapy (median, 17 days vs 21 days).

DISCUSSION

Patients with HVP and SAB with possible PVE, who by IDSA MRSA guidelines are regarded as having complicated SAB, did not receive the 4 weeks of antibiotic treatment suggested, nor did they receive combination treatment for PVE [3, 8]. However, only 3 out of 71 patients with possible PVE who concluded therapy had recurrent SAB, which is comparable to previous research stating a recurrence frequency of 2%–5% for patients with SAB [14, 15]. This suggests that some patients with SAB and HVP can be cured with a treatment duration <4 weeks. In accordance with former reports, we did not

Table 1. Clinical Characteristics of Patients With HVP and SAB With Possible Endocarditis

Patient Characteristics	No. of Patients (n = 97) No. (%) or Median (IQR)
Age, y	81 (71–86)
Male sex	64 (66)
Charlson comorbidity score	2 (2–4)
0–1	20 (21)
2–3	49 (51)
>4	28 (29)
Intracardiac device	31 (32)
ICD	5 (5)
Pacemaker	26 (27)
Risk factors	
Previous endocarditis	15 (15)
Injection drug use	1 (1.0)
Hemodialysis dependent	3 (3.0)
Permanent intravenous catheter	2 (2.0)
Type of valve prosthesis	
Biological	65 (67)
Mechanical	21 (22)
TAVR	9 (9.0)
Missing data	2 (2.0)
Location of valve prosthesis	
Aortic	78 (80)
Mitral	9 (9.0)
Aortic and mitral	6 (6.0)
Tricuspid	2 (2.0)
Pulmonary	1 (1.0)
Missing data	1 (1.0)
Sepsis at presentation	75 (77)
Mode of acquisition	
Community-acquired SAB	17 (18)
Health care–associated SAB	47 (48)
Nosocomial SAB	33 (34)
Established origin of infection	28 (29)
Skin and soft tissue	13 (13)
Bone and joint	2 (2)
Intravascular device	6 (6)
Respiratory tract	4 (4)
Urinary tract	3 (3)
Focal infection not regarded as origin of infection[a]	4 (4)
Investigations	
Echocardiography	80 (82)
TOE	49 (61)
TTE	63 (65)
PET/CT	4 (4.0)
Cardiac CT	1 (1.0)
CT for septic embolization[b]	27 (28)
Signs of treatment failure	
Positive blood culture >48 h after therapy	17 (18)
Persistent fever >38°C >72 h after therapy	12 (12)
Mortality	
Deceased during therapy	26 (27)
1-y mortality[c]	43 (44)

Abbreviations: CT, computed tomography; HVP, heart valve prosthesis; ICD, intracardiac defibrillator; IQR, interquartile range; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography; SAB, *Staphylococcus aureus* bacteremia; TAVR, transcutaneous aortic valve replacement; TOE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]One patient had a spondylodiscitis, and 3 patients had septic arthritis.

[b]CT of the abdomen, brain, or lungs. CT of the lungs was only considered investigation for septic embolization in patients with right-sided heart valve prosthesis.

[c]None of the patients with completed antibiotic therapy who died within a year had a positive blood culture for *S. aureus*, nor suspected endocarditis.
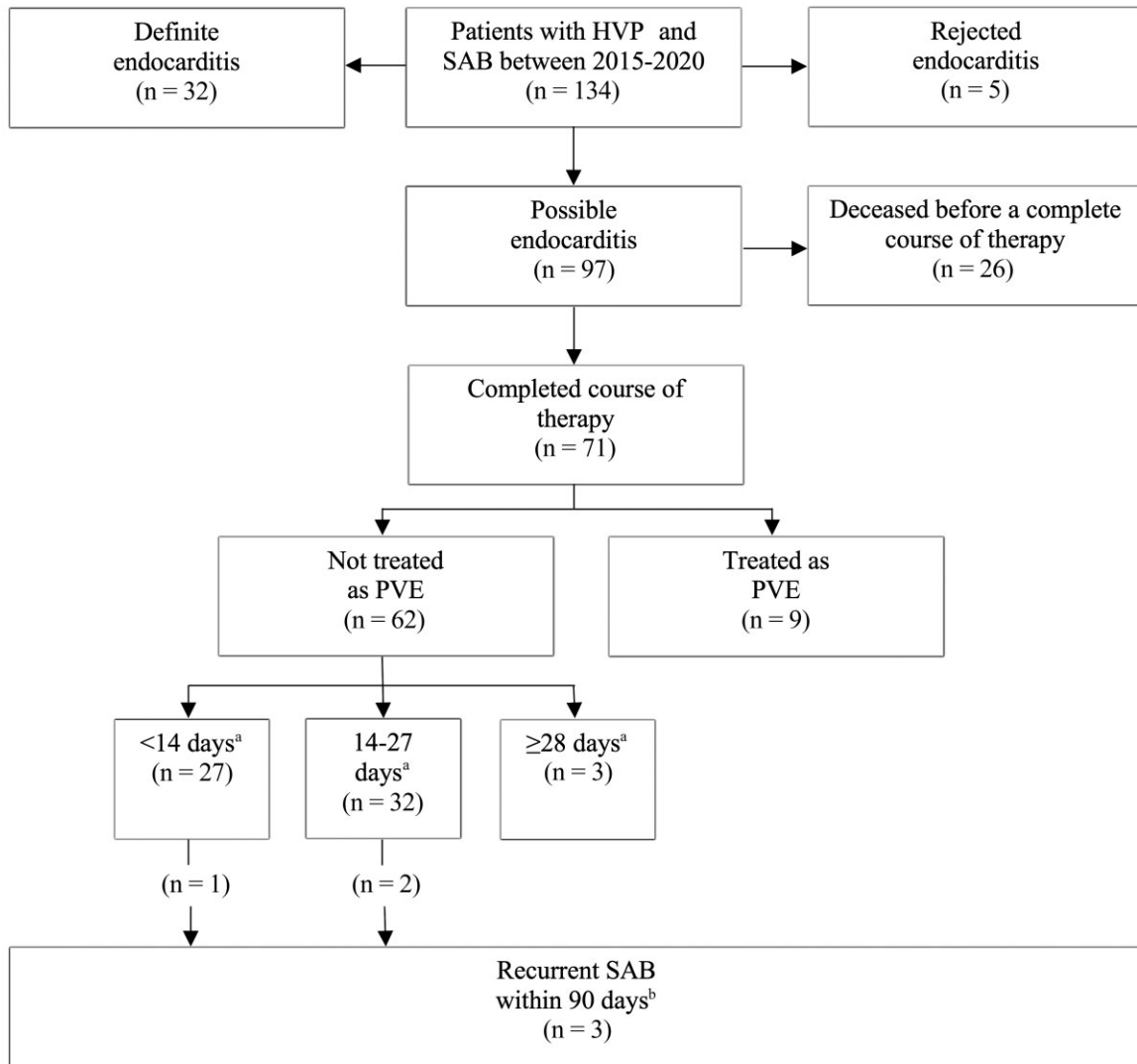
Figure 1. Flowchart representing treatment strategies and recurrences in patients with HVP and SAB with possible endocarditis. [a]Number of days of intravenous antibiotic therapy. [b]No further recurrences of SAB occurred between 90 days and 1 year. Abbreviations: HVP, heart valve prosthesis; PVE, prosthetic valve endocarditis; SAB, *Staphylococcus aureus* bacteremia.

find a difference in treatment duration between patients with recurrence compared with no recurrence [14, 16].

Many patients did not undergo TTE, TOE, or other investigations to detect PVE. Thus, some patients referred to as having possible endocarditis might have had a missed diagnosis of PVE. However, no patient was diagnosed with PVE at recurrence. Therefore, no support was found that further investigation in search for PVE is required in patients with HVP and SAB with negative TOE. Many patients in our cohort died within a year after their initial SAB episode. We cannot exclude the possibility that some patients who died during follow-up had a recurrent SAB or undiagnosed PVE.

To the best of our knowledge, this is the first report regarding patients with HVP and SAB with possible PVE. The main

limitation of the study is its retrospective design, which carries a risk of classification bias due to patients not being properly investigated. Despite being large compared with previous studies, the sample size still limits our analyses for distinguishing patients with recurrence from those without recurrence. The population-based approach is a strength of the study, resulting in a lack of selection bias, which is common in this type of study.

Our results suggest that patients with HVP and SAB with possible PVE are neither investigated nor treated according to international guidelines [8]. The exact reasons for this are likely multifaceted and could not be addressed in this retrospective study, but we found a low recurrence frequency, suggesting that a treatment duration of <4 weeks might be

sufficient for selected patients. More research is needed to determine optimal management.

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