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Microbiological etiology in prosthetic valve endocarditis: A nationwide registry study

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Abstract. Berisha B, Ragnarsson S, Olaison L, Rasmussen M. Microbiological etiology in prosthetic valve endocarditis: A nationwide registry study. *J Intern Med.* 2022;**292:**428–437.

Background. Prosthetic valve endocarditis (PVE) is a feared complication after heart valve surgery. Studies on differences in bacteriology in various types of PVE are limited.

Objectives. This study aimed to investigate the microbiology of PVE depending on the type of prosthetic valve and timing of diagnosis.

Methods. A retrospective study based on the Swedish Registry on Infective Endocarditis focusing on PVE was conducted. The cohort was divided into mechanical and bioprosthetic valves; into endocarditis localization in the aortic, mitral, or tricuspid valve; and into early and late PVE. The microbiology in these groups was compared. Predictors of *Staphylococcus aureus* as the cause of PVE were examined by multivariable logistic regression.

Results. A total of 780 episodes of PVE in 749 patients were compared regarding the distribution of causative microbiological agents. The most common agents included alpha-hemolytic streptococci (29%), *S. aureus* (22%), enterococci (14%), coagulase-negative staphylococci (CoNS) (12%), and *Cutibacterium acnes* (6%). *S. aureus* was more commonly found on mechanical valves compared to bioprosthetic ones (36% vs. 17%, $p < 0.001$) whereas alpha-hemolytic streptococci, enterococci, and CoNS were more common on bioprosthetic valves. There were no significant differences in the microbiology of PVE affecting mitral or aortic valves or in cases of early and late PVE. Predictors for *S. aureus* as the cause of PVE were end-stage renal disease, intravenous drug use, mechanical valve, and tricuspid localization of endocarditis.

Conclusions. The type of prosthetic heart valve is associated with the causative pathogen. Patients with mechanical valves are more likely to have PVE caused by *S. aureus*.

Keywords: microbiological etiology, prosthetic valve endocarditis, registry study, *Staphylococcus aureus*, valve prosthesis

Introduction

The use of prosthetic heart valves in patients with valvular heart disease is increasing worldwide. In aortic valve disease, mechanical heart valves are often used in younger patients whereas older patients usually receive biological or transcatheter aortic valve implantation (TAVI). Likewise, when a repair is not possible in mitral valve disease, a mechanical valve is often chosen in younger patients and a biological valve is used in elderly patients. Prosthetic valve endocarditis (PVE) is commonly defined as either early or late depending on whether the infection occurred within or after 12 months of valve surgery. One to six percent of all patients with heart valve prostheses are diagnosed with PVE, and over 20% of all cases of infective endocarditis (IE) are classified as PVE. In-hospital mortality among patients with PVE is significantly higher than in those diagnosed with native valve endocarditis (NVE) [1–4].

Most cases of PVE are reported to be caused by *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) [5]. Early PVE is most often caused by microorganisms indicating nosocomial

infection, such as *S. aureus*, CoNS, gram-negative bacteria, and fungi, whereas cases of late PVE are usually due to bacteria such as α-hemolytic streptococci and CoNS colonizing various human body surfaces [2, 5]. Information about the association of specific organisms to valve types in PVE is scarce, as are reports about differences in the microbiology of endocarditis affecting the mitral valve as compared to the aortic valve. One report that investigated PVE caused by *S. aureus* found the risk of *S. aureus* as the etiologic agent was similar in patients with late and early PVE and infection localization on mechanical and bioprosthetic valves [6]. A previous study based on the Swedish Registry on Infective Endocarditis (SRIE) focusing on NVE found that *S. aureus* was more commonly a causative pathogen affecting the mitral valve (41% vs. 31%, $p < 0.001$), whereas enterococci and CoNS were more prone to engage the aortic valve [7].

Thus, the state of knowledge around the microbiology in PVE depending on timing and especially the type of valve prosthesis affected is limited. This retrospective nationwide study aimed to describe the differences in microbiological causes of PVE depending on the types of valvular prostheses and the time between valve implantation and PVE diagnosis. Moreover, the factors determining *S. aureus* as the causative agent of PVE were analyzed.

Methods

Study design and population

A retrospective study based on the SRIE was conducted, focusing on patients with PVE. In Sweden, patients with IE are typically treated at departments for infectious diseases, and all Swedish infectious disease departments report cases of patients treated as IE to the SRIE on a voluntary basis [8]. The registry contains information regarding patient characteristics, comorbidities, microbiology, diagnosis according to Duke criteria [9], and treatment. In the registry, there were 4414 episodes of definite IE recorded from January 2008 to June 2020. Information on survival was extracted from the Swedish Population Register. Episodes in patients with vegetations or abscesses in relation to a prosthetic valve or with a prosthetic valve and undetermined localization of IE were classified as PVE. The variable describing microbiology had data on *S. aureus*, α-hemolytic streptococci, *Streptococcus bovis*, CoNS, enterococci, β-hemolytic streptococci, *Streptococcus pneumoniae*, *Haemophilus, Aggregatibacter, Cardiobacterium, Eikinella, Kingella* (HACEK), and a group of "other" microorganisms. We merged episodes caused by α-hemolytic streptococci with episodes of *Streptococcus bovis* and episodes of β-hemolytic streptococci with episodes of *Streptococcus pneumoniae*. Because the date of valve implantation is specified by year only in SRIE, episodes were considered as early PVE if IE occurred either during the same year or within the first half of the following year. No imputations of missing variables were made.

Statistical analysis

Comparisons of PVE episodes affecting different types of valves, different PVE locations, and different times after surgery were performed. Categorical variables are presented as number of episodes and percentages rounded to the nearest integer in parentheses. These variables were compared between episodes in patients with biological valves, including TAVI on the one hand and mechanical valves on the other hand, episodes with IE located on aortic and mitral valves, and episodes with early and late PVE using the Chi-squared test. However, *p*-values for comparisons between categorical variables with at least one cell with a count of less than five were calculated using Fisher's exact test. The continuous variables were regarded as non-normally distributed and presented as median with interquartile range in parentheses when groups had more than 10 subjects. In groups where subjects were fewer than 10, maximum and minimum values were presented in parentheses. Differences between groups were investigated using the Mann–Whitney U test. We compared types of valves in an age-stratified analysis and localization of infection in a sex-stratified analysis.

Next, we performed a univariable logistic regression to identify independent predictors of *S. aureus* as a causative agent on patient characteristics and background variables that were known prior to the current IE episode. All variables with $p < 0.25$ in the univariable analysis were then entered into a multivariable logistic regression model. A subgroup analysis was performed following the exclusion of all patients with a history of intravenous drug use (IVDU). We repeated the above-described univariable and multivariable regression but used a cut-off of $p < 0.2$ for variables to be entered into the multivariable model. All statistical calculations were made with SPSS (V.26.0; IBM, Armonk, New York, USA).

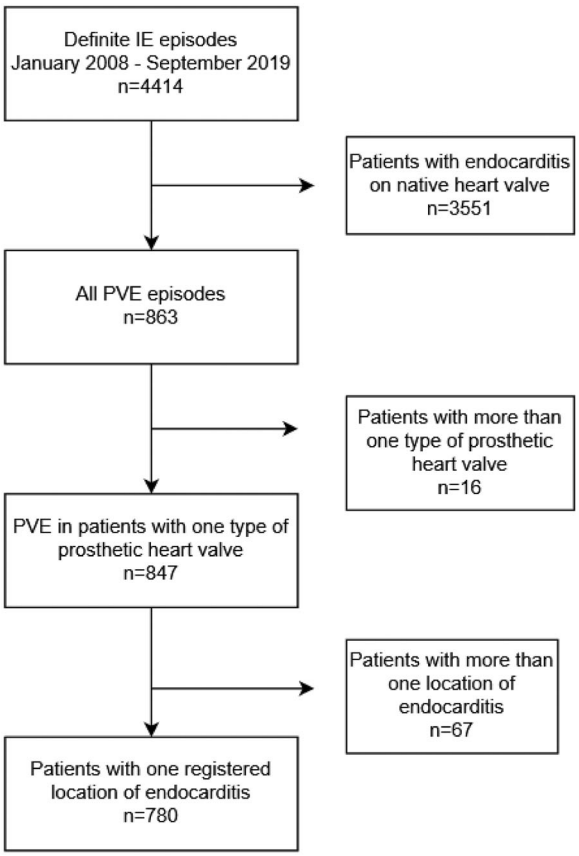

Fig. 1 *Flow chart of inclusion and exclusion criteria in population selection.*

This study was approved by the Regional Ethics Review Board in Lund, Sweden, Ref. 2016/601.

Results

Total population characteristics and microbiology

Of 4414 episodes with definite IE, 3551 were excluded due to having native valve IE. Sixteen episodes were excluded because they had more than one type of prosthetic heart valve, and 67 episodes were excluded because they had more than one localization of IE. The remaining 780 episodes with PVE constituted the final study cohort (Fig. 1). These occurred in 749 patients; 27 patients had two episodes, and two patients had three episodes each. Baseline characteristics, localization of IE, the type of prosthetic heart valve, microbiological etiology, and treatment outcome for the total population included in the study are presented in Table 1. Of all PVE episodes, the

Table 1. *Patient characteristics*

Variables	*N*	Patients with definite PVE ($n = 780$)
Age (years)	780	71 (51–91)
Female	780	196 (25%)
Male	780	584 (75%)
Diabetes mellitus	780	145 (19%)
ESRD	780	18 (2%)
Tumor disease treated within the last 5 years	780	88 (11%)
IVDU	780	54 (7%)
Early PVE	602	149 (19%)
Late PVE	602	453 (58%)
Localization of endocarditis		
Aortic valve only	780	547 (70%)
Mitral valve only	780	123 (16%)
Tricuspid valve only	780	17 (2%)
Pulmonic valve only	780	9 (1%)
Undetermined or missing	780	84 (11%)
Type of prosthetic valve		
Biological, including TAVI	736	503 (68%)
Mechanical	736	197 (27%)
Repaired	736	22 (3%)
Homograft	736	11 (1%)
Other	736	3 (0.4%)
Microbiology		
S. aureus	780	173 (22%)
α-hemolytic streptococci and *S. bovis*	780	224 (29%)
Enterococci	780	113 (14%)
CoNS	780	81 (10%)
C. acnes	780	47 (6%)
β-hemolytic streptococci and *S. pneumoniae*	780	30 (4%)
HACEK	780	25 (3%)
Candida	780	14 (2%)
Corynebacterium	780	13 (2%)
Other	780	36 (5%)
Pathogen unknown	780	24 (3%)
Treatment outcome		
Duration of antibiotic treatment (days)	666	40 (26–54)
Surgical intervention	780	254 (33%)
In-hospital mortality	780	105 (14%)

Abbreviations: CoNS, coagulase-negative staphylococci; ESRD, end-stage renal disease; HACEK, *Haemophilus, Aggregatibacter, Cardiobacterium, Eikinella, Kingella*; IVDU, intravenous drug use; PVE, prosthetic valve endocarditis; TAVI, transcatheter aortic valve implantation.

Table 2. *Patient characteristics depending on the type of prosthetic heart valve*

Variables	*N*	Biological and TAVI ($n = 503$)	Mechanical ($n = 197$)	*p*-Value	Repaired ($n = 22$)	Homograft ($n = 11$)	Other ($n = 3$)
Age (years)	736	74 (58–90)	63 (43–83)	<0.001**	70 (53–87)	60 (28–92)	54 (22–60)
Female	736	128 (25%)	48 (24%)	0.8	10 (46%)	1 (9%)	2 (67%)
Male		375 (75%)	149 (76%)		12 (55%)	10 (91%)	1 (33%)
Diabetes mellitus	736	101 (20%)	28 (14%)	0.07	2 (9%)	3 (27%)	0 (0%)
ESRD	736	13 (3%)	5 (3%)	1.0	0 (0%)	0 (0%)	0 (0%)
Tumor disease treated within the last 5 years	736	70 (14%)	12 (6%)	0.004	1 (5%)	0 (0%)	0 (0%)
IVDU	736	46 (9%)	5 (3%)	0.002	2 (9%)	1 (9%)	0 (0%)
Early PVE	585	111 (22%)	21 (11%)	0.001	10 (45%)	2 (18%)	0 (0%)
Late PVE	585	297 (59%)	130 (66%)		7 (32%)	7 (64%)	0 (0%)
Localization of endocarditis				<0.001*			
Aortic valve	736	387 (77%)	122 (62%)		1 (5%)	9 (82%)	1 (33%)
Mitral valve	736	48 (10%)	47 (24%)		17 (77%)	0 (0%)	1 (33%)
Tricuspid valve	736	14 (3%)	2 (1%)		1 (5%)	0 (0%)	0 (0%)
Pulmonic valve	736	6 (1%)	1 (1%)		0 (0%)	1 (9%)	1 (33%)
Undetermined	736	48 (10%)	25 (13%)		3 (14%)	1 (9%)	0 (0%)
Microbiology				<0.001			
S. aureus	736	87 (17%)	70 (36%)		7 (32%)	1 (9%)	0 (0%)
α-hemolytic streptococci and *S. bovis*	736	164 (33%)	37 (19%)		6 (27%)	3 (27%)	1 (33%)
Enterococci	736	82 (16%)	21 (11%)		2 (9%)	3 (27%)	1 (33%)
CoNS	736	58 (12%)	9 (5%)		3 (14%)	0 (0%)	1 (33%)
C. acnes	736	31 (6%)	15 (8%)		1 (5%)	0 (0%)	0 (0%)
β-hemolytic streptococci and *S. pneumoniae*	736	15 (3%)	12 (6%)		2 (9%)	0 (0%)	0 (0%)
HACEK	736	11 (2%)	11 (6%)		0 (0%)	2 (18%)	0 (0%)
Candida	736	11 (2%)	1 (1%)		0 (0%)	1 (9%)	0 (0%)
Corynebacterium	736	11 (2%)	2 (1%)		0 (0%)	0 (0%)	0 (0%)
Other	736	18 (4%)	13 (7%)		1 (5%)	1 (9%)	0 (0%)
Pathogen unknown	736	15 (3%)	6 (3%)		0 (0%)	0 (0%)	0 (0%)

Abbreviations: CoNS, coagulase-negative staphylococci; ESRD, end-stage renal disease; HACEK, *Haemophilus, Aggregatibacter, Cardiobacterium, Eikinella, Kingella*; IVDU, intravenous drug use; PVE, prosthetic valve endocarditis; TAVI, transcatheter aortic valve implantation.

causative agent was α-hemolytic streptococci in 29%, *S. aureus* in 22%, enterococci in 14%, CoNS in 10%, and *Cutibacterium acnes* (formerly *Propionibacterium acnes*) in 6%.

Characteristics and microbiology depending on the type of prosthetic valve

The correlation of the type of prosthetic valve with patient characteristics, localization of IE, and microbiological etiology is presented in Table 2. PVE episodes in patients with biological valves, including TAVI, were most commonly due to α-hemolytic streptococci (33%), whereas PVE in patients with mechanical valves was most commonly caused by *S. aureus* (36%). The difference in the distribution of *S. aureus*, α-hemolytic streptococci, enterococci, and CoNS depending on whether patients had biological or mechanical valves was statistically significant ($p < 0.001$). The same correlations were investigated in a stratified analysis with

Table 3. *Patient characteristics depending on localization of endocarditis*

Variables	*N*	Aortic only ($n = 547$)	Mitral only ($n = 123$)	*p*-Value	Tricuspid only ($n = 17$)	Pulmonic only ($n = 9$)	Undetermined or missing ($n = 84$)
Age (years)	780	73 (55–91)	68 (50–86)	0.001**	45 (26–64)	36 (22–50)	73 (53–93)
Female	780	113 (21%)	49 (40%)	<0.001	9 (53%)	3 (33%)	22 (26%)
Male	780	434 (79%)	74 (60%)		8 (47%)	6 (67%)	62 (74%)
Diabetes mellitus	780	100 (18%)	26 (21%)	0.5	3 (18%)	0 (0%)	16 (19%)
ESRD	780	11 (2%)	4 (3%)	0.4	0 (0%)	0 (0%)	3 (4%)
Tumor disease treated within the last 5 years	780	71 (13%)	11 (9%)	0.2	1 (6%)	0 (0%)	5 (6%)
IVDU	780	23 (4%)	15 (12%)	0.001	12 (71%)	1 (11%)	3 (4%)
Early PVE	602	107 (20%)	30 (24%)	0.2	4 (24%)	0 (0%)	8 (10%)
Late PVE	602	327 (60%)	66 (54%)		8 (47%)	7 (78%)	45 (54%)
Type of prosthetic valve				<0.001*			
Biological, including TAVI	736	387 (71%)	48 (39%)		14 (82%)	6 (67%)	48 (57%)
Mechanical	736	122 (22%)	47 (38%)		2 (12%)	1 (11%)	25 (30%)
Repaired	736	1 (0.2%)	17 (14%)		1 (6%)	0 (0%)	3 (4%)
Homograft	736	9 (2%)	0 (0%)		0 (0%)	1 (11%)	1 (1%)
Other	736	1 (0.2%)	1 (1%)		0 (0%)	1 (11%)	0 (0%)
Microbiology				0.5			
S. aureus	780	113 (21%)	32 (26%)		11 (65%)	3 (33%)	14 (17%)
α-hemolytic streptococci and *S. bovis*	780	146 (27%)	33 (27%)		2 (12%)	4 (44%)	39 (46%)
Enterococci	780	83 (15%)	15 (12%)		3 (18%)	0 (0%)	12 (14%)
CoNS	780	55 (10%)	16 (13%)		1 (6%)	1 (11%)	8 (10%)
C. acnes	780	44 (8%)	3 (2%)		0 (0%)	0 (0%)	0 (0%)
β-hemolytic streptococci and *S. pneumoniae*	780	24 (4%)	4 (3%)		0 (0%)	0 (0%)	2 (2%)
HACEK	780	16 (3%)	5 (4%)		0 (0%)	1 (11%)	3 (4%)
Candida		11 (2%)	3 (2%)		0 (0%)	0 (0%)	0 (0%)
Corynebacterium		12 (2%)	1 (1%)		0 (0%)	0 (0%)	0 (0%)
Other	780	25 (5%)	7 (6%)		0 (0%)	0 (0%)	4 (5%)
Pathogen unknown	780	18 (3%)	4 (3%)		0 (0%)	0 (0%)	2 (2%)

Abbreviations: CoNS, coagulase-negative staphylococci; ESRD, end-stage renal disease; HACEK, *Haemophilus, Aggregatibacter, Cardiobacterium, Eikinella, Kingella*; IVDU, intravenous drug use; PVE, prosthetic valve endocarditis; TAVI, transcatheter aortic valve implantation.

three different age groups, with similar results (Table S1).

Characteristics and microbiology depending on the localization of IE

Patient characteristics, type of prosthetic heart valve, and microbiological etiology depending on the localization of IE are presented in Table 3. Of patients with aortic valve IE, 387 patients (77%) had biological valves, including TAVI, compared to 48 patients (10%) with mitral localization ($p < 0.001$). There was no statistically significant difference in the distribution of *S. aureus*, α-hemolytic streptococci, enterococci, and CoNS when comparing aortic to mitral localization of PVE. As male sex was significantly more common in aortic PVE, a sex-stratified analysis was performed with largely similar results (Table S2).

Table 4. *Patient characteristics depending on the timing of PVE*

Variables	*N*	Early PVE ($n = 149$)	Late PVE ($n = 453$)	*p*-Value
Age (years)	602	68 (50–86)	72 (51–93)	0.005**
Female	602	37 (25%)	112 (25%)	1.0
Male	602	112 (75%)	341 (75%)	
Diabetes mellitus	602	29 (20%)	89 (20%)	1.0
ESRD	602	3 (2%)	12 (3%)	0.7
Tumor disease treated within the last 5 years	602	24 (26%)	45 (10%)	0.04
IVDU	602	13 (9%)	28 (6%)	0.3
Localization of endocarditis				0.2
Aortic valve only	602	107 (72%)	327 (72%)	
Mitral valve only	602	30 (20%)	66 (15%)	
Tricuspid valve only	602	4 (3%)	8 (2%)	
Pulmonic valve only	602	0 (0%)	7 (2%)	
Undetermined	602	8 (5%)	45 (10%)	
Type of prosthetic valve				0.001
Biological, including TAVI	585	111 (74%)	297 (66%)	
Mechanical	585	21 (14%)	130 (29%)	
Repaired	585	10 (7%)	7 (2%)	
Homograft	585	2 (1%)	7 (2%)	
Other	585	0 (0%)	0 (0%)	
Microbiology				0.1*
S. aureus	602	29 (19%)	105 (23%)	
α-hemolytic streptococci and *S. bovis*	602	38 (26%)	144 (32%)	
Enterococci	602	21 (14%)	61 (13%)	
CoNS	602	20 (13%)	36 (8%)	
C. acnes	602	12 (8%)	32 (7%)	
β-hemolytic streptococci and *S. pneumoniae*	602	3 (2%)	17 (4%)	
HACEK	602	2 (1%)	18 (4%)	
Candida	602	8 (5%)	1 (0.2%)	
Corynebacterium	602	7 (5%)	5 (1%)	
Other	602	6 (4%)	21 (5%)	
Pathogen unknown	602	3 (2%)	13 (3%)	

Abbreviations: CoNS, coagulase-negative staphylococci; ESRD, end-stage renal disease; HACEK, *Haemophilus, Aggregatibacter, Cardiobacterium, Eikinella, Kingella*; IVDU, intravenous drug use; PVE, prosthetic valve endocarditis; TAVI, transcatheter aortic valve implantation.

Characteristics and microbiology depending on the timing of PVE

The characteristics of early and late PVE are presented in Table 4. There was no statistically significant difference in the distribution of *S. aureus*, α-hemolytic streptococci, enterococci, and CoNS depending on whether the episode represented an early or late PVE ($p = 0.13$). There was, however, a higher risk for early PVE among patients with bioprosthetic valves compared to those with mechanical valves ($p < 0.001$).

Predictors of S. aureus *as a causative agent in PVE*

Predictors of *S. aureus* as the causative pathogen in patients with PVE are presented in Table 5. In the univariable screening for predictors of *S. aureus* as the causative pathogen in PVE, we identified the following variables to include in a multivariable model: age, diabetes mellitus, end-stage renal disease (ESRD), IVDU, mechanical valves and repaired valves, and mitral and tricuspid localization of endocarditis. However, following the multivariable analysis, only ESRD, IVDU, mechanical

Table 5. *Logistic regression for S. aureus as a cause of PVE*

			Univariable analysis			Multivariable analysis		
Predictor	*S. aureus* PVE ($n = 173$) $N = 173$	Non–*S. aureus* PVE ($n = 607$) $N = 607$	Wald	*p*-Value	OR (95% CI)	Wald	*p*-Value	OR (95% CI)
Age (years)*	70 (43–97)	68.5 (49.5–87.5)	5.6	0.02	0.99 (0.98–1.0)	1.9	0.2	1.0 (1.0–1.03)
Sex	48 (28%) female 125 (72%) male	148 (24%) Female 459 (76%) Male	0.81	0.4	1.2 (0.81–1.7)			
Diabetes mellitus	23 (13%)	122 (20%)	4.1	0.04	0.61 (0.38–0.99)	1.6	0.2	0.71 (0.42–1.2)
ESRD	8 (5%)	10 (2%)	4.9	0.03	2.9 (1.1–7.5)	7.1	0.01	3.9 (1.4–10)
Tumor disease treated within the last 5 years	18 (10%)	70 (12%)	0.17	0.7	0.89 (0.52–1.5)			
IVDU	22 (13%)	32 (5%)	11	0.001	2.6 (1.5–4.6)	6.9	0.01	2.8 (1.3–6.2)
Late PVE	$N = 134$ 105 (78%)	$N = 468$ 348 (74%)	0.89	0.4	1.2 (0.79–2.0)			
Type of prosthetic valve	$N = 165$	$N = 571$	28	<0.001		34	<0.001	
Biological and TAVI	87 (53%)	416 (73%)			(ref)			(ref)
Mechanical	70 (42%)	127 (22%)	26	<0.001	2.6 (1.8–3.8)	32	<0.001	3.4 (2.2–5.3)
Repaired	7 (4%)	15 (3%)	2.9	0.09	2.2 (0.88–5.6)	3.2	0.07	2.5 (0.92–7.1)
Homograft	1 (1%)	10 (2%)	0.49	0.5	0.48 (0.06–3.8)	0.3	0.6	0.55 (0.1–4.6)
Other	0 (0%)	3 (1%)	N/A	N/A	N/A	N/A	N/A	N/A
Localization of endocarditis	$N = 173$	$N = 607$	17	0.002		14	0.01	
Aortic only	113 (65%)	434 (71%)			(ref)			(ref)
Mitral only	32 (18%)	91 (15%)	1.7	0.2	1.4 (0.86–2.1)	0.1	0.8	0.93 (0.54–1.6)
Tricuspid only	11 (6%)	6 (1%)	14	<0.001	7.0 (2.5–19)	9.0	0.003	5.7 (1.8–18)
Pulmonic only	3 (2%)	6 (1%)	0.83	0.4	1.9 (0.47–7.8)	2.6	0.1	3.8 (0.76–19)
Undetermined	14 (8%)	70 (12%)	0.72	0.4	0.77 (0.42–1.4)	1.7	0.2	0.65 (0.34–1.3)

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; IVDU, intravenous drug use; OR, odds ratio; PVE, prosthetic valve endocarditis; TAVI, transcatheter aortic valve implantation.

valves, and tricuspid localization were associated with an increased risk for *S. aureus* as the cause of PVE. Since the IVDU population is largely different from other patients in the current study cohort, the predictors of *S. aureus* were also investigated in a subanalysis excluding IVDU (Table S3). In this multivariable analysis, mechanical valves and ESRD remained significant predictors of *S. aureus*.

Discussion

This study shows that patients with mechanical valve prostheses have a higher risk of having *S. aureus* as the cause for PVE compared to patients with bioprosthetic valve PVE. On the contrary, patients with bioprosthetic valves are more likely to have α-hemolytic streptococci as the cause for PVE. This finding is novel and potentially important to direct initial investigations and therapy in cases of suspected PVE. Specifically, *S. aureus* was more than twice as common in PVE in patients with mechanical valves compared to biological ones. This finding contrasts with a smaller previous study, which reported that the risk of PVE caused by *S. aureus* was not significantly different in patients with mechanical and bioprosthetic valves [6]. Our finding may be explained by the properties of *S. aureus* that perhaps make these bacteria more likely to adhere to mechanical surfaces compared to the other IE pathogens. However, patients who receive mechanical valves are typically younger, and *S. aureus* infections are more common in younger persons [10]. We made an age-stratified analysis and found that the association between *S. aureus* and mechanical valves was stable across all age groups. In the multivariable analysis, age was not independently associated with *S. aureus* as the cause, whereas the presence of a mechanical valve prosthesis was an independent predictor of *S. aureus* etiology. Importantly, the association between mechanical valves and *S. aureus* remained if the IVDU population, which is typically younger, was excluded from the analysis. This indicates that the apparent predilection of *S. aureus* for mechanical valve prostheses might reflect a true difference in bacterial adhesion and valve colonization. Bioprostheses may have better protection from *S. aureus* adhesion and colonization through the partial endothelialization that occurs in bioprostheses over time [11]. On the other hand, mechanical valves are generally covered in pyrolytic carbon, and they do not mimic the biological and elastomeric properties of native valves. Moreover, the leaflets of mechanical valves are not in direct contact with endothelium, which prevents cell migration [12].

We also show that ESRD, IVDU, and tricuspid localization of IE are all predictors of *S. aureus* as the causative pathogen in patients with PVE. This is in line with previous findings and underlines the mechanisms of *S. aureus* entry into the blood stream and the propensity of the organism to adhere to the tricuspid valve.

Other results of this study are largely in accordance with previous studies conducted on PVE [2, 3, 13]. We identified similar causative pathogens in PVE as other recent studies [2, 5], and the proportion of early PVE and the valve affected was found to be similar to what others have reported [2, 13]. In a study by Bjursten et al. on TAVI PVE, the authors demonstrated that *S. aureus* was significantly more common in early PVE [14]. In contrast to most TAVI procedures that are done through vascular access in the groin, surgically implanted valves are implanted through sternotomy or thoracotomy where disinfection is easier to perform compared to the groin.

We found no statistically significant difference in the distribution of causative pathogens depending on aortic or mitral localization, and this was also the case when comparing early and late PVE. When grouping patients according to localization of IE, we found that males more commonly had an aortic localization, while females predominantly had mitral localization of infection. The same has previously been documented in studies on native IE [7].

A strength of this study is that our population was relatively large and that we present results that are largely similar to previous studies of PVE. The SRIE is a nationwide registry, which has advantages over registries based on reports from tertiary centers with selection of complicated cases. However, reporting to the SRIE is voluntary, and there may certainly be cases missed, possibly also in a nonrandom fashion. The main weaknesses of the current study are that it relies on data entered by many different physicians with potentially incoherent ways of collecting and recording data, and that there were a considerable number of missing data points regarding the type of prosthetic heart

valve and the time between valve implantation and PVE diagnosis. As the majority of cases had only the year of valve implantation recorded, we had to make assumptions (described in the method), making the classification of early and late PVE unprecise. Despite being a relatively large study, we were limited by the scarce data on episodes with PVE on repaired valves, homografts, and tricuspid or pulmonic valves, making it difficult to draw conclusions on these groups. Another limitation is that the SRIE has no formal validation, and that the results of this study are not automatically applicable to other countries and healthcare systems. The retrospective design of our study and the possibility of unknown confounders not registered, such as socioeconomic variables and living conditions, are inevitable weaknesses that may have affected our study results.

Conclusion

The findings of this study suggest that different bacteria predominantly adhere to different types of valve materials. This has implications for the direction of empirical therapy in PVE, and it potentially calls for treatment regimens targeting specific bacterial adherence mechanisms in patients with PVE.

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Author contributions

Blerand Berisha: conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. Sigurdur Ragnarsson: conceptualization; formal analysis; investigation; methodology; writing – review and editing. Lars Olaison: Conceptualization; formal analysis; methodology; resources; writing – original draft; writing – review and editing. Magnus Rasmussen: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; writing – original draft; writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Sensitivity analysis according to age groups.
Table S2: Sensitivity analysis according to sex.
Table S3: Logistic regression for S. aureus as the cause of PVE, subanalysis after exclusion of all intravenous drug users. ■

