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Incidence and outcomes of prosthetic valve endocarditis in adults with tetralogy of Fallot

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ABSTRACT

Background: The risk of endocarditis varies with CHD complexity and the presence of prosthetic valves. The purpose of the study was therefore to describe incidence and outcomes of prosthetic valve endocarditis in adults with repair tetralogy of Fallot. *Methods:* Retrospective review of adult tetralogy of Fallot patients who underwent prosthetic valve implantation, 1990–2017. We defined prosthetic valve endocarditis-related complications as prosthetic valve dysfunction, perivalvular extension of infection such abscess/aneurysm/fistula, heart block, pulmonary/systemic embolic events, recurrent endocarditis, and death due to sepsis. *Results:* A total of 338 patients (age: 37 ± 15 years) received 352 prosthetic valves (pulmonary [n = 308, 88%], tricuspid [n = 13, 4%], mitral [n = 9, 3%], and aortic position [n = 22, 6%]). The annual incidence of prosthetic valve endocarditis was 0.4%. There were 12 prosthetic valve endocarditis-related complications in six patients, and these complications were prosthetic valve dysfunction (n = 4), systemic/pulmonary embolic events (n = 2), heart block (n = 1), aortic root abscess (n = 1), recurrent endocarditis (n = 2), and death due to sepsis (n = 1). Three (50%) patients required surgery at 2 days, 6 weeks, and 23 weeks from the time of prosthetic valve endocarditis diagnosis. Altogether three of the six (50%) patients died, and one of these deaths was due to sepsis. *Conclusions:* The incidence, complication rate, and outcomes of prosthetic valve endocarditis in tetralogy of Fallot patients underscore some of the risks of having a prosthetic valve. It is important to educate the patients on the need for early presentation if they develop systemic symptoms, have a high index of suspicion for prosthetic valve endocarditis, and adopt a multi-disciplinary care approach in this high-risk population.

Patients with repaired tetralogy of Fallot often have residual or develop recurrent valvular lesions, the most common being pulmonary regurgitation.[1–4] These residual or recurrent valvular lesions often require implantation of prosthetic valves.[1–4] The presence of a prosthetic valve is a risk factor for endocarditis, and the guidelines recommend endocarditis prophylaxis for patients with prosthetic valves.[5–8] The risk of endocarditis is also associated with complexity of CHD diagnosis, and patients with complex lesions are at higher risk of endocarditis.[9] Most of the studies reporting incidence and outcomes of endocarditis were derived from cohorts of CHD patients with different types of lesions.[9,10] Since the risk of endocarditis varies by CHD complexity and presence of prosthetic valve/material, the purpose of the study was therefore to describe the incidence and outcomes of prosthetic valve endocarditis in adults with repaired tetralogy of Fallot.

Methods

The MACHD (Mayo Adult Congenital Heart Disease) database was queried for patients (age ≥18 years) with repaired tetralogy of Fallot who underwent prosthetic valve implantation from 1 January, 1990 through 31 December, 2017. The patients with pulmonary atresia were excluded. The Mayo Clinic institutional review board approved this study and waived informed consent for patients that provided research authorisation. The electronic health records were reviewed to identify patients with a diagnosis of infective endocarditis. Among the patients with a diagnosis of infective endocarditis, we performed extensive review of blood culture reports, tissue culture/histology reports, images of transthoracic echocardiogram and transesophageal echocardiogram, computed tomography, positron emission tomography scan report, infectious disease consult notes, and surgical operation notes. The patients who met the criteria for *definite* endocarditis based on the modified Duke criteria[11] were selected as the study cohort.

We defined prosthetic valve endocarditis-related complications as prosthetic valve dysfunction, perivalvular extension of infection such as abscess/aneurysm/fistula, heart block, pulmonary or systemic embolic events, recurrent endocarditis, and death due to sepsis. Prosthetic valve dysfunction

Table 1. Baseline characteristics.

	n = 338
Age (years)	37 ± 15
Male	172 (51%)
Body mass index (kg/m^2)	27 ± 6
Body surface area (m^2)	1.9 ± 0.3
Age at TOF repair (years)	5 (2–9)
Prior palliative shunt	144 (43%)
DiGeorge syndrome	6 (2%)
Down syndrome	1 (0.3%)
Comorbidities	
Atrial fibrillation	92 (27%)
Atrial flutter	80 (24%)
Hypertension	83 (25%)
Hyperlipidemia	138 (41%)
Coronary artery disease	43 (13%)
Current or prior smoker	60 (19%)
Diabetes mellitus	55 (16%)
Sleep apnea	97 (29%)
Prior stroke	31 (9%)
Laboratory tests	
Hemoglobin (g/dl)	14.1 ± 1.8
Creatinine (mg/dl)	0.97 ± 0.31
NT-proBNP (pg/ml)	241 (122–837)
Echocardiography	
≥ Moderate RV enlargement*	254 (75%)
≥ Moderate RV systolic dysfunction*	108 (32%)
Fractional area change (%)	39 ± 10
LV ejection fraction (%)	57 ± 9

LV = left ventricle; NT-proBNP = N-terminal pro b-type natriuretic peptide; RV = right ventricle; TOF = tetralogy of Fallot.
*Qualitative assessment.

was defined as new moderate prosthetic obstruction (mean gradient of >25 mmHg for aortic and pulmonary prostheses, or >7 mmHg for tricuspid and mitral prostheses), new moderate prosthetic regurgitation, or any degree of periprosthetic regurgitation based on qualitative Doppler assessment.[12] Prosthetic valve was defined as artificial or non-native valve prosthesis.

Data were presented as mean ± standard deviation, median (interquartile range), or counts (%), and between-group comparisons were performed using t-test, chi-square test, and Fisher exact test as appropriate. For the analysis of incidence density, each episode of prosthetic valve endocarditis was counted as a separate event and expressed as event per patient-years. The *at-risk* period was calculated from the time of initial prosthetic valve implantation to the diagnosis of prosthetic valve endocarditis or last clinic visit. All statistical analyses were performed using JMP software (version 13.0; SAS Institute Inc., Cary, North Carolina, United States of America) and $p < 0.05$ was considered statistically significant.

Results

A total of 338 patients received 352 prosthetic valves within the study period at a mean age of 37 ± 15 years. These prostheses were implanted in the following positions: pulmonary (n = 308, 88%), tricuspid (n = 13, 4%), mitral (n = 9, 3%), and aortic (n = 22, 6%). Of the 352 prostheses, 40 (11%) were mechanical prostheses. Table 1 shows the baseline clinical data of the patients with prosthetic valves. Of the 338 patients with prosthetic valves, 6 (2%) patients (5 males, 1 female) developed prosthetic valve endocarditis, while another 3 (1%) patients had bacteremia (2 cases of *Enterococcus faecalis* and 1 case of *Staphylococcus epidermidis*) without evidence of endocarditis. All six patients had at least one positive blood culture and imaging finding consistent with endocarditis. Compared to the patients without prosthetic valve endocarditis, the patients with prosthetic valve endocarditis had a higher prevalence of atrial fibrillation (25% versus 83%, p = 0.002), but otherwise there were no other significant differences in clinical characteristics between the groups. All of the patients were on antiplatelet therapy, while four of them were on warfarin at the time of prosthetic valve endocarditis diagnosis.

The median follow-up (*at-risk* period) was 79 (12–165) months, cumulative follow-up was 2225 patient-years, and during this period, eight episodes of prosthetic valve endocarditis occurred in six patients. The mean interval from valve implantation to diagnosis of endocarditis was 6.6 ± 2.8 years (median 6.2 years). The incidence of prosthetic valve endocarditis was 0.4 events per patient-years (95% confidence interval 0.2–0.7).

Of these eight prosthetic valve endocarditis events, the pulmonary and aortic prostheses were involved in five and three cases, respectively, Table 2. Prosthetic valve endocarditis was due to methicillin-sensitive *Staphylococcus aureus* (n = 4, 50%), *Staphylococcus epidermidis* (n = 1, 12.5%), *Streptococcus agalactiae* (n = 2, 25%), and *Enterobacter* species (n = 1, 12.5%). All patients had transthoracic echocardiogram, transesophageal echocardiogram, and cardiac computed tomography scans. None of the patients had positron emission tomography scan.

There were 12 prosthetic valve endocarditis-related complications in all six patients, and these complications were prosthetic valve dysfunction (n = 4), systemic or pulmonary embolic events (n = 2), heart block (n = 1), aortic root abscess (n = 1), recurrent endocarditis (n = 2), and death due to sepsis in patient 6 (n = 1). All six patients received at least 6 weeks of intravenous antibiotics, and three (50%) patients required surgical valve replacements at 2 days, 6 weeks, and 23 weeks from the time of prosthetic valve endocarditis diagnosis. Altogether three of the six (50%) patients died at 2 months, 4 years, and 5 years from the time of initial prosthetic valve endocarditis diagnosis, and two deaths (33%) were due to sepsis. The clinical data of the six patients with prosthetic valve endocarditis are shown here.

Patient 1: 50-year-old male with a history of aortic valve replacement with #27 Bjork-Shiley mechanical valve at the age of 17 years, pulmonary valve replacement with 31 mm Hancock II porcine bioprosthesis at the age of 44 years, and atrial septal defect closure with Amplatzer septal occluder at the age of 45 years. He developed *Staphylococcus epidermidis* (oxacillin-sensitive) endocarditis of the aortic valve prosthesis resulting in severe aortic prosthetic valve obstruction with mean gradient of 40 mmHg. He had multiple septic emboli to the brain, spleen, and right leg at the time of initial presentation. He developed aortic root enlargement on echocardiogram concerning for abscess despite broad-spectrum antibiotics' coverage with nafcillin, rifampin, and

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Table 2. Characteristics of patients with endocarditis.

Patient	Age	Prosthesis	Organism	Surgical intervention
1	50	Aortic-#27 Bjork-Shiley mechanical valve Pulmonary-31 mm Hancock II porcine bioprosthesis	*Staphylococcus epidermidis*	Yes
2	55	Pulmonary-24 mm aortic homograft	*Streptococcus agalactiae*	Yes
3	28	Pulmonary-porcine pulmonary valve conduit	*Staphylococcus aureus*	Yes
4	35	Pulmonary-29 mm Carpentier-Edwards bioprosthesis	*Staphylococcus aureus*	No
5	36	CarboMedics mechanical prostheses: Aortic (27 mm) Pulmonary (31 mm)Tricuspid (35 mm)	*Staphylococcus aureus*	No
6	66	CarboMedics mechanical prostheses: Aortic (25 mm) Pulmonary (29 mm)	*Enterobacter*	No

gentamicin. The surgical report described a blind pouch in the aortic root consisted with an old abscess cavity. This was patched with a piece of bovine pericardium followed by aortic valve re-replacement with 23 mm CarboMedics mechanical prosthesis at 41 days from the time of prosthetic valve endocarditis diagnosis. His post-operative course was complicated by heart block for which he received a dual chamber pacemaker 14 days post-operatively. He died 5 years later from end-stage heart failure.

Patient 2: 55-year-old male with 22q11 deletion and a history of pulmonary valve replacement with 24 mm aortic homograft and implantation of dual-chamber pacemaker at the age of 39 years. He developed *Streptococcus agalactiae* endocarditis of the pulmonary valve without prosthetic valve dysfunction for which he received a 6-week course of intravenous ceftriaxone with good clinical response. He subsequently developed recurrent *Streptococcus agalactiae* endocarditis of the pulmonary valve homograft resulting in severe prosthetic valve regurgitation at the age of 59 years. He received a 6-week course of intravenous cefepime therapy and subsequently underwent pulmonary valve re-replacement with 27 mm Medtronic freestyle prosthesis at 23 weeks after prosthetic valve endocarditis diagnosis.

Patient 3: 28-year-old male with a history of pulmonary valve conduit implantation and prior history of *Staphylococcus aureus* endocarditis at the age of 16 years. He presented with methicillin-sensitive *Staphylococcus aureus* endocarditis of the pulmonary valve resulting in severe prosthetic obstruction and regurgitation. He underwent pulmonary valve re-replacement with 26 mm pulmonary homograft 2 days after presentation and received a 6-week course of intravenous nafcillin.

Patient 4: 35-year-old female with a history of pulmonary valve replacement with 29 mm Carpentier-Edwards bioprosthesis at the age of 34 years. She presented with methicillin-sensitive *Staphylococcus aureus* endocarditis of the pulmonary valve without prosthetic valve dysfunction. Her clinical course was complicated by multiple septic pulmonary emboli resulting in hemoptysis, and this resolved with conservative management. She received a 6-week course of intravenous nafcillin followed by a 6-month course of cefadroxil.

Patient 5: 36-year-old male with chronic liver disease and end-stage renal failure on haemodialysis who underwent pulmonary, tricuspid, and aortic valve replacements with 27, 31, and 25 mm CarboMedics mechanical prostheses, respectively, at the age of 33 years. He developed methicillin-sensitive *Staphylococcus aureus* endocarditis of the aortic prosthesis resulting in moderate prosthetic/periprosthetic aortic regurgitation and stenosis at the age of 36 years. He was deemed inoperable because of multiple comorbidities and therefore received medical therapy with cefazolin and rifampin for 6 weeks with initial clearance of bacteremia. He had recurrence of methicillin-sensitive *Staphylococcus aureus* endocarditis of the aortic prosthesis 2 years later, which was again treated with medical therapy resulting in clearance of bacteremia. He died at the age of 40 years from *Corynebacterium septicemia* resulting multi-system organ failure.

Patient 6: 66-year-old male with prior bioprosthetic aortic valve replacement that presented with severe aortic, pulmonary, and tricuspid valve regurgitation. He underwent aortic valve replacement with 25 mm CarboMedics valve conduit, pulmonary valve replacement with 29 mm CarboMedics mechanical valve, and tricuspid valve repair. He developed *Enterobacter* endocarditis of the aortic valve prosthesis 2 months post-operatively and died from multi-system organ failure despite intensive antibiotic therapy. This was considered as endocarditis-related death.

Discussion

In this study of adult tetralogy of Fallot patients with a history of prosthetic valve implantation, the incidence of prosthetic valve endocarditis was 0.4% per year, and the most common organism was methicillin-sensitive *Staphylococcus aureus*. Patients with CHD have a 20-fold increase in the risk for endocarditis compared to the general population.[13] This risk is even higher in the patients with complex congenital heart lesions and patients with prosthetic valves[9,10,14] In a multi-centre study from the CONCOR registry (a multi-centre Dutch national registry of CHD patients), the incidence of endocarditis was 0.13% per year with a 17-fold increase in risk for patients with prosthetic valves.[10] The most common causative organism for prosthetic valve endocarditis in that study was also *Staphylococcus aureus*. This multi-centre study was based on a large cohort of CHD patients with different diagnoses, in contrast to the current study that focused specifically on adults with tetralogy of Fallot and prosthetic valve. In a different study of more than 26,000 patients who received aortic valve prostheses, Glaser et al[14] reported prosthetic valve endocarditis incidence of 0.6% per year with higher incidence in patients with bioprosthesis compared to mechanical prosthesis, and high risk of prosthetic valve endocarditis occurring within the first 6 months after valve implantation. In contrast to these previous studies, the current study provides prosthetic valve endocarditis risk that is specific to the tetralogy of Fallot patients with prosthetic valves, a population that has a high prevalence of right-sided valve prostheses.

All six patients had prosthetic valve endocarditis-related complications such as prosthetic valve dysfunction, aortic root abscess,

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high-grade heart block, and systemic or pulmonary embolic events, and half of patients with prosthetic valve endocarditis required surgical interventions. Two of the six patients (33%) died from sepsis and multi-system organ failure. Perivalvular extension such as aortic root abscess is a known complication of prosthetic valve endocarditis especially with coagulase negative staphylococcal infection involving aortic valve prosthesis, and is an indication for surgery[8,15–18] The only case of perivalvular extension observed in our cohort was due to *Staphylococcus epidermidis* prosthetic valve endocarditis of the aortic prosthesis, and the infection resolved after surgical drainage of aortic root abscess and aortic valve re-replacement. Several studies, including a recent study from our institution, have reported mortality related to prosthetic valve endocarditis ranging from 17 to 24%.[19–21] The 33% sepsis-related mortality reported in the current study is higher than that of previous studies, but may be related to complexity of these patients. The two patients who died both underwent triple valve replacements, which may reflect disease complexity.

Limitations

The major limitation of this study was the small sample size and consequently small number of events. As a result, we were unable to perform more in-depth analysis to determine differences of prosthetic valve endocarditis risk for different prostheses as well as the differences in the incidence of prosthetic valve endocarditis based on the interval from prosthetic valve implantation. We only included diagnosis of definite prosthetic valve endocarditis, and as a result the disease incidence may have been underestimated. Due to the retrospective study design, we were unable to provide data about dental procedures and other events that can potentially increase the risk of endocarditis.

Conclusions

We reviewed 338 adult tetralogy of Fallot patients with prosthetic valves and reported an annual incidence of prosthetic valve endocarditis of 0.4%. All the affected patients had at least one prosthetic valve endocarditis-related complication, 50% required surgery, and 17% died from sepsis. This study was limited by small sample size and hence low event rates. However, the incidence and outcome data presented this study underscore the need to educate patients on the importance of good dental hygiene and endocarditis prophylaxis as well as early evaluation and blood cultures if they develop systemic symptoms. The clinician should have a high index of suspicion for prosthetic valve endocarditis when caring for this high-risk population.

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Conflicts of Interest. None.

Ethical Standards. The study methodology adhered to ethical standards stipulated by the institutional review board.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Mayo Clinic).

Author's Contribution. Study design, data analysis, manuscript drafting, and final revision: Alexander C. Egbe.

Data collection, manuscript drafting, and final revision: Raja Jadav, Muhammad Masood, Maria Najam, Srikanth Kothapalli, and Mounika Angirekula.

Manuscript drafting and final revision: William R. Miranda, Daniel C. Desimone, and Heidi M. Connolly.

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