Chapter 2

Prosthetic Valve Endocarditis

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Introduction

Structural valve diseases, which include valvular stenosis and regurgitation are a common indication for valve replacement and repair. An estimated 275,000 to 370,000 operations are performed world-wide each year for these conditions [1]. Although the risks of open-heart surgery have decreased over time secondary to improved patient selection, surgical technique, and postoperative care, significant complications after valve replacement and repair do occur. One of the most dreaded complications and a source of significant morbidity and mortality after valve surgery is prosthetic valve endocarditis (PVE). PVE is the infection of a surgically implanted prosthetic valve or repaired native valve with an annuloplasty ring, with an incidence of 3 % to 6% over a patient’s lifetime [2]. Both mechanical and bioprosthetic valves can be affected and the mortality rate remains high despite aggressive medical and surgical treatments. Mortality with medical treatment ranges between 26% to 75% while mortality with surgical treatment ranges between 23% to 43% [3].

Over the last decade, the introduction and increasing popularity of transcatheter valve replacements and transcatheter valve repairs in patients deemed unsuited for cardiac surgery has led to the emergence of a new body of literature. Outcomes related to PVE in patients who have received a transcatheter valve replacement for severe stenosis and transcatheter valve repair for regurgitation are now being published. In this chapter, we will discuss PVE in the setting of surgical and endovascular valve replace-
ment and repair. We will discuss a brief history, epidemiology, microbiology, medical and surgical treatments and complications of PVE. Lastly, we will discuss the latest antimicrobial prophylaxis guidelines to prevent PVE.

### History of Surgical Valves and Transcatheter Devices

#### Valve Replacement

Surgical valve replacements were first successfully performed in 1960, with Braunwald et al. reporting on the first mitral valve replacement and Harken et al. reporting on the first aortic valve replacement [4,5]. Since then, the field has rapidly evolved and there are currently a large number of prosthetic valve types available. These valves can be grouped into two main categories: mechanical and bioprosthetic. Mechanical valves are comprised of metal or carbon alloys and are very durable, with life spans of 20 to 30 years. Conversely, bioprosthetic valves are available as either heterografts, which are made of porcine or bovine tissue mounted on a metal cage or homografts, which are preserved human valves. These bioprosthetic valves have a shorter life span of 10 to 15 years. While mechanical valves are thrombogenic and require lifelong anticoagulation, bioprosthetic valves have very low thrombogenic potential and thus do not require anticoagulation [2].

In 2002, Cribier et al. performed the first transcatheter aortic valve replacement (TAVR) after an unsuccessful balloon valvuloplasty. The patient was deemed to be a poor surgical candidate given his hemodynamic instability and significant medical comorbidities. Although the patient’s hemodynamics improved following implantation, he died 17 weeks later of noncardiac complications [6]. This was followed by the PARTNER trials, which led to the USA Food and Drug Administration (FDA) approval of the TAVR in 2011 [7,8]. In the PARTNER B trial, patients who were poor candidates for surgery were divided into a standard medical therapy and a TAVR cohort. At one year, the rate of death from cardiovascular causes was 44.6% in the standard cohort and 20.5% in the TAVR cohort (p<0.001). Amongst survivors, the rate of cardiac symptoms (New York Heart Association class III or IV) was 58% in the standard cohort and 25.2% in the TAVR cohort (p<0.001) [7]. This trial showed both a survival and symptomatic benefit of TAVR over medical treatment alone for severe, inoperable aortic stenosis.

This was followed by the PARTNER A trial, which compared surgical aortic valve replacement with TAVR. At one year, both cohorts had a similar rate of mortality (26.8% vs. 24.2%, p=0.44). Morbidity at 30 days differed between the two cohorts with increased vascular complications and neurologic events noted in the TAVR cohort and increased incidence of major bleeding and new-onset atrial fibrillation noted in the surgical cohort [9].

#### Valve Repair

Surgical valve repair was first introduced in 1968. Using a prosthetic ring annuloplasty, Carpentier repaired a regurgitant mitral valve and ushered in the era of surgi-
cal valve repair with prosthetic rings [10]. The era of transcatheter mitral valve repair using the MitraClip (Abbott Vascular, Abbott Park, IL, USA) was started after the EVEREST II trial. In that trial, transcatheter mitral valve repair was compared with surgical valve repair. Transcatheter valve repair was found to have a lower incidence of major adverse events at 30 days (15% vs. 48%, p<0.001). The primary efficacy endpoint of freedom from death, surgery for mitral valve dysfunction and mitral regurgitation grade 3+ or 4+ at 12 months following intervention was observed in 55% of the transcatheter cohort and 73% of the surgical cohort (p=0.007) [11].

In a subsequent study at five years, the endpoint of freedom from death, surgery for mitral valve dysfunction, and mitral regurgitation grade 3+ or 4+ was observed in 44.2% of the transcatheter cohort and 64.3% of the surgical cohort (p=0.01). Although no difference in mortality was observed at five years, the patients who underwent transcatheter mitral valve repair had a statistically significant increased need for surgery and were found to have 3+ to 4+ mitral regurgitation more frequently than the surgical cohort [12].

**Epidemiology and Microbiology**

**Surgical Devices**

PVE accounts for 10% to 30% of all cases of infective endocarditis. Its incidence is reported to be 0.3% to 1.2% per patient year [13]. Early PVE is defined as occurring within one year of intervention, while late PVE is defined as occurring after one year. This timing is important since the causative agents differ between these two time periods [14]. It has been shown that mechanical valves are at higher risk of PVE than bioprosthetic valves in the first three months after surgical valve implantation. At 5 years post implantation, the incidence of PVE in both valve types is about the same at 5.7% [15]. Hammermeister et al. showed a similar finding that in long-term survivors (patients who survived at least 15 years) the incidence of PVE was the same between mechanical and bioprosthetic valves [16].

Given that early PVE is likely acquired intraoperatively or during the hospital stay, normal skin flora are typically involved. Staphylococci species, particularly *Staphylococcus aureus*, has been shown to be involved in early PVE. Tan et al. showed that *Staphylococcus aureus* PVE was an independent factor associated with in hospital mortality [17]. Coagulase negative staphylococci including *Staphylococcus epidermidis* and *Staphylococcus capitis* are also frequently isolated in patients with early onset PVE. In a study of 172 non-drug users with PVE, Lopez et al. showed that coagulase negative staphylococci were involved in 37% of cases of PVE within one year, while only being implicated in 18% of cases after one year (p=0.005) [14].

Late PVE is often secondary to seeding from transient bacteremia. The causative microbiology includes dental flora such as *Streptococcus viridans* and less frequently,
gram negative bacteria and fungi [3]. Since these patients often have multiple medical comorbidities, they frequently are readmitted to the hospital and undergo a variety of procedures. Consequently the bacteria that have been associated with early PVE (Staphylococcal species) are now being isolated more commonly in patients who develop late PVE [18].

Transcatheter Devices

The literature on transcatheter valve replacement and repair is still evolving, since these devices have been in clinical practice for a short period of time. The incidence of PVE after transcatheter intervention has been reported to be 0-2.3%. Eisen et al. reviewed 10 cases of TAVR endocarditis in 2012 and found that the mean time for developing PVE was 186 days. Although it was a small study looking at individual case reports and case presentations, they found the causative bacteria to be most commonly Staphylococcus species followed by Streptococcus species [19]. Another review of 28 studies with 60 patients examined PVE after TAVR and transcatheter pulmonic valve replacement (TPVR). The median time to developing endocarditis was 5 months. In the TAVR cohort, Enterococcus was most frequently isolated (34.4%), while in the TPVR cohort, Staphylococcus aureus was the predominant organism (29.4%) [20].

PVE after transcatheter mitral valve repair has only been described in two case reports. In the first, an 88 year-old male with severe mitral regurgitation underwent a transcatheter mitral valve repair with the placement of two clips. After one month, the patient was diagnosed with PVE with large vegetations secondary to *Staphylococcus aureus* and required surgical mitral valve replacement. The patient was ultimately discharged to a rehabilitation center [21]. In the second case report, a patient who underwent a transcatheter mitral valve repair with three clips had a recurrence of mitral regurgitation after three years. He was found to have PVE with large vegetations secondary to *Staphylococcus epidermidis* and required a surgical mitral valve replacement. After a prolonged hospital course, the patient was discharged [22]. Undoubtedly as the experience with transcatheter mitral valve repairs increases, the epidemiology and microbiology of PVE in this group of patients will become available.

Medical and Surgical Management

**Surgical Devices**

The optimal management of PVE remains unclear. Multiple factors have been identified that serve as negative prognostic markers in patients with PVE and these may warrant more aggressive interventions. These include advanced age, diabetes, infection with *Staphylococcus aureus*, stroke, intracardiac abscess, and congestive heart failure [13,23]. Studies have been unable to identify whether medical therapy alone or a combined surgical-medical approach is superior. Akowuah et al. showed a mortality of
29% in a medical group versus 24% in the surgical - medical group (p=0.15) [24]. Wang et al. showed an in-hospital mortality rate of 23.4% in a medical group versus 25% in the surgical - medical group (p =0.729) [25].

Many patients with PVE can be successfully treated with antibiotics alone. Truninger et al. showed that patients with non-staphylococcal PVE who were hemodynamically stable could be treated with antibiotics alone without an increased risk of operation, reinfection or death. These patients however need to be monitored closely during the course of treatment for late complications [26].

Surgical intervention is indicated in the presence of complicated PVE resulting in heart failure or severe valvular dysfunction. Most recommendations for early surgery are for high-risk subgroups with poor outcomes from antimicrobials alone such as staphylococcal PVE and complicated PVE [27,28]. Subset analyses in patients with PVE caused by Staphylococcus aureus, a known negative prognostic indicator, has failed to show a survival benefit between medical and surgical groups [27,29]. On the other hand, subset analyses in patients with heart failure caused by their PVE showed a survival benefit in patients who underwent surgery [30].

In patients who require surgery, a large meta-analysis failed to show a survival benefit between early and non-early surgery for PVE. Early surgery was defined as occurring during the initial hospitalization before the completion of a course of antibiotics. For patients with PVE, in-hospital mortality did not differ between patients who underwent early surgery and those who underwent non-early surgery (OR=0.83, 95% CI 0.65-1.06, p=0.413) [31].

When it comes to PVE, the mainstay in treatment is radical debridement of all infected material along with the original prosthesis and implantation of a new valve on viable, healthy tissue [23,32]. Historically homografts were considered the gold standard of treatment for aortic valve endocarditis. In 2002, Lytle et al. published their experience with utilizing homografts to replace the aortic valve and ascending aorta. Both the hospital mortality rate and the rate of recurrent PVE after surgery was 3.7% [33]. This study supported the use of homografts for reconstruction of the aortic valve and ascending aorta after PVE. However, a more recent study by Kim et al. showed that there was no benefit in using homografts. They had an early mortality rate of 19.8% in their series and found that the use of homografts had no effect on mortality or reinfection [34]. Additionally, valved Dacron conduit and pulmonary autografts (Ross procedure) can be considered for endocarditis of the aortic position [23,35]. For mitral PVE, paravalvular abscesses and the need to reconstruct the annulus make operative management of mitral PVE very difficult. Operative mortality for mitral valve replacement for mitral PVE is as high as 13% [36].
Transcatheter Devices

While PVE of TAVR bioprosthesis is a rare complication, it clearly carries a high morbidity and mortality rate in a population of older, high-risk individuals. Given the high operative risk conferred by surgical removal of the infected valve, many centers are choosing to treat these patients conservatively with long-term IV antibiotics and close monitoring with serial blood cultures and echocardiography. There have been multiple documented cases of successful PVE treatment using this approach, even when large vegetations or heart failure are present. In one case report, a 77 year-old male developed PVE of his TAVR bioprosthesis 17 months after his procedure. A transesophageal echocardiogram showed an obstructive 1.5 cm vegetation of the aortic valve and blood cultures grew *Streptococcus viridans*. He was treated non-operatively with levofloxacin, oral penicillin, and intravenous penicillin [37]. Loh et al. published a similar case report in which an 85 year-old male with a TAVR bioprosthesis was successfully treated for PVE with antibiotics [38]. Latib et al. investigated a TAVR cohort of 2,572 patients of whom 29 patients developed PVE. In this study, in-hospital mortality from PVE was 44.8% and overall mortality was 62%. Surgery was performed in 10.3% of patients (with a 67% mortality rate), TAVR in TAVR in 3.4%, and 86.2% were treated with medical management alone [39].

Successful management of PVE with surgery has been less frequently reported. Currently there are no large studies reporting on surgical management in patients with a TAVR bioprosthesis who developed PVE. Head et al. presented a patient who underwent a TAVR and then developed PVE secondary to infection with Histoplasmosis. This was successfully managed with surgical aortic valve replacement [40]. Amat-Santos et al. reported on patients who underwent TAVR and TPVR and developed PVE. In their review of 28 publications with 60 patients, 41% of TAVR and 75% of TPVR patients required surgery for their PVE [20].

Complications

The complications that occur with PVE are similar to those seen with native valve endocarditis, albeit more difficult to manage. They can range from positive blood cultures in an asymptomatic patient to stroke, myocardial infarction, heart failure, and death. Many of the complications occur directly because of the vegetations formed on the valve. The presence of vegetations can cause outflow obstruction or acute heart failure due to valvular dysfunction. Decompensated heart failure related to valvular dysfunction or obstruction is an indication for surgery in these patients. In a study by Lopez et al., the incidence of congestive heart failure in patients with left sided PVE was approximately 56%. Heart failure was a predictive factor for in-hospital mortality in patients with PVE, with an odds ratio of 3 (p=0.001) [30].

Septic emboli from an infected prosthetic valve can also result in significant morbidity and mortality. These
can result in cerebral abscesses, soft tissue abscesses, and abscesses in the liver, spleen and kidneys. A retrospective review found the incidence of stroke to be 23% in 111 patients with PVE. Most of these patients were anticoagulated and 42% of them developed hemorrhagic conversion of their embolic stroke [41].

PVE can directly extend into the wall of the heart or the perivalvular aorta leading to abscess in these areas. There are a multiple reports of perivalvular aortic abscesses following prosthetic valve endocarditis being managed surgically with good outcome. Perivalvular or myocardial abscesses are high risk for causing acute heart failure and aortic root aneurysm. A study looking at risk factors for mortality in PVE identified abscess formation as one of the most important risk factors for mortality with a rate of 55% [42].

Case reports of prosthetic valve partial or full dehiscence can be found when looking at rare but severe consequences of PVE. Krishna et al. present a case of a patient who presented 3 months after aortic valve replacement with shortness of breath and low-grade fever and was diagnosed with staphylococcal PVE. On TTE and TEE, the patient was found to have a freely mobile prosthetic aortic valve with a severe paravalvular leak. The valve had detached and became lodged at the sinotubular level [43]. Another case report by Patsouras et al. presented an elderly gentleman who had undergone an aortic valve replacement and developed staphylococcal PVE. He was quickly noted to have perivalvular involvement, leading to partial valve dehiscence and an aorto-left atrial fistula [44]. This is an extremely rare but difficult to treat complication. As expected, prosthetic valve dehiscence has been found to be an independent predictor of mortality in patients with PVE [28].

While many of the complications remain similar, there is a difference in outcome of surgical intervention in PVE and native valve endocarditis. When comparing surgical valve replacement across these groups, post-operative complications and the need for reoperation were higher in the patients who underwent valve replacement for PVE. Reoperation-free survival was significantly lower in these patients. Those who underwent valve replacement for PVE were more likely to have recurrent endocarditis or non-infectious periprosthetic dehiscence compared with their native valve counterparts [45].

Antimicrobial Prophylaxis

The American Heart Association (AHA) published Prevention of Bacterial Endocarditis in 1997, which recommended prophylaxis for individuals with heart murmurs, prosthetic valves, congenital heart defects, previous bacterial endocarditis and acquired valvular disease who underwent dental procedures, gastrointestinal tract procedures (colonoscopy, endoscopy), and genitourinary procedures (prostate surgery, cystoscopy). An update to these recommendations by the AHA was released in 2007. Reviews of studies from 1950 to 2006 revealed that there was no benefit to using prophylactic antibiotics except
in those in the highest risk category [46]. The groups included patients with prosthetic valves, previous infective endocarditis, cardiac transplant patients who develop valvular pathology, and certain congenital heart defects. This statement also narrowed prophylactic antibiotics to only dental procedures. Penicillin is the recommended antibiotic except for those with penicillin allergies.

It is estimated that 277 patients would need to be treated with prophylactic antibiotics to prevent one single case of infective endocarditis [47]. The 2015 guidelines published by the European Society of Cardiology states that antibiotics should be considered for the highest risk individuals undergoing the highest risk dental procedures [23].

Despite multiple consensus statements against routine prophylactic antibiotics, they are still widely used for prophylaxis. Pant et al. studied patients in the United States since the AHA recommended restricting the use of prophylactic antibiotics. They showed that there has been an increase in infective endocarditis, in particular Streptococcus, since the guideline updates. However, there has not been an associated increase in hospitalization or valve surgery [48]. Dayer et al. recently showed in a survey of clinicians that many patients who are perceived to be high risk continue to receive antibiotic prophylaxis. This study showed that 39% of cardiologists and cardiothoracic surgeons continue to provide prophylaxis whereas most dentists (87%) follow guidelines [49].

**Conclusion**

All valvular devices and repairs, whether performed surgically or via transcatheter technology are susceptible to PVE. Medical treatment with a prolonged course of antibiotics remains the mainstay of treatment. Heart failure and valve dysfunction often require surgical intervention. Although several studies related to transcatheter valve implantations and repairs were highlighted, the long-term effects and optimal management of PVE in this population remains to be seen. Since patients who undergo transcatheter interventions are poor surgical candidates and often have multiple medical comorbidities, these patients are especially difficult to manage when they develop PVE.

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**Figure 1:** PVE in the tricuspid valve prior to resection.
Figure 2: PVE in a tricuspid valve after resection.

References


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