

# Prosthetic valve endocarditis: state of the heart

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Prosthetic valve endocarditis (PVE) is a rare but serious complication of cardiac valve replacement surgery and is associated with high rates of morbidity and mortality. Despite significant advances in our understanding of the pathogenesis and management of this disease process, the rates of undesirable outcomes, including mortality directly attributable to infection, remain unacceptably high. The purpose of this article is to provide an up-to-date review of the changing epidemiology, microbiology and pathogenesis of PVE as well as review state-of-the-art diagnostic approaches and treatment for PVE, including the controversies surrounding the role of surgery for optimal management.

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## Introduction & epidemiology

Prosthetic valve endocarditis (PVE) is a dire complication of cardiac valve replacement surgery as it is associated with high rates of morbidity and mortality. Reported incidence of PVE varies based on the study population and year of publication. While overall risk of PVE was found to be 3.1% at 12 months and 5.7% at 60 months in an earlier study [1], a more recent investigation reported a lower risk of 1% at 12 months and 3% at 60 months among patients who underwent aortic valve replacement [2]. The overall incidence rate of PVE has been reported to be between 0.3 and 1.2% per patient per year [3]. Interestingly, the cumulative risk of PVE appears to be similar in mechanical and bioprosthetic valves [1,4]. As compared with allografts, mechanical and prosthetic valves have a higher hazard for development of endocarditis in the first 6 months and 10–15 years following the initial surgery for infective endocarditis [5]. In general, the incidence of infective endocarditis increases with age and is higher in males [6].

With the increasing frequency of valve replacement and an aging population in the industrialized world, PVE now represents an increased proportion of overall endocarditis cases. In the most recent analysis from the International Collaboration on Endocarditis (ICE) Prospective Cohort Study (PCS), PVE represented 20.1% of all endocarditis cases [7]. Although one could argue that the ICE cohort could potentially represent a recruitment bias as most of the enrolled sites are tertiary referral centers, a recent French population-based cohort also had a similar percentage of patients with PVE [8]. In a separate analysis of the ICE-PCS registry, development of PVE was found to be an independent predictor of in-hospital mortality [9].

Mortality rates associated with PVE have also changed over time. The earliest reports describing the epidemiology of PVE emerged in the 1970s and the mortality in these publications ranged from 56 to 60% [10,11]. Three decades

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later, the ICE-PCS observational database reported an overall mortality rate of 22.8% [7]. Although the mortality rate has declined with time, it continues to be unacceptably high despite the significant advances in diagnostic techniques and improvements in medical and surgical management. The rate of complications from PVE also remains significantly high. According to the ICE-PCS database, patients with PVE were more likely to have an abscess compared with native valve endocarditis (NVE; 29.7 vs 11.7%) and had longer hospital stays (mean length of stay 33 days) compared with patients with NVE (mean length of stay 29 days) [7]. Almost half (48.9%) of the PVE patients underwent cardiac surgery during index hospitalization in this study. This number was comparable with the number of patients with NVE who underwent surgery (46.4%) during index hospitalization [7].

Traditionally, PVE has been classified as early, intermediate or late depending on the onset of symptoms of endocarditis following valve replacement surgery. This classification is based on the observational data that the microbiology, pathogenesis and many clinical features of the disease are directly linked to the timing of infection relative to valve replacement surgery [1,12,13].

Early-onset PVE is defined as that occurring within 60 days of surgery and it is usually a manifestation of healthcare-acquired infections. *Staphylococcal aureus* is the most common etiology during this time period [14]. Intermediate-onset PVE occurs from 60 to 365 days following valve replacement surgery. The microbiological profile of infections during this time represents a mix of healthcare- and community-acquired infections. The incidence of coagulase-negative *Staphylococcus* (CoNS) PVE is highest during this period [14]. Patients may present with low-grade clinical manifestations, a greater delay in diagnosis and a longer periannular extension of infection during this period and thus may carry a poorer prognosis [15]. Finally, late-onset PVE is classified as occurring more than 1 year following valve replacement surgery. Although *S. aureus* and CoNS remain important causes of PVE in this timeframe, primarily due to frequent exposures of the healthcare system in these patients, the microbiology of these late-onset infections resembles more closely that of NVE.

Based on published data, more than two-thirds of PVE cases occur within the first year following valve replacement surgery [7]. In the ICE-PCS study, median time to diagnosis of healthcare-associated PVE following a valve replacement procedure was 83.5 days, with 71% being diagnosed within the first

year of valve replacement [7]. It has been hypothesized that this is due to that fact that endothelialization of the mechanical valves takes about 1 year to complete and during this time period prosthetic valve material is exposed to pathogens in the bloodstream and prone to seeding or colonization by various bacterial species.

Interestingly, the long-term risk of endocarditis appears to be similar in bioprosthetic and mechanical valves [1,16]. This may seem contrary to the common wisdom that bioprosthesis have a lower risk of bacterial seeding and infection. However, it has been postulated that as bioprosthetic valves age, they are more prone to leaflet degeneration, which may translate into a higher risk of endocarditis, comparable with mechanical prosthesis.

The rate of PVE also varies based on geographic location and the healthcare delivery system. According to ICE-PCS data, the USA has a higher rate of healthcare-associated PVE infections as compared with Europe, Australia and South America [7]. While precise reasons for this difference are unclear, this may be partly attributable to greater use of intravenously (iv.) access devices and increased rates of complications in the US cohort.

In addition, the risk of PVE also varies based on the location of the valve prosthesis. The aortic valve is the most commonly infected (69.1%) prosthesis in PVE cases, followed by mitral valve or ring (50.4%). The tricuspid valve/ring and pulmonary valve are less frequently infected (9.4 and 5.6%, respectively) [7]. This may be secondary to a higher number of aortic valve replacements in general and the differences in flow dynamics and pressure gradients across these valvular prostheses.

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## Microbiology

Overall, *S. aureus* is the most common pathogen responsible for PVE, accounting for 23.0% of total cases (Figure 1). Recent data suggest that an increasing number of these isolates are methicillin resistant. In the overall ICE-PCS database, 14.7% of all strains were methicillin-susceptible *S. aureus* (MSSA) and 6.5% were methicillin-resistant *S. aureus* (MRSA) [7]. However, rates of methicillin-resistance among *S. aureus* were disproportionately higher in the US population. CoNS are the next most common group of organisms responsible for PVE, accounting for 16.9% of all cases, followed by enterococci at 12.8%. Among CoNS, the most common species implicated in PVE is *Staphylococcus epidermidis*. Therefore, *S. epidermidis* bloodstream infection in patients with underlying prosthetic heart valves should be taken very seriously and consideration of underlying PVE is warranted. *Staphylococcus lugdunensis* is less frequently the

species responsible for CoNS in PVE cases, but has been associated with a more aggressive clinical course [17]. Unlike NVE, viridans group streptococci account for only 12.1% of all PVE cases.

The reported rate of culture-negative PVE in the ICE-PCS database was 11.2% [7]. The majority of these patients had received antibiotics within 7 days prior to the diagnosis of endocarditis, and thus prior antimicrobial use was the most common cause of culture-negative endocarditis cases.

Another important observation in this cohort was the high frequency of healthcare-associated infections. Overall, healthcare-associated PVE accounted for 36.5% (203 of 556 cases) of total infections. Of these, 141 were thought to be nosocomial and 62 were non-nosocomial healthcare-associated infections. Presence of an intravascular device was presumed to be associated with 42.9% of these infections, although the actual rate of causal association could be lower. As expected, staphylococci were responsible for the majority of healthcare-associated PVE cases; *S. aureus* accounted for 34.0% of all healthcare-associated infections (including MRSA in 13.3%). CoNS were responsible for 25.6% of the healthcare-associated PVE cases. In contrast with early PVE, healthcare-associated PVE was found to have higher rates of CoNS infections.

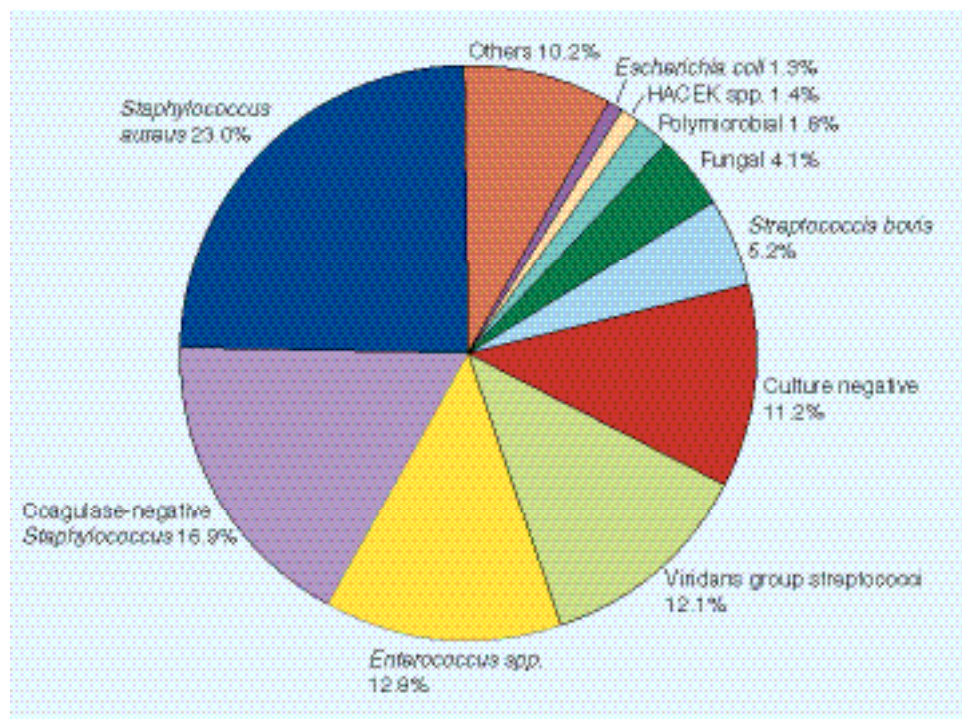
### Pathogenesis

The ability of a particular organism to cause infection in a foreign body is influenced by a number of different host, device and microbial factors. As discussed earlier, the incidence of mechanical valve infections are higher in the first year likely due to a lack of endothelialization. In contrast, bioprosthetic valves are at higher risk of causing PVE in the later years, which may be related to tissue degeneration over time. However, some of the key pathogenic mechanisms for PVE are related to the ability of a particular microorganism to adhere, persist and grow in a suitable environment in order to establish infection. In this regards, Gram-positive organisms such as *S. aureus*, CoNS and certain streptococcal species, possess a variety of unique mechanisms that

enhance their ability to perform these tasks.

The initial adherence of the organism to endothelial tissue is a critical event in establishing an infection. Since streptococci mostly adhere to damaged endothelium, while *S. aureus* is capable of infecting intact endothelial tissue, it is postulated that there are two separate pathways that are operating in this initial step of bacterial adherence to the heart valve [18]. The basic mechanism involved in adherence of bacteria to the endothelial tissues involves interaction between host extracellular matrix and microbial surface components recognizing adhesive matrix molecules (MSCRAMMs). Multiple different MSCRAMMs have been described in the literature (e.g., surface glucans, fimA, FBP-130, ssaB, scaA, PsaA for various species of streptococci; EfaA for *Enterococcus faecalis*; and clumping factor A and B, coagulase, fibrinogen-binding protein A and B for *S. aureus*) [18]. Multiple complex molecular interactions between these proteins enable the various bacterial strains to establish the initial colonization of the damaged or undamaged cardiac tissue.

The next step in the pathogenetic pathway is *in situ* bacterial persistence. This involves local production of tissue factor by monocytes, endothelial cells and fibroblasts. Tissue factor production triggers a coagulation cascade that ultimately leads to formation of fibrin from polymerization of fibrinogen. Platelets



**Figure 1. Common pathogens responsible for prosthetic valve endocarditis.**  
Adapted with permission from [7].

are also activated during this time. The subsequent platelet aggregation and fibrin deposition lead to growth and maturation of endocarditis vegetation.

As the vegetation grows further, it may become fragmented by multiple factors including mechanical stress and dissolution by proteolytic enzymes. These fragments can then be carried hematogenously to other organs, such as the lungs, brain, spleen and kidneys, where the cycle of adherence, persistence and growth is repeated.

Besides knowledge of bacterial virulence factors, a basic understanding of microbial resistance mechanisms is critical for optimal management of PVE. Clinically, the resistance profile that is encountered most often is the one involving resistance of *S. aureus* to methicillin. The mechanism of this resistance involves alteration of PBP2a through a *mecA* gene encoded on the staphylococcal cassette chromosome *mec* (SCC*mec*) element. This leads to resistance of all the commonly used  $\beta$ -lactam class of antibiotics and cephalosporins. Traditionally, vancomycin has been the drug of choice for treating these organisms. However, more recently, reports of increasing minimal inhibitory concentrations (MICs) of MRSA to vancomycin have attracted attention [19,20]. Some studies have linked this elevated MIC amongst MRSA isolates with adverse clinical outcomes [21–24]. Moreover, subpopulations of *S. aureus* isolates with heteroresistance to vancomycin (hVISA) have been described and their clinical significance is being explored [25]. Given these concerns, recent guidelines have recommended that the goal trough levels of vancomycin should be increased to 15–20  $\mu\text{g/ml}$  for certain infections including infective endocarditis [26]. Whether this approach of striving for higher vancomycin trough levels will be adequate in improving outcomes with hVISA infections remains to be seen. In a recent report, investigators described worse outcomes in patients infected with MSSA isolates who were treated with higher *in vitro* vancomycin MICs compared with active agents other than vancomycin [27]. This observation suggests that there are factors other than just reduced vancomycin susceptibility responsible for poor clinical outcomes in patients infected with hVISA isolates.

### Clinical features

Clinical manifestations of PVE vary depending on the virulence of the causative microorganism and severity of the illness. The most common presenting symptom in patients with PVE is fever. However, other classic signs described with subacute bacterial endocarditis, such as Osler's nodes (painful,

violaceous nodules in the pulp of fingers), Janeway lesions (macular, blanching and painless lesions on palms and soles) and Roth's spots (exudative and edematous lesions on the retina), are infrequent in PVE cases due to acute presentation and the fact that *S. aureus*, which now accounts for the majority of these infections, has a more aggressive clinical course [7,28–30]. Also, clinicians should be aware that elderly and immunocompromised individuals commonly present with atypical features and this can lead to a delay in diagnosis.

Early-onset PVE may present unique challenges in making the diagnosis. A high index of suspicion for PVE needs to be maintained during the early post-operative period following valve replacement surgery as fever and other constitutional symptoms, such as fatigue, poor appetite and weakness, are common during this time. Findings of a new regurgitant murmur, new onset or worsening heart failure, conduction abnormalities on the EKG (Figure 2) or stroke in the presence of fever, with or without documented bacteremia, should prompt immediate evaluation for development of PVE.

Presence or absence of intra- and extra-cardiac complications of the disease also contribute to varying clinical manifestations of PVE. According to the ICE-PCS data, heart failure occurred in 32.9%, intra-cardiac abscess in 29.7%, stroke in 18.2% and other systemic embolization in 14.9% of the PVE cases. As compared with NVE, patients with PVE also had longer mean duration of hospitalization (33 vs 29 days) and higher in-hospital mortality (22.8 vs 16.8%) in this cohort. Complications in the form of congestive heart failure, intra-cardiac abscess and stroke, were all found to be associated with increased risk of in-hospital mortality (adjusted odds ratio of 2.33 [95% CI: 1.62–3.34], 1.86 [95% CI: 1.10–3.15] and 2.25 [95% CI: 1.25–4.03], respectively) in this cohort [7].

### Diagnosis

The nonpathological, clinical diagnosis of infective endocarditis relies on the demonstration of major findings of continuous bloodstream infection due to characteristic organisms and evidence of cardiac valvular involvement by echocardiography or clinical examination, supplemented by 'minor' findings including risk factors, fever, and evidence of immunologic or vascular phenomena. The Duke criteria were initially developed in 1994 [31] and it stratified patients with suspected infective endocarditis into three categories; namely definite, possible and rejected cases of endocarditis based on a predefined set of criteria. This criterion was

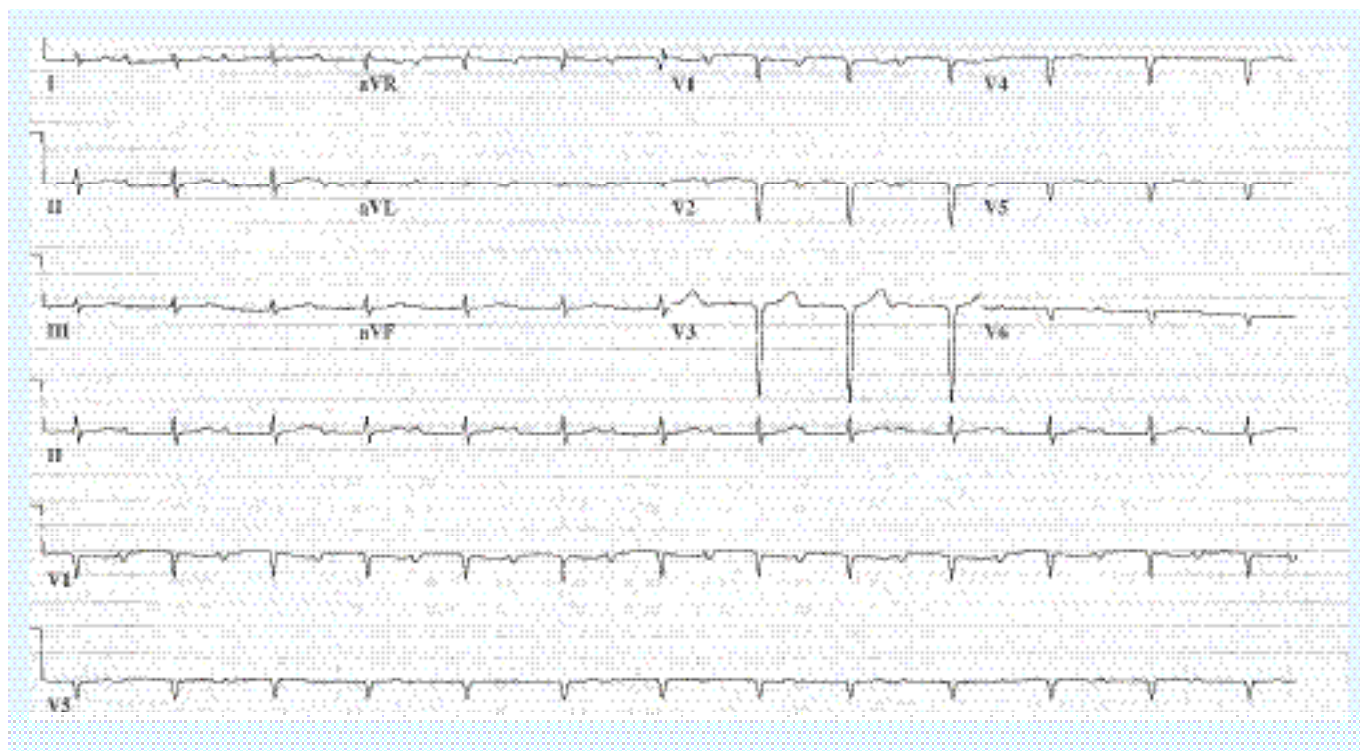


Figure 2. EKG showing first-degree heart block due to paravalvular extension of infection.

subsequently validated in a number of clinical studies [32–38].

With the availability of additional data, high proportion of cases that were categorized as ‘possible’ endocarditis, and development of a newer serological diagnostic techniques in the late 1990s, some modifications to the original Duke criteria were proposed in 2000 [39]. These revised criteria along with definitions are outlined in **Boxes 1 & 2**.

Despite the availability of this well-studied and published clinical criteria, diagnosis of infective endocarditis can be quite difficult in certain situations. Thus, it is important for clinicians to familiarize themselves with certain pearls and pitfalls associated with the diagnosis of PVE.

One of the most commonly encountered and frustrating clinical situations is administration of empiric antibiotics, without first obtaining blood cultures, when patients with prosthetic heart valves present to clinicians in outpatient or emergency room settings with fever. The importance of obtaining serial blood cultures, before initiating empiric antibiotic therapy, cannot be over-emphasized as identification of the causative organism is critical in choosing the appropriate antibiotic therapy for the patient. Even in situations where the patient is hemodynamically unstable and initiation of empirical antibiotics is of paramount importance, at least two sets of blood

cultures should still be drawn prior to the first dose of antibiotics.

Ideally, two different sets of blood cultures should be drawn 12 h apart. In more urgent situations, serial sets can be obtained 1 h apart. Multiple sets not only improve the yield of blood cultures, but also help to differentiate between contamination versus true bloodstream infection. Blood cultures are highly specific if separate sets of cultures are positive for the same organism. In cases where multiple blood culture were obtained prior to administration of any antibiotic therapy and are negative, serological tests for *Coxiella burnetii*, *Bartonella*, *Brucella*, *Mycoplasma*, *Legionella* and *Chlamydia* should be considered [40].

Whenever a patient has a high pretest probability of endocarditis (e.g., persistent bacteremia or fever of unknown origin in the presence of a prosthetic valve), an echocardiogram should be obtained. Transesophageal echocardiography (TEE) enables better visualization of the cardiac structures such as the atrial side of the mitral prosthesis, compared with trans-thoracic echocardiography (TTE) [41]. TEE is especially helpful in assessing the perivalvular extension of infection and detection of vegetations on prosthetic heart valves and cardiovascular implantable electronic devices leads. However, the advantages of TEE are not limited to patients with prosthetic heart valves and cardiac devices. Compared

**Box 1. Classification of infective endocarditis according to the modified Duke criteria.****Definite infective endocarditis**

## ■ Pathologic criteria

- Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen
- Pathologic lesions, vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

## ■ Clinical criteria

- Two major criteria
- One major criterion and three minor criteria
- Five minor criteria

**Possible infective endocarditis**

## ■ One major criterion and one minor criterion

## ■ Three minor criteria

**Rejected**

- Firm alternate diagnosis explaining evidence of infective endocarditis
- Resolution of infective endocarditis syndrome with antibiotic therapy for <4 days
- No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for <4 days
- Does not meet criteria for possible infective endocarditis, as above

Adapted with permission from [39].

with TTE, TEE has better diagnostic yield for NVE (>95 vs 55%), prosthetic mitral valve endocarditis (82 vs 36%) [42], prosthetic valve abscesses (87 vs 28%) [43], and perivalvular regurgitation (95 vs 45%) [44]. Based on these data, TEE has become the imaging test of choice in the diagnosis of PVE.

In some instances, a TEE can be negative during the early stages of infection. Thus, if clinical suspicion of PVE persists, a repeat TEE should be performed in 7–10 days. This may allow visualization of previously undetected vegetations or abscesses that may have grown in size over time. TEE results may also be negative following embolization of previously present vegetation. Despite its relative superiority over TTE, TEE, in some cases, can still be negative and absence of vegetations should not be regarded as proof of absence of PVE.

In situations where pretest probability of endocarditis is low, and TEE is being performed to ‘rule out’ endocarditis, such as patients with short-lived nosocomial *S. aureus* bacteremia due to a vascular access device, it may be prudent to delay echocardiography until the bloodstream is rendered negative. This strategy may obviate unnecessary repeat echocardiography in situations where TEE is first obtained the very same day the positive blood culture is first reported and initial imaging is negative.

Other complimentary tests may help in the characterization of the disease by identifying associated complications and may help in deciding management interventions. For example, visualization of multiple focal lung nodules or infiltrates on a chest x-ray of a patient with tricuspid

or pulmonary PVE suggests the possibility of septic pulmonary emboli. Similarly, presence of a heart block on a EKG may indicate extension of the infective process to the adjacent myocardium and presence of ischemia or infarction on a EKG may indicate septic emboli to the coronary arteries [40]. Computed tomography (CT) or MRI of the head should be performed on a patient with underlying PVE and new neurological deficits as they may represent septic emboli to the brain. Similarly, in patients with underlying PVE, a new onset of left upper quadrant or flank pain or hematuria may indicate septic embolization to the spleen and kidneys, which can be investigated by performing a CT scan of the abdomen.

Newer imaging techniques, such as Gallium-67 citrate single photo emission computed tomography (SPECT) have been used to demonstrate the presence of peri-prosthetic abscesses in some case reports, but data regarding their routine use in diagnosis of local complications and cost-effectiveness are lacking [45–47].

Newer molecular diagnostic methods, developed in the last decade, appear to have some promising roles in the diagnosis of endocarditis. Most prominent among these is the broad range PCR assay utilizing the 16S ribosomal DNA gene for amplification followed by sequencing, which allows for identification of causative microorganisms without the aid of standard culturing techniques. This method has been found to be more sensitive than either the blood or the valve tissue culture for the diagnosis of endocarditis in cases where the infection is either caused by fastidious and slow growing or difficult to culture organisms, such as

*Tropheryma whippelii*, *Bartonella* sp. and *Coxiella* sp., or where the growth of an organism on culture media is hampered by prior administration of antibiotics [48–50]. However, there are certain limitations inherent to the PCR method and these include the possibility of contamination, inability to address viability of the detected organisms (bacterial DNA can persist in the valvular tissue even after completion of antimicrobial therapy), lack of standardization across different laboratories, unavailability of tissue in patients who do not undergo surgery and limited number of organisms available in the test library database. Most importantly, pure growth of the causative organism is still required for susceptibility analysis and the determination of MICs, unless resistance gene-specific PCR assays are used simultaneously to detect commonly occurring resistance patterns [50].

Fluorescence *in situ* hybridization is another molecular technique that can be used for the diagnosis of infective endocarditis. It involves the use of fluorescent-labeled probes to detect DNA and RNA. The most common target is the bacterial 16S ribosomal RNA. The probes can be applied to a fixed tissue or smear sample. The unique advantage of this technique is that it allows visualization and identification of microorganisms in the context of the surrounding environment and

thus can help distinguish between contaminants and true pathogens. Since it also has the potential to measure ribosomal content of bacteria *in situ*, it has the potential use in assessing treatment efficacy [50]. However, similarly to PCR assays, this technique also has certain limitations, including lack of standardization, limited library of probes and inability to study susceptibility and resistance profiles of etiological microorganisms.

### Surgical treatment

The optimal management of PVE is a subject of great debate as there have been no randomized-controlled trials comparing efficacy of medical treatment with the combined medical–surgical approach. Although there are multiple case series that describe outcomes with various approaches, the selection of patients for surgery is never standardized. Thus, the characteristics of patients managed with the medical–surgical approach are quite different from those managed with medical treatment alone. Therefore, practice guidelines have been published by a panel of experts convened by the American Heart Association and American College of Cardiology to aid clinicians in critical decision making regarding need for surgical intervention (Box 3) [51].

#### Box 2. Definition of terms used in the modified Duke criteria for the diagnosis of infective endocarditis.

##### Major criteria

- Blood culture positive for IE
  - Typical microorganisms consistent with IE (Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus* or community-acquired enterococci; in the absence of a primary focus) from two separate blood cultures
  - Microorganisms consistent with IE from persistently positive blood cultures, defined as follows. At least two positive cultures of blood samples drawn 12 h apart; all of three or a majority of >four separate cultures of blood (with first and last sample drawn at least 1 h apart); or **single positive blood culture for *Coxiella burnetii* or anti-phase I IgG antibody titer >1: 800**
- Evidence of endocardial involvement
  - Echocardiogram positive for IE (**TEE recommended in patients with prosthetic valves, rated at least ‘possible IE’ by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients**), defined as follows. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve
  - New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

##### Minor criteria

- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature >38°C
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages and Janeway’s lesions
- Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, and rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE
- **Echocardiographic minor criteria eliminated**

Bold text indicate the modifications.

IE: Infective endocarditis; TEE: Transesophageal echocardiography; TTE: Trans-thoracic echocardiography.

Adapted with permission from [39].

**Box 3. American Heart Association and American College of Cardiology practice guidelines to aid clinicians in critical decision making regarding need for surgical intervention.**
**Class I**

- Consultation with a cardiac surgeon is indicated for patients with infective endocarditis of a prosthetic valve (Level of Evidence C)
- Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with heart failure (Level of Evidence B)
- Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with dehiscence evidenced by cine fluoroscopy or echocardiography (Level of Evidence B)
- Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with evidence of increasing obstruction or worsening regurgitation (Level of Evidence C)
- Surgery is indicated for patients with infective endocarditis of a prosthetic valve who present with complications, such as, abscess formation (Level of Evidence C)

**Class IIa**

- Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with evidence of persistent bacteremia or recurrent emboli despite appropriate antibiotic treatment (Level of Evidence C)
- Surgery is reasonable for patients with infective endocarditis of a prosthetic valve who present with relapsing infection (Level of Evidence C)

**Class III**

- Routine surgery is not indicated for patients with uncomplicated infective endocarditis of a prosthetic valve caused by first infection with a sensitive organism (Level of Evidence C)

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses; Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies; Level of Evidence C: Only consensus opinion of experts, case studies, or standard of care.

Adapted with permission from [51].

In each individual case, the risks and benefits of surgery need to be carefully weighed. Surgical intervention is most beneficial when patients present with complications of PVE, such as worsening heart failure, prosthetic valve dehiscence, worsening regurgitation or perivalvular leak, valvular obstruction and cardiac abscess formation.

Surgery should also be considered in PVE cases with persistent bacteremia or relapse of infection after completion of an appropriate antibiotic course. The precise definition of persistent bacteremia is unclear as the duration of bacteremia varies depending on the causative organisms. While blood cultures usually turn negative within 48 h of initiating antibiotic therapy in cases of susceptible viridans group streptococci, they frequently remain positive for 7 days or more in cases of MRSA endocarditis despite appropriate vancomycin therapy [52].

Other relative indications of surgery include relapsing bacterial infection despite adequate therapy, fungal endocarditis, intracardiac abscess resulting in heart block, culture-negative endocarditis with recalcitrant fever despite 10 days of antibiotic therapy and recurrent emboli despite optimal antibiotic treatment. Similar to fungal endocarditis, *S. aureus* PVE is also considered to be a surgical disease by some surgeons [51,53].

The role of surgical intervention to prevent systemic embolization is not clearly defined. Vegetations greater than 10 mm at the aortic or mitral valve have a significantly higher association with embolization

as compared with the ones that measure less than 10 mm [54,55], especially during the first 2 weeks of therapy [56]. Thus, benefit of surgical intervention may be highest in this subset of patients in the earlier phase of their disease. Other echocardiographic features that may indicate the possible need for surgery are an increase in size of vegetation despite embolization and an increase in vegetation size despite appropriate antimicrobial therapy [57].

Surgery is not performed when the possibility of recovery is remote. This is usually seen in patients with high operative risks due to cardiopulmonary and neurological status, poor prognosis due to other severe comorbid conditions, a major cerebrovascular event with intracranial hemorrhage and history of multiple and technically difficult surgery with inoperability defined during a previous surgery [40,58].

Higher rates of operative intervention in patients with PVE require special attention to management of anticoagulation. Patients with PVE who are on warfarin should be switched to heparin, so that the anticoagulated state does not become a contraindication should the need for emergency surgery arise in these patients. Likewise, aspirin should also be discontinued in these patients [51]. Moreover, if neurological symptoms develop, anticoagulation should be discontinued until an intracranial hemorrhagic event has been excluded by appropriate imaging procedures, such as CT scanning.



## Medical treatment

### ■ General principles

Antimicrobial therapy for PVE should be guided by the susceptibility profile of the causative organism. Blood cultures should be drawn prior to administration of any empiric antibiotics. Specific antimicrobial regimens depending on the causative microorganisms have been published by the American Heart Association and European Society of Cardiology and are readily available on their respective websites [3,57].

Initial antimicrobial therapy for PVE should be initiated in a hospital setting under close observation. If available, an infectious diseases expert should be consulted to guide antimicrobial management. The patient should be carefully monitored for any symptoms or signs suggestive of a worsening condition or development of intra- or extra-cardiac complications. Clinicians should also watch for any adverse effects from antimicrobial therapy that may necessitate use of supportive care or a change in treatment regimen.

In general, patients with PVE are treated with 6 weeks of antibiotic therapy, counting from the day of the first negative blood cultures. At least two sets of blood cultures should be obtained every 24–48 h until the bloodstream is cleared. The time to positivity may increase with ongoing antimicrobial therapy and thus premature conclusion of a negative blood culture should be avoided until the results are finalized, which is usually at 5 days for most microbiologic laboratories. When combination therapy is used, the drugs should be administered in close proximity to each other in order to maximize the synergistic effect.

If valve replacement surgery is performed during the course of antimicrobial treatment, valve and other infected tissues obtained during surgical procedure should be submitted for Gram stain and culture. If the tissue culture reveals bacterial growth despite negative blood cultures, antimicrobial therapy should be continued for 6 additional weeks, beginning from the day of surgery. However, positive-Gram stain alone (negative culture) may simply represent nonviable organisms and does not warrant restarting the entire treatment course.

Below we discuss some key issues regarding the antibiotic selection, including the need for combination therapy, and the duration of treatment for the most common pathogens responsible for PVE.

### ■ Staphylococcal PVE

Approximately 90–95% of clinical *S. aureus* isolates are resistant to penicillin [44]. Additionally, an increasing number of staphylococcal strains are resistant to methicillin (31% of *S. aureus* and 68% of

CoNS in the ICE-PCS database) [59]. For all practical purposes, the antibiotic choices for both *S. aureus* and CoNS PVE are similar. The recommended treatment for methicillin-susceptible staphylococcal strains in patients with normal renal function is nafcillin (or oxacillin) 12 g/24 h iv. in six equally divided doses with rifampin 900 mg/24 h iv./orally in three equally divided doses for 6 weeks. In general, gentamicin 3 mg/kg/24 h iv./intramuscularly (im.), in equally divided doses is also recommended for the first 2 weeks of therapy. For methicillin-resistant strains, vancomycin in a dose of 30 mg/kg/24 h iv., in two equally divided doses, adjusted for renal function, should be used instead of nafcillin (or oxacillin).

The recommendation for the use of rifampin is based on experimental models of endocarditis in animals where combination antimicrobials with rifampin were shown to sterilize biofilm-associated foreign bodies infected by *S. aureus* [60]. This effect is partly attributable to better biofilm penetration by rifampin and its ability to interfere in replication of slowly growing bacteria where cell wall agents are not very effective. However, rifampin should never be used as a monotherapy because of a low barrier to emergence of resistance. Some experts believe that it may be prudent to wait and add rifampin only once the bloodstream has cleared.

If a patient has had a prior non-anaphylactic reaction to penicillin, a first generation cephalosporin, such as cefazolin can be substituted for nafcillin. For strains of staphylococci resistant to gentamicin, susceptibility testing should be performed for another aminoglycoside such as streptomycin. If the strain is resistant to all aminoglycosides, then either the treatment with aminoglycoside should be omitted or consideration may be given to using fluoroquinolones instead.

*S. aureus* strains that are fully resistant to vancomycin are very rare and a subject of case reports. However, there are increasing reports of creeping MICs in clinical *S. aureus* isolates that are associated with poor response to treatment as discussed above. In such cases, where clinical failure of vancomycin is apparent, and other scenarios where vancomycin cannot be used due to associated renal toxicity, few other options are available, but data are extremely limited. Recent reports have described successful treatment with daptomycin [61,62], which is approved by the US FDA for *S. aureus* bacteremia and right-sided endocarditis and is noninferior to vancomycin for left-sided endocarditis. Linezolid is another alternative agent for which limited data are available [63,64]. In general, bacteriostatic agents, such as linezolid, are best avoided in PVE if bactericidal

agents are available. Moreover, PVE usually requires at least 6 weeks of antimicrobial therapy and such prolonged administration of linezolid carries the risk of bone marrow suppression, irreversible optic or peripheral neuropathy and lactic acidosis.

#### ■ Streptococcal PVE

In general, uncomplicated PVE due to streptococci, most often caused by viridans group streptococci or *Staphylococcus bovis*, can be managed with medical therapy alone. Antibiotic choices for Streptococcal PVE vary based on penicillin MIC data. Depending on their susceptibility to penicillin, viridans group streptococci (*Staphylococcus sanguis*, *Staphylococcus oralis*, *Staphylococcus salivarius*, *Staphylococcus mutans* and *Staphylococcus anginosus*) and *S. bovis* are divided into three different categories; namely highly penicillin susceptible (MIC  $\leq 0.12$   $\mu\text{g/ml}$ ), relatively resistant to penicillin (MIC  $>0.12$ – $\leq 0.5$   $\mu\text{g/ml}$ ) and highly resistant to penicillin (MIC  $>0.5$   $\mu\text{g/ml}$ ). Patients with PVE due to highly susceptible penicillin strains should be treated with 6 weeks of iv. penicillin 12–18 million units/24 h in four to six equally divided doses or as a continuous infusion. Alternatively, ceftriaxone 2 g iv./im. every 24 h can be used for the same 6 weeks duration with comparable outcomes.

Strains that are relatively or highly resistant to penicillin should be treated with 6 weeks of combination antimicrobial therapy consisting of iv. penicillin 24 million units/24 h, in four to six equally divided doses or ceftriaxone 2 g iv./im. every 24 h with gentamicin 3 mg/kg/24 h iv./im., in three equally divided doses.

PVE caused by nutritionally variant streptococci, such as *Abiotrophia defectiva*, *Granulicatella* sp. and *Gemella* sp., is rare and similarly to enterococcal PVE, is associated with a higher rate of complications and is difficult to cure. Moreover, susceptibility data can be difficult to interpret and even when available, may not correlate with clinical outcomes. Thus, infections with these organisms should be treated with combination antimicrobial therapy with penicillin or ceftriaxone along with gentamicin for 6 weeks, similar to PVE caused by enterococcal species.

Of note, bacteremia with *S. bovis* has been associated with gastrointestinal pathology, including malignancy [65–68]. Therefore patients with *S. bovis* PVE should undergo colonoscopy to look for the presence of an underlying occult gastrointestinal malignancy.

#### ■ Enterococcal PVE

*E. faecalis* followed by *Enterococcus faecium* are the

major enterococcal species of clinical importance in PVE. Enterococci are relatively resistant to the bactericidal action of  $\beta$ -lactam agents as they express penicillin-binding proteins with lower affinity to these drugs. Therefore, synergistic actions of aminoglycoside are required for treatment of enterococcal PVE. *E. faecium* in particular is frequently resistant to penicillin due to increased expression of low affinity PBP5 [69]. Penicillin resistance is somewhat less common in *E. faecalis*.

Besides penicillin resistance, high-level resistance to vancomycin is an emerging problem in enterococci. Six different phenotypes of vancomycin resistance are recognized [70]. Of these, VanA and VanB phenotypes can be harbored on plasmids and thus are the most clinically relevant. VanA phenotype confers high-grade resistance to vancomycin and teicoplanin. VanB phenotype confers variable resistance to vancomycin but retains susceptibility to teicoplanin. In addition, enterococci can acquire high-level aminoglycoside resistance through plasmid-mediated expression of aminoglycoside-modifying enzymes. This diminishes the affinity of aminoglycosides to their target sites. Another mechanism of resistance is through ArmA-mediated 16S ribosomal methylation, which blocks the target of aminoglycoside.

Some *E. faecium* strains can be resistant to both  $\beta$ -lactam agents and aminoglycosides. Others, such as *Enterococcus gallinarum* and *Enterococcus casseliflavus*, constitutively express VanC phenotype and thus are intrinsically resistant to vancomycin.

Antimicrobial therapy for enterococcal PVE is best guided by susceptibility testing. Penicillin susceptible strains should be treated with 6 weeks of combination therapy with iv. penicillin and gentamicin. If the strain is penicillin resistant, vancomycin can be used along with gentamicin. Rarely, penicillin resistance in *Enterococcus* spp. is caused by production of  $\beta$ -lactamase and in those cases ampicillin–sulbactam can be used along with gentamicin.

For gentamicin-resistant strains, susceptibilities should be obtained for streptomycin and if found to be susceptible, streptomycin should be used. A double  $\beta$ -lactam combination of ceftriaxone and ampicillin has been used for *E. faecalis* strains with high-level aminoglycoside resistance with reported microbiological and clinical cure [71]. This double  $\beta$ -lactam combination may also be useful in patients who have other contraindications to aminoglycoside use or have worsening renal function on therapy, but experience is limited.

Enterococci resistant to penicillin, aminoglycosides and vancomycin present a particularly difficult challenge. Case reports of successful treatment with

linezolid and quinupristin–dalfopristin have been published [63,72–74]. However, due to publication bias, reports of unsuccessful treatment are generally not available.

#### ■ HACEK PVE

*Haemophilus parainfluenzae*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae* constitute a group of slow-growing Gram-negative microorganisms that are part of normal oral flora. Collectively, these are known as HACEK organisms. Antimicrobial susceptibility can be difficult to perform in these slow-growing organisms and treatment is usually initiated while awaiting susceptibility data. Due to frequent occurrence of  $\beta$ -lactamase-producing strains, ampicillin resistance should be assumed and treatment with ceftriaxone, ampicillin–sulbactam or fluoroquinolones should be initiated. Recommended duration of treatment is 6 weeks.

#### ■ Non-HACEK Gram-negative bacilli PVE

Infections due to these organisms are rare, accounting for just over 2% of PVE cases in the ICE-PCS database [7]. Among these, *Escherichia coli* is the most frequently reported organism followed by *Pseudomonas* and *Serratia*. Infection usually occurs in the early phase following valve surgery and is frequently healthcare associated. Rate of complications and mortality is high with Gram-negative bacilli PVE. Susceptibility-guided antimicrobial therapy with third- or fourth-generation cephalosporins, extended spectrum penicillins, fluoroquinolones or carbapenems with or without aminoglycosides, and frequently surgical intervention, are the cornerstone of treatment.

#### ■ Fungal PVE

Fungal PVE is extremely rare. *Candida* species and *Histoplasma capsulatum* are the most commonly reported fungal organisms responsible for PVE in the USA. *Candida* seeding of prosthetic heart valves is frequently a consequence of healthcare-associated bloodstream infection in patients with vascular access devices or surgery involving the gastrointestinal tract. Fungal PVE is usually characterized by large, dense and heterogeneous vegetations on the heart valves and is associated with a high rate of complications [75,76]. Outcomes are often poor even with the combined medical–surgical approach and relapse of infection is frequent.

For candida PVE, the recommended treatment approach consists of an initial parenteral induction with liposomal amphotericin B 5 mg/kg iv. once-daily

and 5-flucytosine 25–37.5 mg/kg every 6 h for 6–8 weeks followed by chronic long-term oral suppressive therapy with an azole (fluconazole 400 mg orally daily if susceptible). Echinocandins, such as caspofungin, micafungin or anidulafungin, can be used for *Candida* species if patients are unable to tolerate liposomal preparation of amphotericin B, which although better tolerated than amphotericin B, is still commonly associated with nephrotoxicity and electrolyte wasting, specifically potassium depletion. Echinocandins, however, are not active against dimorphic fungi such as histoplasma.

Fungal endocarditis should always be managed in close collaboration with an infectious diseases expert and an experienced cardiac surgeon.

#### ■ Adverse effect monitoring

Treatment of PVE involves long courses of parenterally administered antimicrobial therapy and thus close follow-up of patients is essential for successful outcomes. Patients should ideally be enrolled in an outpatient parenteral antibiotic treatment program to ensure a safe and effective treatment course. Infectious Diseases Society of America has published practice guidelines for outpatient parenteral antibiotic treatment [77], which are easily accessible at [101]. Clinicians should familiarize themselves with common side effects of antibiotics that are prescribed in the outpatient setting so as to monitor and detect any adverse effects and take corrective action when necessary.

#### Outcomes

In the ICE-PCS database, increasing age, healthcare-associated PVE, *S. aureus* PVE, complications in the form of heart failure, persistent bacteremia and stroke, were all associated with a higher in-hospital mortality rate of 30.5%. The mortality rate during the index hospitalization was 22.8% and approximately half the patients required surgical management [7]. In-hospital mortality rates following surgery for PVE have been reported to be 13–48% [30]. As compared with NVE, surgical intervention for PVE has been found to have higher rates of 30-day mortality (13 vs 5.6%) but long-term survival does not appear to be significantly different [78]. Also, redo aortic valve surgery for PVE has been shown to be associated with significantly higher in-hospital mortality as well as higher 1-, 3-, 5- and 10-year mortality as compared with redo aortic valve surgery for non-endocarditic causes [79]. In this group of patients, 5-year actuarial freedom from endocarditis was only 80% in patients who underwent redo surgery for PVE as compared with 95% in patients who underwent redo surgery for

non-endocarditic causes. Furthermore, surgery for active PVE, defined as having been performed prior to completion of a standard course of antibiotics, has been shown to be associated with an increased risk of in-hospital mortality (overall response: 4.16; 95% CI: 1.14–12.2) in multivariate analysis of a single-center cohort of 141 patients operated upon by the same surgical team [80]. Mechanical respiratory and cardiac support, preoperation higher doses of catecholamines, emergent surgery, mitral valve replacement and age at operation, were found to be predictors of early mortality in another recent retrospective analysis [81].

Many of these studies are limited by a number of factors including being single-center retrospective observational studies. Additionally, lack of standardization in patient selection and procedure makes the results difficult to interpret. However, there appears to be a trend towards mortality benefit from surgery among patients who develop complications of PVE [30,82].

### Prevention

American Heart Association guidelines for prevention of infective endocarditis have undergone numerous iterations over the last few years. The latest update to these guidelines was released in 2007

[83]. These revisions identify subgroups of patients who might be at a highest risk of complications if they were to develop infective endocarditis. People with prosthetic valves are recognized as one of these subgroups and thus perioperative prophylaxis with either amoxicillin 2 g orally or ampicillin 2 g iv./im. are considered reasonable for procedures that carry the highest risks of transient bacteremias, such as all dental procedures that involve manipulation of gingival tissue or periapical region of teeth or perforation of oral mucosa. Similarly, prophylaxis is also reasonable for these patients who are undergoing procedures involving incision or biopsy of respiratory mucosa, genitourinary and gastrointestinal procedures in the presence of an established infection and procedures on infected skin and skin structures.

Clindamycin, azithromycin, cephalexin, ceftazidime or vancomycin, may be used in patients who are known to be allergic to penicillins. Of these, only vancomycin is active against *Enterococcus sp.*, which is frequently a cause of gastrointestinal and genitourinary infections.

### Challenges & future perspective

Although significant progress has been made in

## Executive summary

### Epidemiology

- Prosthetic valve endocarditis (PVE) accounts for approximately a fifth of all cases of infective endocarditis.
- PVE is associated with high rates of morbidity and mortality (22.8%).
- PVE can be early-onset (within 60 days of surgery), intermediate-onset (60–365 days) and late-onset (after 1 year of valve surgery).

### Microbiology

- *Staphylococcus aureus* is now the most common cause of PVE.
- Healthcare-associated infections account for most cases of PVE.

### Pathogenesis

- Most cases of PVE occur within the first year after surgery, likely due to incomplete endothelialization of the mechanical valve during this timeframe.

### Diagnosis

- Diagnosis of PVE is guided by the modified Duke's criteria.
- Transesophageal echocardiography is the preferred imaging modality for PVE.

### Treatment

- Treatment often involves a combined medical and surgical approach.
- Surgery is most beneficial for patients who present with acute heart failure symptoms, paravalvular extension of infection, valve dehiscence, worsening stenosis or regurgitation, recurrent emboli or persistent bloodstream infection despite appropriate therapy, and relapse of infection after an adequate treatment course.
- More invasive organisms, such as *Staphylococcus aureus*, non-HACEK Gram-negative bacilli and fungi, are associated with a more severe presentation and frequently require surgical management.
- Antibiotic therapy is usually given for 6 weeks or longer.
- Organism-specific antibiotic treatment guidelines have been published by the American Heart Association and European Society of Cardiology and should be followed in most cases of PVE.
- Infection due to resistant organisms, especially multidrug-resistant pathogens, poses an immediate and challenging problem in the management of these complicated infections.

our understanding and management of PVE, many unanswered questions remain. High-quality evidence in the form of randomized-controlled trials is lacking due to the rare occurrence of these infections. Nevertheless, the most important questions that remain unanswered involve decisions regarding the timing of surgical intervention and optimal duration of antimicrobial therapy. Molecular methods described above that are currently available need to be refined further and their role in the diagnosis of PVE needs to be clearly defined. Finally, we should continue to implement strict infection-control practices specifically pertaining to prevention of surgical-site infections and healthcare-associated bloodstream infections, in order to reduce the burden of early and intermediate cases of PVE.

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