

## VALVE DISEASE

## Prosthetic valve endocarditis

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After 40 years of continuous improvements in the design and materials used for prosthetic heart valves, valve replacement surgery is now performed with low morbidity and mortality. These advantages have been hampered by a few but severe adverse effects; in particular, infections of the prosthetic material continue to be an extremely serious complication occurring with a relatively low but increasing frequency ranging from 0.1–2.3% per patient year.<sup>1–3</sup> The prosthesis obviously predisposes to device related infections, especially those caused by novobiocin susceptible, coagulase negative staphylococci, which are able to adhere to a variety of surfaces<sup>4</sup> and produce an antibiotic resistant biofilm.<sup>5,6</sup>

## Definition and frequency

Prosthetic valve endocarditis (PVE) is an endovascular, microbial infection occurring on parts of a valve prosthesis or on reconstructed native heart valves.<sup>7</sup> It is recommended to determine whether (a) a mechanical prosthesis, (b) a bioprosthetic xenograft, stented or unstented, (c) an allograft, (d) a homograft, or (e) a repaired native valve with or without implantation of an annular ring is involved.<sup>8</sup> Although clinical relevance and therapeutic considerations may be similar, infections of devices or lines placed inside the heart but not connected to the endocardial structures should

be classified as “polymer associated infections” rather than PVE.

PVE should be classified as either being acquired perioperatively, and thus nosocomial (early PVE), or as community acquired (late PVE).<sup>8</sup> Because of significant differences in microbiology of PVE observed within the first year of operation and later on, the time cut off point between early and late PVE should be regarded as one year.<sup>9</sup>

The risk for early PVE is higher (approximately 5%) in patients with replacement surgery during active infective endocarditis, especially if the causal organism is unknown or the antibiotic treatment is insufficient. The incidence of late PVE is lower for mechanical prostheses than for bioprostheses. The weighted mean incidence for infections of bioprostheses calculated from published series is 0.49% per patient year for mitral valves and 0.91% per patient year for aortic valves. For mechanical prostheses, the incidence is 0.18% per patient year for mitral, 0.27% per patient year for aortic, and 0.29% per patient year for multiple implants.<sup>10</sup>

Comparing different periods of implantation, hazard functions reveal a significant decline in early PVE cases in recent years, contrasting with a slight increase in the hazard for late PVE (fig 1).

## Pathogenesis

Prostheses made from metal, pyrolyte or other materials do not allow adherence of microorganisms as long as they are free from thrombotic material. Infections of mechanical prostheses generally originate from the sewing cuff or from thrombi located near the sewing ring downstream in recirculation areas. Inflammatory periprosthetic leaks, ring abscesses, and invasion of the infective process into the adjacent tissue are common findings. The pathogenesis of bioprosthetic infections may be similar to that of native valves. In these cases, the infection is restricted to the cusps, eventually initiating secondary bioprosthetic failure but with only a low tendency to invade the sewing cuff or to result in periprosthetic abscesses.<sup>10</sup> If the sewing cuff, however, is involved, the pathogenesis and clinical course are more or less the same as in PVE involving mechanical prostheses.

## Microbiology

The microbiology of PVE is very different from that of native valve endocarditis (NVE). Streptococci and enterococci occur less frequently, while staphylococci, bacteria of the HACEK group (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*), and fungi are found more frequently in cases of PVE. Novobiocin susceptible, coagulase negative staphylococci have a particularly high affinity for implanted or indwelling foreign surfaces, especially polymers.<sup>4</sup> They are the most frequent

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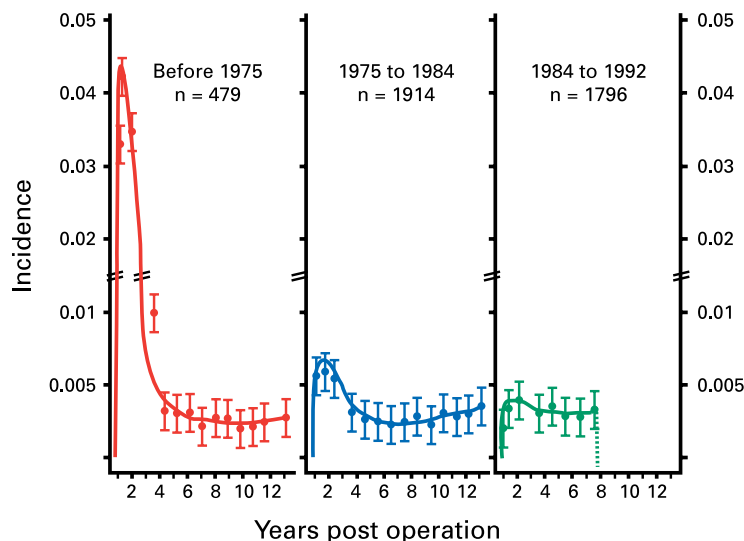


Figure 1. Hazard functions for prosthetic valve endocarditis in 4189 consecutive patients during three successive follow up periods.

### Definition, pathogenesis, and microbiology of prosthetic valve endocarditis (PVE)

- Microbial infection of parts of a prosthetic valve or reconstructed native heart valve
- Early PVE is usually acquired perioperatively (nosocomial)
- Late PVE is mostly community acquired
- Time cut off point between early and late PVE should be one year (notable differences in microbiology)
- The risk of early PVE is higher (approximately 5%) in patients with replacement surgery during active infective endocarditis
- Mechanical prosthesis infections originate from the sewing cuff or from nearby located thrombi → periprosthetic leaks, ring abscesses, invasion of adjacent tissue
- Bioprosthesis infections mostly are restricted to the cusps → secondary bioprosthetic failure
- Staphylococci (especially novobiocin susceptible, coagulase negative staphylococci), bacteria of the HACEK group, and fungi occur more frequently in PVE
- Streptococci and enterococci are found more frequently in native valve endocarditis

pathogens causing PVE. The usual spectrum for Europe is given in table 1.

### Diagnostic approach

The diagnostic approach in PVE does not differ from that in NVE, as both are systemic infections maintaining a continuous bacteraemia. Hence, the diagnosis is established if in addition to typical clinical signs and symptoms and positive blood cultures, the device can be shown to be affected by echocardiography, preferably using multiplane transoesophageal (TOE) probes. TOE should be performed without delay in all patients with suspicion of PVE.<sup>11</sup> For the diagnosis of PVE, TOE is of such immense importance that institutions without this facility are best advised to ask for assistance from a specialised centre. With TOE the size of vegetation can be defined more precisely than with transthoracic echocardiography (TTE), and periannular complications indicating a locally uncontrolled infection (for example, abscesses, dehiscence, fistulas) may be detected earlier. Both size of vegetations and infection morphology significantly influence therapeutic decisions (namely duration of antimicrobial treatment and the need for urgent surgical intervention).

In otherwise unproven cases, gallium-67 scans or indium-111 leucocyte scintigraphy have been reported to be useful in detecting myocardial abscesses or diffuse tissue infiltrations. Their diagnostic impact has not been established so far.<sup>12</sup>

### Treatment

#### Antimicrobial treatment

The basic principles of antimicrobial treatment in PVE do not differ from those for NVE. Some special aspects need to be considered, however.

PVE is usually associated with vegetations larger than those found in NVE. Consequently, antibiotics have to be used in dosages which result in maximum, non-toxic serum concentrations in order to penetrate the total vegetation. The duration of treatment usually has to be longer than for the treatment of NVE and should consider vegetation size as determined by TOE as well as the minimal inhibitory concentration (MIC) of the most efficient combination of antibiotics (table 2). Antibiotic sterilisation of large vegetations is unlikely with an MIC  $\geq 4$   $\mu\text{g/ml}$ .

In PVE caused by coagulase negative staphylococci, complex interactions between the microorganism and the synthetic material—for example, irreversible adhesion and production of a biofilm, which inhibit the host defence mechanisms—protects against antimicrobial treatment and makes antibiotic sterilisation extremely difficult.<sup>5,6</sup>

The presence of (micro-) abscesses is likely in PVE caused by coagulase negative staphylococci, and triple therapy including rifampicin (900 mg/day divided into three doses) is

Table 1 Microbiology of early and late PVE. Authors' own findings compared to a recent European literature review<sup>9</sup>

	Early PVE (%)		Late PVE (%)	
	Own experience (n=34)	Europe (n=68)	Own experience (n=132)	Europe (n=194)
<i>Staphylococcus epidermidis</i>	29	43	21	28
<i>Staphylococcus aureus</i>	18	13	19	13
Streptococci	6	3	15*	20
Enterococci	6	2	18	7.5
HACEK	18	17	8	7
Fungi	9	6	5	4
Mixed infections	6	–	3	–
Others	6	12	7	9
Culture negative	3	4	4	12

\*Viridans group n=13 (10%),  $\beta$  haemolytic streptococci n=3 (2%), and *Streptococcus bovis* n=4 (3%).

HACEK, *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*.

Table 2 Duration of antimicrobial treatment in prosthetic valve endocarditis with respect to vegetation size and minimal inhibitory concentration (MIC)

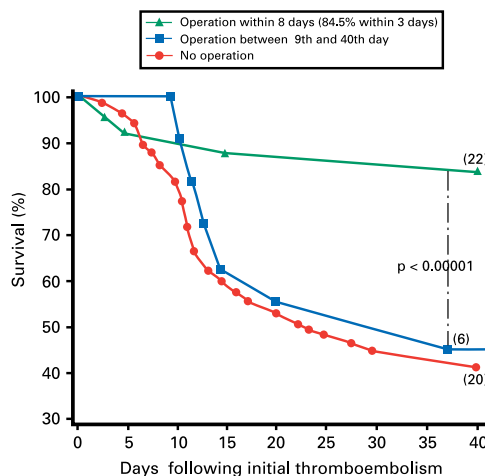
	Vegetation size*		
	< 4 mm	5–9 mm	> 10 mm
MIC $\geq 4$ $\mu\text{g/l}$	Antibiotic cure unlikely		
4 $\mu\text{g/ml}$ > MIC $\geq 2$ $\mu\text{g/ml}$	> 6 weeks	Antibiotic cure unlikely	
2 $\mu\text{g/ml}$ > MIC $\geq 0.5$ $\mu\text{g/ml}$	6 weeks	> 6 weeks	Antibiotic cure unlikely
0.5 $\mu\text{g/ml}$ > MIC $\geq 0.1$ $\mu\text{g/ml}$	6 weeks	6 weeks	> 6 weeks
MIC < 0.1 $\mu\text{g/ml}$	4 weeks	4 weeks	> 6 weeks

\*Actual size of vegetation during treatment; MIC, minimal inhibitory concentration of the most effective antibiotic combination.

recommended.<sup>13</sup> Rifampicin is actively taken up by granulocytes and becomes effective against intracellular staphylococci and staphylococci inside abscesses.<sup>4</sup>

When PVE is clinically apparent and blood cultures are not yet positive, empiric treatment should be initiated with vancomycin and gentamicin.<sup>8</sup> For PVE caused by penicillin sensitive streptococci ( $MIC_{PEN} < 0.1 \mu\text{g/ml}$ ), it is advisable to combine penicillin (20–24 million units/24 hours intravenously (iv) divided into 4–6 doses) with an aminoglycoside (preferably gentamicin, 3 mg/kg/24 hours iv, divided into 2–3 doses), treating for at least two weeks with this combination and at least a further two weeks with penicillin alone. In the case of penicillin allergy, vancomycin as a single drug treatment (30 mg/kg/24 hours iv divided into two doses) or ceftriaxone (2 g/24 hours iv as single dose) in combination with gentamicin should be given. PVE caused by streptococci less sensitive to penicillin ( $MIC_{PEN} \geq 0.5 \mu\text{g/ml}$ ) or enterococci ( $MIC_{PEN} \leq 8 \mu\text{g/ml}$ ) are best treated with a combination of penicillin and gentamicin for at least four weeks. Vancomycin can replace penicillin, if the patient is allergic to penicillin or if  $MIC_{PEN} > 8 \mu\text{g/ml}$ . Vancomycin resistant strains susceptible to teicoplanin ( $MIC_{TEICOP} \leq 4 \mu\text{g/ml}$ ) may be treated with teicoplanin (10 mg/kg iv divided into two doses) plus gentamicin. If the isolates are highly resistant to gentamicin or multiresistant to the standard antimicrobial agents, alternative combinations of drugs (for example, quinolones) must be considered in consultation with an expert in clinical microbiology. Enterococcal PVE is often complicated by periprosthetic dehiscence, annular abscesses or fistulas. In these cases, if antibiotic treatment fails an early surgical intervention should be considered.

If the pathogen is an oxacillin susceptible staphylococcus ( $MIC \leq 0.1 \mu\text{g/ml}$ ), gentamicin should be combined with dicloxacillin/flucloxacillin (12 g/24 hours iv, divided into six doses) for two weeks; thereafter dicloxacillin/flucloxacillin should be given for an additional four weeks. In oxacillin resistant strains, vancomycin (see above for doses) should replace oxacillin derivatives. There is no valid evidence to prove that teicoplanin is superior to the established antistaphylococcal drugs. Early surgery in most cases is indicated to prevent secondary complications.<sup>8, 13</sup>



**Figure 2.** Influence of the timing of surgery on the prognosis of patients with cerebral thromboembolism complicating prosthetic valve endocarditis.

### Antithrombotic treatment

Antithrombotic management in patients with PVE has been discussed widely.<sup>14</sup> There seems to be a consensus that oral anticoagulation treatment should be suspended and replaced by intravenous heparin. The dosage of heparin depends on the presence and nature of secondary complications (for example, thrombocytopenia) and varies between 7–30 U/kg body weight. Low molecular weight heparins may be advantageous, as side effects (especially thrombocytopenia) are less frequent.

### Surgical reintervention

If PVE is complicated, it has to be decided whether medical treatment should be continued or urgent surgical intervention is required. The indications for surgery in PVE are similar to those in NVE: large (> 10 mm), mobile vegetations, thromboembolic events with vegetations still demonstrable, sepsis persisting for more than 48 hours despite effective antibiotic treatment (guided by blood cultures and MICs), and acute renal failure. A cerebral embolic event is not a contraindication for open heart surgery provided that there is no cerebral haemorrhage and the time between embolic event and surgery is short (preferably < 72 hours) so that the blood–brain barrier can be expected not to be significantly disturbed (fig 2).<sup>15</sup> Periprosthetic dehiscence with or

**Table 3** Guidelines for endocarditis prophylaxis in patients with biological or prosthetic heart valves, categorised according to the patient population at high risk of acquiring endocarditis

	Oropharynx, gastrointestinal tract, urogenital tract		
	No penicillin allergy	In case of penicillin allergy	Skin, heart catheterisation
1 hour before the procedure	<ul style="list-style-type: none"> <li>Outpatient: 2 g (3 g &gt; 70 kg bodyweight) amoxicillin orally</li> <li>Hospitalised: 2 g amoxicillin iv + 1.5 mg/kg gentamicin</li> </ul>	<ul style="list-style-type: none"> <li>Outpatient: 600 mg clindamycin orally or 1 g vancomycin iv for 1 hour or 800 mg teicoplanin</li> <li>Hospitalised: vancomycin 1 g iv for 1 hour + 1.5 mg/kg gentamicin</li> </ul>	<ul style="list-style-type: none"> <li>600 mg clindamycin orally or 1 g vancomycin iv for 1 hour or 800 mg teicoplanin</li> </ul>
6 hours after the procedure	<ul style="list-style-type: none"> <li>Outpatient: 1 g amoxicillin orally</li> <li>Hospitalised: 1 g amoxicillin + 1.5 mg/kg gentamicin</li> </ul>	<ul style="list-style-type: none"> <li>Outpatient: 300 mg clindamycin orally</li> <li>Hospitalised: vancomycin 1 g iv for 1 hour + 1.5 mg/kg gentamicin</li> </ul>	<ul style="list-style-type: none"> <li>300 mg clindamycin</li> </ul>

iv, intravenous.

### Treatment and prophylaxis of prosthetic valve endocarditis (PVE)

- Duration of treatment for PVE is usually longer than for native valve endocarditis
- Antibiotic sterilisation of coagulase negative staphylococci or enterococci PVE is extremely difficult
- Early surgical intervention is necessary in most cases to prevent secondary complications
- Oral anticoagulation should be replaced by intravenous heparin or low molecular weight heparin
- For PVE prophylaxis, antibiotics should be taken one hour before and six hours after the interventional procedure
- In hospitalised patients, antibiotics may be administered intravenously in combination with aminoglycosides

without myocardial failure has a poor prognosis. If congestion is not promptly removed by medical treatment, surgical intervention is mandatory. Allograft aortic root replacement is a valuable technique in the complex setting of PVE with involvement of the periannular region.<sup>16</sup>

### Prophylaxis

As the risk for an infection is much higher in patients with prosthetic heart valves than in patients with valvular heart disease, more intensive prophylaxis is needed in these patients. In patients with prosthetic valves, the antibiotics should be taken one hour before the interventional procedure and a repeat but reduced dosage administered six hours after the procedure. If patients are hospitalised, the antibiotics may be applied intravenously in combination with aminoglycosides one hour before and six hours after the procedure (table 3).

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