Early-onset prosthetic valve endocarditis

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- **BACKGROUND** Endocarditis following cardiac valve implantation is a rare but serious complication.
- **OBJECTIVE** To determine the risk and outcome of early-onset prosthetic valve endocarditis (EO-PVE) in adult patients at The Cleveland Clinic.
- **METHODS** Retrospective review of a 5-year case series of patients who acquired bloodstream infections within 60 days of surgery identified through a prospective surveillance program.
- **RESULTS** Sixty-eight of approximately 2100 patients acquired bloodstream infections; 16 (24%) contracted EO-PVE and 52 (76%) did not. Risk factors for EO-PVE included younger age, at least three sets of positive blood culture results, and an organism other than a gram-negative bacillus. The majority of patients with EO-PVE had a recognized source of infection (wound or vascular catheter site), but no infections were attributed to a pulmonary or urinary tract site. Eleven patients (69%) were cured, including six who underwent emergent second operations.
- **CONCLUSION** Patients with multiple blood cultures positive for organisms other than gram-negative bacilli are at risk of EO-PVE, even when a primary wound infection or vascular catheter site infection is recognized and treated.

■ INDEX TERMS: BACTEREMIA; ENDOCARDITIS, BACTERIAL; HEART VALVE PROSTHESIS ■ CLEVE CLIN J MED 1993; 60:455–459

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EARLY-ONSET PROSTHETIC valve endocarditis (EO-PVE) occurring within 60 days of surgery has always been worrisome. Death occurred in 88% of patients who contracted EO-PVE after undergoing valve replacement at the Mayo Clinic from 1963 to 1974.[1] Despite advancing surgical expertise and antibiotic prophylaxis, this complication still occurs in approximately 1% of patients with implanted heart valves, and mortality remains in the range of 30% to 50%.[2]

Bloodstream infections after cardiac valve surgery may cause life-threatening problems. In 1972, Sande and colleagues[3] described 22 patients who acquired bacteremia following mechanical valve implantation. Eleven patients contracted endocarditis and all 11 died. No patient underwent a second operation. The infecting organisms were all gram-positive cocci, usually *Staphylococcus aureus*, coagulase-negative staphylococci, or streptococci. Cases often presented later than 2 weeks after surgery; in no case was a source of bacteremia recognized. In contrast, gram-negative bacteremia was documented in nine patients, and none of them

TABLE 1
CLINICAL AND LABORATORY FINDINGS IN PATIENTS WITH BLOODSTREAM INFECTIONS AFTER SURGERY

	EO-PVE* (n=16)	No EO-PVE (n=52)	*P* value
Age 18-64	8	13	
Age ≥ 65	8	39	.06
Female	7	21	
Male	9	31	.81
Onset after surgery			
1-14 days	5	25	
15-60 days	11	27	.24
Temperature ≥ 38.5°C	8	25	.89
Three or more positive blood cultures	13	21	.004
Gram-negative bacteria	2	20	.05

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TABLE 2
ORGANISMS THAT CAUSED BLOODSTREAM INFECTIONS AFTER CARDIAC VALVE SURGERY

Organism	EO-PVE* (n=16)	No EO-PVE (n=52)
Gram-positive bacteria		
Staphylococcus aureus	6	11
Coagulase-negative staphylococci	0	2
Enterococcus faecalis	4	10
Other streptococci	0	1
Diphtheroids	1	1
Gram-negative bacteria		
Pseudomonas aeruginosa	0	7
Enterobacter species	1	4
Serratia marcescens	0	5
Escherichia coli	0	2
Other	1	2
Candida species	3	7

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TABLE 3
SOURCE OF BLOODSTREAM INFECTIONS AFTER CARDIAC VALVE SURGERY

Source	EO-PVE* (n=16)	No EO-PVE (n=52)
Surgical wound	6	15
Intravenous catheter site	3	12
Pneumonia	0	8
Urinary tract	0	6
Unknown	7	11

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contracted endocarditis. This condition was usually recognized within 2 weeks of surgery, and a primary source for the infection was often apparent (wound, vascular site, or respiratory tract). The majority of these infections responded to antibiotic therapy. The investigators concluded that late postoperative bacteremia, when caused by gram-positive organisms and without a recognized source, indicates endocarditis. Antibiotic therapy without surgical intervention was likely to be ineffective. However, gram-negative bacteremia, especially within 2 weeks of surgery, responded to antibiotic therapy for the primary infection. The risk of endocarditis appeared to be low in the latter instance.

Despite major advances in technology and supportive care since this report, nosocomial bloodstream infections continue to be of concern. Many patients who incur this complication already have severe underlying disease requiring life-support measures in an intensive care unit following surgery. The decision to treat such patients with prolonged courses of antibiotics is often based on the fear that endocarditis may be present. We report The Cleveland Clinic's recent experience with this problem, focusing on the risk and outcome of endocarditis.

MATERIALS AND METHODS

All adult patients who acquired bloodstream infections within 60 days of cardiac valve surgery from 1986 to 1990 were identified through a prospective surveillance program maintained by the Infection Control Department. During this period, approximately 2100 patients underwent cardiac valve replacements. The standard antibiotic prophylaxis was cefamandole, 1 g intravenously during induction of anesthesia and every 6 hours thereafter for 48 hours, followed by a 3-day course of oral cephalexin. Documentation of bacteremia required at least two sets of blood culture results positive for the same microorganism within a 48-hour period. Each blood culture set involved inoculating 10 mL of blood into a lysis-centrifugation system (Dupont Isolator) and another 10 mL into a companion 100 mL nonvented broth bottle.

Information was abstracted from the medical record regarding temperature during the event, heart murmurs, embolic events, echocardiographic results, and source of infection (when recognized). Endocarditis was considered "definite" if there was gross

TABLE 4
SUMMARY OF EIGHT CASES OF DEFINITE EARLY-ONSET PROSTHETIC VALVE ENDOCARDITIS*

Age	Sex	Implant	Post-operative day	Organism	Positive cultures	Days positive	Site	Positive echocardiogram†	Emboli present	Surgery	Outcome (duration of follow-up)
42	M	AVR‡	2	*Candida albicans*	8	5	Intravascular catheter	No	No	Yes	Relapsed and died (24 months)§
66	F	MVR§	11	Methicillin-resistant *Staphylococcus aureus*	6	3	Wound	Yes	No	Yes	Cured (16 months)
73	F	MVR	18	Methicillin-sensitive *S aureus*	6	4	Wound	Yes	No	Yes	Cured (39 months)
64	F	M-ring	20	Methicillin-resistant *S aureus*	7	2	Intravascular catheter	Yes	No	Yes	Cured (14 months)
34	M	AVR/MVR	21	*Acinetobacter anitratus*	2	1	Wound	Yes	Yes	Yes	Cured (24 months)
23	F	T-ring	22	Methicillin-sensitive *S aureus*	2	1	Wound	No	No	No	Died (15 days)‖
62	M	MVR	32	*Enterococcus*	5	3	Unknown	Yes	Yes	Yes	Cured (25 months)
38	M	AVR	43	C *albicans*	4	4	Unknown	No	Yes	Yes	Cured (42 months)

*See text for definition of definite early-onset prosthetic valve endocarditis
†Conclusive evidence of vegetation or abscess
‡Aortic valve replacement
§Mitral valve replacement
‖Active endocarditis at autopsy

and histologic proof of infection at surgery or postmortem examination; it was considered "probable" if there was a documented regurgitant or newly appreciated heart murmur and a clinical profile consistent with endocarditis. Cases were also classified according to whether a bloodstream infection was "recent" (recognized within 2 weeks after surgery) or "delayed" (recognized from 15 to 60 days after surgery). Surviving patients were followed-up for at least 6 months after completion of antibiotic therapy.

Univariate comparison included a *t* test for the comparison of mean age and Fisher's exact test for association of risk factors with prosthetic valve endocarditis compared with bloodstream infections without endocarditis. *P* values less than .05 were considered statistically significant; *P* values from .05 to .10 were considered marginally significant.

RESULTS

Sixty-eight patients with bloodstream infections qualified for study, and EO-PVE was diagnosed in 16 (24%). Eight had definite cases, eight had probable cases, and the remaining 52 patients (76%) did not have evidence of endocarditis. Clinical and laboratory findings in patients with and without endocarditis are compared in *Table 1*. Patients with EO-PVE were more likely to be younger than age 65 than patients without endocarditis ($P = .06$), but were no more likely to have had positive blood cultures within 2 weeks of surgery ($P = .24$). Neither sex predominated ($P = .81$).

Temperatures ≥ 38.5° were noted in eight patients with EO-PVE and in 25 with bacteremia ($P = .89$). Thirteen of 16 patients with EO-PVE had three or more blood culture results positive for the same organism; this occurred in only 21 of 52 patients with bacteremia ($P = .004$).

The organisms in bloodstream infections causing EO-PVE included *S aureus*, *Enterococcus faecalis*, diphtheroids, gram-negative bacilli, and *Candida* species (*Table 2*). Of interest, no case of EO-PVE was caused by coagulase-negative staphylococci, and only two infections were noted in the patients without endocarditis. There were two cases of EO-PVE caused by gram-negative bacilli (*Acinetobacter anitratus* and *Enterobacter cloacae*), while these organisms were present in 20 patients who had bacteremia without endocarditis ($P = .05$).

A source of bloodstream infection was recognized in 9 of 16 patients with EO-PVE and in 41 of 52 without endocarditis (*Table 3*). Surgical wounds and

TABLE 5
SUMMARY OF EIGHT CASES OF PROBABLE EARLY-ONSET PROSTHETIC VALVE ENDOCARDITIS*

Age	Sex	Implant	Post operative day	Organism	Positive cultures	Days positive	Site	Positive echocardiogram†	Emboli present	Surgery	Outcome (duration of follow-up)
82	M	AVR‡	8	Methicillin-sensitive *Staphylococcus aureus*	6	4	Wound	No	No	No	Cured (10 months)
64	F	MVR§/T-ring	8	*Enterobacter cloacae*	3	2	Unknown	...	No	No	Cured (6 months)
77	F	AVR	10	*Enterococcus*	2	1	Wound	No	No	No	Cured (22 months)
88	M	AVR	20	*Candida albicans*	6	4	Unknown	No	No	No	Died (1 month)
77	M	M-ring	31	Methicillin-sensitive *S aureus*	7	3	Intravascular catheter	Yes	No	No	Died (6 days)
78	M	AVR	34	*Enterococcus*	4	1	Unknown	Yes	Yes	No	Died (6 weeks)
71	F	AVR/MVR	43	*Enterococcus*	9	2	Unknown	Yes	Yes	No	Cured (8 months)
57	M	AVR	48	JK Diphtheroids	13	15	Unknown	Yes	Yes	No	Cured (20 months)

*See text for definition of probable early-onset prosthetic valve endocarditis
†Conclusive evidence of vegetation or abscess
‡Aortic valve replacement
§Mitral valve replacement

vascular catheter site infections were recognized sources in both groups of patients. However, no case of EO-PVE was attributed to a respiratory or urinary tract source.

Table 4 summarizes the eight cases of definite EO-PVE, including follow-up and outcome. Careful chart review did not demonstrate a site of infection prior to the documentation of bacteremia, except in one case of gram-negative endocarditis. This patient, a 34-year-old man, underwent replacement of failed aortic and mitral valve prostheses originally implanted 17 years earlier. Two days before surgery, a small anterior mediastinal loculus was drained. This lesion was adjacent to old ventricular pacing wires from the previous surgery. Operative culture results were negative, but the patient had been receiving cefamandole during specimen collection. On postoperative day 21, the patient presented with an acute arterial obstruction to the right foot that required an emergency embolectomy. A newly recognized grade 2 precordial systolic heart murmur was recorded at time of readmission. The resected embolus and blood cultures grew *A anitratus*. The patient returned to surgery, and a large ring abscess was found surrounding the freshly implanted aortic valve. Culture results of the resected valve were also positive for *A anitratus*. Following valve replacement, the patient was treated with a 5-week course of intravenous antibiotic therapy, and has remained well without evidence of relapse for over 3 years.

The eight cases of probable EO-PVE are summarized in *Table 5*. Only one case of endocarditis due to gram-negative bacilli was noted in this group.

Altogether, 11 of 16 patients (69%) with EO-PVE were cured, including six of seven patients who underwent emergent surgery. Four of the patients who were cured were infected with *S aureus*; three of them had surgery. Five patients died (31%), two of overwhelming infection due to *S aureus*; neither had surgery. Two deaths were caused by *Candida albicans*, one despite valve replacement. The remaining death occurred in a patient who suffered respiratory arrest after completing antibiotic therapy for enterococcal endocarditis.

Twenty-nine of the 52 patients with bacteremia without endocarditis (56%) died in the hospital, often during prolonged life support in an intensive care unit. It was difficult to determine the role of bacteremia in the demise of these patients because they had prolonged and irreversible multiple organ failure. Thirteen (45%) underwent postmortem examinations. All prostheses were intact and functional and there was no evidence of infection in these patients.

DISCUSSION

In our series, 16 of 68 patients (24%) with documented bloodstream infections within 60 days of cardiac valve surgery acquired EO-PVE. Factors that favored this diagnosis included younger age, at least three blood culture results positive for the same organism, and an organism other than a gram-negative bacillus. Cases of endocarditis were as likely to present within 2 weeks of surgery as later.

This study confirms the sobering fact that EO-PVE remains a small but significant risk for patients undergoing valvular heart surgery. In contrast to Sande and colleagues' report,[3] the majority of our patients had a recognized source of bacteremia, either a surgical wound or a vascular-catheter site. Clearly, vascular-catheter site infections are increasing in frequency in patients who require invasive monitoring while in intensive care units. Banerjee and associates[4] noted a significant rise in primary bloodstream infections in American hospitals from 1980 to 1989. The most frequent pathogens have been coagulase-negative staphylococci, *S aureus*, *E faecalis*, and *Candida* species.

It is important to emphasize that three of our cases of endocarditis arose from infections at vascular-catheter sites. When sepsis is suspected, particularly in patients who have undergone recent valvular heart surgery, vascular catheters should be removed. Changing central venous and pulmonary artery catheters over a guide-wire is not recommended.[5] The use of antimicrobial-impregnated cuffs may reduce the likelihood of infection complications, especially in cases requiring prolonged intravascular monitoring.[6]

Our study appears unique in that no cases of EO-PVE due to coagulase-negative staphylococci were identified and only two cases of bacteremia were attributed to these organisms. Cefamandole, which has demonstrated in vitro activity against coagulase-negative staphylococci,[7] was used for standard perioperative prophylaxis. Although bacteremic surgical wound infections are occasionally caused by coagulase-negative staphylococci, in our experience they are more often due to *S aureus*. In addition, when sepsis is suspected, it is our standard practice to initiate broad-spectrum antistaphylococcal therapy promptly with vancomycin, after obtaining appropriate cultures. This practice may minimize the likelihood of sustained bacteremia caused by these organisms.

Our study, however, does agree with Sande and colleagues'[3] observation that patients with postoperative gram-negative bacteremia are unlikely to have EO-PVE. This finding, also noted by Dismukes and associates,[8] may be related to the lack of adherence that gram-negative bacilli have for endovascular surfaces compared with gram-positive cocci.[9] But, when bacteremia is caused by gram-positive cocci or yeasts, EO-PVE must be considered even when a primary source of infection is recognized such as a wound or vascular-catheter site. If, in addition, a patient has three or more sets of blood culture results positive for the same microorganism and a regurgitant or newly-appreciated heart murmur, aggressive therapy is warranted, including consideration for emergent repeat operation. In contrast to the 100% mortality reported by Sande and associates,[3] there were only five (31%) deaths in our series. Eleven patients were cured, including six who underwent prosthetic valve replacement at repeat operation.

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REFERENCES

1. **Wilson WR, Jaumin PM, Danielson GK, Giuliani ER, Washington JA II, Geraci JE.** Prosthetic valve endocarditis. Ann Intern Med 1975; **82:**751–756.
2. **Threlkeld MG, Cobbs CG.** Infectious disorders of prosthetic valves and intravascular devices. In: Mandell, Douglas, Bennett, editors. Principles and practice of infectious diseases. 3rd ed. New York, Churchill Livingston Inc, 1990:706–721.
3. **Sande MA, Johnson WD Jr, Hook EW, Kaye D.** Sustained bacteremia in patients with prosthetic cardiac valves. N Engl J Med 1972; **286:**1067–1070.
4. **Banerjee SN, Emori TG, Culver DH, et al.** Secular trends in nosocomial primary bloodstream infections in the United States. Am J Med 1991; **91(3B Suppl):**86S–89S.
5. **Cobb DK, High KP, Sawyer RG, et al.** A controlled trial of scheduled replacement of central venous and pulmonary artery catheters. N Engl J Med 1992; **327:**1062–1068.
6. **Maki DG, Cobb L, Garman JK, et al.** An attachable silver-impregnated cuff for prevention of infection with central venous catheters: a prospective randomized multicenter trial. Am J Med 1988; **85:**307–314.
7. **Yourassowsky E, Van Der Linden MP, Crokaert F.** Inoculum effect of growth-delay time of oxacillin-resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* exposed to cefamandole, cefazolin and cefuroxime. Antimicrob Agents Chemother 1990; **34:**505–509.
8. **Dismukes WE, Karchmer AW, Buckley MJ, Austen WG, Swartz MN.** Prosthetic valve endocarditis. Analysis of 38 cases. Circulation 1973; **158:**365–377.
9. **Sullam PM, Drake TA, Sande MA.** Pathogenesis of endocarditis. Am J Med 1985; **78(6B Suppl):**110–115.