

The use and effect of surgical therapy for prosthetic valve infective endocarditis: A propensity analysis of a multicenter, international cohort

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Background Although surgical intervention is often used in the treatment of prosthetic valve infective endocarditis (PVIE), an understanding of its effect on survival has been limited by the biases of observational studies and lack of controlled trials.

Methods The International Collaboration on Endocarditis Merged Database is a large, multicenter, international registry of patients with definite endocarditis by Duke criteria, including 367 patients with PVIE. Clinical, microbiologic, and echocardiographic variables were analyzed to determine those factors associated with the use of surgery for PVIE. Logistic regression analysis was performed to create a propensity model of predictors of surgery use. Patients who underwent surgery during initial hospitalization were matched by propensity score with patients treated with medical therapy alone. Logistic regression analysis was performed to determine variables independently associated with inhospital mortality in this matched subset.

Results Surgical therapy for PVIE was performed in 148 (42%) of 367 patients. Inhospital mortality was similar for patients treated with surgery compared with those treated with medical therapy alone (25.0% vs 23.4%, $P = .729$). Surgical therapy was independently associated with patient age, microorganism, intracardiac abscess, and congestive heart failure. After adjustment for these determinants, inhospital mortality was predicted by brain embolization (OR 11.12, 95% CI 4.16-29.73) and *Staphylococcus aureus* infection (OR 3.67, 95% CI 1.29-9.74), with a trend toward benefit for surgery (OR 0.56, 95% CI 0.23-1.36).

Conclusions Despite the frequent use of surgery for the treatment of PVIE, this condition continues to be associated with a high inhospital mortality rate in the contemporary era. After adjustment for factors related to surgical intervention, brain embolism and *S aureus* infection were independently associated with inhospital mortality and a trend toward a survival benefit of surgery was evident. (Am Heart J 2005;150:1086-91.)

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Guest editor of this manuscript is Lawrence H. Cohn, MD.

This study was supported in part by the following: American Heart Association GIA 0455802U (AW) and BGIA 0265405U (CHC); National Institutes of Health K23 AI-01647 (VGF) and K23 HL70861-01 (CHC); Tenet Healthcare Foundation (Santa Barbara, Calif) (EA); Red Española de Investigación en Patología Infecciosa (V-2003-REDC14A-O) (JMM); Fundación Privada Máximo Soriano Jiménez (Barcelona, Spain) (JMM); and Institut d'Investigacions Biomèdiques August Pii Sunyer (Barcelona, Spain) (JMM).

No authors have any conflict of interest to disclose regarding the work presented in this manuscript.

Submitted August 30, 2004; accepted January 18, 2005.

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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2005.01.023

Prosthetic valve infective endocarditis (PVIE) is a well-recognized complication of the >150 000 prosthetic heart valves implanted each year in the United States and Europe.^{1,2} The overall risk of PVIE is approximately 1% to 2% per patient-year.³⁻⁵ Treatment options for these patients include medical (predominantly antimicrobial) therapy alone or medical therapy in combination with prosthetic valve replacement. Despite advances in antimicrobial therapy and surgical techniques, the mortality rate of PVIE remains extremely high, with short-term mortality rates of 20% to 40%.⁶⁻¹⁰

The effect of surgical therapy on outcome of PVIE remains poorly understood. The most formal guidelines for the management of infective endocarditis, developed jointly by the American College of Cardiology and American Heart Association in 1998, recommend surgery for complications of infective endocarditis or for those patients in whom there is a low likelihood of cure with medical therapy alone.¹¹ However, the

management of PVIE is largely unaddressed in these guidelines. Recently, the effect of surgical therapy on outcome in *native* valve infective endocarditis has been evaluated; by creating propensity-matched groups of patients treated with surgical and/or medical therapy, surgical therapy was found to be significantly associated with a lower mortality (hazard ratio 0.40, 95% CI 0.18-0.91).¹² To date, no such evaluation of the treatment of PVIE has been performed.

The objective of this study was to evaluate the use and effect of surgery in a large, international multicenter database of patients with PVIE. Specifically, we sought to evaluate the predictors of cardiac surgery for PVIE and the effect of surgery on in-hospital mortality compared with medical therapy alone after adjustment for differences in these groups.

Methods

Study population

Approval of research protocols by local institutional review boards were obtained at applicable sites. The methods used to create the International Collaboration on Endocarditis Merged Database (ICE-MD) have been described previously.^{13,14} In brief, ICE investigators from 7 sites in 5 countries contributed prospectively collected data in an electronic format. The database from each center was provided to the coordinating center (Duke Clinical Research Institute) for characterization and merger. Key domains, containing core variables common to the individual databases, were determined. These domains included the following: patient demographics, preexisting conditions, focus of infection, previous endocarditis episodes, initial valve status, clinical course, echocardiographic data, microbiologic data, serologic data, complications, and outcome. Standard definitions for each core variable were developed and merger was accomplished using a hierarchical variable structure.¹³ For example, for cerebral embolic events, the most specific information provided by individual sites was used to code a dichotomous variable as present or absent. In addition, qualitative or descriptive data (eg, ischemic, hemorrhagic, or ischemic plus hemorrhagic) were retained as a subclassification under cerebral embolic event. In this way, the presence or absence of core variables was assessed and important qualitative data were also included in the merged database. Data from each site were then converted to the set of core variables. Once the variables from each individual database were converted, the individual databases were merged to form the ICE-MD.

For the purposes of this study, only patients with definite PVIE by Duke criteria^{15,16} were included in the analysis. Patients with PVIE and a recent history of intravenous drug use were excluded because of the possible treatment bias against repeat surgical intervention in this setting.

Definitions

Definite infective endocarditis was defined and confirmed using Duke criteria.^{15,16} Etiologic microorganism was defined as that microorganism grown from blood or tissue culture sources determined to be the causative agent for the PVIE

episode. Immune suppression was defined by the use of systemic corticosteroid therapy (≥ 10 mg/d of prednisone or equivalent for >30 days) or other immune suppressive therapy (eg, organ transplantation or cancer chemotherapy). Chronic intravascular catheters were defined as catheters designed to be left in place on a permanent or semipermanent basis (eg, Hickman or percutaneous dialysis catheters). Nosocomial, health care-associated (nosohusial), or community-acquired infective endocarditis was defined as described by Friedman et al.¹⁷ An abscess was defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance by echocardiography¹⁸ or the presence of pus by direct visualization at the time of surgery. The presence of congestive heart failure (CHF) was based on the presence of symptoms and signs and determined by clinicians at the individual sites. Systemic embolism included an embolus in any major arterial vessel, excluding the pulmonary artery. Brain embolism was defined as a cerebral infarction or hemorrhage attributed to cardioembolic source in PVIE. Early surgery and mortality were defined as cardiac surgery or mortality, respectively, during the initial hospitalization for PVIE.

Statistical analysis

Descriptive statistics for continuous variables were expressed in terms of medians and interquartile ranges. For each individual categorical variable the number of patients affected is reported in relation to the total sample size for that variable (%). Variables that were available for $<50\%$ of the total patient population because of differences in data collection between the sites were not included in the analysis. Wilcoxon rank-sum and χ^2 tests were used to evaluate group differences for continuous and categorical variables, respectively. A 2-sided P value of $<.05$ was established as the level of statistical significance for all tests.

To account for nonrandom treatment assignment, we adjusted for factors favoring selection of surgical treatment using propensity scores.¹⁹ Using multivariable logistic regression, a propensity score model was created to estimate the likelihood of surgical treatment. Variables included in the propensity models included the following: age, sex, year of diagnosis, site of enrollment, microbiologic causative organism, vegetation location, intracardiac abscess, CHF, systemic embolization, and cerebral embolization. Patients treated with cardiac surgery during hospitalization were then matched based on propensity score with patients treated with medical therapy only for PVIE. Patients were matched by propensity score to 5 digits; if a match was not available, attempts were made for a 4-, 3-, 2-, and 1-digit match. If this threshold was exceeded, the patient with PVIE who had surgery was excluded. Multivariable logistic regression analyses were performed (1) on this matched subset of patients with PVIE and (2) a subset of the overall cohort with a high propensity for surgery (the 2 quintiles with highest propensity scores) to determine predictors of in-hospital mortality in PVIE. All analyses were performed using SAS software (versions 6.12 and 8.2, SAS Institute, Cary, NC).

Results

Of 2212 patients in the merged database, definite PVIE was present in 355 (16.0%) patients without a history of

Table I. Characteristics of patients with PVIE

	Total (n = 355)	Surgery (n = 148)	No surgery (n = 207)	P
Age	66.5 (53-74)	62.0 (50-71)	70.0 (56-76)	<.001
Male sex	64.8 (230/355)	71.6 (106/148)	59.9 (124/207)	.023
Diabetes mellitus	14.1 (30/213)	7.8 (8/102)	19.8 (22/111)	.012
Chronic IV catheter	3.7 (7/189)	3.2 (3/93)	4.2 (4/96)	.732
Congenital heart disease	9.2 (24/260)	5.7 (7/123)	12.4 (17/137)	.062
History of cancer	6.6 (14/213)	6.9 (7/102)	6.3 (7/111)	.870
Dialysis dependent	1.4 (3/213)	1.0 (1/102)	1.8 (2/111)	.611
Other chronic disease	27.5 (52/189)	21.5 (20/93)	33.3 (32/96)	.069
Community acquisition	70.9 (151/213)	65.7 (67/102)	75.7 (84/111)	.109
Hospital referral	46.9 (100/213)	56.9 (58/102)	37.8 (42/111)	.005
Microbiology				
Viridans group streptococci	16.9 (60/355)	10.1 (15/148)	21.7 (45/207)	.040
<i>Staphylococcus aureus</i>	16.3 (58/355)	12.8 (19/148)	18.8 (39/207)	.132
Coagulase-negative staphylococci	15.2 (54/355)	25.0 (37/148)	8.2 (17/207)	<.001
Enterococci	12.1 (43/355)	9.5 (14/148)	14.0 (29/207)	.195
<i>S bovis</i>	6.8 (24/355)	2.0 (3/148)	10.1 (21/207)	.003
No growth	4.5 (16/355)	6.1 (9/148)	3.4 (7/207)	.227
Echocardiography				
Transsthoracic only	19.4 (69/355)	19.6 (29/148)	19.3 (40/207)	.949
Transesophageal only	27.0 (96/355)	29.1 (43/148)	25.6 (53/207)	.471
Both transsthoracic and transesophageal	42.8 (152/355)	43.9 (65/148)	42.0 (87/207)	.723

Table II. Complications and outcomes of patients with PVIE

	Total (n = 355)	Surgery (n = 148)	No surgery (n = 207)	P
CHF	38.6 (137/355)	53.4 (79/148)	28.0 (58/207)	<.001
Systemic embolization	27.3 (97/355)	25.0 (37/148)	29.0 (60/207)	.406
Brain embolization	18.9 (61/323)	19.4 (27/139)	18.5 (34/184)	.830
Intracardiac abscess	19.4 (69/355)	35.1 (52/148)	8.2 (17/207)	<.001
Inhospital death	24.1 (83/345)	25.0 (36/144)	23.4 (47/201)	.729

injection drug use. Among these 355 patients with PVIE, 148 (42%) patients underwent cardiac surgery at a median time of 12 days from hospital admission. Clinical characteristics of this cohort and subgroups based on use of surgery are shown in Table I.

Inhospital complications of PVIE are depicted in Table II. Prosthetic valve infective endocarditis was associated with complications in a significant percentage of patients, including clinical evidence of heart failure in 38.6%, systemic embolization in 27.3% (including brain embolization in 18.9% of the cohort), intracardiac abscess in 19.4%, and in-hospital mortality in 23.4%. Patients who received cardiac surgery were significantly more likely to have heart failure symptoms (28.0% vs 53.4%, respectively, $P < .001$) and intracardiac abscess (8.2% vs 35.1%, respectively, $P < .001$) compared with patients who did not undergo repeat surgery.

Using multivariable logistic regression, a propensity score model was created to determine the factors predictive of cardiac surgery for PVIE (Table III). In

addition to the presence of heart failure and intracardiac abscess, surgical treatment was independently associated with younger patient age, causative microbiologic organism (coagulase-negative *Staphylococcus* and *Staphylococcus aureus* infection), and year of diagnosis. The area under the receiver operating characteristic (ROC) curve for this propensity score model was 0.829.

Sixty-eight patients who underwent cardiac surgery for PVIE were individually matched by propensity score with 68 patients treated only with medical therapy during initial hospitalization. Among these 136 patients, in-hospital mortality occurred in 37 (27.2%) patients; 15 (22.1%) patients treated with surgery died in-hospital compared with 22 (32.4%) treated with medical therapy alone ($P = .178$). Multivariable logistic regression analysis demonstrated that only brain embolization and *S aureus* infection were independently associated with in-hospital mortality (Table IV). When surgical treatment was included in the model, there was a nonsignificant trend toward a survival benefit of surgery. In a separate

Table III. Propensity analysis of surgical treatment of PVIE

Variable	Wald χ^2	P
Intracardiac abscess	33.95	<.001
CHF	20.45	<.001
Age	18.06	<.001
Coagulase-negative staphylococci	7.88	.005
Year of diagnosis	6.14	.013
<i>S aureus</i> infection	3.92	.048
Mitral valve vegetation	3.06	.080

Area under ROC curve = 0.829.

multivariate analysis of 137 patients of the total cohort who had a high propensity score for surgery, similar results were found to be predictive of in-hospital death: *S aureus* infection (OR 4.28, 95% CI 1.23-14.91), brain embolization (OR 2.52, 95% CI 1.02-6.21), and surgical treatment (0.61, 95% CI 0.26-1.44).

Discussion

The present study, involving a large, multicenter, international cohort of patients with PVIE, offers important insights regarding the treatment and outcome of this condition. Despite contemporary diagnostic methods, including the Duke criteria^{16,20} and use of transesophageal echocardiography, and modern surgical techniques at experienced centers, the in-hospital mortality rate of PVIE remains high. In the current investigation, almost half of the patients with PVIE underwent cardiac surgery, predominantly those with complicated endocarditis (eg, presence of abscess, heart failure). Although the unadjusted in-hospital mortality rates were similar for patients receiving surgical therapy versus medical therapy alone, a trend toward a survival benefit for surgical intervention was evident after adjustment for the high-risk characteristics of these patients.

Surgical therapy as an adjunct to medical (antimicrobial) therapy has been described since these early studies of PVIE. In 1978, Karchmer et al proposed that surgical intervention for late PVIE should be considered for patients who had clinical features associated with a poor response to medical treatment, specifically those who had nonstreptococcal etiology, new regurgitant murmur, or significant heart failure.²¹ Numerous subsequent studies have described the outcome of PVIE for these therapeutic strategies (Table V). Whereas some studies have reported improved short- and long-term survival for patients treated with surgical reoperation,⁶ others have found similar, high rates of mortality for both treatment approaches.^{8-10,22,23} These conflicting results of the effect of surgical therapy may reflect publication bias (702 of 835 patients, or 84%, underwent surgery for PVIE in these studies) and the limitations of

Table IV. Logistic regression analysis of variables independently associated with in-hospital mortality in patients with PVIE and matched propensity for surgical treatment

Variable	OR	95% CI	P
<i>S aureus</i> infection	3.67	1.39-9.74	.009
Brain embolization	11.12	4.16-29.73	<.001
Surgery	0.56	0.23-1.36	.198

Area under ROC curve = 0.797.

these investigations. Most of these studies were small, retrospective, single-center cohort studies. The Duke criteria for infective endocarditis,^{15,16} a diagnostic classification for infective endocarditis that has improved sensitivity over earlier diagnostic criteria because of incorporating echocardiographic findings, were applied in only 2 of these studies.^{6,24} Along these lines, the potential relationship between echocardiographic findings and the use and outcome of surgical therapy for PVIE has not been thoroughly assessed. Finally, because of the observational design of these studies, differences in baseline characteristics may have influenced the outcome of these treatments, and adjustment for these differences was not performed in previous studies.

The use of propensity analysis in the present study provided a better understanding of the factors that favor cardiac surgery for PVIE. Most of the variables predictive of surgery in the model were characteristics associated with a higher mortality in infective endocarditis and were consistent with clinical experience and current guidelines for surgery in native valve endocarditis.¹¹ However, patients with *S aureus* infection were less likely to undergo repeat cardiac surgery, as only one third of these patients were treated with surgery. The reason for this finding is unclear but may be related to the severity of illness of these patients, the presence of complications (eg, stroke), or undetermined treatment bias.

This propensity model, which strongly predicted the use of surgery for PVIE, also offered a clearer perspective on its effect on outcome. In unadjusted bivariate analysis of the entire cohort, the in-hospital mortality rate was similar for patients treated with surgery versus medical therapy for PVIE. This finding suggests that surgical treatment of *complicated* PVIE reduces the in-hospital mortality rate to that of *uncomplicated* PVIE treated with medical therapy alone. Moreover, after adjustment for factors associated with the use of surgery, a trend toward a survival benefit of surgery was evident.

This difference illustrates the effect of treatment bias in an observational study. The lack of a statistically significant benefit of surgery after adjustment may be a reflection of the smaller sample size of the propensity-matched subset. In addition, longer term follow-up may be necessary to demonstrate a significant benefit. The

Table V. Recent studies of PVIE

First author	Year published	Total number of PVIE cases	Number treated with surgery	Number treated without surgery	Overall hospital mortality rate	Surgery hospital mortality rate	Medical hospital mortality rate
Present study	2004	355	148	207	0.24	0.25	0.23
Akokuwah ⁶	2003	66	38	28	0.33	0.24	0.44
Sasaki ²²	2001	30	30	0	0.13	0.13	NA
Grunenfelder ²³	2001	73	73	0	0.15	0.15	NA
Truninger ²⁴	1999	49	39	10	0.14	0.18	0
Edwards ⁷	1998	322	322	0	0.20	0.20	NA
Tornos ¹⁰	1997	59	17	42	0.25	0.29	0.24
Schulz ⁹	1996	24	14	10	0.20	0.21	0.17
Lytle ³⁰	1995	146	146	0	0.13	0.13	NA
Grover ⁸	1994	66	23	43	0.45	0.48	0.41

NA, not available because of lack of control group.

need for a longer-term end point is likely due to the early excess risk of surgery (perioperative mortality) compared with medical therapy and the possible increased delayed mortality in the medically treated patients. Indeed, the results of a study using similar propensity score methodology to evaluate surgery for complicated, *native valve* endocarditis found a survival benefit at 6 months.¹² Furthermore, in a recent single-center study, a survival benefit of surgery for PVIE was apparent only in long-term follow-up.⁶

The factors found to be predictive of inhospital mortality in PVIE—*S aureus* infection and brain embolization—were consistent findings in both a propensity-matched analysis and among patients with a high likelihood of cardiac surgery. These findings reiterate the prognostic importance of these characteristics, as demonstrated by our previous study including both native and prosthetic valve endocarditis.²⁵ *S aureus* was a predominant cause of endocarditis in this and other investigations.^{26,27} Prior studies have had differing results regarding the effect of surgery on outcome of *S aureus* PVIE. In a recent analysis of *S aureus* PVIE from the present merged database, early surgical treatment was found to offer a survival benefit largely in those patients with cardiac complications.²⁸ In contrast, an earlier, retrospective study reported a survival benefit of early surgery in *S aureus* PVIE regardless of the presence of cardiac complications.²⁹ These disparate conclusions were likely because of significant differences in study designs, populations, and particularly, timing of the survival end points (in-hospital vs 90 days, respectively).

Our study had several limitations. Because the International Collaboration on Endocarditis database was a merger of separate and distinct data sets, the collection of certain variables was incomplete. Characteristics such as the acute physiology of the patients, time from initial prosthetic valve implantation to PVIE diagnosis (ie, early

vs late PVIE), type of valve involved (bioprosthetic vs mechanical vs annuloplasty ring), echocardiographic determination of the presence of vegetation and perivalvular regurgitation, and timing of surgical intervention were not thoroughly collected by the multiple sites and therefore were not included in the analysis.

However, it is unlikely that these variables would have affected the analyses significantly, given the excellent predictive ability of both models. The year of diagnosis may have also confounded the survival analysis because advancements in diagnosis and treatment may have influenced outcome. However, adjustment for the year of diagnosis, which was associated with the use of surgical therapy, was performed in the propensity analysis. Although propensity analysis adjusts for treatment biases in an observational cohort, it does not completely avoid confounding, especially from factors not evaluated in the cohort. A randomized, controlled trial of surgical treatment of PVIE represents the ideal design to evaluate its effect on outcome, but significant ethical and logistical issues make such a trial improbable.

In conclusion, a high percentage of cases of PVIE are treated with cardiac surgery in the contemporary era. Patients treated with cardiac surgery for PVIE have clinical characteristics associated with a higher mortality in infective endocarditis and yet, have similar inhospital mortality rates as those treated with medical therapy alone. After adjustment for these treatment biases, a trend toward a survival benefit of surgical treatment is evident but longer term follow-up is needed.

References

- Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med* 1996;335:407-16.
- Ghosh P, Unger F. Cardiac surgery and catheter based coronary interventions in Europe 2002. *Cardiovascular Forum Online* 2004;0001-19.

3. Kloster FE. Complications of artificial heart valves. *JAMA* 1979;241:2201-3.
4. Blackstone EH, Kirklin JW. Death and other time-related events after valve replacement. *Circulation* 1985;72:753-67.
5. Vlessis AA, Khaki A, Grunkemeier GL, et al. Risk, diagnosis and management of prosthetic valve endocarditis: a review. *J Heart Valve Dis* 1997;6:443-65.
6. Akowuah EF, Davies W, Oliver S, et al. Prosthetic valve endocarditis: early and late outcome following medical or surgical treatment. *Heart* 2003;89:269-72.
7. Edwards MB, Ratnatunga CP, Dore CJ, et al. Thirty-day mortality and long-term survival following surgery for prosthetic endocarditis: a study from the UK heart valve registry. *Eur J Cardiothorac Surg* 1998;14:156-64.
8. Grover FL, Cohen DJ, Oprian C, et al. Determinants of the occurrence of and survival from prosthetic valve endocarditis. Experience of the Veterans Affairs Cooperative Study on Valvular Heart Disease. *J Thorac Cardiovasc Surg* 1994;108:207-14.
9. Schulz R, Werner GS, Fuchs JB, et al. Clinical outcome and echocardiographic findings of native and prosthetic valve endocarditis in the 1990's. *Eur Heart J* 1996;17:281-8.
10. Tornos P, Almirante B, Olona M, et al. Clinical outcome and long-term prognosis of late prosthetic valve endocarditis: a 20-year experience. *Clin Infect Dis* 1997;24:381-6.
11. Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;98:2936-48.
12. Vikram HR, Buenconsejo J, Hasbun R, et al. Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis. *JAMA* 2003;290:3207-14.
13. Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis. Early lessons from the International Collaboration on Endocarditis Investigation. *Infect Dis Clin North Am* 2002;16:255-72.
14. Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis. Lessons from the International Collaboration on Endocarditis. *Cardiol Clin* 2003;21:147-58.
15. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994;96:200-9.
16. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633-8.
17. Friedman N, Kaye K, Stout J, et al. Health care-associated blood stream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;137:791-7.
18. Mugge A, Daniel WG, Frank G, et al. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. *J Am Coll Cardiol* 1989;14:631-8.
19. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: Analytic strategies using propensity scores. *Ann Intern Med* 2002;137:693-5.
20. Durack DT. Evaluating and optimizing outcomes of surgery for endocarditis. *JAMA* 2003;290:3250-1.
21. Karchmer AW, Dismukes WE, Buckley MJ, et al. Late prosthetic valve endocarditis: clinical features influencing therapy. *Am J Med* 1978;64:199-206.
22. Sasaki Y, Isobe F, Kinugasa S, et al. Early and late outcomes after reoperation for prosthetic valve endocarditis. *Jpn J Thorac Cardiovasc Surg* 2001;49:224-9.
23. Grunenfelder J, Akins CW, Hilgenberg AD, et al. Long-term results and determinants of mortality after surgery for native and prosthetic valve endocarditis. *J Heart Valve Dis* 2001;10:694-702.
24. Truninger K, Attenhofer Jost CH, Seifert B, et al. Long term follow up of prosthetic valve endocarditis: what characteristics identify patients who were treated successfully with antibiotics alone? *Heart* 1999;82:714-20.
25. Chu VH, Cabell CH, Benjamin Jr DK, et al. Early predictors of in-hospital death in infective endocarditis. *Circulation* 2004;109:1745-9.
26. Cabell CH, Jollis JG, Peterson GE, et al. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med* 2002;162:90-4.
27. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA* 2002;288:75-81.
28. Chirouze C, Cabell CH, Fowler Jr VG, et al. Prognostic factors in 61 cases of *Staphylococcus aureus* prosthetic valve infective endocarditis from the International Collaboration on Endocarditis Merged Database. *Clin Infect Dis* 2004;38:1323-7.
29. John MD, Hibberd PL, Karchmer AW, et al. *Staphylococcus aureus* prosthetic valve endocarditis: optimal management and risk factors for death. *Clin Infect Dis* 1998;26:1302-9.
30. Lytle BW. Surgical treatment of prosthetic valve endocarditis. *Semin Thorac Cardiovasc Surg* 1995;7:13-9.

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