Surgical Therapy for *Staphylococcus aureus* Prosthetic Valve Endocarditis: Proceed With Caution (Caveat Emptor)

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(See the Major Article by Chirouze et al on pages 741–9.)

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Embraced by treatment guidelines from various organizations (eg, the American Heart Association, the European Society of Cardiology), the role of surgery in the treatment of left-sided infective endocarditis (IE) has been expanding in recent decades. The generally accepted indications for surgical intervention are based almost entirely on observational studies, and in some instances on expert opinion. Recent studies utilizing large datasets of patients with native valve IE have used sophisticated analytic techniques to assess the benefits of surgical treatment of IE. These studies adjust for treatment selection bias (propensity for surgery), prognostic variables, and comorbidities, as well as survival bias expressed as the time of surgery. At least 2 of these investigations have demonstrated survival benefits of early valve surgery (EVS) in terms of mortality in hospital and/or at 6 months after surgery [1, 2].

Prosthetic valve infective endocarditis (PVIE) represents a special management category, given its distinct pathogenesis and severe complications, especially in early PVIE (ie, within 12 months after valve implantation). Current guidelines [3, 4] and some studies advocate aggressive surgical intervention for patients with early PVIE, particularly when caused by *Staphylococcus* or complicated by severe heart failure (New York Heart Association [NYHA] class III–IV), valve dehiscence, or paravalvular abscess. At large tertiary hospitals with cardiac surgical programs, surgical intervention occurs in 42%–49% of patients with PVIE [5, 6]. This is not unexpected given the above-mentioned severe complications, which are unlikely to respond to antimicrobial therapy alone [5, 7]. Nevertheless, Lalani et al [7] were unable to demonstrate reduced in-hospital or 1-year mortality with valve replacement compared with medical therapy for PVIE. Using data collected prospectively between 1 January 2000 and 31 December 2006 by the multicenter International Collaborative on Endocarditis–Prospective Cohort Study (ICE-PCS), these investigators examined mortality rates among 1025 patients with definite PVIE, 490 (47.8%) of whom underwent surgery during their index hospitalization. After controlling for therapy selection bias using the inverse probability of treatment weighting, a propensity variable, in regression models, EVS was associated with lower mortality during hospitalization and at 1 year. However, when controlling for both treatment selection, as well as for survivor bias by including surgery as a time-dependent variable in a Cox proportional hazards model, the survival benefit of EVS was lost.

The issue of whether all patients with *Staphylococcus aureus* (SA) PVIE should undergo early prosthetic valve replacement, irrespective of the presence or absence of heart failure and/or intracardiac complications, remains controversial. For example, both John et al [8] and Attaran et al [9] concluded that SA PVIE was an indication for prompt valve surgery even in the absence of intracardiac complications. Habib et al [10] similarly identified SA PVIE as a marker for poor early and late outcomes, and strongly recommended EVS for such patients. In contrast, Sohail et al [11] recommended EVS for SA PVIE only in the presence of the above-mentioned hemodynamic or periannular complications.

In the current issue of *Clinical Infectious Diseases*, Chirouze and colleagues studied 168 well-characterized cases of
Duke criteria–definite SA PVIE from the ICE-PCS database; they explored the impact of valve replacement within 60 days after the index admission on all-cause mortality 1 year after hospital discharge. Patients with SA PVIE more frequently had healthcare-associated infection, stroke, and echocardiographic evidence of prosthesis dehiscence vs those with non-SV PVIE. Moreover, SA PVIE was associated with a higher 1-year mortality compared with patients with PVIE caused by other organisms (48.2% vs 32.9%; F = .003). Using a Cox model, these investigators assessed the impact of EVS for patients with SA PVIE on 1-year mortality. After adjusting for propensity factors, prognostic and comorbidity metrics (age, stroke, and NYHA class III–IV heart failure), and survivor bias (using valve surgery as a time-dependent variable), they were unable to demonstrate a benefit of EVS on in-hospital or 1-year mortality.

Where does this leave clinical “teams” caring for these complex patients with SA PVIE? The findings of Chirouze et al raise cautionary flags for the decision-making process. EVS is not of universal benefit for these patients, but rather must be carefully weighed and individualized. Clearly, SA PVIE patients can survive with medical therapy alone, as in the current study (41%), as well as in that of Sohail et al (52%) [1]. In this latter report, favorable outcome with medical therapy alone was highest among patients <50 years of age, with American Society of Anesthesiologist class III physical status, and no cardiac or central nervous system complications [11]. Having said that, many patients with SA PVIE will have clinical and echocardiographic evidence of heart failure and intracardiac complications unlikely to be curable with medical therapy alone. It seems intuitive that such patients will fare better with EVS than medical therapy alone. However, because this current investigation was an observational study dependent on review of the ICE-PCS database, and due to relatively limited study size, lack of information on cause(s) of death and indications for valve replacement, Chirouze et al were unable to identify a subpopulation where EVS increased survival in SA PVIE.

Although not conclusive, data from other studies may help identify biomarkers for a subpopulation of SA PVIE patients that would benefit from EVS. For example, John et al [8] found that mortality at 3 months after diagnosis was associated with intracardiac complications, and that valve replacement during antibiotic therapy was associated with significantly decreased mortality. Hill et al [12], studying 23 SA PVIE patients, reported survival with surgical therapy for 7 of 12 (58%) patients with classical indications for EVS (severe valve dysfunction with or without heart failure, abscess or paravalvar infection, failure of medical treatment after 7 days of appropriate antimicrobial therapy, or large vegetations with high risk for embolization). In contrast, all 6 patients with similar surgical indications, but in whom surgery was precluded because of operative risk, died. Furthermore, among those patients with all-cause PVIE who had more notable intracardiac complications and hemodynamic dysfunction, Lalani et al [7] found reduced in-hospital and 1-year mortality with surgical as opposed to only medical treatment Taken together, these studies suggest that a survival benefit may accrue from EVS in SA PVIE in those with major intracardiac complications or NYHA class III–IV heart failure.

Many questions remain in the management of SA PVIE. For example, is persistent staphylococcalemia alone or infection caused by methicillin-resistant strains an indication for EVS? Of particular controversy, should patients with SA PVIE and large vegetations (≥1 cm) alone undergo EVS? The recent study by Desch et al [13] would suggest that, at least in native valve IE, EVS in such patients is associated with excess all-cause mortality [3]. Even the well-chronicled recent randomized trial of EVS in IE by Kang et al [14] provided little insight into management of SA PVIE: (i) it was a small study of native valve IE only; (ii) patients were relatively young, without comorbidities and resultant low Euroscores; (iii) there was mitral valve dominance; (iv) it was “strepococcal-centric,” with few cases of SA IE; and (v) three-quarters of the patients in the “conventional” treatment group also underwent relatively early surgery during the index hospitalization, with nearly one-quarter undergoing valve surgery within the first week after admission.

In summary, Chirouze et al are to be congratulated for calling attention to the need for nuanced and individualized decision-making in selecting EVS vs medical therapy alone for SA PVIE. Their study further underscores the need for additional research (ideally, randomized interventional trials) to define optimal treatment of this challenging infection.

Notes

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