Surgical Timing in Infectious Endocarditis
Wrestling With the Unrandomized

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Endocarditis is a rare and highly variable disease, with a dramatic mortality that has not improved significantly despite progress in diagnosis and treatment. Strategies for prevention and management have generally been based on relatively small, usually single-center, experiences or, in the case of prophylaxis guidelines, been extrapolated from animal models of disease. Randomized controlled studies are unavailable and seem unlikely to inform our practices any time soon. How can we hope to make better therapeutic choices and improve outcomes in their absence?

Article see p 1005

The International Collaboration on Endocarditis—Prospective Cohort Study registry is an international collaborative effort among 61 centers in 28 countries that has compiled data from 2760 patients with definite infective endocarditis diagnosed according to the modified Duke criteria. Observational data from these patients creates the opportunity to examine some of the critical questions in endocarditis management, including the question whether surgical intervention during the acute hospitalized phase of endocarditis will improve survival. Lalani and colleagues address this topic in this issue of Circulation.

Surgical timing is one of the hardest clinical issues in treating patients with endocarditis. The traditional indications for surgery include heart failure, paravalvular extension of infection, and recurrent embolization. These have been based on observational studies and have generally been borne out by patient outcomes. As anyone who cares for these patients well understands, however, the decision to commit to a surgical procedure that might possibly be avoided is quite difficult for the patient, the surgeon, and the referring physician. An understanding of the degree of probable benefit of surgery would be extremely useful, if the benefit could be assessed in a way that was highly tailored to the individual patient’s circumstances. Because patients with endocarditis span such a wide range of comorbidities, complications, and manifestations, generalization from a disparate population is unsatisfying.

To address this question, the International Collaboration on Endocarditis investigators first limited the scope of their population by excluding users of illicit intravenous drugs and patients with infections of nonnative valves, including heart rhythm devices. The excluded individuals represented 44% of their patient set, so it must be recognized that their subsequent findings will not inform choices in a large proportion of the patients whom a practitioner may treat. They did not separate right-sided from left-sided valvular infections, although in practice isolated right-sided heart endocarditis is less often an indication for surgery. This is reflected in the low percentage (6.1%) of patients with tricuspid valve vegetation among their study participants who underwent early surgery. Excluding those patients might have further tightened the clinical match to patients outside of the study for the purposes of decision making.

Given the absence of randomization in observational datasets, underlying differences in the treatment groups are a major barrier to drawing valid causal inferences from treatment effects. Such treatment biases, or “confounding by indication,” may be addressed by the use of propensity-score matching, a well-established statistical technique that seeks to balance the probability of treatment assignment as determined by confounding factors. This approach may simulate the conditions of randomized treatment assignment, assuming that each and every important confounding factor is known and measured. Naturally, this assumption is fragile, and causal inference may still be limited by “hidden biases” from unknown or unmeasured confounders.

The authors contend that a strength of their study, and an explanation for why their conclusions differ from those of prior studies, is that they specifically address these hidden biases. They accomplish this with an instrumental variable technique that attempts to identify upstream predictor variables that could alter the outcome of interest only through the treatment effect in question. Instrumental variables are notoriously hard to find, however, and the inclusion of poorly selected instruments may exacerbate, rather than eliminate, hidden bias.

The authors developed a combined instrument using a spectrum of candidate variables. However, the robustness of some of these predictors as instrumental variables is doubtful. For example, whereas the site-specific rate of early surgery might be expected to affect outcome through the actual performance of surgery, it may also be a marker for other factors that could affect outcome, such as clinical volume, physician’s experience, or quality of facilities. The instrumentality of preoperative transesophageal echocardiography,
which the authors also included in their combined instrument, is even less obvious.

The authors performed extensive subgroup analysis demonstrating that clinical details such as paravalvular complication, systemic embolization, stroke, *Staphylococcus aureus* infection, or higher scores of propensity for surgery (quintiles 4 and 5) identified patients likely to benefit from early surgery. Surprisingly, neither valve perforation nor congestive heart failure predicted a survival benefit of early surgery. This goes against prior assumptions and experiences, and it bears additional consideration.

An unfortunate and acknowledged limitation in the extensive International Collaboration on Endocarditis database is the lack of stratification of the severity of heart failure or its response to treatment. Clinically, it is often the case that patients who present with mild heart failure caused by mitral or aortic insufficiency respond promptly to medical therapy, including diuresis and afterload reduction. Are these patients comparable, from the perspective of a need for surgery, to patients who present in more severe failure, who are not readily responsive to medical therapy, or both? Does underlying cardiovascular disease play a role, and should we expect that patients with preexisting impairment in ventricular function will have a more complicated and recalcitrant course? These questions, unfortunately, cannot be addressed with the data available in this registry, although it is one of the most important clinical considerations in the decision relative to early surgical treatment.

Similarly, it is interesting that valvular perforation, which is presumably a permanent and potentially progressive mechanical disruption, did not predict a survival benefit from early surgery. One of the important differences of the study by Lalani et al from prior reports is that the Lalani et al limited their investigation to mortality during the initial hospitalization. Extending the outcome horizon to include the first 6 months after infection or longer, as some studies have done, might provide an interesting perspective on this issue. It has been suggested that the majority of patients with valvular infections that are successfully treated medically will eventually require valve replacement because of the valvular damage sustained. Avoiding early surgery, therefore, does not spare many patients from the risks of morbidity and mortality of eventual valve replacement.

The institutional experience with early surgery for endocarditis is an important issue that can influence the application of these findings in the broader context. The contributing International Collaboration on Endocarditis centers have demonstrated interest and experience with this disease, which certainly extends to both medical and surgical providers. Their level of experience and skill may not be available in all settings. These data, which underscore the importance of having an early surgical option for a subset of endocarditis patients, may serve to bolster early interactions with the surgical team.

Armed with these new insights into the predictors of benefit from early surgery, how will our decision making shift? Whereas absolute risk reduction is a gold standard for the expression of public health impact of treatment choices, the “number needed to treat” that it provides becomes difficult to interpret when the treatment is something as dramatic as surgery, with its attendant risk and lifelong consequences. Among patients with endocarditis who will adequately match the inclusion criteria for this study (far less than half, in our urban hospital experience), a subset will present with the clinical determinants of paravalvular extension of infection, systemic or central nervous system embolization, or *S aureus* infection. For these patients, we may be able to more clearly present the benefits of an early surgical approach to patient and surgeon alike. The conclusion by Lalani et al on heart failure has less impact; these results are unlikely to diminish the clinical impetus to move quickly to surgery in patients with significant or recalcitrant heart failure.

Despite the known risks of infective endocarditis, our success in improving outcomes has faltered for lack of evidence base and tools for decision making for the individual patient. It is encouraging that in this field, seemingly confined for the foreseeable future to observational data, refined statistical methods such as those presented by Lalani and colleagues can provide evidence that we’re willing to take to the mat.

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**References**


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