Editorial Commentary

Infective endocarditis and outcomes of valve surgery: the bug, the valve, the host and the unknown

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Infective endocarditis (IE) is becoming growing national epidemic in the US (1). The etiology of this substantial increase in IE prevalence is multifactorial, but is likely due to the increasing number of intravenous drug users, patients with prosthetic valves and/or implantable devices, immune-compromised patients, and patients with chronic indwelling catheters (2). Although antibiotic therapy has been a cornerstone in the treatment of IE, timely valve surgery remains a key life-saving intervention in many patients. Indeed, recent years have witnessed not only a significant increase in the number of valve operations for IE, but also an increasing trends towards valve repair *vs.* replacement and early *vs.* late surgery (3). Given the upward temporal trends in the incidence of IE, and in IE-related valve surgery, identifying predictors of mortality after surgery is essential to achieve optimal patient selection and operative outcomes. Prior risk prediction schemes (mainly the STS PROM score) have evolved into very comprehensive tools that incorporate a large number of patient- and hospital-characteristics. However, the causative pathogen has not been included in risk prediction models, despite historical data suggesting worse outcomes with fungal *vs.* bacterial, and with *Staphylococcus vs.* non-*staphylococcus* endocarditis (2,4,5).

In a recent issue of *The Annals of Thoracic Surgery*, Williams *et al.* sought to assess the impact of the causative pathogen on the short-term outcomes of valve surgery in patients with IE. The authors utilized a large North American clinical database (STS—Society for Thoracic Surgeons) that included ~23,000 patients who underwent valve surgery for IE between 2011 and 2016. Right-sided valves were infected in 7%, and prosthetic valves were involved in 17% of patients. Patients with left-sided IE were older, had more comorbidities, and more cardiogenic shock on presentation than those with right-sided IE. In patients with left-sided IE, the most common pathogens were *Streptococcus* (32%), *Staphylococcus* (26%), and *Enterococcus* (11%). On the other hand, *Staphylococcus* was far the dominant pathogen in right-sided lesions (65%), followed by *Streptococcus* (10%). A fungus was identified only in 1%, and in 6% of patients with left-sided *vs.* right-sided IE, respectively. The main finding of the study is that the microbiology of IE strongly impacts the morbidity and mortality of surgery for left-sided IE, but has a minimal impact on the outcomes of surgery for right-sided IE. As expected, compared with streptococcal infections, fungal infections, Staphylococcal, and Culture-negative infections were associated with 290%, 41%, and 35% increase in operative mortality following surgery for left-sided IE. On the contrary, no statistically significant differences were observed in the operative mortality of valve surgery for right-sided IE according to the infective agent. The authors also documented worse outcomes after valve surgery for left-sided IE, and for prosthetic *vs.* native valve IE.

The study offers a glimpse into real-world data on an increasingly relevant topic using a very large dataset. How do these data compare to what we already know from prior studies and what are their practical implications?

Using a large contemporary dataset, the STS adult cardiac surgery database Williams *et al.* have shed light on the impact of "the bug" and mortality. The observation though not novel confirms the association of microbial virulence with mortality. Traditional risk scores like the STS and EuroSCORE are developed for cardiac surgeries overall and have been shown to have suboptimal prognostic ability (6). The cohort of native valve endocarditis (NVE) can be associated with unique complications like abscess formation, acute valve dysfunction and associated conditions like embolic events, stroke, septicemia and septic shock that impact outcomes. Endocarditis specific scores have been developed to better prognosticate surgical outcomes.

The authors mention STS-IE score with regards to a risk score to predict operative mortality (7). However, multiple risk scores have been developed to better predict the early and late outcomes in these patients, although not frequently used in clinical context. The Costa score (8) and De Feo-Cotrufo score (9) are some of the other dedicated risk models for the IE cohort that do not include microbial organism in the risk model. Limited validation was performed of these risk models in 2 studies with varying results with regards to discriminative power (10,11). The IE specific scoring systems PALSUSE, and 2 other scoring systems have a weighting for microbial organism with *S. aureus* associated with worse mortality (5,12,13). The risk scores have also been shown to predict in-hospital mortality even in patients treated without surgery (14,15). Databases like the STS provide a unique opportunity to not only develop risk models but also validate them in a large dataset. The current study adds to the evidence with regards to the virulent nature of both *S. aureus* and fungal infections and underscores the need for risk scores to take into account the type of involved pathogen in assessing surgical risk.

The last decade has seen the rise of *S. aureus* as a leading pathogen for native valve IE not only in the US but also in countries like Brazil and France (2,4,8,16,17). The increased incidence of *S. aureus* endocarditis is secondary to hemodialysis related access, cardiac implantable devices and intravenous drug abuse. ACC/AHA guidelines on management of IE recommend surgical management in patients with virulent organism like *S. aureus* or fungal etiology as medical therapy alone may not eradicate the infection (18). The current study showed Streptococcal endocarditis to be the most common organism in patients undergoing surgery for IE during the study period 2011–2016 in the US. What could be the potential explanation with Streptococcal endocarditis being the leading pathogen in the surgical cohort? The likely explanation for the predominance of Streptococcal etiology is that *S. aureus* endocarditis is less likely to be treated surgically (19). Some of the reasons cited for non-surgical management were poor prognosis, hemodynamic instability, death before surgery, stroke. Staphylococcal endocarditis is associated with a higher operative risk and is also an independent predictor of mortality in addition to fungal endocarditis (13,19). Despite evidence with regards to early surgery in patients with left sided IE, studies have shown that nearly a quarter of those patients with surgical indications do not undergo surgery (19).

Studies have shown lower incidence of right sided IE compared to left sided IE. Several physiologic aspects are unique to the valves on the right side of the heart that have been proposed as causal for this finding. The right sided valves reside in a low-pressure pulmonic circuit whereas left sided valves residing in a high-pressure circuit are subject to turbulence and more prone to endothelial damage. Also, oxygen saturation is lower in the right sided chambers and the higher oxygen saturation in the left sided chambers is more supportive of growth aerobic organisms (20). Isolated right sided IE is also increasing in incidence due to indwelling catheters, cardiac devices and intravenous drug abuse with *S. aureus* being the leading pathogen. The optimal management of isolated right sided endocarditis is unknown as guidelines focus on left sided endocarditis. Despite the significantly lower numbers of patients with isolated right sided IE compared to those with left sided IE a type 1 error is less likely with regards to the non-significant impact of virulence on mortality. Small retrospective studies so far have reported lower mortality in isolated right sided IE compared to combined right and left sided IE (21). It is also known that right sided IE with *S. aureus* is not a risk factor mortality (21). Severe tricuspid valve (TV) regurgitation and large vegetations with septic embolic burden that could cause downstream septic process in the lungs are indications for which surgery is commonly performed. With regards to surgical strategy, TV repair if feasible is recommended over TV replacement as there is a mortality benefit to TV replacement (22). Early surgery may be able to salvage the valve with repair alone compared to late surgery where the valve may not be amenable to repair. Overall the results of the current study support prevailing knowledge with regards to better outcomes of isolated right sided endocarditis compared to left sided or mixed IE with the largest surgical patient population studied to date.

Prosthetic valve endocarditis (PVE)

PVE is a challenging entity with high mortality rate. There is a clinical equipoise with regards to surgical management over medical therapy alone in patients with PVE. Early valve replacement has not shown to be definitively associated with lower mortality compared to medical therapy (23). Observational data points to roughly 50% undergoing early surgery (23).

The outcomes for PVE can be variable with data largely from retrospective and single center studies. Studies to date have shown either no difference in outcome or multi-fold increase in mortality with PVE compared to NVE (24-27). The factors affecting retrospective studies like bias, site experience and lack of adjustment for confounding factors decrease the generalizability of such results. Williams *et al.* confirm the higher mortality with surgery for PVE compared to native valve IE. However, the reasons for increased mortality in this important subgroup of PVE alone needs further study. *S. aureus* is the leading cause of PVE but data with regards to association with mortality in this patient population is circumspect at best (28,29). Certain characteristics of PVE are associated with worse prognosis like persistent bacteremia, heart failure, intracardiac abscess and stroke (30). The prevalence of these complications in the PVE cohort, the pathogen distribution in the PVE cohort would have been helpful in confirming the reasons behind this observation.

The current study is the largest with regards to the association of the "bug" with mortality and also with regards to the surgical outcomes of PVE. There exists an unmet need with regards to the risk stratification and optimal treatment strategy in patients with IE, both in NVE and PVE cohorts. The study does suggest association of microbial virulence with outcomes and is supportive of inclusion of this factor in risk stratification. Given the substantial rise in the incidence of IE across the world, optimizing the physician tool kit to facilitate decision making at bed side with risk scores is direly needed. There are still unanswered questions like the optimal timing of surgery in left sided PVE and factors contributing to increased mortality with PVE. Analysis of big data like the authors have used may expedite our learning of IE and impact surgical outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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