

## Letter to the Editor: Timing of Surgery for Fungal Infective Endocarditis

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Dear Editor,

Fungal endocarditis rarely occurs and is difficult to treat. Taguchi et al described that a 55-year-old man, who developed severe mitral regurgitation with persistent fungal infective endocarditis (IE) 8 months after coronary artery bypass grafting, was cured with mitral valve replacement via the anterolateral right thoracotomy without cross-clamping method [Taguchi 2016].

We have some comments regarding this case report. Early diagnosis and early treatment is quite difficult for fungal IE. Although fungal endocarditis rarely occurs, it has a high morbidity and mortality rate [Richardson 1978]. Antifungal therapy is often insufficient in patients who develop fungal IE, and surgical treatment is not advisable due to its difficulty and high mortality [Babayigit 2015]. Before the antibiotic era, IE was fatal. During the penicillin era in the 1940s, the number of deaths was reduced, but the mortality rate did not decrease substantially. At the end of the 1960s, early valvular surgery became an answer to the most serious cases, especially heart failure (HF) [Wallace 2014]. Mortality has been affected by modifications in therapeutic management. However, the effect of surgery has not been confirmed by large-scale randomized trials for ethical reasons and due to selection biases and survival biases. The optimal timing of surgery is still unclear. The 2015 European Society of Cardiology (ESC) guidelines and the 2015 American Heart Association/American College of Cardiology (AHA/ACC) guidelines have different recommendations on the timing of surgery. The 2015 ESC guideline divided the timing of surgery into 3 categories: emergent, urgent, and elective. Emergent surgery is defined as an operation within 24 hours, urgent surgery is performed within few days, and elective surgery is performed within 1-2 weeks of antibiotic treatment [2015 ESC Guidelines]. The 2015 AHA/ACC guideline defines early surgery as surgery during initial hospitalization and before the completion of a full course of antibiotics [Baddour 2015]; because of that, most of the previous observational studies defined early surgery as surgery that was performed during the initial hospitalization for IE. There was no consensus about the definition of early surgery due to a lack of evidence. Over decades, expert panels have made recommendations based on observational trials, and despite the availability of new studies, the indications did not change over time [Habib 2009]. The indications of early surgery in IE can be classified into 3 scenarios: heart failure, uncontrolled

infection, and prevention of embolism. However, the details are not the same. The data supporting early surgery mostly comes from observational studies and randomized trials, which are scarce due to ethical concerns [Kang 2012]. Numerous studies have attempted to identify the predicting factors of early and late mortality, but there is great heterogeneity in the patient characteristics and study method. Liang et al. reported that early surgery was associated with lower in-hospital and long-term mortality compared with non-early surgical treatment for IE, especially in native valve endocarditis [Liang 2015]. However, the optimal timing of surgery remains unclear. Additional larger prospective clinical trials will be required to clarify the optimal timing for surgical intervention and determine its efficacy in prosthetic valve endocarditis (PVE).

Heart failure is the most frequent complication of IE and is the strongest indication for surgery. Studies from the 1970s and 1980s demonstrated a reduction in mortality after surgery from 56-86% to 11-35% [Richardson 1978]. The International Collaboration of Endocarditis Prospective Cohort Study reported an in-hospital mortality of 21% in patients with IE and HF who were treated with surgery compared with 45% mortality in the medical therapy group [Murdock 2009]. Surgery must be performed emergently irrespective of the infection status in cases of refractory pulmonary edema and cardiogenic shock that persists despite medical therapy [Habib 2007]. Patients with mild congestive heart failure at the beginning may progress insidiously despite antibiotic therapy. Delayed surgery is associated with a dramatic increase in mortality because of progressive cardiac decompensation [Middlemost 1991]. Therefore, the AHA guidelines recommended that the timing should be decided by the Heart Valve Team. If severe valve regurgitation is well tolerated (NYHA I-II) and there are no other indications for surgery, medical therapy and careful echocardiographic monitoring are recommended. Elective surgery should be considered after the IE is resolved.

Uncontrolled infection is the second most common indication for surgery in IE. Surgery indications include persistent infection, locally uncontrolled infection, and microorganism(s) with a low likelihood of being controlled by antibiotics. Persistent infection is defined as fever and positive blood culture that persists for 7-10 days after an appropriate antibiotic therapy has been administered and extracardiac abscess was excluded. A recent study demonstrated that persistent blood culture 48-72 hours after appropriate antibiotic therapy is an independent risk factor for hospital mortality [Lopez 2013]. Locally uncontrolled infection includes aortic abscess, fistula, and heart block. The weakest portion of the heart is near the membranous septum and the atrioventricular node, which explains why abscesses occur in this location

Received January 28, 2017; revised form August 16, 2017; accepted August 17, 2017

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and why heart block is a frequent sequela [Arnett 1976]. The sensitivity of transthoracic echocardiogram (TTE) for detecting perivalvular abscess is low (18-63%) in prospective and retrospective studies, whereas transesophageal echocardiography (TEE) has 76-100% sensitivity, 95% specificity, 87% positive predictive values, and 89% negative predictive values [Rohmann 2007; Leung 1994]. The AHA guidelines recommended that TEE should be repeated at intervals of 2, 4, and 8 weeks after the completion of antibiotic therapy. Both guidelines recommended surgery in fungal, multiresistant organism (e.g., methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus) and non-HACEK GNB (including *Hemophilus* species as well as *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* species) IE. The ESC guidelines recommended that PVE caused by *S. aureus* should be considered an urgent surgical indication even without complications [Attaran 2012]. We also want to emphasize that fungal IE should be considered an urgent surgical indication even without complications. Additionally, we want to mention that iatrogenic infectious disorders after coronary artery bypass graft might occur later and could be lethal. It is recommended to use a method that accommodates the available resources and data needs when post-discharge surveillance is used to detect surgical site infection (SSI) following coronary artery bypass grafting.

The Guideline for Prevention of Surgical Wound Infections was published in 1982 [Simmons 1982]. Then, the guideline adopted the term “surgical site infection” to describe both the incisional (from skin to deep soft tissues) and organ/space infections in 1991 [Mangram 1999]. The update represented a consensus of the Centers for Disease Control and Prevention (CDC) and its new advisory committee on infection control in 2015 [U.S. Centers for Disease Control and Prevention 2015]. The dependence solely on inpatient case-finding will result in an underestimation of SSI rates for coronary artery bypass grafting [Emori 1998]; hence, it was recommended to use a method that accommodates the available resources and data needs when post-discharge surveillance is used to detect SSI following coronary artery bypass grafting (category II) [Mangram 1999]. Although the duration (eight months) after coronary artery bypass grafting is longer than the definition for healthcare-associated infection, we still want to mention that iatrogenic infectious disorders after coronary artery bypass grafting are an infrequent entity but might occur late and could be lethal.

In conclusion, fungal IE has a high morbidity and mortality rate, although fungal IE rarely occurs. Antifungal therapy is often insufficient in cases that develop fungal IE, and surgical treatment is not preferred due to its difficulty and high mortality. We want to emphasize that fungal IE should be considered an urgent surgical indication even without complications.

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