Optimal Timing of Surgery for Patients with Active Infective Endocarditis

Takeshi Kitai, MD, PhD[a,*], Akiko Masumoto, MD[a], Taiji Okada, MD, PhD[a], Tadaaki Koyama, MD, PhD[b], Yutaka Furukawa, MD, PhD[a]

KEYWORDS

• Infective endocarditis • Surgery • Complication • Stroke

KEY POINTS

- As delays in diagnosis and initiation of therapy could lead to worse outcomes in patients with infective endocarditis (IE), identification of indication for surgical intervention and its optimal timing are crucial.
- Indications for surgery are based on cardiac and extracardiac complications.
- One of the most common clinical dilemmas regarding surgical intervention for IE is optimal timing of surgery for patients with concomitant neurologic complications such as stroke, intracranial hemorrhage, and mycotic aneurysm.
- Once IE is diagnosed or even suspected, 4 sets of examinations, including transthoracic echocardiography, transesophageal echocardiography, contrast-enhanced computed tomography, and cerebral MRI should be performed to comprehensively assess the necessity of further management, including surgery.

INTRODUCTION

Infective endocarditis (IE) is a rare but serious condition with a dismal prognosis. The incidence of IE has increased over the past few decades to 3 to 10 cases per 100,000 people annually.[1–4] The highest incidence is observed among persons aged 70 to 80 years, with a twofold to threefold higher male predominance. It should be noted that almost half of IE cases occur in individuals without a diagnosed structural disease of the heart.[1] Despite improvements in diagnostic modalities and therapeutic methods, including antibiotic therapy and surgical techniques, IE still poses a clinical challenge to both diagnosis and management and leads to a high mortality rate. The in-hospital mortality rate was reported to be 18% to 25%, with the 1-year mortality rate reaching up to 40%.[5–14] A recent study indicated that the mortality rate for IE was 2.4 per 100,000 people in the United States.[15]

The keys to improving outcomes include an early diagnosis of definite IE, a prompt identification of high-risk patients who have intracardiac and extracardiac complications, and appropriate management, including surgery for high-risk patients. Delays in diagnosis and initiation of therapy lead to complications and worse clinical outcomes.[16] The main complications of IE are embolic events and subsequent bleeding, persistent bacteremia, and heart failure mainly

Funding: None.
Conflicts of interest: None.
[a] Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-minamimachi, Chuo-ku, Kobe 6500047, Japan; [b] Department of Cardiovascular Surgery, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-minamimachi, Chuo-ku, Kobe 6500047, Japan
* Corresponding author.
E-mail address: t-kitai@kcho.jp

Cardiol Clin 39 (2021) 197–209
https://doi.org/10.1016/j.ccl.2021.01.002
0733-8651/21/© 2021 Elsevier Inc. All rights reserved.

because of valvular regurgitation. Historically, there have been controversies surrounding the optimal indication and timing for surgery, especially for patients presenting with neurologic complications.

This article reviews the necessary workup for patients with suspected IE and proposes a state-of-art patient flow chart to guide subsequent clinical management, focusing on surgical indications (Fig. 1). When indications for surgery arise after evaluation proposed by the algorithm *and* the patients present with concomitant neurologic complications, an additional evaluation process is necessary before arrangements for surgery are made (Fig. 2).

INITIAL ASSESSMENT AND DIAGNOSIS OF INFECTIVE ENDOCARDITIS

IE develops from underlying valvular or nonvalvular cardiac structural abnormalities and results in blood flow turbulence and disruption of the endocardial endothelium. Subsequently, platelet aggregation and fibrin disposition are induced to the damaged endothelium, causing lesions defined as nonbacterial thrombotic endocarditis, which serve as a foundation for adhesion by circulating bacteria or fungi in the bloodstream.[17–19] The lesions predominantly involve the valves, but also can involve the mural endocardium.[20,21] Besides the infection damaging the valve, there is also a risk of embolization and stroke.

Diagnosis of IE is difficult and is often delayed until serious infection or complications are evident.[22–24] The modified Duke criteria are the most commonly used and validated criteria for IE diagnosis and classification.[25] However, considering the vast heterogeneity of clinical presentations of IE, the modified Duke criteria should be used in combination with circumspect clinical judgment. Two major components of the Duke

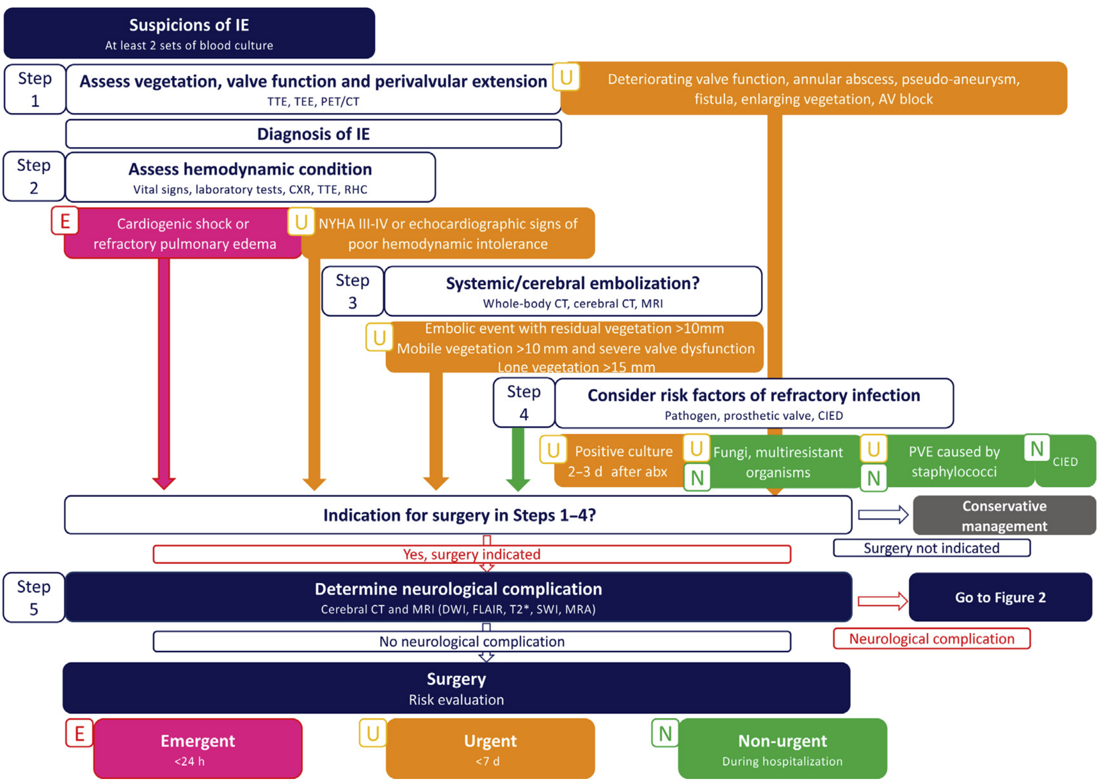

Fig. 1. State-of-the-art patient algorithm for evaluation of suspected IE. After the initial assessment of vegetation, valve function, and perivalvular extension in step 1, the evaluations in steps 2 to 4 are conducted to seek indications for surgery. Special consideration should be given to PVE and cardiac device infection (CDI). When indications for surgery arise after evaluations in steps 1 to 4, and the patient presents with concomitant neurologic complications, the evaluations in step 5 are added (see Fig. 2) before surgery. Before surgery, surgical risk should be considered and weighed against the benefits of avoiding further complications with early surgery. Abx, antibiotics; AV block, atrioventricular block; CIED, cardiac implantable electronic device; CXR, chest radiograph; DWI, diffusion-weighted imaging; E, emergent surgery within 24 hours; FLAIR, fluid-attenuated inversion recovery; Lac, lactate; N, nonurgent surgery or elective surgery during hospitalization; RHC, right heart catheterization; sBP, systolic blood pressure; SWI, susceptibility-weighted imaging; U, urgent surgery within 7 days.

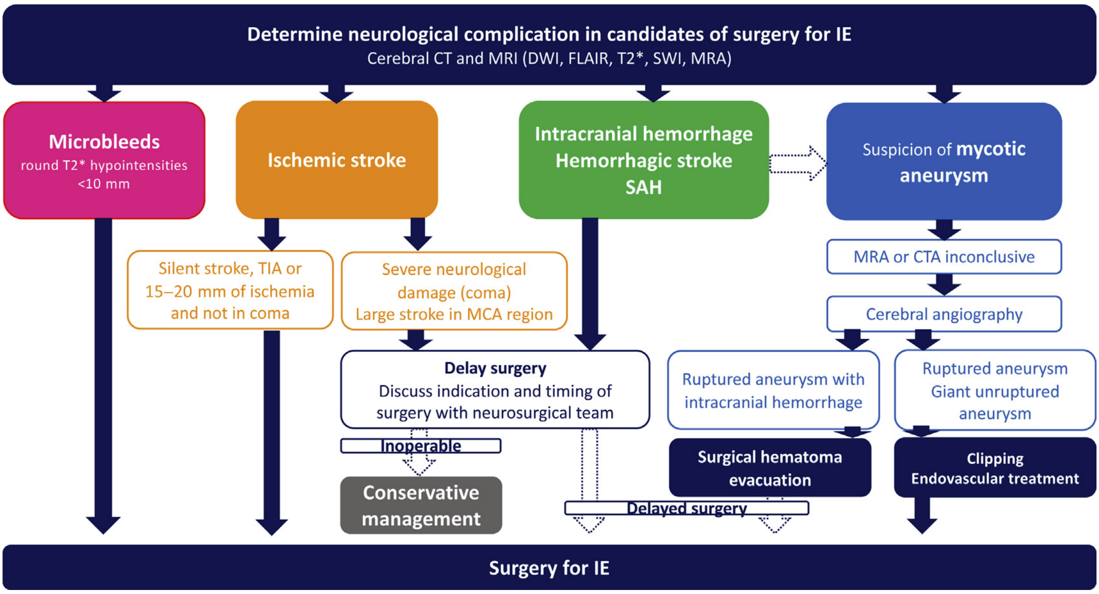

Fig. 2. Indications for surgery in patients with neurologic complications. When indications for surgery arise *and* concomitant neurologic complications are detected on cerebral CT and/or cerebral MRI, each neurologic complication should be evaluated and managed to determine if cardiac surgery is feasible. DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MCA, middle cerebral artery; SAH, subarachnoid hemorrhage; SWI, susceptibility-weighted imaging; TIA, transient ischemic attack.

criteria include the results from blood culture and echocardiography.

Positive Blood Culture and Culture-Negative Endocarditis

In addition to the diagnostic purposes, results from blood culture are also crucial for determining appropriate antibiotic therapy, which is the mainstay in the management of IE. Antibiotic therapy should be initiated promptly and targeted to the organism isolated from the blood cultures with a prolonged duration regardless of the timing of surgery. Although *Streptococcus viridans* was the most commonly identified pathogen in the 1960s, the epidemiologic profile of IE has changed recently, with *Staphylococcus aureus* being the predominant causative organism.[20] Causative organisms are associated with the development of both intracardiac and extracardiac complications. *S aureus* is reported to be associated with more frequent stroke, systemic emboli, and persistent bacteremia.[26] A recent study using propensity-matched analysis including more than 700 patients with *S aureus* left-sided native valve endocarditis (NVE) showed that intracardiac abscess and left ventricular ejection fraction less than 40% were independent predictors of in-hospital mortality, whereas intracardiac abscess and valve perforation were independent predictors of 1-year mortality.[27] Moreover, the characteristics of the patients have also evolved, with a trend toward increased age, more frequent presence of prosthetic valve endocarditis (PVE), and higher frequency of cardiac implantable electric device (CIED) infection, which result in the increasing severity of the patient's condition. Accordingly, antibiotic therapy alone is sometimes insufficient for these high-risk patients, and the number of surgeries performed for IE has been increasing.[28]

Although the diagnosis of IE is contingent on positive blood cultures, 5% to 10% of infections are found to be culture negative. This condition, known as culture-negative endocarditis, is very challenging in terms of the selection of antibiotic therapy. Fastidious bacterial organisms, including fungi or nonbacterial pathogens, can cause culture-negative endocarditis; however, most cases of culture-negative endocarditis in clinical practice are often caused by prior administration of antibiotics before blood culture collection. The condition of negative or unknown causative organisms can influence the indication of surgery. Withdrawal of antibiotics and repeated blood cultures until an organism is isolated might be a consideration to improve diagnosis.

Role of a Complete Echocardiographic Evaluation

Another important component of the modified Duke criteria is the echocardiographic evaluation.

Echocardiography is an important tool for the diagnosis of IE, and is recommended as an initial and essential imaging modality in all patients with suspected IE. Transthoracic echocardiography (TTE), which is often the initial study, should be used to assess valve dysfunction, ventricular function, and hemodynamic conditions. Initial TTE should be conducted within 24 hours of suspected IE. However, the sensitivity of TTE in NVE is reported to be 82% to 89% and its specificity as 70% to 90%,[29,30] whereas the sensitivity of transesophageal echocardiography (TEE) in NVE is reported to be higher at 90% to 100% and specificity 90%.[31] Therefore, TTE should always be corroborated with TEE as a more comprehensive evaluation for IE only in the absence of contraindications for TEE. Even when TEE is also negative, repeat echocardiography should be considered in cases in which IE is strongly suspected based on clinical judgment.[32,33]

TTE provides information not only on location, size, and mobility of vegetation, but also on the indication of the development of more extensive complications such as annular abscess, pseudoaneurysm, fistula formation, and disruption of the integrity of native or prosthetic valves. However, TTE is not suitable for the detection of small vegetations or for evaluations on prosthetic valves, and it may be technically inadequate in the presence of lung disease or body habitus.[34]

Conversely, TEE has higher sensitivity than TTE and is better suited for the detection of cardiac complications with sensitivity, specificity, and positive and negative predictive values of 87%, 95%, and 91% and 92%, respectively.[34] Therefore, TEE is indicated when TTE is positive or nondiagnostic or inconclusive.[35] In one report, TEE resulted in a shift from possible to definite endocarditis in 42% of cases with PVE.[36] Although TEE is essential for the positive or negative diagnosis of IE, the importance of TTE examination as a first step should be noted. The absence of valvular abnormalities or vegetation on TTE has been reported to be associated with a reduced incidence of complications.[37]

Real-time 3-dimensional (3D) TEE adds information on the vegetation morphology and size, and is particularly useful in the assessment of perivalvular extension of the infection, prosthetic valve dehiscence, and valve perforation.[38,39]

ASSESSMENT OF INDICATIONS FOR SURGERY

Hemodynamic Conditions

Among the complications of IE, congestive heart failure has the greatest impact on prognosis. Emergent surgery within 24 hours is indicated regardless of the status of the infection when evidence of pulmonary edema or cardiogenic shock is present. The usual cause of heart failure in a patient with IE is valvular regurgitation resulting from infection-induced valvular damage. Embolization of valvular vegetation can cause acute myocardial infarction and subsequent heart failure.[40] For patients who remain in class III or IV in the New York Heart Association (NYHA) classification of heart failure, even after initial management for acute heart failure, delayed surgery is unacceptable. It is associated with a dramatic rise in operative mortality as a consequence of progressive cardiac decompensation and exposure of the patient to secondary risks of the disease and its treatment.[41] In patients with no signs of congestive heart failure and with severe valvular regurgitation, elective surgery should be considered depending on the tolerance of the valve lesion and should be performed in accordance with the recommendations of the guidelines on the management of valvular heart disease.[42–46]

Refractory Infections

Uncontrolled infection encompasses persistent infection, infection due to resistant microorganisms, and locally uncontrolled infection. Persistent infection is arbitrarily defined as fever and persistent positive blood cultures after 7 to 10 days of appropriate antibiotic treatment. In a study of 256 patients with positive blood culture at admission, persistent positive cultures after 48 to 72 hours from the initiation of antibiotic treatment were associated with higher in-hospital mortality.[47] Urgent surgery is warranted to remove the source of infection.

S aureus IE is characterized by an aggressive clinical course associated with severe valvular damage, large vegetation, embolic complications, and overall poor prognosis.[48] Fungal IE, secondary to infection with *Candida* or *Aspergillus*, is often complicated by bulky vegetation, metastatic infection, periannular spread, and embolic events.[49] Surgery is the only means of eradication of infection when IE is caused by multiresistant organisms, including methicillin-resistant *S aureus* and vancomycin-resistant enterococci. Careful microbiological liaison is essential to determine appropriate antibiotic management during the postoperative period.

Cardiac Complications

Cardiac complications of IE are causes of uncontrolled infection associated with increased mortality. Cardiac complications include congestive heart failure caused by valvular damage from the infection, annular abscess, extension of infection into the conduction system leading to atrioventricular blocks, and mycotic aneurysms of the sinus of Valsalva, which can result in pericarditis, hemopericardium, cardiac tamponade, or fistulas to the cardiac chambers.[20] Urgent surgery is recommended when cardiac complications are detected to reduce the morbidity and mortality of this disorder.[50–52] Representative cases with cardiac complications requiring surgical interventions are summarized in **Fig. 3**.

In a study including 4681 IE cases, the incidence of fistulous intracardiac complications was 1.6%.[53] The incidence of perivalvular abscess is reported to be 30% to 40%. Perivalvular abscess is associated with a higher mortality and a higher risk of systemic and cerebral embolization.[34,54,55] In addition, perivalvular abscess can extend into adjacent cardiac conduction tissues, leading to atrioventricular block. Involvement of the conduction system by IE is most common in the setting of aortic valve infection, especially vegetation and/or abscess, and is observed between the right and noncoronary cusp, which overlies the intraventricular septum containing the proximal ventricular conduction system. Conversely, perivalvular abscesses should be suspected in the setting of conduction abnormalities in patients with IE.[56] It also should be noted that the aortic valve and annulus are more susceptible to abscess formation and associated complications than the mitral valve and annulus.[34,54,57]

Even if the diagnosis of IE has been achieved, TEE is encouraged to obtain further evaluation of valvular lesions and perivalvular complications. TEE is more sensitive for the detection of myocardial abscesses than TTE.[28] The sensitivity of TEE for the diagnosis of PVE is greater than that of TTE (86%–92% vs 17%–52%, respectively), particularly for assessing mitral valve prosthesis or paravalvular complications.[58–62] However, careful assessment is always required, as even TEE may fail to identify an abscess in difficult imaging situations such as calcification, prosthetic valves, or poor image acquisition. Patients with negative TEE for whom the clinical suspicion for IE is high should undergo repeat TEE 7 to 10 days later.

Systemic Emboli

Prevention and treatment of recurrent or primary embolic events represent a major impetus for surgical intervention in the management of IE.

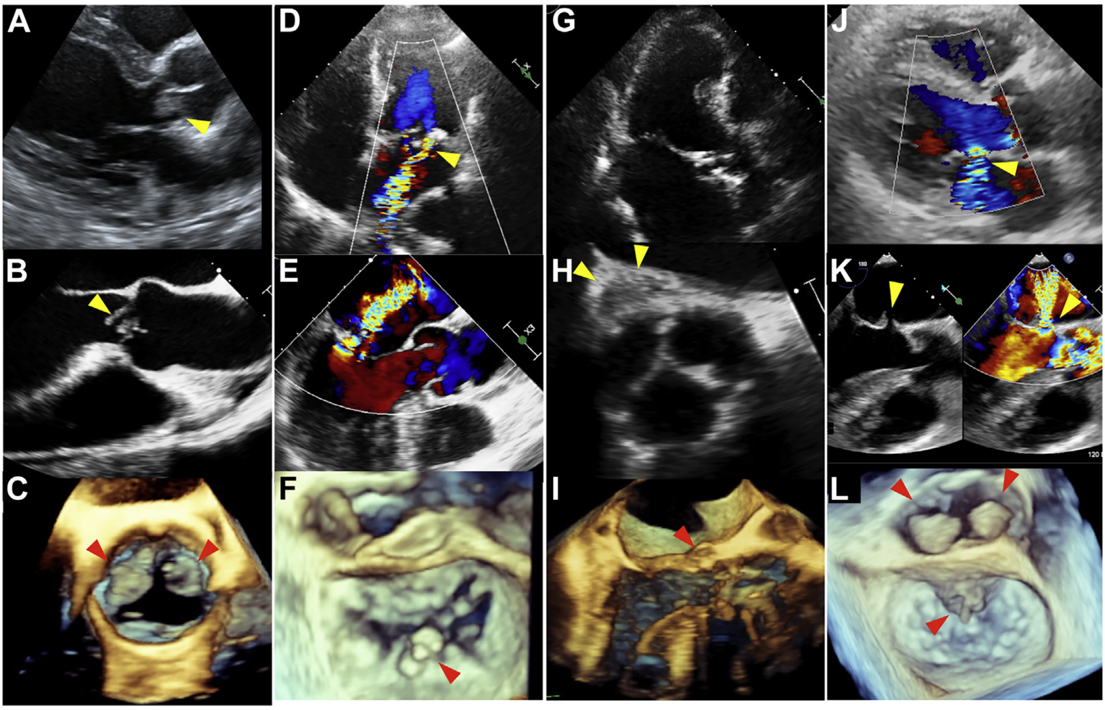

Fig. 3. Representative cases of cardiac complications of IE. (*A–C*) Leaflet aneurysms (*arrowhead*) with perforation in the aortic valves on TTE (*A*), TEE (*B*), and 3D-TEE (*C*). (*D–F*) Leaflet perforation (*arrowhead*) and severe mitral regurgitation in the posterior mitral valve on TTE (*D*), TEE (*E*), and 3D-TEE (*F*). (*G–I*) Periannular abscess (*arrowhead*) in the aortic annulus on TTE (*G*), TEE (*H*), and 3D-TEE (*I*). (*J–L*) Perforation of aorto-mitral curtain (*arrowhead*) and severe mitral regurgitation on TTE (*J*), TEE (*K*), and 3D-TEE (*L*).

Systemic embolism can occur in end organs and/or in soft tissues, including the coronary arteries, kidneys, spleen, liver, lungs, peripheral vasculature, and psoas muscles,[20,63] and may lead to formation of extracardiac abscesses. Embolization has been described in 13% to 44% of patients with IE.[64–66] The known risk factors for embolism are vegetation size, mitral valve involvement, vegetation mobility, and *S aureus* infection. Vegetation size larger than 10 mm is a predictor of embolic events, and the risk of embolization is particularly high for very large (>15 mm) vegetation.[67,68] Embolism before antimicrobial therapy is a risk factor for new emboli. An increase in vegetation size, despite antimicrobial treatment, may predict subsequent embolic events.[67] The guidelines recommend early surgery if patients experience recurrent embolic events or demonstrate large, mobile vegetation, respectively (**Fig. 4**).[69] However, the role of vegetation size as the sole indication for surgery has yet to be determined. Similar to the presence of neurologic complications, the incidence of systemic emboli diagnosed by contrast-enhanced computed tomography (CT) is much higher than the incidence diagnosed by symptoms alone. Therefore, contrast-enhanced whole-body CT should be considered in all cases with IE as soon as possible in the absence of contraindications for contrast material. Although antibiotic therapy alone was reported to decrease the incidence of stroke,[70] a recent study showed that early surgical intervention within 48 hours from diagnosis was associated with decreased risk of 6-week embolic

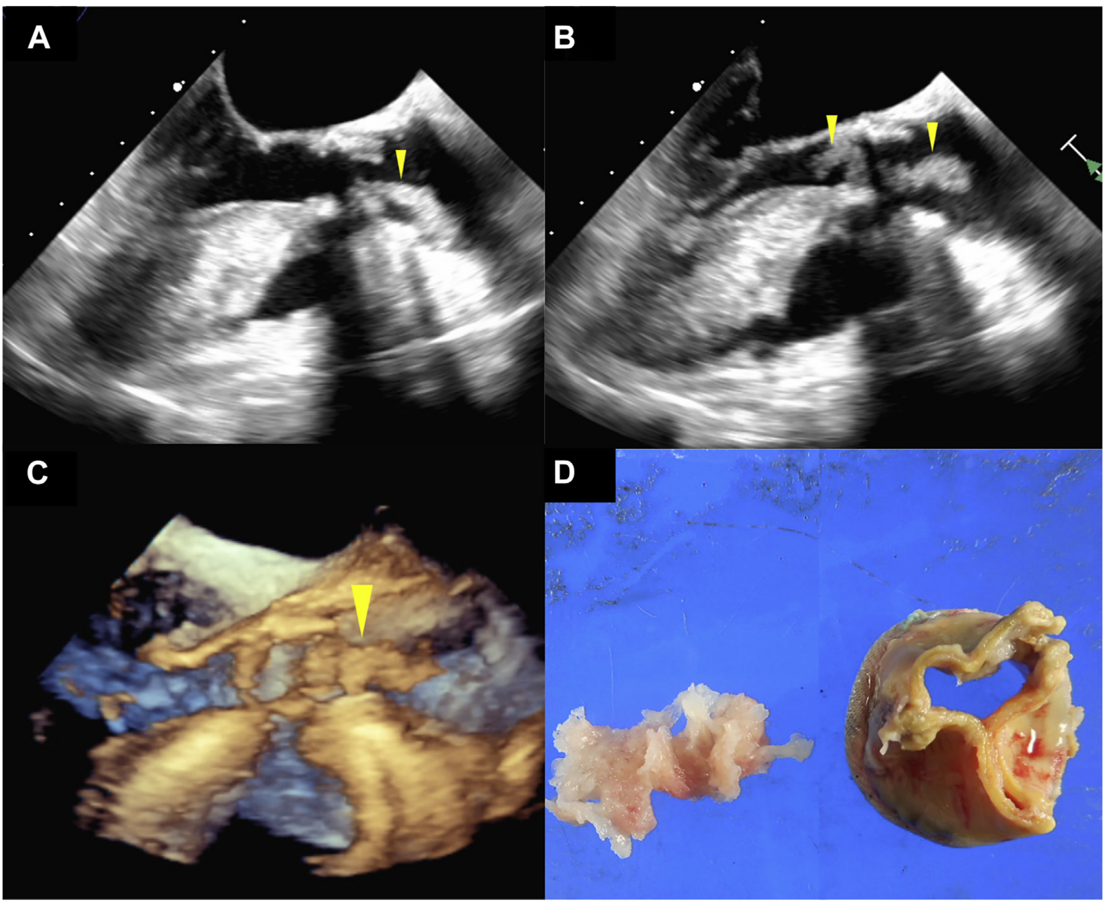

Fig. 4. A case of a large mobile vegetation on the aortic bioprosthesis. A 78-year-old woman with a history of aortic valve replacement with a bioprosthesis presented with a 4-week history of fever, and was diagnosed with PVE. On the mid-esophageal long-axis view, TEE showed a high-echoic 33-mm-long vegetation (*arrowhead*) attached to the prosthesis (*A*, *B*). The 3D TEE showed vegetation on the aortic side of the prosthesis (*C*). The patient underwent urgent resection of the vegetation (*D*, *left*) and removal of the infected prosthesis (*D*, *right*). The culture obtained from vegetation indicated *Enterococcus faecalis*. The patient was discharged without neurologic deficits after the completion of antibiotic treatment.

events as well as the risk of in-hospital mortality.[71] Furthermore, the incidence of embolic events was reported to be greater with mitral valve vegetation than with aortic valve vegetation. Specifically, the anterior mitral leaflet had the highest risk of embolization.[72,73]

Accordingly, the surgical considerations relative to systemic or neurologic emboli are as follows: (1) surgery is indicated in patients with previous emboli and ongoing high risk of second embolism; (2) surgery is recommended, based on evidence from randomized-controlled trials, in patients at risk of first embolism (vegetation >10 mm in size) when associated with severe valvular regurgitation or stenosis[71]; and (3) surgery may be considered for the primary prevention of embolism in patients without severe valve dysfunction who are considered high risk, such as vegetation greater than 15 mm. Considering that the risk of embolism in left-sided IE is highest during the first week of antibiotics, surgery to prevent embolism must be performed urgently.[67]

Neurologic Complications

IE is complicated by stroke in 20% to 40% of cases, accounting for 65% of embolic events, 90% of which arise in the distribution of the middle cerebral artery (**Fig. 5**).[70] Patients with neurologic complications of IE have been reported to be associated with worse clinical outcomes.[74–77] In transient ischemic attack or silent embolism, surgery is recommended without delay. Although cerebral CT scanning is most often performed, the higher sensitivity of MRI allows for better detection and analysis of cerebral lesions in patients with neurologic symptoms, and this may have a direct impact on the timing of surgery.[78,79] Symptomatic strokes as a complication of IE occur in up to 35% of patients,[66,74,75,80–82] whereas asymptomatic cerebrovascular complications, including ischemic stroke and microhemorrhage may occur in up to 80% of patients.[66,83–85] Therefore, we encourage routine cerebral MRI in all cases with IE with specific sequences, including diffusion-weighted imaging, gradient-recalled fluid-attenuated inversion recovery sequences, T2* sequences, susceptibility-weighted imaging, and magnetic resonance angiography (MRA) with 3D reconstruction to detect mycotic aneurysms. Surgery should not be delayed when indicated, provided that cerebral hemorrhage has been excluded by cranial CT and neurologic damage is not severe.[75]

The most difficult issues surround patients with IE with stroke who require surgery, as there is a risk of hemorrhagic transformation when patients undergo anticoagulation treatment for cardiopulmonary bypass. Patients with intracranial cerebral hemorrhage or complex stroke have significantly higher surgical mortality, and the conventional approach is to defer surgery for at least 4 weeks if indicated in these patients (**Fig. 6**).[75,82] Cerebral microbleeds, defined as hypointense lesions smaller than 10 mm in diameter, seen on T2* or susceptibility-weighted imaging, have been reported to be a risk factor for intracranial cerebral hemorrhage.[86] However, in a study comparing outcomes of surgery performed in 25 (63%) patients with microbleeds and in 24 (71%) patients without microbleeds, there was no significant difference in the de novo stroke incidence postoperatively (16% vs 17%).[87] Although careful monitoring of neurologic deterioration should be performed in patients with microbleeds, its presence is not a contraindication for surgery. **Fig. 1** proposes a state-of-the-art patient flow chart for the evaluation of suspected IE to guide subsequent clinical management, especially for surgical indications, and **Fig. 2** shows an approach for patients with IE with concomitant neurologic complications.

Mycotic aneurysms are uncommon complications of IE that result from septic embolization of vegetation to the arteries, with subsequent spread of infection through the intima and outward through the vessel wall. Mycotic aneurysm can usually develop at points of vessel bifurcation,[88] and are often detected with angiography, and/or CT and MRA with 3D reconstructions (**Fig. 7**). The overall mortality rate among patients with IE with mycotic aneurysms is as high as 60%. Because mycotic aneurysm can rupture and cause intracranial hemorrhage and sudden death,[20,24] it should be treated immediately and appropriately. Early cardiac surgery may be considered in patients with cerebral bleeding from an isolated mycotic aneurysm, in whom neurosurgical or endovascular intervention may produce a sufficient reduction in the risk of recurrent bleeding to permit cardiopulmonary bypass.[89,90]

TIMELY INDICATION AND RISK EVALUATION OF SURGERY

The goal of surgery is resection and debridement of infected tissue, reconstruction of cardiac structures, and removal of the source of embolism. When indications for surgery arise after evaluations in steps 1 to 4 of the algorithm (see **Fig. 1**), and there are no neurologic complications, surgery should be arranged in a timely manner. When there is an indication for surgery *and* concomitant neurologic complications, additional

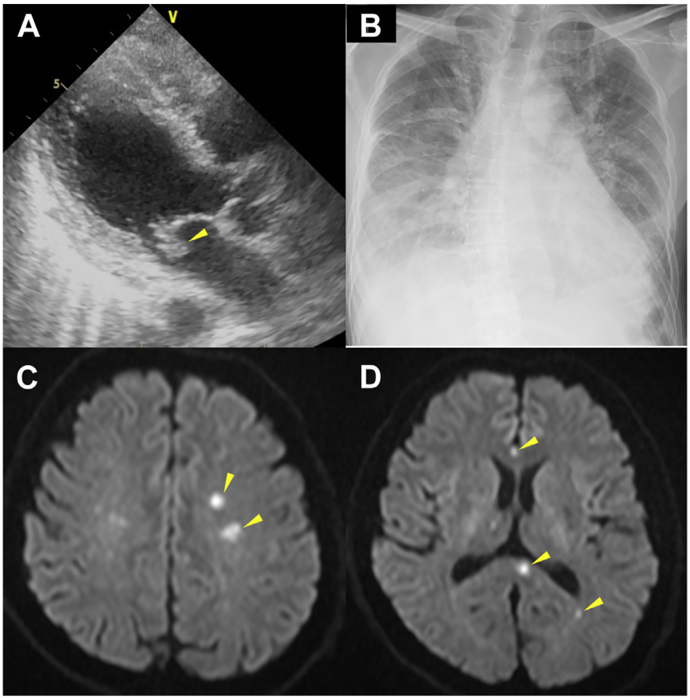

Fig. 5. A case of mitral valve endocarditis complicated with multiple embolic stroke. A 57-year-old man with atopic dermatitis presented with a 3-day history of fever and malaise. Blood culture was positive for methicillin-susceptible *S aureus*, and he presented plantar petechiae. Transthoracic echocardiography revealed highly mobile vegetation (*arrowhead*) attached to the anterior leaflet of the mitral valve and severe mitral regurgitation (*A*). The patient developed acute pulmonary edema on the third day of admission. Chest radiography showed bilateral congestion (*B*). Cerebral MRI showed multiple bihemispheric acute ischemic lesions as hyper-intensity signals (*arrowhead*) in diffusion-weighted image sequences (*C*, *D*). The patient underwent emergent mitral valve replacement and developed no further neurologic complications after surgery.

assessment should be performed (see Fig. 2), and surgery should be planned if surgical risks are acceptable compared with the benefits of surgery. Ironically, the presence of cardiac and extracardiac complications indicating surgery adds to the surgical risk for active IE, as these conditions

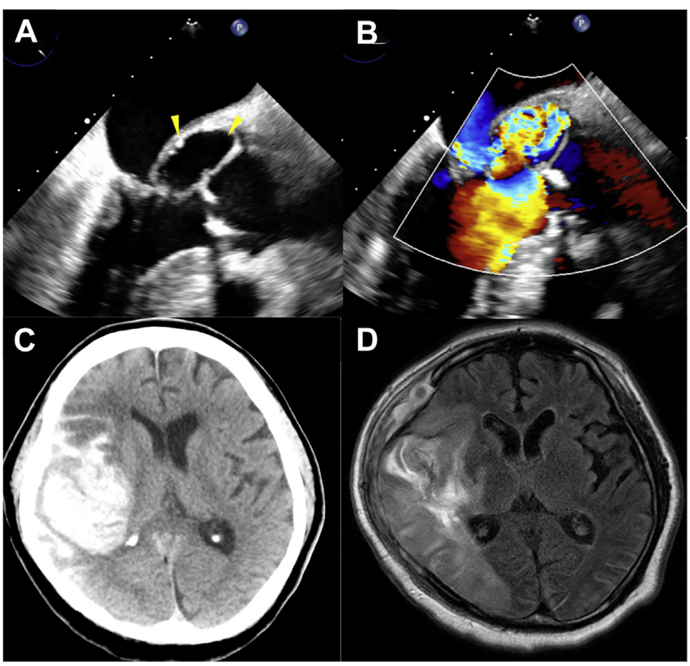

Fig. 6. A case of bicuspid aortic valve endocarditis with large hemorrhagic stroke. A 72-year-old man who was initially treated with antibiotics for Group B streptococcal bacteremia in another institution developed dysarthria and left-sided hemiparesis. Emergent cerebral angiography showed occlusion of the right M2 segment, where thrombus was successfully retrieved. TTE showed vegetation attached to the leaflet of the bicuspid aortic valve and perforation (*arrowhead*) of the aorto-mitral curtain (*A*). TEE revealed severe regurgitation from the sinus of Valsalva to the left atrium (*B*). The patient experienced coma 3 days after the angiography. Cerebral CT images showed hemorrhagic transformation of large lobar infarctions in the right middle cerebral artery region (*C*). Cerebral MRI showed bleeding in fluid-attenuated inversion recovery sequences (*D*). A decompressive craniotomy was conducted, but the patient remained unconscious. Because of the large hemorrhagic infarction and coma, cardiac surgery was deemed unfeasible. Conservative therapy with antibiotics was resumed, and the patient died of respiratory failure 1 month later.

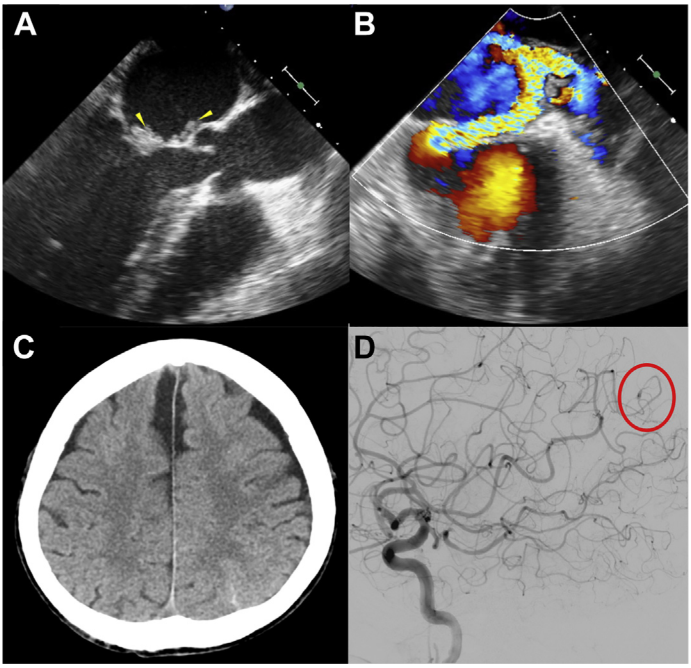

Fig. 7. A case of mitral valve endocarditis complicated with subarachnoid hemorrhage and mycotic aneurysm. A 59-year-old man with known mitral valve P3 prolapse presented with a 3-day history of fever and finger agnosia. TEE showed mobile vegetation (*arrowhead*) attached to the jet lesion of the mitral regurgitant flow (*A*). Severe mitral regurgitation was observed on TEE (*B*). Based on these findings, urgent cardiac surgery was warranted to prevent further embolization; however, subarachnoid hemorrhage was observed in the left occipital lobe with cerebral CT (*C*). Therefore, double-subtraction angiography (DSA) was planned. DSA of the left internal carotid artery showed 2 mycotic aneurysms each at the end of the left angular artery (*circle*) and in the left anterior cerebral artery A2 portion (*D*). The patient was scheduled for embolization of the mycotic aneurysm using N-butyl 2-cyanoacrylate before the cardiac surgery. On day following the embolization, the patient underwent resection of vegetation and mitral valve repair without any additional complications.

deteriorate hemodynamic status and organ dysfunction. Ultimately, the perceived risk of the operation determines the threshold for surgery; surgical procedures for active IE present high risk, with an overall in-hospital mortality of 20%. However, merely delaying surgery might lead to possible harm due to the occurrence of additional lethal complications. Thus, one must weigh anticipated surgical risk against the benefits of avoiding further complications with early surgery. When surgery is not indicated, or is indicated and the existing neurologic complications or comorbidities pose too high a risk, conservative therapy with antibiotics is pursued. In the case of a worrisome clinical course, evaluation with TTE and assessments in steps 2 to 4 should be repeated to search for new cardiac and extracardiac complications.

Special Considerations

PVE accounts for 10% to 20% of most cases. In early (within 1 year of surgery) PVE, spread of infection beyond the points of attachment of the valve prosthesis is almost inevitable, and root abscesses and valve dehiscence arise in 60% of cases. Surgical treatment results in improved survival at both immediate and long-term follow-up and a reduced incidence of relapse or need for repeat surgery compared with medical therapy.[91] When indicated, surgery is best performed urgently, especially when infection is caused by *S aureus*.[92] In late PVE (after 1 year of surgery), aggressive tissue destruction is less frequent, and early antibiotic therapy can affect a cure in many patients for whom surgery is often unnecessary. An exception is late PVE due to *S aureus*, for which the prognosis is dismal,[93] thus, urgent surgery is indicated.[94–96]

CIEDs include permanent pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices. CIED infection may involve the generator pocket, device leads, or endocardial surfaces. IE may originate from a pocket infection or occur by seeding of infection to the leads via the bloodstream. Management of CIED infection is difficult, and complete system removal is necessary.[97] Advances in percutaneous techniques have lowered the risk of device extraction.[98]

SUMMARY

We can summarize important keys features for the successful management of IE as follows: (1) prompt and adequate diagnosis of IE itself and initiation of antibiotics; (2) prompt and adequate identification of complications and indications for surgery; and (3) prompt initiation of surgery when faced with surgical risks, especially those with neurologic and hemorrhagic complications. Once IE is diagnosed or even suspected, 4 sets of examinations, including TTE, TEE, contrast-enhanced CT, and cerebral MRI, should be performed to assess the necessity of further management, including surgery, unless there are contraindications for these examinations.

Although robust evidence in the future is required to resolve the controversies regarding the surgical indications for IE, benefits of early surgery have emerged in the past decades. Physicians should promptly assess the patient's conditions and complications with existing modalities in order to recognize the optimal timing for surgery for patients with IE.

CLINICS CARE POINTS

- As delays in diagnosis and initiation of therapy lead to worse outcomes in patients with infective endocarditis (IE), identification of indication for surgical intervention and its optimal timing are crucial.
- Indications for surgery are based on cardiac and extracardiac complications. Once IE is diagnosed, 4 sets of examinations, including transthoracic echocardiography, transesophageal echocardiography, contrast-enhanced computed tomography, and cerebral MRI should be performed.
- One of the most common clinical dilemmas regarding surgical intervention for IE is optimal timing of surgery for patients with concomitant neurologic complications such as stroke, intracranial hemorrhage, and mycotic aneurysm.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet 2016;387:882–93.
2. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review. PLoS One 2013;8:e82665.
3. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol 2015;65:2070–6.
4. Bustamante-Munguira J, Mestres CA, Alvarez P, et al. Surgery for acute infective endocarditis: epidemiological data from a Spanish nationwide hospital-based registry. Interact Cardiovasc Thorac Surg 2018;27:498–504.
5. Wang A, Gaca JG, Chu VH. Management considerations in infective endocarditis: a review. JAMA 2018;320:72–83.
6. 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.
7. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463–73.
8. Toyoda N, Chikwe J, Itagaki S, et al. Trends in infective endocarditis in California and New York State, 1998-2013. JAMA 2017;317:1652–60.
9. Thornhill MH, Jones S, Prendergast B, et al. Quantifying infective endocarditis risk in patients with predisposing cardiac conditions. Eur Heart J 2018;39:586–95.
10. Wallace SM, Walton BI, Kharbanda RK, et al. Mortality from infective endocarditis: clinical predictors of outcome. Heart 2002;88:53–60.
11. Chu VH, Cabell CH, Benjamin DK Jr, et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004;109:1745–9.
12. Hasbun R, Vikram HR, Barakat LA, et al. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. JAMA 2003;289:1933–40.
13. Hill EE, Herijgers P, Claus P, et al. Infective endocarditis: changing epidemiology and predictors of 6-month mortality: a prospective cohort study. Eur Heart J 2007;28:196–203.
14. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA 2007;297:1354–61.
15. Roth GA, Dwyer-Lindgren L, Bertozzi-Villa A, et al. Trends and patterns of geographic variation in cardiovascular mortality among US counties, 1980-2014. JAMA 2017;317:1976–92.
16. Cahill TJ, Baddour LM, Habib G, et al. Challenges in infective endocarditis. J Am Coll Cardiol 2017;69:325–44.
17. Holland TL, Baddour LM, Bayer AS, et al. Infective endocarditis. Nat Rev Dis Primers 2016;2:16059.
18. Moreillon P, Que YA. Infective endocarditis. Lancet 2004;363:139–49.
19. Werdan K, Dietz S, Loffler B, et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. Nat Rev Cardiol 2014;11:35–50.
20. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med 2001;345:1318–30.
21. AATS Surgical Treatment of Infective Endocarditis Consensus Guidelines Writing Committee Chairs,

Pettersson GB, Coselli JS, et al. 2016 the American Association for Thoracic Surgery (AATS) consensus guidelines: surgical treatment of infective endocarditis: executive summary. J Thorac Cardiovasc Surg 2017;153:1241–58.e29.
22. Rogolevich VV, Glushkova TV, Ponasenko AV, et al. Infective endocarditis causing native and prosthetic heart valve dysfunction. Kardiologiia 2019;59:68–77 [In Russian].
23. Jillella DV, Wisco DR. Infectious causes of stroke. Curr Opin Infect Dis 2019;32:285–92.
24. Sotero FD, Rosario M, Fonseca AC, et al. Neurological complications of infective endocarditis. Curr Neurol Neurosci Rep 2019;19:23.
25. 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.
26. Fowler VG Jr, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. JAMA 2005;293:3012–21.
27. Lauridsen TK, Park L, Tong SY, et al. Echocardiographic findings predict in-hospital and 1-year mortality in left-sided native valve Staphylococcus aureus endocarditis: analysis from the International Collaboration on Endocarditis-Prospective Echo Cohort Study. Circ Cardiovasc Imaging 2015;8: e003397.
28. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132: 1435–86.
29. Casella F, Rana B, Casazza G, et al. The potential impact of contemporary transthoracic echocardiography on the management of patients with native valve endocarditis: a comparison with transesophageal echocardiography. Echocardiography 2009;26: 900–6.
30. Nadji G, Rusinaru D, Remadi JP, et al. Heart failure in left-sided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment. Eur J Heart Fail 2009;11:668–75.
31. Banchs J, Yusuf SW. Echocardiographic evaluation of cardiac infections. Expert Rev Cardiovasc Ther 2012;10:1–4.
32. Morguet AJ, Werner GS, Andreas S, et al. Diagnostic value of transesophageal compared with transthoracic echocardiography in suspected prosthetic valve endocarditis. Herz 1995;20: 390–8.
33. Sochowski RA, Chan KL. Implication of negative results on a monoplane transesophageal echocardiographic study in patients with suspected infective endocarditis. J Am Coll Cardiol 1993;21:216–21.
34. Daniel WG, Mugge A, Martin RP, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med 1991;324:795–800.
35. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075–128.
36. Vieira ML, Grinberg M, Pomerantzeff PM, et al. Repeated echocardiographic examinations of patients with suspected infective endocarditis. Heart 2004;90:1020–4.
37. Sanfilippo AJ, Picard MH, Newell JB, et al. Echocardiographic assessment of patients with infectious endocarditis: prediction of risk for complications. J Am Coll Cardiol 1991;18:1191–9.
38. Berdejo J, Shibayama K, Harada K, et al. Evaluation of vegetation size and its relationship with embolism in infective endocarditis: a real-time 3-dimensional transesophageal echocardiography study. Circ Cardiovasc Imaging 2014;7:149–54.
39. Liu YW, Tsai WC, Lin CC, et al. Usefulness of real-time three-dimensional echocardiography for diagnosis of infective endocarditis. Scand Cardiovasc J 2009;43:318–23.
40. Millaire A, Van Belle E, de Groote P, et al. Obstruction of the left main coronary ostium due to an aortic vegetation: survival after early surgery. Clin Infect Dis 1996;22:192–3.
41. Middlemost S, Wisenbaugh T, Meyerowitz C, et al. A case for early surgery in native left-sided endocarditis complicated by heart failure: results in 203 patients. J Am Coll Cardiol 1991;18:663–7.
42. Saikrishnan N, Kumar G, Sawaya FJ, et al. Accurate assessment of aortic stenosis: a review of diagnostic modalities and hemodynamics. Circulation 2014; 129:244–53.
43. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/ EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.
44. Kitai T, Okada Y, Shomura Y, et al. Early surgery for asymptomatic mitral regurgitation: importance of atrial fibrillation. J Heart Valve Dis 2012;21:61–70.
45. Kitai T, Okada Y, Shomura Y, et al. Timing of valve repair for severe degenerative mitral regurgitation and long-term left ventricular function. J Thorac Cardiovasc Surg 2014;148:1978–82.
46. Kitai T, Furukawa Y, Murotani K, et al. Therapeutic strategy for functional tricuspid regurgitation in patients undergoing mitral valve repair for severe mitral regurgitation. Int J Cardiol 2017;227:803–7.
47. Lopez J, Sevilla T, Vilacosta I, et al. Prognostic role of persistent positive blood cultures after initiation of antibiotic therapy in left-sided infective endocarditis. Eur Heart J 2013;34:1749–54.

48. Yoshinaga M, Niwa K, Niwa A, et al. Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. Am J Cardiol 2008;101:114–8.
49. Nguyen MH, Nguyen ML, Yu VL, et al. Candida prosthetic valve endocarditis: prospective study of six cases, review of the literature. Clin Infect Dis 1996;22:262–7.
50. Fernando RJ, Johnson SD, Augoustides JG, et al. Simultaneous right-sided, left-sided infective endocarditis: management challenges in a multidisciplinary setting. J Cardiothorac Vasc Anesth 2018;32:1041–9.
51. Hitzeroth J, Beckett N, Ntuli P. An approach to a patient with infective endocarditis. S Afr Med J 2016; 106:145–50.
52. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation 2010;121: 1141–52.
53. Anguera I, Miro JM, Vilacosta I, et al. Aorto-cavitary fistulous tract formation in infective endocarditis: clinical, echocardiographic features of 76 cases and risk factors for mortality. Eur Heart J 2005;26: 288–97.
54. Omari B, Shapiro S, Ginzton L, et al. Predictive risk factors for periannular extension of native valve endocarditis. Clinical and echocardiographic analyses. Chest 1989;96:1273–9.
55. Cosmi JE, Tunick PA, Kronzon I. Mortality in patients with paravalvular abscess diagnosed by transesophageal echocardiography. J Am Soc Echocardiogr 2004;17:766–8.
56. Molavi A. Endocarditis: recognition, management, and prophylaxis. Cardiovasc Clin 1993;23:139–74.
57. Arnett EN, Roberts WC. Valve ring abscess in active infective endocarditis. Frequency, location, and clues to clinical diagnosis from the study of 95 necropsy patients. Circulation 1976;54:140–5.
58. Bruun NE, Habib G, Thuny F, et al. Cardiac imaging in infectious endocarditis. Eur Heart J 2014;35: 624–32.
59. Pizzi MN, Roque A, Fernandez-Hidalgo N, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with 18F-fluordeoxyglucose positron emission tomography/computed tomography angiography: initial results at an infective endocarditis referral center. Circulation 2015;132:1113–26.
60. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 guidelines for the clinical application of echocardiography). Circulation 2003;108: 1146–62.
61. Stewart WJ, Shan K. The diagnosis of prosthetic valve endocarditis by echocardiography. Semin Thorac Cardiovasc Surg 1995;7:7–12.
62. Roe MT, Abramson MA, Li J, et al. Clinical information determines the impact of transesophageal echocardiography on the diagnosis of infective endocarditis by the Duke criteria. Am Heart J 2000; 139:945–51.
63. Heiro M, Nikoskelainen J, Engblom E, et al. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med 2000;160:2781–7.
64. Steckelberg JM, Murphy JG, Ballard D, et al. Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med 1991;114: 635–40.
65. De Castro S, Magni G, Beni S, et al. Role of transthoracic and transesophageal echocardiography in predicting embolic events in patients with active infective endocarditis involving native cardiac valves. Am J Cardiol 1997;80:1030–4.
66. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis 2008;47:23–30.
67. Vilacosta I, Graupner C, San Roman JA, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol 2002;39: 1489–95.
68. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005;112:69–75.
69. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017; 135:e1159–95.
70. Dickerman SA, Abrutyn E, Barsic B, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J 2007;154: 1086–94.
71. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012;366:2466–73.
72. Rohmann S, Erbel R, Gorge G, et al. Clinical relevance of vegetation localization by transoesophageal echocardiography in infective endocarditis. Eur Heart J 1992;13:446–52.

73. Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. Circulation 1998;98:2936–48.
74. Roder BL, Wandall DA, Espersen F, et al. Neurologic manifestations in *Staphylococcus aureus* endocarditis: a review of 260 bacteremic cases in nondrug addicts. Am J Med 1997;102:379–86.
75. Ruttmann E, Willeit J, Ulmer H, et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke 2006;37:2094–9.
76. Anderson DJ, Goldstein LB, Wilkinson WE, et al. Stroke location, characterization, severity, and outcome in mitral vs aortic valve endocarditis. Neurology 2003;61:1341–6.
77. Murai R, Funakoshi S, Kaji S, et al. Outcomes of early surgery for infective endocarditis with moderate cerebral complications. J Thorac Cardiovasc Surg 2017;153:831–40.e8.
78. Goulenok T, Klein I, Mazighi M, et al. Infective endocarditis with symptomatic cerebral complications: contribution of cerebral magnetic resonance imaging. Cerebrovasc Dis 2013;35:327–36.
79. Hess A, Klein I, Iung B, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. AJNR Am J Neuroradiol 2013;34:1579–84.
80. Jones HR Jr, Siekert RG. Neurological manifestations of infective endocarditis. Review of clinical and therapeutic challenges. Brain 1989;112(Pt 5):1295–315.
81. Parrino PE, Kron IL, Ross SD, et al. Does a focal neurologic deficit contraindicate operation in a patient with endocarditis? Ann Thorac Surg 1999;67:59–64.
82. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation 2013;127:2272–84.
83. Cooper HA, Thompson EC, Laureno R, et al. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. Circulation 2009;120:585–91.
84. Klein I, Iung B, Labreuche J, et al. Cerebral microbleeds are frequent in infective endocarditis: a case-control study. Stroke 2009;40:3461–5.
85. Duval X, Iung B, Klein I, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Ann Intern Med 2010;152:497–504. W175.
86. Okazaki S, Sakaguchi M, Hyun B, et al. Cerebral microbleeds predict impending intracranial hemorrhage in infective endocarditis. Cerebrovasc Dis 2011;32:483–8.
87. Murai R, Kaji S, Kitai T, et al. The clinical significance of cerebral microbleeds in infective endocarditis patients. Semin Thorac Cardiovasc Surg 2019;31:51–8.
88. Bisdas T, Teebken OE. Mycotic or infected aneurysm? Time to change the term. Eur J Vasc Endovasc Surg 2011;41:570 [author reply: 570–1].
89. Chapot R, Houdart E, Saint-Maurice JP, et al. Endovascular treatment of cerebral mycotic aneurysms. Radiology 2002;222:389–96.
90. Fukuda W, Daitoku K, Minakawa M, et al. Management of infective endocarditis with cerebral complications. Ann Thorac Cardiovasc Surg 2014;20:229–36.
91. Gordon SM, Serkey JM, Longworth DL, et al. Early onset prosthetic valve endocarditis: the Cleveland Clinic experience 1992-1997. Ann Thorac Surg 2000;69:1388–92.
92. Wolff M, Witchitz S, Chastang C, et al. Prosthetic valve endocarditis in the ICU. Prognostic factors of overall survival in a series of 122 cases and consequences for treatment decision. Chest 1995;108:688–94.
93. 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.
94. Lopez J, Sevilla T, Vilacosta I, et al. Clinical significance of congestive heart failure in prosthetic valve endocarditis. A multicenter study with 257 patients. Rev Esp Cardiol (Engl Ed) 2013;66:384–90.
95. Habib G, Tribouilloy C, Thuny F, et al. Prosthetic valve endocarditis: who needs surgery? A multicentre study of 104 cases. Heart 2005;91:954–9.
96. Lalani T, Chu VH, Park LP, et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. JAMA Intern Med 2013;173:1495–504.
97. Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint working party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS), British Society for Echocardiography (BSE). J Antimicrob Chemother 2015;70:325–59.
98. Fu HX, Huang XM, Zhong LI, et al. Outcomes and complications of lead removal: can we establish a risk stratification schema for a collaborative and effective approach? Pacing Clin Electrophysiol 2015;38:1439–47.