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Surgical Management of Infective Endocarditis Complicated by Embolic Stroke

Practical Recommendations for Clinicians

ABSTRACT: There has been an overall improvement in surgical mortality for patients with infective endocarditis (IE), presumably because of improved diagnosis and management, centered around a more aggressive early surgical approach. Surgery is currently performed in approximately half of all cases of IE. Improved survival in surgery-treated patients is correlated with a reduction in heart failure and the prevention of embolic sequelae. It is reported that between 20% and 40% of patients with IE present with stroke or other neurological conditions. It is for these IE patients that the timing of surgical intervention remains a point of considerable discussion and debate. Despite evidence of improved survival in IE patients with earlier surgical treatment, a significant proportion of patients with IE and preexisting neurological complications either undergo delayed surgery or do not have surgery at all, even when surgery is indicated and guideline endorsed. Physicians and surgeons are caught in a common conundrum where the urgency of the heart operation must be balanced against the real or perceived risks of neurological exacerbation. Recent data suggest that the risk of neurological exacerbation may be lower than previously believed. Current guidelines reflect a shift toward early surgery for such patients, but there continue to be important areas of clinical equipoise. Individualized clinical assessment is of major importance for decision making, and, as such, we emphasize the need for the functioning of an endocarditis team, including cardiac surgeons, cardiologists, infectious diseases specialists, neurologists, neurosurgeons, and interventional neuroradiologists. Here, we present 2 illustrative cases, critically review contemporary data, and offer conceptual and practical suggestions for clinicians to address this important, common, and often fatal cardiac condition.

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The overall outcomes of patients with infective endocarditis (IE) are improving possibly because of a more proactive, earlier surgical approach.[1] Surgery is currently performed in approximately half of all cases of IE and is correlated with clinical benefits from improving heart failure and preventing embolic sequelae.[2] Furthermore, earlier surgery may confer a survival benefit.[3–5] In a propensity-matched analysis of patients with IE that underwent early surgery versus medical therapy, early surgery was associated with an impressive reduction in mortality (absolute risk reduction, 5.9%; P<0.001). A recent meta-analysis of 21 studies confirmed a survival advantage for early surgery (<7 days) for unmatched (odds ratio [OR], 0.61; 95% confidence interval, 0.50–0.74; P<0.001) and propensity-matched cohorts (OR, 0.41; 95% confidence interval, 0.31–0.54; P<0.001).[5] In the only prospective randomized trial in this field, Kang et al[3] compared early surgery (<48 hours) versus conventional management in patients with uncomplicated left-sided IE, vegetation >10 mm, and severe valvular disease. Early surgery was associated with a reduced composite end point of all-cause mortality and embolic events (hazard ratio, 0.10; 95% confidence interval, 0.01–0.82; P=0.03), driven by lower systemic embolism. Similar findings were shown in a prospective study of critically ill patients with IE and neurological injury, although there likely was selection bias.[6] These studies support an emerging consensus that, for the majority of IE patients, once there is an indication for surgery, there is little benefit in delaying the operation. Rather, delay carries the potential for harm from worsening heart failure, repeat embolic events, and even death.

The predominant cerebral insult from septic emboli is ischemic stroke, but may also include intracerebral hemorrhage, either subarchnoid or subdural hemorrhage, infectious aneurysm, brain abscess, and rarely meningitis (Table 1).[7–22] As many as 40% of patients with IE present with clinically evident neurological sequelae, but brain MRI of IE patients has identified embolic lesions in as many as 60% to 80% of patients.[13,14,23,24] A retrospective series of 102 patients with IE found clinical neurological deficits in 34%, but demonstrated lesions in 63% by diffusion-weighted imaging MRI.[7] Similarly, in a series of 56 patients with IE, clinical stroke was diagnosed in 25%, but evidence of embolization was identified by MRI in 80% of patients.[13] Because cerebral embolic events pose an independent risk factor for mortality in IE, even subclinical neurological injury may have prognostic importance.[6]

The decision on surgical timing in patients with IE and neurological injury requires a balance between the urgency of the operation for cardiac indications versus the perceived risk of exacerbation of neurological injury by intracerebral hemorrhage, hypotension, or further embolization from cardiopulmonary bypass, and diffuse cerebral ischemia from altered vasoregulation, as well (Figure 1). The indications for urgent surgery include severe heart failure, unresponsive or poorly controlled infection, highly virulent and resistant organisms, perivalvular extension or abscesses, development of heart block, prosthetic valve infection with unstable prosthesis, recurrent embolism, and large vegetation(s) associated with imminent risk of embolism. Regarding this latter point, there are established risk factors related to infective agent, vegetation size, mobility, and location and history of embolism that place a patient at higher risk of further embolism based on observational data (Table 2).[18,25–33] On the other hand, it has been reported that the risk of stroke falls once antibiotic therapy has been established.[34] Although surgical timing should be individualized and decided with input from multiple specialists, we believe more patients could benefit from early surgery. Despite emerging trends in the recent literature that can help to guide this decision, currently, a significant proportion of patients with IE and neurological complications (eg, ischemic stroke) and a cardiac indication for surgery either have their operation delayed or not performed at all.[11]

In this review, we discuss the neurological complications seen in IE patients and present the contemporary

Table 1. Neurological Sequelae of Infective Endocarditis and Approximate Proportion

Complication	Approximate Proportion	Reference
Ischemic stroke	70%	Snygg-Martin et al[14]
		Cooper et al[13]
		Barsic et al[15]
		Thuny et al[16]
		Ting et al[17]
Intracerebral hemorrhage	10%	Derex et al[18]
		Diab et al[19]
		Garcia-Cabrera et al[11]
		Okita et al[10]
Subarachnoid hemorrhage	5%	-
Meningoencephalitis	5%	Sonneville et al[20]
		Garcia-Cabrera et al[11]
		Lucas et al[21]
Intracerebral abscess	5%	Garcia-Cabrera et al[11]
		Sonneville et al[20]
Infectious intracranial aneurysm	5%	Peters et al[22]
Encephalopathy	–	Garcia-Cabrera et al[11]

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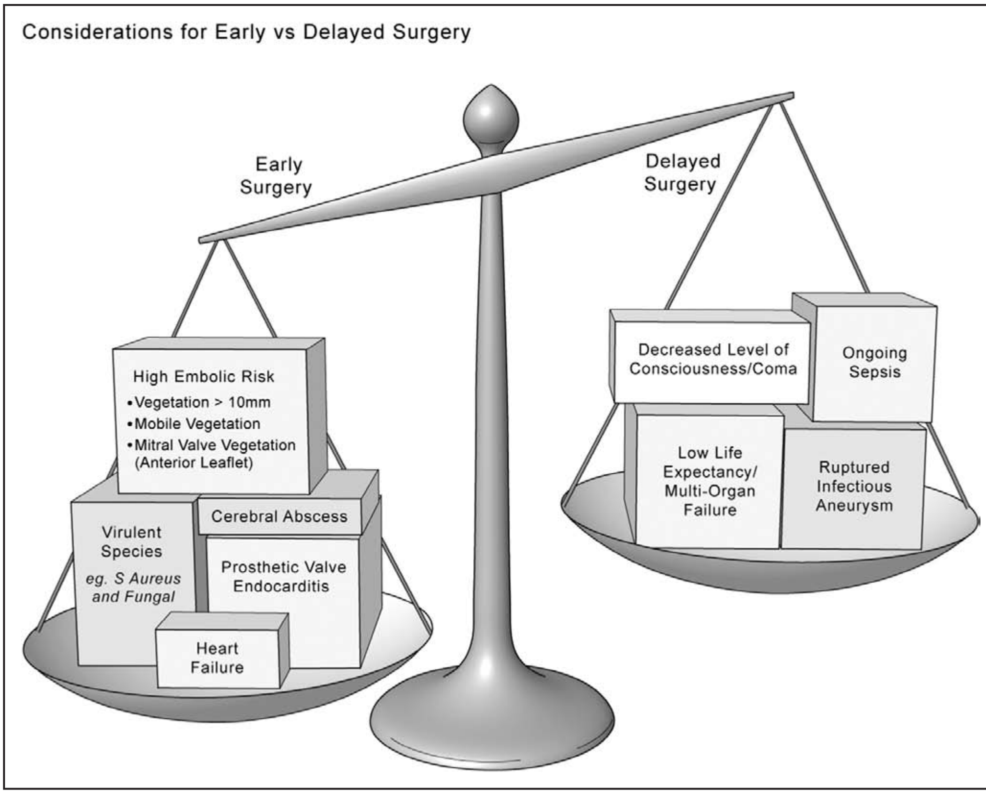

Figure 1. Conceptual diagram of arguments for early and delayed surgery in patients with infective endocarditis with stroke and other cerebral complications.

data that inform the optimal timing of surgery. This document seeks to expand on the recent guidelines by the American Heart Association (AHA), European Society of Cardiology/European Association for Cardio-Thoracic Surgery/European Association of Nuclear Medicine, and the Society of Thoracic Surgeons (Table 3).[31,35,36] Thus, the development of the present document involved a comprehensive literature review based largely on recent observational trials, and review and specific adaptation of recent AHA, European Society of Cardiology, and Society of Thoracic Surgeons guideline statements, as well.

In the next sections, we illustrate 2 cases of surgical management of IE and embolic stroke that reflect the range of clinical presentation and challenges in decision making in these patients. Our recommendations, however, are based on evidence in case series, cohort studies, and meta-analysis, not only by these illustrative cases.

CASE 1

A 70-year-old patient was referred for a *Streptococcus mitis* infective endocarditis of the aortic valve. Transesophageal echocardiography showed a perforated aneurysm of the left coronary cusp with massive aortic insufficiency and a large vegetation (Figure 2A). Eight hours after admission, he presented with an ischemic stroke manifested by dysarthria and right hemiparesis. Brain MRI showed a hyperintense lesion of the left frontoinsular area without mycotic aneurysm (Figure 2B; MRI-fluid-attenuated inversion recovery and MR angiogram). Computed tomography (CT) scan confirmed the ischemic lesion without hemorrhagic conversion (Figure 2B; CT scan). ^{18}F Positron emission tomography (PET) demonstrated uptake in the ischemic area (Figure 2B; PET-CT). Although the patient improved clinically, repeat preoperative CT scan at day 7 revealed hemorrhagic conversion of the ischemic lesion (Figure 2C, white arrow), which delayed the planned valvular surgery for 3 weeks to ensure stability of the hemorrhagic conversion by weekly CT scan. Intraoperatively, the valvular lesion was confirmed (Figure 2D) and bioprosthetic aortic valve replacement (25 mm Edwards Lifescience Perimount) was performed without cerebral complication.

This case illustrates a comprehensive neurological evaluation and surgical timing that was based on serial neurological imaging.

CASE 2

A 39-year-old patient with a history of aortic valve replacement and pacemaker implantation and reoperation for fungal (*Aspergillus* species) prosthetic valve endocarditis 6 months previously presented with recurrent fungal endocarditis with large vegetations in the

Table 2. Risk Factors for Embolism in Left-Sided Infective Endocarditis

Risk Factors	Reference
Vegetation size >10 mm or >13 mm	Wilbring et al[25]
	Rizzi et al[26]
	Mylonakis et al[27]
	Mugge et al[28]
	Vilacosta et al[29]
	Thuny et al[30]
Vegetation mobility	Thuny et al[30]
Infective agent: *Staphylococcus aureus*	Derex et al[18]
	Baddour et al[31]
	Rizzi et al[26]
	Thuny et al[30]
Infective agent: *Streptococcus bovis*	Thuny et al[30]
Infective agent: fungal	Baddour et al[31]
Location: anterior mitral valve > aortic valve	Derex et al[18]
	Rohmann et al[32]
	Anderson et al[33]
Prior history of embolism	–

proximal aorta and small vegetations on the prosthetic valve (Figure 3A and 3B). He embolized to the lower extremities requiring emergency embolectomy. A CT scan of the head revealed multiple 6- to 7-mm infarcts (Figure 3C and 3D) including one with hemorrhagic conversion (Figure 3D) and 2 smaller mycotic aneurysms (the larger embolized just before her heart operation) (Figure 3E1 and 3E2, with Glue Cast). The risk of additional embolization was considered very high, justifying urgent cardiac surgery despite a perceived high risk of complications, including exacerbation of cerebral hemorrhage. A multidisciplinary endocarditis team agreed to the urgent timing of the operation. Intraoperatively, the aortic vegetation was predominantly found at the previous aortotomy, which had been repaired with pledgets and bovine pericardium. The prosthetic aortic valve itself had minimal vegetations. Complete debridement and homograft root replacement were performed. The pacemaker leads in the right atrium were not convincingly infected but leads and pacemaker were removed. Specimens identified *Aspergillus terreus*, resistant to Amphotericin B. The postoperative course was uneventful with stable neurological symptoms and followed up with serial brain imaging. The patient was treated with 6 weeks of intravenous antifungals and, at 2 years, the patient is doing well.

This case illustrates that early surgery can be performed successfully even in the setting of multiple small cerebral infracts, including one with hemorrhagic extension.

EARLY STUDIES OF ISCHEMIC STROKE AND SURGICAL TIMING

Ischemic stroke attributable to septic embolism is the most common neurological complication with IE. Early studies demonstrated higher mortality with surgery in IE patients with neurological signs in the acute period following ischemic stroke.[9,37–39] A multicenter Japanese study of 181 patients with cerebral complications with IE reported neurological deterioration in 44% of patients when surgery was done between 2 and 7 days, 16.7% for surgery between 1 and 2 weeks, and 2.3% for >4 weeks after the neurological injury.[9] Furthermore, mortality was greater for patients having early surgery in comparison with between 1 and 2 weeks and >4 weeks (44%, 17%, and 7%, respectively). Angstwurm et al[39] in 2004 reported that the risk of neurological exacerbation with surgery was 20% when surgery was undertaken within 3 days of presentation, 20% to 50% between 4 and 14 days, but <10% when surgery was performed >14 days and <1% when surgery was performed >4 weeks after an embolic event. Interpretation of this last finding is challenging, because significant treatment selection bias was present, because those patients undergoing surgery had greater hemodynamic compromise and ongoing sepsis, thus representing a higher-risk cohort. Furthermore, most observational series have lacked clinical imaging data to determine the extent of stroke, the causative bacterial organism, and the size, mobility, and location of vegetation, all of which should influence surgical timing and outcome. Despite these limitations, these and other early studies, which showed that delay in surgery was correlated with better outcomes, had an important influence on the early guidelines.

MORE RECENT STUDIES ON THE IMPACT OF EARLY SURGERY ON OUTCOMES

Important evidence from several more recent observational studies demonstrates that the overall risk of hemorrhagic conversion and mortality may be lower than previously reported.[40,41] When propensity matching is performed to adjust for inherent selection biases, risk is no longer significantly greater with early surgery.[7,8,42,43] Piper et al[42] in 2001 suggested that surgery can be performed with low risk within a 72-hour window of the neurological insult. A retrospective review by Morita et al[43] of 253 patients with IE with ischemic stroke found no difference in overall mortality (8.6% versus 9.5%) and perioperative complications (42.9% versus 37.8%) between unmatched early (<7 days) and delayed (>7 days) surgery cohorts. The propensity-matched analysis confirmed no difference between groups. In the unmatched comparison, there was a nonsignificant higher risk of cerebral hemorrhage in the early surgery group (6.7%

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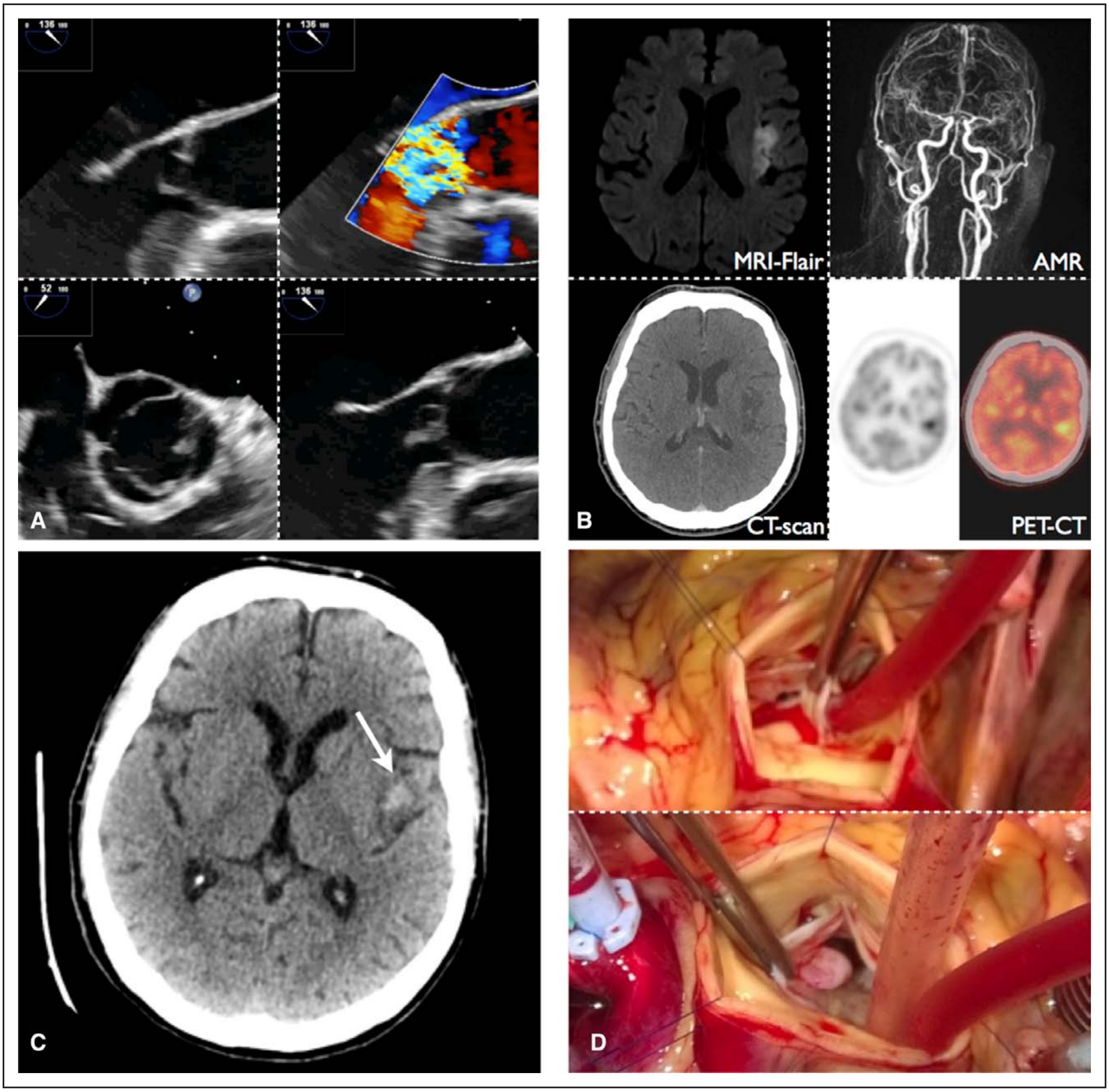

Figure 2. Aortic valve infective endocarditis and stroke with hermorrhagic conversion.
Aortic valve vegetation by TEE (**A**), left frontoinsular infarct by brain MRI (**B**; MRI-Flair and AMR), CT scan (**B**; CT-scan), and ^{18}F positron emission tomography (**B;** PET-CT). Hemorrhagic conversion on follow-up CT scan (**C;** white arrow). Intraoperative valvular lesions (**D**). AMR indicates magnetic resonance angiography; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; PET, positron emission tomography; and TEE, transesophageal echocardiography.

versus 2.0%, *P*=0.1), but this was not found in the propensity-matched analysis. In a recent retrospective Japanese multicenter study of 568 IE patients (n=118 with ischemic stroke and n=54 with hemorrhagic stroke), in the ischemic stroke group, delaying surgery between 2 and 4 weeks and >4 weeks resulted in a trend to a higher incidence of hospital death (OR, 5.90; *P*=0.107 and OR, 4.92; *P*=0.14) in comparison with early surgery within 7 days.[10] The International Collaboration on Endocarditis-Prospective Cohort Study (2013) included 4794 patients with IE, of which 857 (17.9%) had an ischemic stroke and only 198 (23%) underwent cardiac surgery.[15] The propensity-matched analysis found that early surgery correlated with a nonsignificant trend of increased in-hospital (OR, 2.3; 95% confidence interval, 0.94–5.7) and 1-year mortality (27.1% versus 19.2%, *P*=0.3). Thus, more recent studies, including those with propensity-matched analyses, have not found a significant increased risk of mortality or neurological exacerbation for early surgery in patients with ischemic stroke sec-

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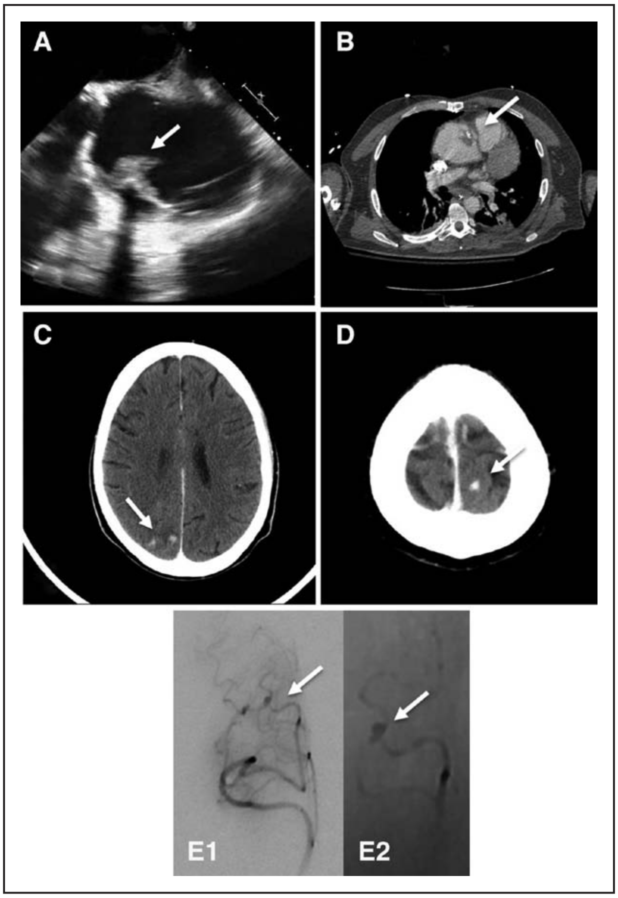

Figure 3. ***Aspergillus*** **endocarditis with large fungal vegetations in a dilated ascending aorta on the old aortotomy suture line (arrows) seen by TEE (A) and CT scan (B), brain infarct by CT scan (C and D, arrows), and mycotic aneurysms (E1 and E2).**
CT indicates computed tomography; and TEE, transesophageal echocardiography.

ondary to IE. However, when interpreting these data, we need to be aware of the era. Contemporary outcomes have improved because of a trend toward early surgery guided by improved brain imaging. With earlier surgery, the patient is less likely to sustain additional embolization while awaiting surgery. It is our opinion that, on balance, more patients with IE and ischemic strokes should be considered for earlier surgical intervention.

RISK OF NEUROLOGICAL EXACERBATION

Because cardiopulmonary bypass requires high-dose anticoagulation, concerns have long been raised about the risk for hemorrhagic conversion of ischemic stroke, or exacerbation of small hemorrhage, when early surgery for IE is performed in patients with cerebral embolism. The true impact of heart surgery on neurological status and lesions is difficult to address, because few series have measured the extent of cerebral injury with MRI before and after surgery. In an observational study of 102 patients with IE and cerebral embolism, 34 patients underwent early surgery (mean, 4.1±4.2 days) and 30 patients underwent delayed surgery (mean, 34.2±17.1 days).[7] There were no differences in the maximum size (18.3±21.4 mm versus 21.2±19.4 mm) and number of infarcts (2.9±1.7 versus 2.8±2.0) between those that had early and delayed surgery. The incidence of neurological exacerbation was lower in patients that underwent early surgery (35.3% versus 73.3%, P=0.003). In comparison with hemorrhagic conversion rates of 20% to 50% in older series, more recent studies suggest rates of <10%.[7,8,16,17] Yoshioka et al[7] report a 2% overall hemorrhagic conversion rate, whereas Rutmman et al[8] found only 1 patient with hemorrhagic conversion among 65 patients with ischemic strokes undergoing surgery. Collectively, these reports using comprehensive neurological imaging confirm that patients with ischemic embolic strokes secondary to IE have a more favorable prognosis with early surgery and a much lower risk of hemorrhagic conversion of ischemic infarcts than previously reported.

In the general stroke population, the baseline incidence of spontaneous hemorrhagic conversion for all strokes ranges from 38% to 71% in autopsy studies and from 13% to 43% in CT studies, whereas the incidence of symptomatic hemorrhagic conversion is between 0.6% and 20%.[44] Most patients who developed hemorrhagic conversion are asymptomatic. Prognostic tools such as the Ischemic Stroke Predictive Risk Score (eg, www.sorcan.ca/iscore) may be useful when assessing the risk of bleeding and overall stroke outcomes, although they have not been validated in patients with IE who will be exposed to anticoagulation for cardiac surgery.[45–47]

The location and extent of the initial stroke may impact the risk of neurological exacerbation. A proposed classification of stroke related to IE using MRI with diffusion-weighted imaging is the following: (1) single lesion, (2) an infarction isolated to a single cerebral vascular territory, (3) disseminated punctate lesions, and (4) numerous small (<10 mm) and medium (10–30 mm) or large (>30 mm) lesions in multiple territories.[44] Although larger lesions are likely more worrisome for hemorrhagic conversion, other patterns such as multiple cerebral infarcts were not correlated with increased risk of hemorrhagic conversion in comparison with single lesions.[42] With regard to the affected brain region, the most commonly affected is the middle cerebral artery territory (40%), frontoparietal (20%), multifocal (10.8%), and thalamus (4.6%).[8,45] Of patients that underwent surgery, those with the middle cerebral artery territory affected have less complete neurological recovery in comparison with non–middle cerebral artery (50% versus 83%, P=0.01). Garcia-Cabrera et al[11] performed a retrospective review of 1345 patients with IE at 8 Spanish centers of whom 25.3% had neurological complications (n=340); 72%

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were minor (silent embolism, transient ischemic attack, or stroke <30% of a single lobe) and 28% were moderate to severe (stroke involving >30% of a lobe or multiple emboli). Of those with moderate-to-severe strokes, 28% underwent surgery (15/54 patients) overall, with 40% mortality (2/5) when operated on within the first 2 weeks and a 20% mortality (2/10) when operated on after 2 weeks. However, for those with a minor ischemic injury, there was no difference in mortality between patients that underwent surgery within 2 weeks and later than 2 weeks (47% versus 50%), and hemorrhagic conversion was seen in 11% for surgery within 1 week, in 10% in the second week, and in 27% in the third week.

In summary, for most patients with ischemic stroke, early surgery offers better outcomes and survival with a relatively low cumulative risk of neurological worsening. Patients with severe neurological deficits, altered level of consciousness, and large parenchymal hemorrhage require more individualized decisions because the risk of neurological deterioration is greater.

INTRACEREBRAL HEMORRHAGE AND SURGICAL TIMING

Intracerebral hemorrhage indicates primary bleeding with or without concomitant ischemic stroke. Not surprisingly, the presence of intracerebral hemorrhage is correlated with a significantly higher risk of surgical mortality.[17,19] Garcia-Cabrera et al[11] reported new cerebral bleeding and mortality in 50% and 75% of patients with cerebral hemorrhage undergoing surgery within 2 weeks, 33% and 67% for surgery between 2 and 3 weeks, and 20% and 40% for surgery later than 3 weeks, respectively. Eishi et al[9] report an overall mortality of 19% and exacerbation of neurological deficits in 19% of patients with hemorrhagic stroke who underwent surgery after 4 weeks. Mortality was 20% in 5 patients between 2 and 3 weeks, 0% in 6 patients between 3 and 4 weeks, and 19% in 21 patients >4 weeks. In the Japanese Adult Cardiovascular Surgery Database, patients with IE and cerebral hemorrhage had trends toward lower incidence of hospital death when operated on between 1 and 3 weeks (OR, 0.79; P=0.84) or >3weeks (OR, 0.12; P=0.2) in comparison with those who had surgery within 7 days.[10] The overall surgical mortality in patients with cerebral hemorrhage, ischemic cerebral infarction, or with no cerebral complication was low in all groups, ≤9.1%. Thus, hemorrhagic strokes confer a worse prognosis, and some form of surgical delay is likely prudent, guided by serial neurological imaging as in our patient in Case 1. Optimal patient selection and timing of surgery remain open questions and may ultimately depend on the size and other characteristics of the hemorrhagic lesions.

On the other end of the spectrum are those patients with large ischemic stroke and space-occupying intracerebral hemorrhage with potential for real herniation. Although this is a less common scenario because of the underlying pathophysiological mechanisms in stroke secondary to IE, such patients require hemorrhagic evacuation and further investigation of the underlying cause of intracerebral hemorrhage (eg, ruptured infectious aneurysm) with delayed surgery following discussion with the endocarditis team.

In our patient in Case 1, planned early surgery was delayed for stabilization of a small hemorrhagic conversion of an ischemic stroke as assessed by serial CT scans. The timing of cardiac surgery should involve the endocarditis team and is usually not performed before 4 weeks. In Case 2, urgent surgery was required, despite multiple strokes and hemorrhagic conversion. This surgery was performed without worsening the neurological injury. A mycotic aneurysm was embolized just before the heart operation to reduce the risk of rebleeding.

OTHER CEREBRAL COMPLICATIONS AND SURGICAL TIMING

Patients with IE face a range of neurological insults as a result of sepsis, immune-mediated vasculitis, and septic embolism. Taken together, they contribute to the peri- and postoperative risk attributable to vascular friability, infectious aneurysm, secondary injury from an ischemic stroke, or progression of microhemorrhages.[48]

Silent Cerebral Embolism

Silent infarctions detected only by neurological imaging and transient ischemic attacks can affect clinical outcomes and cognition. The precise long-term outcome in comparison with clinically evident strokes is unclear. A prospective MRI study of 109 IE patients without neurological manifestations showed occult abnormalities in 71.5% including ischemic lesions (37%) and cerebral microhemorrhages (57%), subarachnoid hemorrhage (3%), microabscesses (3%), and infectious aneurysm (3%).[24] Several reports suggest that the risk of mortality with silent infarctions is low and approaches that of patients without any neurological injury.[7,13,14,16] Such ischemic lesions appeared mostly as multiple small infarcts in watershed territories. However, Misfeld et al,[49] found that silent embolic events were just as harmful as symptomatic events with similar hazards for long-term mortality. Also, a small percentage of patients with no obvious preoperative neurological insult will have a postoperative intracranial hemorrhage, suggesting that subclinical insults may be prognostically important.[11] Routine cerebral imaging should be considered for all patients presenting with IE to help assess risk, but cardiac surgery should not be delayed or deferred when indicated in the presence of silent stroke.

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Infectious (Mycotic) Intracranial Aneurysms

Infectious intracranial aneurysms, commonly called mycotic aneurysms, which implies a fungal etiology, are found in 2% to 4% of patients with IE and account for 5% to 15% of those with neurological presentation.[22,49] However, given that most events are subclinical, the true incidence may be higher. Diagnosis, risk assessment, and treatment require vascular imaging: CT angiography or cerebral angiography. Vascular imaging is indicated for all patients with central nervous system bleeding more than microhemorrhages to rule out a ruptured aneurysm. Detection of an infectious aneurysm is very unlikely in a patient without hemorrhage. Only an initial liberal policy with regard to indication for angiography can eventually disclose the true incidence and associated risk. Deciding need for angiography and management requires involvement of neurological and neurosurgical expertise.

The management of unruptured intracranial aneurysms depends on the risk of rupture based on absolute size, growth rate, presence of symptoms, and other anatomic characteristics. Smaller aneurysms may be monitored clinically and with serial imaging and may not have an impact on surgical timing.[50] The mortality of ruptured in comparison with unruptured intracranial aneurysms is very high, 80% versus 30%, respectively.[51] There are rare reports of patients who have had successful endovascular repair of ruptured and large unruptured aneurysms (>7–10 mm) who then go on to have definitive valvular surgery within a week with good outcome.[52–56] Importantly, endovascular stenting necessitates short-term administration of clopidogrel, which may impact surgical timing.

In summary, for the vast majority of patients with unruptured infectious aneurysms, no specific treatment is needed and cardiac surgery should not be delayed. For ruptured infectious aneurysm and hemorrhage, surgery is often delayed and based on serial imaging and clinical progression.

Cerebral Abscess

Cerebral abscesses are seen as multiple rim-enhancing lesions on CT or MRI, which may cause edema, mass effect, or hemorrhage. Large abscesses with mass effect require serial imaging and possible neurosurgical intervention, particularly when there is poor response to antibiotics. If the abscess is large and symptomatic, causing neurological deterioration, the management of the abscess drainage may take precedent over cardiac surgical intervention. Smaller abscesses should not impact the timing of surgical intervention.

Meningoencephalitis

Patients with meningitis and encephalitis represent a high-risk cohort of patients with IE.[45] In a multicenter study of 1345 patients with IE, encephalopathy occurred in 5% and meningitis occurred in 1.2%.[21] However, meningitis or meningeal reaction was found in 20% of critically ill patients with IE.[20] There are no data to suggest that meningitis or encephalitis should impact the timing of surgery.

In summary, there is a wide variety of neurological complications of IE. Silent cerebral microemboli are found in the majority of patients with left-sided IE by MRI but their clinical significance is unknown. Other complications, including intracranial aneurysms, arteritis, abscess, and meningoencephalitis, are less common and scant data exist regarding their impact on prognosis.

CURRENT GUIDELINES

There is general agreement in current practice guidelines from the United States and Europe regarding surgery for IE complicated by cerebral injury (Table 3).[31,35,36] In a Scientific Statement from the AHA titled "Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications," no delay for surgery may be reasonable if the neurological damage is not severe (class IIb; level of evidence [LOE] B) and a delay of at least 4 weeks for major ischemic stroke is recommended (class IIa; LOE B).[31] In the 2015 European Society of Cardiology Guidelines for the Management of Infective Endocarditis, the recommendation is no delay of surgery to manage heart failure, uncontrolled infection, abscess, or a persistently high embolic risk in the absence of coma (class IIa; LOE B).[35] The Society of Thoracic Clinical Practical Guidelines suggests that delay of less than <4 weeks may be reasonable for cardiac dysfunction, recurrent stroke, or systemic embolism or uncontrolled infection (class IIb; LOE C) and recommends a delay of at least 4 weeks for major ischemic stroke (class IIa; LOE C).[36] For transient ischemic attack and silent ischemic stroke detected by neurological imaging, the ECS and AHA guidelines do not recommend delay of surgery. Thus, overall, the guidelines suggest it may be reasonable in some circumstances to consider surgery within 4 weeks for minor neurological injuries/events (class IIb recommendation), and to provide a stronger recommendation to delay of surgery beyond 4 weeks for major neurological injury unless there is an imminent risk of death (class IIa recommendation). For stroke with hemorrhagic conversion, all 3 guidelines are consistent in recommending at least 4 weeks delay for surgery, but they did not differentiate based on the etiology of the hemorrhage (eg, high-risk ruptured infectious aneurysm).

ENDOCARDITIS TEAM

The American and European Guidelines strongly endorse shared decision making by a multidisciplinary

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Table 3. Current Endocarditis Management Guidelines

Guideline	Year	Timing of Surgery		
		Silent Embolism/TIA	Ischemic Stroke	Hemorrhagic Stroke
AHA	2015	No delay (class IIb; LOE B)	No delay if neurological damage is not severe (class IIb; LOE B) At least 4 wk for major ischemic stroke (class IIa; LOE B)	At least 4 wk (class IIa; LOE B)
ESC	2015	No delay (class I; LOE B)	No delay for heart failure, uncontrolled infection, abscess, persistent high embolic risk in absence of coma (class IIa; LOE B)	>1 mo (class IIa; LOE B)
STS	2011	-	Delay of <4 wk for cardiac dysfunction, recurrent stroke or systemic embolism or uncontrolled infection despite adequate antibiotic therapy (class IIb; LOE C) At least 4 wk from the stroke, if possible, for major ischemic stroke (class IIa, LOE C)	At least 4 wk from the stroke, if possible (class IIa, LOE C)

Table data from Baddour et al[31], Habib et al[35], and Byrne et al.[36]

AHA indicates American Heart Association; ESC, European Society of Cardiology; LOE, level of evidence; STS, Society of Thoracic Surgeons; and TIA, transient ischemic attack.

Heart Team for management of complex coronary revascularization[57,58] and for valvular heart disease.[59,60] Similarly, an International Working Group has recommended that patients with complex IE should be treated by a dedicated team of multidisciplinary experts.[61] The Working Group on Infective Endocarditis at the Hospital Clínic de Barcelona has also published recommendations based on their 30-year experience with a dedicated endocarditis team.[62] The team should include cardiac surgeons, cardiologists, infectious disease specialists, neurologists, interventional neuroradiologists, and other specialists as necessary. Additional specialists may include nephrology, orthopedic surgery for spine involvement, cardiovascular pathologists, home care support for outpatient parenteral antibiotic treatment, and specialists to manage intravenous drug abuse. Given that patients with IE and cerebral embolism are among the highest-risk surgical candidates, we advocate for referral to tertiary centers with an experienced endocarditis team. Currently, the Hospital Clínic de Barcelona experience is an exception and not the rule, because the development of an endocarditis team requires a significant investment of time, which is often not financially reimbursed. Finally, it is important that such meetings should not cause delays in decision making and treatment.

AREAS OF UNCERTAINTY

Evidence regarding the optimal time interval between stroke and cardiac surgery remains incomplete because of the lack of controlled studies and the diverse patient population with variable combinations of cardiac and cerebral pathologies. Earlier reports of the treatment of IE patients with neurological complications did not have the benefit of modern imaging technology, which is so much more sensitive and specific than what was available even 10 years ago. In addition, IE patients are encountered relatively infrequently in most institutions, and large series of IE patients have only been available in multicenter studies. Such collective series have reflected wide variations in experience, patient selection, and outcomes among the participating institutions.

So why are the outcomes in patients with IE and neurological complications better than they used to be? We believe there are many reasons for this: greater experience, earlier surgery in general means less damage to the heart and less sick patients, the operations are technically better and more expeditious and shorter than what they used to be, and anesthesia management and perfusion technology are improved. In addition, greater attention to neurological complications results in the use of more sensitive imaging modalities with visualization of smaller lesions than previously were undetected. These smaller lesions correlate with lower risk of hemorrhagic conversion and worsening of deficits. Better processes of care, particularly in tertiary care institutions, also likely contribute to improvement of clinical outcomes after stroke. To prove this, we need carefully designed prospective studies with pre- and postoperative brain imaging. Some of these questions may be answered by well-designed randomized studies.

Clinical judgment is still critical in weighing the severity of the cardiac symptomatology and pathology versus the risk to the brain of surgery at a given time. The clinical judgment will take all the factors into consideration and judge the risk associated with the neurological lesions by size, number, location, amount of hemorrhage and symptoms, and match that with the urgency of the needed operation and the risk of more emboli from the heart to the brain. The final decision should be taken by the multidisciplinary endocarditis team. We offer an algorithm to guide decision making for patients with IE and ischemic stroke (Figure 4). However, there are uncertainties, which the management team has to fill in with local expertise.

The recommendations for anticoagulant therapy in patients with IE are based on a low level of evidence. The

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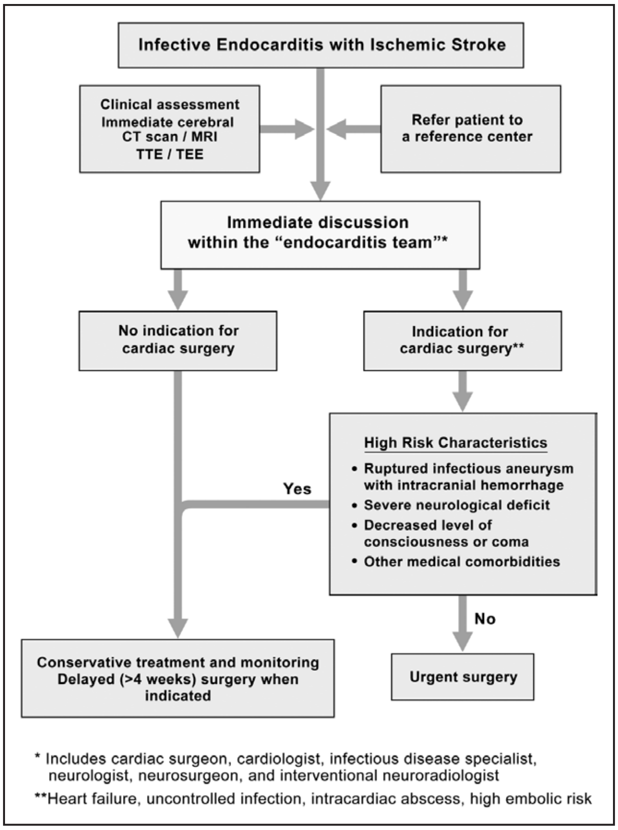

Figure 4. Algorithm for management of patients with infective endocarditis complicated by embolic stroke.
CT indicates computed tomography; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiogram.

AHA guidelines suggest, for patients with mechanical valve IE with embolic stroke, anticoagulation should be discontinued for at least 2 weeks of antibiotic therapy to prevent hemorrhagic conversion (class IIa; LOE C).[31] Heparin should be used with caution in patients with IE. In terms of valve prostheses in the context of cerebral embolism, we generally prefer the use of bioprosthetic valves to avoid the need for postoperative oral anticoagulation.

Finally, it is unclear who should have specialized imaging to rule out intracranial infectious aneurysms. We suggest the use of noninvasive CT or MRI angiography for IE patients with neurological symptoms and verified intracerebral bleeding, but, if these investigations are negative and suspicion remains high, conventional 4-vessel angiography should be considered.

PRACTICAL RECOMMENDATIONS FOR CLINICIANS

1. The managing endocarditis team for patients with IE should include infectious disease, cardiology, and cardiac surgery with input from neurology, neurosurgery, radiology, and other specialists as indicated and needed.
2. Preoperative neurological imaging should be performed for all patients with IE. Vascular imaging (CT angiography or angiography) should be performed in patients with a cerebral hemorrhage to rule out ruptured infectious aneurysm.
3. For patients with neurological symptoms and deficits, a thorough neurological evaluation, complete workup, and prognostication should guide further management.
4. Timing of surgery in patients with symptomatic ischemic stroke should be a balance of the severity of cardiac decompensation and pathology and the severity of neurological symptoms.
5. Patients without neurological symptoms but positive imaging suggesting cerebral embolism should also be evaluated by a neurologist preoperatively.
6. Patients with severe cardiac decompensation and severe mechanical cardiac lesions should be operated on emergently or urgently unless the neurological status (eg, coma, large intracranial hemorrhage) precludes heparinization or when neurological recovery to reasonable quality of life is very unlikely (eg, multiple stroke or severe neurological deficits in patients with preexisting comorbidities).
7. For patients with IE and silent microembolism, transient ischemic attack, and ischemic strokes without more than minimal hemorrhagic conversion, we recommend no delay in surgery. The presence of large vegetations (>10 mm) on the aortic or mitral valve add to the urgency.
8. For patients with IE and ischemic stroke, it is reasonable to proceed with surgery without delay, unless there is severe neurological impairment or decreased level of consciousness/coma.
9. For patients with IE and parenchymal hemorrhage, it is reasonable to proceed for small lesions or to delay surgery, typically between 0 and 4 weeks, depending on the size of involvement and the urgency of the operation. Vascular imaging should be performed.
10. For patients with IE and cerebral abscess, we recommend no delay in surgery.
11. Patients with unruptured infectious intracranial aneurysms should be evaluated by a neurosurgeon preoperatively with the underlying goal of avoiding delays in cardiac surgery.
12. In the uncommon event that hemorrhagic evacuation is needed to treat a malignant infarct, we recommend a reassessment for cardiac surgery in consultation with the neurosurgical team in 2 weeks.

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CONCLUSIONS

IE remains the most serious complication of valvular heart disease. Any neurological complication of IE adds to the mortality risk and morbidity from residual neurological deficits. The decision to operate, and the optimal timing of surgery, as well, in this complex subset of patients should be based on a team approach including infectious disease, cardiology, cardiac surgery, and neurology. Earlier retrospective studies of surgical management of IE patients with cerebral complications suggested that delayed surgery was correlated with improved outcomes. However, more recent studies applying propensity matching have found lower overall mortality, lower risk of cerebral exacerbation, and no evidence for worse outcomes with earlier surgery. We present practical suggestions to guide clinicians when facing this common and often catastrophic presentation. In addition, it may be reasonable to refer complex IE patients to larger centers with a special interest and expertise in all aspects of the management, especially centers with advanced cardiac and neurointerventional capabilities.

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DISCLOSURES

None.

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FOOTNOTES

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