REVIEW ARTICLE

Neurological complications in infective endocarditis. What does the cardiac surgeon need to know?

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Neurological complications of infective endocarditis have an incidence of 15-30% of patients that present neurologic symptoms but the incidence of silent cerebral is even higher (reported to be up to 80%). The indication for cardiac surgery must be taken for a multidisciplinary team (Endocarditis Team) in order to achieve the best possible outcome. Although specific recommendations are always tailored to the individual patient, there are guiding principles that can be used to help the decision-making process. The purpose of this paper is to review the pathophysiology, epidemiology, clinical manifestations, diagnosis of neurological complications of infective endocarditis, and the final clinical decision making process for cardiac surgery.

***Key words*: Infective endocarditis; Neurological complications; Stroke; Intracranial hemorrhage; Infectious vascular aneurysm.**

Las complicaciones neurológicas de lal endocarditis infecciosa tienen una incidencia de 10 al 15% de los pacientes que presentan manifestaciones neurológicas. No obstante, la incidencia del fenómeno silemte cerebral es aun mayor (de hasta un 80%). La indicación quirúrgica debe tomarse desde la perspectiva de un equipo multidisciplinario (Team de Endocarditis) para lograr el mejor resultado posible. Aunque las recomendaciones específicas van acorde a cada paciente, existen principios como guías clínicas que pueden ser utilizados para ayudar en el proceso de toma de decisiones. El propósito de este artículo es revisar la fisiopatología, epidemiología, manifestaciones clínicas, diagnóstico de la complicaciones neurológicas de la endocarditis infecciosa, así como le proceso de toma de decisiones para aplicar la indicación de cirugía cardiaca.

***Palabras clave:* Endocarditis infecciosa; Complicaciones neurológicas; Stroke; Hemorragia intracraneal; Aneurisma vascular infeccioso.**

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In order to understand all concepts regarding the mitral valve Infective endocarditis (IE) is an infectious disease associated with high morbidity and mortality. Despite the great advances in cardiovascular medicine, it is still one of the most challenging acute cardiovascular pathologies. IE has remained as a prevalent disease in general and tertiary hospitals, with a fairly constant incidence over the last five decades, accounting for one case per 1000 hospital admission. In developed countries [1], the incidence of IE ranges from 3 to 9 cases per 100,000 per year, and is more common in men [2,3]. Intracardiac vegetations may result in life-threatening embolic events. The overall risk of peripheral embolism is 20-50%, and once antibiotic therapy is started, this risk decreased to 6-21% [4]. The brain and the spleen are the most frequent sites of embolization in the left-side IE, while pulmonary embolism is frequent in native right- sided and pacemaker lead IE.

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Neurological complications (NC) are the most common extra cardiac complications of IE with and incidence of 15-30% of patients that present symptomatic neurological complications but in recent years, thanks to advances in neuroimaging technology [5], silent cerebral complications can be detected; and their incidence is much higher than expected, reported to be up to 80% [6].

The risk of developing NC from IE depends mainly on characteristics of the vegetations and duration of antibiotic therapy. Larger, left-sided lesions on the anterior leaflet of the mitral valve are more common to embolize, and this is more likely to occur before antibiotics are started or within the first

week after the antibiotic initiation. The presence of NC, and their type and severity have a huge impact the management of valvular lesions and the timing of surgery for active IE.

NC of IE can arise through the following mechanisms, frequently associated in the same patient: occlusion of cerebral arteries by emboli secondary to endocardial vegetation; cerebral hemorrhage because of vasculitis or mycotic aneurysm; infection of the meninges; sepsis related encephalopathy and brain abscess [7].

*Table 1. Summary of neurological complications in Infective Endocarditis**

NEUROLOGIC COMPLICATION	EPIDEMIOLOGY	CLINICAL MANIFESTATION	TREATMENT	RECOMMENDATIONS FOR CARDIAC SURGERY
Ischemic stroke	Symptomatic (20 to 40% of patients) Asymptomatic (30 to 40% patients)	Focal deficits, encephalopathy, and seizure	Avoid IV tPA, antiplatelet agents, and anticoagulation	Clinically silent/small infarcts should not delay cardiac surgery Larger infarcts may warrant delaying surgical intervention for up to 4 weeks if there is not a strong indication for surgery
Intracerebral hemorrhage	Hemorrhage 4 to 27% of patients Microhemorrhage is present in up to 57% of patients with IE	Focal deficits, headache, encephalopathy, and seizure	NVE: avoid all antiplatelets and anticoagulants PVE: prophylactically, convert oral anticoagulants to IV heparin and should hemorrhage develop stop anticoagulation for 10 to 14 days	Postpone cardiac surgery for 4 weeks following clinically significant hemorrhage
Infectious intracranial aneurysm	Present in 2% to 4% of patients	Headache, seizures, focal deficit, encephalopathy, ophthalmoplegia, and rarely proptosis	Antibiotics and serial imaging for stable, small, unruptured aneurysms. Endovascular repair of large or enlarging unruptured aneurysms if amenable. Open surgical clipping for large or enlarging unruptured aneurysms not amenable to endovascular techniques or in eloquent areas where surgical anastomoses may spare function	Postpone cardiac surgery for 1 to 2 weeks following aneurysmal repair
Cerebral abscess	1% to 7% of patients	Focal deficits, headache, encephalopathy, persistent fever, and seizures	Antibiotics alone for small or multifocal abscesses. Surgical drainage for abscesses that are large or do not respond to antibiotics. Neurosurgical intervention as appropriate for hydrocephalus or significant mass effect	Usually, will not interfere with surgical planning. Prioritize neurosurgical intervention in the setting of hydrocephalus or significant mass effect. If hemorrhage accompanies, manages as mentioned above
Meningitis	1 to 20% of patients	Headache, encephalopathy, seizure, neck/back pain, nuchal rigidity, and photophobia	At least 4 weeks of antibiotics	Usually, will not interfere with surgical planning

Abbreviations: IE, infective endocarditis; IV, intravenous; tPA, tissue plasminogen activator; PVE, prosthetic valve endocarditis; NVE, native valve endocarditis. *Adapted from [62].

Neurological Complications **(Table 1)**

Stroke

Acute ischemic stroke is the most common NC of IE, and the mechanism of acute cerebral ischemia is very likely to be embolic. Ischemic strokes in IE most commonly occur in the middle cerebral artery territory [8], likely as a result of the high percentage of blood volume in these territories. However, multifocal infarction is also common and frequently involves the end arterial territories of cerebral vessels. Cerebral emboli result from dislodgment or fragmentation of cardiac vegetations, followed by vessel occlusion; this results in various degrees of ischemia and infarction depending on the size vessels and the collateral blood flow. Occlusion of cerebral arteries, with either stroke or transient ischemic attack, accounts for 40% to 50% of the NC of IE.

The main risk of neurologic complications is the absence of appropriate antibiotic therapy. Most neurologic complications are already evident at the time of hospitalization or develop within a few days. The probability of developing these complications decreases rapidly once antimicrobial therapy has been started [9]. In the ICE-PCS study [10], the incidence of stroke in patients receiving antimicrobial therapy was 4.82/1,000 patient days in the first week of therapy and decreased to 1.71/1,000 patient days in the second week. This rate continued to decline with additional therapy [11]. Moreover, recurrent neurologic events, although possible even late, are uncommon. The localization of the infection has been found to influence the occurrence of neurologic events in some but not all studies, with a higher risk in patients with mitral valve vegetation [12]. Obviously, patients with large vegetations, measuring more than 10 or 15 mm and those with mobile vegetations are at increasing risk for embolism [13]. When neurologic complication rates were assessed as a function of the causative agent, the frequency of NC involvement was two to three times higher with S. aureus than with other pathogens [12]. However, in IE caused by less frequent pathogens, such as Streptococcus agalactiae and fungi, the incidence of emboli is high and is explained by the large size of the vegetations [14,15]. Summarizing the medical literature, the most common scenarios in which the risk of cerebral ischemia is more likely are: 1) anterior mitral valve leaflet endocarditis confers the highest risk [16]; 2) left-sided endocarditis associated with a much higher risk of stroke; 3) S Aureus infection before or less than 1 week after initiation of antibiotics.

Emboli may cause a wide variety of clinical symptoms and signs, including impaired consciousness or focal deficits, depending on their size, location, and number. When systematic MRI is performed, large systematized and small ischemic lesions are seen in one third and two thirds of embolic episodes, respectively.

Management of stroke in the setting of IE differs from that of stroke due to noninfective mechanisms insofar as anticoagulation and antiplatelet agents are contraindicated, at least [5,13]. The management differences to other types of ischemic stroke pose a potential clinical conundrum in the scenario whereby stroke is the presenting symptom of IE. If a patient appears with a stroke that is amenable to thrombolytic treatment, antiplatelet agents, or anticoagulation, one could inadvertently use a thrombolytic drug in a patient with occult endocarditis, thereby precipitating devastating results.

Symptomatic and silent NC are a major cause of morbidity and mortality in IE and may interact with the decision for surgery, and due for the importance of this complications currently is recommended by guidelines [17-19], systematic neuroimaging procedures such as brain MRI or CT scan to look for these kinds of complications. The impact of detection of silent NC on the prognosis of patients is not well known and differs according to studies [6,20,21].

Cerebral Hemorrhage

Cerebral hemorrhage accounts for 12% to 30% of neurologic complications of IE. Hemorrhage in the brain in patients with IE could be localized in the parenchyma or subarachnoid space. The cerebral hemorrhage may be the result of different mechanisms; can be caused by transformation of ischemic infarcts caused by septic emboli that is involved in approximately one third of patients with cerebral bleeding, due to vascular friability, or rupture of an infectious aneurysm either at the early phase of emboli or later. Quoted frequencies of cerebral hemorrhage in the literature may vary based on inclusion criteria of the aforementioned mechanisms.

A recent case-control study, using diffusion weighted MRI has revealed a high incidence of very small foci of hemorrhage. Cerebral microbleeds were observed in 57% of patients with IE compared with 15% of control subjects [22]. These lesions may reflect a subacute microvascular process leading in some cases to the development of intracranial mycotic aneurysms on distal or pial arteries. Brain hemorrhage is more frequent during the bacteremic phase of S. aureus IE and is made more likely by severe thrombopenia and anticoagulant therapy [23]. Other mechanisms of bleeding are ruptured intracranial mycotic aneurysms and septic erosion of the arterial wall without a well-identified aneurysm. The latter complication is mainly seen in patients with S. aureus IE. Cerebral hemorrhage may be the first manifestation of IE and should be suspected in a febrile patient with sudden coma and/or neurologic deficit. Another series of 198 patients who defined cerebral hemorrhage as primary intracerebral hemorrhage, hemorrhagic conversion of a prior ischemic infarct, or rupture of infectious aneurysm found the rate of cerebral hemorrhage in 27% of the patients [24]. Other study of 113 patients with a similar definition found the rate of cerebral hemorrhage to be only 4% [25]. The risk of hemorrhage may be higher in those who are on anticoagulant drugs at the time of presentation [26] or who are treated with anticoagulation or antiplatelet agents early after diagnosis. Infection as well as concomitant medications may prolong the international normalized ratio (INR), and not surprisingly patients with a supratherapeutic INR seem to be at particularly high risk of fulminant hemorrage. Nonetheless, the decision to continue anticoagulation in prosthetic valve endocarditis remains controversial. At least one study showed a higher mortality in those patients maintained on anticoagulation, several other studies report contradictory findings [27]. For instance, one series of 50 cases of prosthetic valve endocarditis found an increased rate of neurological complications in patients with prosthetic valve endocarditis who were not adequately anticoagulated [28]. A previous study of prosthetic valve endocarditis that include 52 patients reported a good outcome in mortality and morbidity in in patients who were kept on adequate anticoagulation [29].

Cerebral microhemorrhage is a silent complication of

endocarditis and recently has been implicated in predicting overt hemorrhage. Cerebral microhemorrhage has been detected in 57% of cases with IE, usually located cortically and with an average of about 8 microbleed per patient [30]. The proposed mechanism to cause these microhemorrhages is a vasculitis secondary to an infectious process [31].

In the current practice, the majority of Endocarditis Team around the world do not recommend acutely treating patients with native valve IE and ischemic stroke or microhemorrhage with anticoagulation but if the patients have another indication for anticoagulation such as atrial fibrillation, deep venous thrombosis (DVT), or pulmonary embolism, the decision must be individualized. In general, the medical literature favor delaying anticoagulation for at least 14 days following treatment initiation in ischemic stroke. An inferior vena cava filter may act as a temporizing measure in patients with DVT. In prosthetic valve endocarditis, the experts usually bridge patients from oral anticoagulants to IV heparin immediately with lower intensity than in patients without IE. In patients with prosthetic valve endocarditis and moderate to large ischemic strokes, we usually recommend discontinuing anticoagulation for at least 10 to 14 days. For smaller strokes in patients with prosthetic valve endocarditis, such as asymptomatic punctuate infarcts seen only on magnetic resonance imaging, we may continue anticoagulation using heparin with serial surveillance imaging. As anticoagulation is often required during or after a surgical procedure, neurologic deterioration is much more likely when surgery for valve replacement or repair is undertaken too soon in the setting of intracranial blood as is described.

Intracranial mycotic aneurysms (ICMA)

Although the term "mycotic aneurysm" has historically been used to describe septic aneurysms from any microorganism, the word "mycotic" connotes a fungal etiology. Since fungi can produce intracranial aneurysms as well as bacteria, "infectious intracranial aneurysm" is a preferred term. The infection intracranial aneurysm (IICA) are relatively rare, accounting for less than 10% of neurologic complications of IE [32]. They usually result from septic embolization to the vasa vasorum or to the intraluminal space of the vessel itself. Septic emboli are responsible for an inflammatory lesion starting on the adventice surface and ultimately destroying the intima. IICA are multiple in 25% of the cases and are mostly located in the distal branches of the middle artery. The mechanism is likely due to destruction of the vessel wall through interaction of organism with the immune inflammatory response of host (vasculitis process) [32-34]. Streptococci, and to a lesser extent S. aureus are responsible for most ICMA. Non-ruptured IICA are responsible for fever, headache, seizures, and focal deficit. Patients with ruptured ICMA have sudden arachnoid or intracerebral bleeding, associating decreased level of consciousness, intracranial hypertension, and focal deficit. Rupture generally occurs at the early phase of IE; but in some patients, especially those with streptococcal IE, rupture may be observed during antibiotic course or even after the end of therapy. CT scan angiography and MR angiography are of equal value to detect ICMA >5 mm. Although conventional angiography may still be useful for the detection of very small ICMA, two-dimensional and three-dimensional helical CT also have high sensitivity [35].

Management of IICA depends on several factors: size, location, rupture (mortality up to 80% in rupture IICA) and expertise of the medical team. The rupture IICA may be managed by open or endovascular procedures following 2-3-weeks delay for cardiac surgery. In the unruptured IICA there is more disagreement in cases where there is an emergent or urgent indication for cardiac valve replacement. A 2002 study reported on 5 patients who had endovascular repair for unruptured aneurysms and underwent valve repair within a week without complication [36]. A more recent review suggests the use of antibiotics and serial imaging for stable, small, unruptured aneurysms or antibiotics and endovascular treatment for large, enlarging, or symptomatic unruptured aneurysms [37]. If endovascular intervention is unfeasible, clip reconstruction or proximal vascular occlusion with or without bypass is recommended. Anticoagulation, antiplatelet, and thrombolytic therapy should not be used in the setting of a known IICA, as there would be very few scenarios in which the risk of aneurysm rupture is outweighed by the need for acute anticoagulation.

Meningitis and brain abscess

Meningitis or sterile inflammatory reaction to infection or brain ischemia or hemorrhage occurs in 2% to 20% of patients with IE and up to 40% of those with neurologic complications [38]. Meningitis may occur during bacterial endocarditis caused by pyogenic organism such as S. aureus and enterococci. In subacute bacterial endocarditis, sterile emboli to the brain may lead to signs of meningeal irritation and cerebral fluid pleocytosis. In most cases, except in the rare cases of Streptococcus pneumoniae IE, the cerebrospinal fluid (CSF) is not purulent and the presence of pathogens is very transient. A typical ICU candidate has an acute febrile and toxic illness with heart murmur, petechiae, and meningeal signs. CSF examination finds moderate pleocytosis and Gram-positive cocci. Blood cultures yield S. aureus, and echocardiography confirms left-sided IE. Choice of treatment of IE related meningitis should be guided by standard principles of bacterial meningitis management just with the difference that in cases of meningitis related with IE the duration of the treatment is longer (4-6 weeks instead of 10-14 days) [39].

Brain abscess is considered to be a rare complication of IE affecting between 1-7% of patients with IE [4,24]. This complication should be suspected in the absence of obvious source and when multiple abscesses are present. Most brain abscesses observed in the setting of IE are caused by methicillin-resistant S. aureus. By MRI, these are usually seen as multiple rim-enhancing lesions at the gray-white junction, which can be the cause of significant edema, hemorrhage, and mass effect.

The treatment for brain abscess is first and foremost with antibiotics to include MRSA coverage if the organism is not known. As they are most commonly multifocal, surgical resection may not be feasible. However, when significant hydrocephalus or impending herniation is present, supportive surgical interventions may be necessary.

In general, following the guidelines for non-IE-associated bacterial brain abscesses, we recommend at least 4 weeks of IV antibiotics for those who have been surgically managed and 6 to 8 weeks for those medically managed [40], monitored by serial imaging to assess the size and diffusion restriction of the abscess. A longer period of treatment can be necessary to achieve resolution.

Encephalopathy

Encephalopathy is a common complication of IE that should prompt further workup. Encephalopathy may be secondary to systemic insults such as fever, azotemia, electrolyte disturbances, or hypercarbia or point to underlying central nervous system involvement in the form of ischemic stroke, hemorrhage, cerebral abscess, or meningitis as discussed previously.

Neurological complications of infective endocarditis and cardiac surgery

The first thing that we must have in mind and know is that IE is not a single disease, but rather may present with very different aspects depending on the first organ involved, the underlying cardiac disease, the microorganism involved, the presence or absence of complications and the patients characteristics, make to this pathology very hard to treat; so no single practitioner will be able to manage and treat a patient in whom the main clinical symptoms might be cardiac, rheumatological, infectious, neurological or other. For these reasons a very high-level expertise is needed from several specialties and the first recommendation to decrease the morbi-mortality in IE is that any patient with the diagnosis of IE must be managed in a tertiary center or reference center by an Endocarditis Team (Cardiologists, Neurologists, Cardiac surgeons, Neurosurgeon, Infection disease specialist, Rheumatologist and other), the Task Force on the management of IE of the ESC strongly supports the management of patients with IE in reference centers by specialized teams (Endocarditis Team) [41,42]. A multidisciplinary approach can substantially reduce the still unacceptably high morbidity and mortality in patients with IE, as it allows early diagnosis and appropriate comprehensive management. Decision-making within the Endocarditis Team must follow a standard protocol that is based on current clinical guidelines for the management of IE. If surgery is indicated, it is best performed sooner than later in most instances.

Patients with IE are at high risk for embolic events, and at high risk for bleeding complications as was described above. The available limited data suggest that neither anticoagulant therapy nor aspirin reduces the risk of embolism in patients with IE. Therefore, neither anticoagulant therapy nor antiplatelet therapy is indicated to reduce the risk of thromboembolic complications in IE. Patients with IE frequently have one or more coexistent conditions that pose a risk of thrombotic complications others than IE; in such patients, we weigh the risk of withholding antithrombotic therapy against the risk of receiving antithrombotic therapy.

Currently no study has evaluated the effect of systematic neuro-imaging on clinical decisions in patients with IE. Cerebral MRI with angiography performed up to 7 days after admission led to a modification of therapeutic plans, including surgical plan modifications, for 24 (18%) of 130 patients mostly non-ICU patients [21]. However, because silent neurologic complications do not alter outcome, the role of systematic neuroimaging should be further evaluated. Although the majority of neurologic events are already present at ICU admission [7], some may occur later. Because clinical modifications may be difficult to evaluate in those ICU patients who are sedated, systematic CT scan or MRI should be performed when cardiac surgery is considered.

Patients who benefit the most from cardiac surgery are those operated on for heart failure caused by severe aortic or mitral regurgitation, fistula into a cardiac chamber or valve obstruction [43]. Other indications are uncontrolled infection and prevention of embolism in high-risk patients (vegetation >10 mm). In recent series [5,44], 48% to 50% of patients (up to 75% in specialized medical-surgical centers) undergo valve replacement during the acute phase of IE (i.e., before the completion of antibiotic treatment). In many studies, but not all, surgery is independently associated with a lower risk of mortality.

However, in patients with neurological complications, the safety of cardiopulmonary bypass has been controversially debated for years. Anticoagulation during cardiac surgery may increase the risk of hemorrhagic transformation of an asymptomatic ischemic stroke. Moreover, episodes of hypotension during procedure might exacerbate a pre-existing ischemic brain lesion. Finally, the need for anticoagulation in patients with mechanical valves increases the risk of cerebral bleeding. However, after a neurological event, most patients still have at least one indication for cardiac surgery. From studies published during the mid 1990s [45,46], an interval of at least 2 weeks between an embolic event and cardiac surgery was recommended. Several recent studies have challenged this statement and their results suggest that early cardiac surgery, when indicated, is possible even after a neurologic event. In a consecutive series of 214 patients undergoing cardiac surgery for IE, 61 had computed tomography or magnetic resonance imaging-verified stroke. In those patients, early surgery (median 4 days) was not associated with more new neurologic events (3.2%) compared with late surgery, and the percentage of complete recovery was similar. However, in the case of middle cerebral artery stroke, recovery was only 50% and was significantly lower compared with non-middle cerebral artery stroke. Moreover, in comparison with non-stroke patients, the age-adjusted perioperative mortality risk was 1.7-fold higher and long-term mortality risk was1.23-fold higher in stroke patients [47]. Two other studies showed that urgent cardiac surgery in patients with embolic events was feasible with worsening of neurologic status in 6% and 0%, respectively [20,48]. Moreover, in a series of 48 patients with prosthetic valve IE, survival was better in patients operated within 8 days of diagnosis compared with those operated later [49]. In addition, the risk of neurologic deterioration after cardiac surgery in patients with silent neurological complications is probably very low [20]. Neurologic recovery depends on preoperative status, with a percentage of good recovery of 80% when National Institute of Health Stroke Score (NIHSS) is <9 but only 35% in patients with NIHSS >15 [47]. Among 108 ICU patients with neurologic complications of IE, 52 underwent cardiac surgery (median 10 days) at the acute stage of IE. Ten (19%) experienced new neurologic events after cardiac surgery and 33 (63%) survived, the majority with good functional outcome [9]. Finally, among 1,552 patients with native valve IE included in the ICE-PCS, cardiac surgery was found to confer a survival benefit among several groups of patients, including those with stroke [50].

The recommendations from "The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology" are: 1) after a silent cerebral embolism or transient ischemic attack, surgery is recommended without delay if an indication remains; 2) after a stroke, surgery indicated for heart failure, uncontrolled

infection, abscess or persisting high emboli risk, should not be delayed. This recommendation does not apply to comatose patients; and 3) after intracranial hemorrhage, surgery must be postponed for at least 1 month [1,51] (**Table 2**).

Neurologic complications may alter directly the outcome, increasing mortality and morbidity or indirectly by contraindicating early cardiac surgery. Indeed, in ICU patients with IE, mortality reached 88% in patients who were denied surgery, partly because of neurologic complications, despite a validated indication. Early surgery (within 7 days of diagnosis) was recently shown to increase free-event survival [20,52]. Many, but not all, studies showed that neurologic complications are associated with increased mortality during IE [1,5,13,53-58]. However, results of recent studies have provided more precise information with regard to the impact of neurologic events on outcome. First; patients with only silent or transient stroke had a better prognosis than patients with symptomatic events [20]. The former have mild or moderate brain lesions, which allow early surgery to be performed with a low operative risk. Second; rather than the neurologic event per se, a better predictor of mortality is neurologic dysfunction, which is associated with location and extension of brain damage. In non-ICU patients, two studies [20,59] showed that impaired consciousness, evaluated by the Glasgow Coma score [60] or clinically, was a predictor of neurologic mortality. In ICU patients, survival with or without neurologic events was not different, whereas there were more deaths in

Table 2. Comparison of recommendations for surgical procedures in patients with infective endocarditis and neurological complications by American College of Cardiology (2015), European Society of Cardiology (2015) and American Association for Thoracic Surgery (2016).

item	ACC	ESC	AATS
IE with persistent emboli despite appropriate antibiotic therapy	Surgery is indicated (Class IIa)	Urgent surgery is indicated (Class I)	Surgery is indicated (Class Ib)
IE with large left-sided vegetations	Surgery must be considered in NVE with mobile vegetations >10 mm (Class IIb)	Class I indication for urgent surgery with vegetations > 10 mm plus other predictors of complicate course such as HF, persistent infection, abscess (Class I). Urgent surgery should be considered for isolated vegetations > 15mm (Class IIb)	Urgent or even emergency surgery may be considered in patients with NVE or PVE (Class IIb)
After silent cerebral embolism or TIA	Valve surgery may be considered in IE patients with stroke or subclinical cerebral emboli and residual vegetation without delay if intracranial hemorrhage has been excluded by imaging studies and neurological damage is not severe (ie, coma) (Class IIb)	Surgery should proceed without delay if an indication remains (Class I)	Early surgery is reasonable for patients with silent stroke (Class IIb)
After intracranial hemorrhage		Surgery must be postponed for a least 1 month (Class I)	A delay of operation for 3 or more weeks (Class IIa)
After clinically relevant stroke	In patients with major ischemic stroke or intracranial hemorrhage, it is reasonable to delay valve surgery for at least 4 weeks (Class IIa)	Surgery for HF, uncontrolled infection, abscess, or persistent high embolic risk should not be delayed. Surgery should be considered in absence of coma and CT evidence of hemorrhage (Class IIa)	Early surgery is indicated when exists a strong cardiac indication for urgent surgery (Class I)

Abbreviations: IE, infective endocarditis; ACC, American College of Cardiology; ESC, European Society of Cardiology, AATS, American Association for Thoracic Surgery.
Recommendations; NVE, native valve endocarditis; HF, heart failure; TIA, transient ischemia attack; CT, computed tomography.
a Per ESC guidelines, "urgent" surgery should be performed "within a few days".
Class I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, and effective.
Class II: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb: usefulness/efficacy is less well established by evidence/opinion.
Class III: evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful.

patients with neurologic failure defined by a neurologic Sequential Organ Failure Assessment score >2 [9], which corresponds to a Glasgow Coma score <10 [60]. Third; patients with severe neurological impairment and those with brain hemorrhage have the worse outcome. Besides mortality, neurologic recovery is a main concern. Among 106 ICU patients with neurologic complications assessed at follow-up (3-8.5 months), only 31 (29%) had a modified Rankin Scale score <3 (ability to walk without assistance) [9]. Like mortality, neurologic outcome depends on the severity of brain damage as suggested by a study conducted in patients with neurologic complications of IE. Full neurologic recovery was observed in 78% of patients with NIHSS at admission of 4-9 but in only 33% when the score was >15 [61].

Conclusions

Infective endocarditis is an important and serious disorder that is frequently complicated by neurological events including ischemic and hemorrhagic stroke, IIA, brain abscess, meningitis, an all of them contribute to severe prognosis that represent a conflicting situation for the treating team. In order to have good outcome is necessary a multidisciplinary approach to optimize medical treatment and decision-making concerning valve surgery.

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