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NEUROLOGY OF SYSTEMIC DISEASES (J. BILLER, SECTION EDITOR)

Neurological Complications of Infective Endocarditis

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Abstract

Purpose of Review The purpose of this narrative review and update is to summarize the current knowledge and provide recent advances on the neurologic complications of infective endocarditis.

Recent Findings Neurological complications occur in about one-fourth of patients with infective endocarditis. Brain MRI represents a major tool for the identification of asymptomatic lesions, which occur in most of the patients with infective endocarditis. The usefulness of systematic brain imaging and the preferred treatment of patients with infective endocarditis and silent brain lesions remains uncertain. The basis of treatment of infective endocarditis is early antimicrobial therapy. In stroke due to infective endocarditis, anticoagulation and thrombolysis should be avoided. Endovascular treatment can be useful for both acute septic emboli and mycotic aneurysms, but evidence is still limited. In patients with neurological complications, cardiac surgery can be safely performed early, if indicated.

Summary The optimal management of a patients with neurological complications of infective endocarditis needs an individualized case discussion and the participation of a multidisciplinary team including neurologists, cardiologists, cardiothoracic surgeons, neuroradiologists, neurosurgeons, and infectious disease specialists.

Keywords Infective endocarditis · Mycotic aneurysm · Neurological complications · Stroke · Cardiac surgery · Thrombectomy

Introduction

Infective endocarditis (IE) is a disease of the endocardial surface of the heart, native or prosthetic heart valves, or indwelling cardiac devices caused by a variety of infectious agents. The latest population surveys estimate that the annual incidence ranges from 3 to 10 per 100,000 persons per year [1–3].

The causes and epidemiology have changed in recent decades and reflect important medical advances, mainly in high-income countries. The frequency of IE related to rheumatic valve disease has decreased significantly. Most of the current cases are related to degenerative valvulopathies, prosthetic valves, and cardiovascular devices. Staphylococci have exceeded streptococci as the most common pathogenic agents. Meanwhile, the average patients' age has doubled [4•].

Clinical manifestations of IE include systemic, cardiac, and extracardiac multiorgan symptoms and signs. Neurological complications are the most frequent and severe extracardiac complications of IE. About 25% of patients with IE experience at least one neurological event [5].

Neurological complications of IE can be grouped as cerebrovascular (ischemic stroke, transient ischemic attack, intracranial hemorrhage, mycotic aneurysm), infectious (meningitis, brain abscess, vertebral osteomyelitis with spinal cord and/or radicular involvement, and encephalopathy), and systemic (encephalopathy, seizures) (Table 1).

Despite recent advances in diagnostic tools, antimicrobial therapy and surgical treatment of IE, morbidity, and mortality

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Table 1 Neurological complications of infective endocarditis

Neurological complications of infective endocarditis
Cerebrovascular
Ischemic stroke
Single or multiple
Intracranial hemorrhage
Hemorrhagic transformation of ischemic infarct
Septic necrotic arteritis
Anticoagulant related
Rupture of mycotic aneurysm
Subarachnoid hemorrhage
Subdural hematoma
Microbleeds
Unruptured mycotic aneurysm
Infectious
Meningitis
Brain abscesses
Single or multiple
Spondylodiscitis/vertebral osteomyelitis
Epidural, subdural, and spinal cord abscess
Systemic
Encephalopathy
Septic
Metabolic
Toxic
Due to seizures
Due to cerebrovascular complications
Due to infectious complications
Seizures

[1, 6] remain high, especially in patients with neurological complications [5]. Independent predictors of mortality include older age, cerebrovascular events, *Staphylococcus aureus* infection, and healthcare-associated IE [7].

For previous comprehensive reviews on the topic, see references [8–10].

Diagnosis of IE

The diagnosis of infective endocarditis is based on clinical, echocardiographic, and microbiological findings. The modified Duke criteria are recommended for the diagnosis of infective endocarditis [8].

The diagnosis of IE is straightforward in only a minority of patients who present with a consistent history (previous valve disease or prosthetic valve, fever) and classical manifestations (new heart murmur, splenomegaly, and multiorgan emboli). Instead, patients' complaints may focus on constitutional symptoms, primary cardiac effects, or secondary phenomena. Examples of the last include focal neurological symptoms due to embolic stroke or back pain associated with spondylodiscitis or vertebral osteomyelitis.

It may be clinically challenging to identify IE in the setting of an acute ischemic stroke within the short time window for intravenous thrombolysis. The "red flags" that may alert the clinician for the possibility of IE include the following: young age with no vascular risk factors, unexplained symptomatic or asymptomatic ischemic or hemorrhagic brain lesions (especially if multiple or simultaneous), multiple cranial abscesses, multiple cerebral microbleeds on blood-sensitive MR sequences, heart disease (previous IE, known valve disease) or non-cardiac risk factors (intravenous drug use, immunosuppression or recent dental procedure), preceding non-specific systemic symptoms, clinical stigmata of embolism, immune complex formation, or very high inflammatory markers.

The variability in clinical presentation and the importance of an early accurate diagnosis require a high suspicion rate and a prompt diagnostic strategy.

The key point of the diagnosis is to identify the causative microorganism in order to guide the antimicrobial treatment. Blood cultures should be routinely performed before the administration of antibiotics. *Staphylococcus aureus* is now the most common causative organism, being isolated in up to 30% of cases of IE [6]. This high frequency of *Staphylococcus aureus* is related to the increased proportion of healthcare-associated IE.

Transthoracic and transesophageal echocardiography can reveal vegetations in up to 90% of cases [6]. The yield of transesophageal is superior to that of transthoracic echocardiography. If IE remains a possibility, repeated examinations should be performed in patients with negative findings on the initial echocardiogram. Large, mobile vegetations in the mitral valve are associated with an increased risk of brain embolization [5, 11].

Neuroimaging can be helpful to depict patients with asymptomatic neurological complications and to identify patients in whom neurological complications may influence further therapeutic decisions.

There is insufficient information on whether all patients with IE, irrespective of neurological symptoms, should undergo brain imaging, with magnetic resonance imaging (MRI) or at least with cranial computed tomography (CT), to screen for asymptomatic embolism and to exclude intracerebral hemorrhage [12•, 13].

Although there are no studies directly comparing CT and MRI for the evaluation of neurological complications of IE, MRI discloses lesions not visible on CT, including embolic infarction, abscess, and subtle petechial hemorrhage.

In a large recent study, preoperative MRI revealed at least one cerebral lesion in 65% of patients [14]. Occult ischemic lesions were identified in up to 37% of IE patients with a normal neurological examination [15]. Preoperative MRI

revealed acute ischemic lesions in 47 patients (55%), of whom only 19 had neurological symptoms [14]. For each millimeter increase in the size of a vegetation, there is a 10% increase in the rate of ischemic lesions detected by brain MRI [16].

Cerebral microbleeds appear as hypointense foci on T2*-weighted or susceptibility-weighted imaging (SWI) MR. About 60% of patients with infective endocarditis have cerebral microbleeds on blood-sensitive MR sequences These usually have a cortical distribution [15] and can be present as lesions of different ages.

Cerebral microbleeds result septic embolism causing endothelial injury and blood-brain barrier disruption, which leads to an inflammatory subacute microvascular vasculitis and small-vessel rupture.

In patients with IE, sulcal SWI lesions with or without contrast enhancement are associated to mycotic aneurisms and might guide patient selection for performing digital subtraction angiography (DSA) [17•].

Some MRI findings, such as ischemic lesions and cerebral microbleeds with or without contrast enhancement seem to be associated with a high risk of perioperative neurological deterioration due to cranial hemorrhage, but their prognostic role is still unclear [14, 17•]. In patients undergoing valve replacement surgery, preoperative MRI findings were not associated with significant differences in the rates of postoperative complications [18•]. However, in the study of Goulenok et al., who evaluated the contribution of MRI to cerebral involvement staging and therapeutic planning, early brain MRI provided additional information that led to modifications of diagnostic or therapeutic decisions in up to 27% of cases [19].

Neurological Complications of IE

Ischemic Stroke

Stroke is the most common neurological complication of IE, affecting up to 35% of all patients [20]. Risk factors for brain embolization include vegetation size and mobility [5], *Staphylococcus aureus* infection, and mitral valve involvement.

IE increases stroke risk for longer time periods than previously thought. In a population-based study [21], stroke risk began to increase approximately 4 months before the diagnosis of IE, peaked in the first month after IE, and then declined, to stabilize by 5 months onwards. The risk of cerebral embolic events in IE decreases dramatically in the second week after the initiation of effective antimicrobial therapy [6].

Acute ischemic lesions are usually multiple cortical and subcortical infarcts, disseminated in multiple vascular territories, often with different ages (Fig. 1). Inflammatory reactions may play an important role in the development of ischemic lesions in IE patients [14].

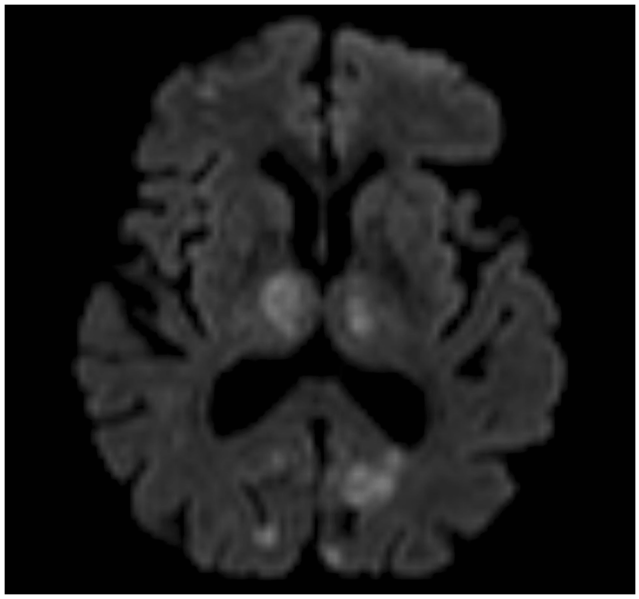

Fig. 1 Diffusion weighed imaging (DWI) brain magnetic resonance imaging showing multiple ischemic lesions involving both thalamus and occipital lobes

Mycotic Aneurysms

Mycotic aneurysms are localized arterial dilatations caused by septic emboli. Their most common location is on peripheral branches of the middle cerebral artery (Fig. 2). Mycotic aneurysms result from septic arterial embolism to the intraluminal space or vasa vasorum and subsequent acute inflammatory involvement of the vessel wall [22]. Mycotic aneurysms are detected in 2 to 4% of patients with IE and in 5 to 12% of patients who present with neurologic symptoms [23, 24]. They are usually asymptomatic unless they rupture, causing intracranial, intraventricular, or subarachnoid hemorrhages.

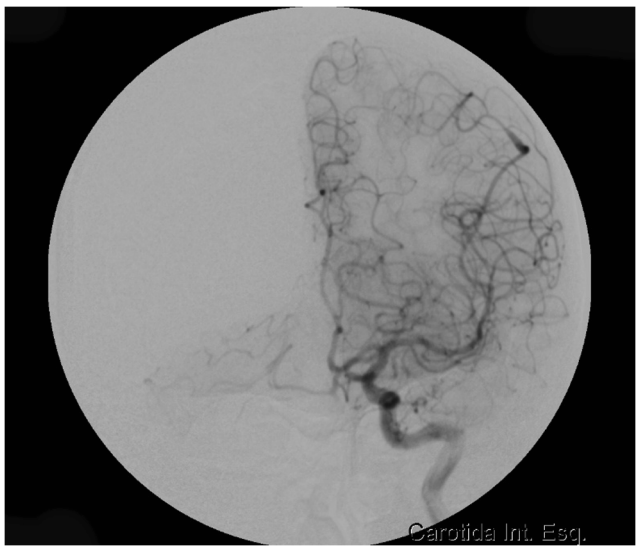

Fig. 2 Digital subtraction angiography (DSA) showing a fusiform mycotic aneurysm of distal (parietal branch) left middle cerebral artery

Rupture of mycotic aneurysms represents 5% of the neurological complications in patients with IE [25] and is associated to a poor outcome and high mortality rate [26]. Patients with mycotic aneurysms and identified *S. aureus* bacteremia are more prone to develop intracerebral hemorrhage, mostly in the first 48 h after hospital admission [26].

CT angiography (CTA) and MR angiography (MRA) have low sensitivity for detecting mycotic aneurysms (42.9% for CTA, 33.3% for MRA [23], 45.5% for cross-sectional imaging (CTA and MRA) [27]). Intra-arterial cerebral angiography remains the "gold standard" for mycotic aneurysm detection [12•]. As vessel imaging is not systematically performed in patients with IE, mycotic aneurisms are probably underdiagnosed. Nevertheless, the absence of an intracranial hemorrhage on CT or MRI has a high negative predictive value for mycotic aneurysm detection [25]. Twenty-two percent of patients with IE that present with brain hemorrhage have an mycotic aneurism compared with only 1% that do not have brain hemorrhages [23]. Thus, brain hemorrhage seems to be the best indicator for the presence of mycotic aneurisms in patients with IE. Some studies suggest that angiography should be reserved for patients with intracranial hemorrhage on CT or MRI, focal neurological deficits, or altered mental status [23].

Mycotic aneurysms are typically fusiform shaped, thin walled, multiple, with a distal location, and they usually change in size on follow-up angiography. They often have a wide or absent neck making endovascular and surgical treatment difficult.

Hemorrhagic Stroke

Hemorrhagic stroke accounts for nearly 20% of cerebrovascular complications of IE, with 15% of brain hemorrhages being hemorrhagic transformations of ischemic lesions [5]. Other possible causes of hemorrhagic stroke include rupture of mycotic aneurysms and septic necrotic arteritis with rupture of the vessel wall.

In a cohort of 1345 patients with IE, hemorrhagic complications were strongly associated with *Staphylococcus aureus* infection and anticoagulant therapy. In such patients, a larger number of hemorrhagic events occurred, even after 1 week of antimicrobial therapy [5].

Brain Abscess and Meningitis

Brain abscesses and meningitis are rare neurological manifestations of IE and may be present in 1% and 6% of patients with IE, respectively. They result directly from septic embolism and are most frequently observed in *Staphylococcus aureus*–related IE [5]. On MRI, brain abscesses are typical multiple rim-enhancing lesions at the gray-white matter junction, which cause significant edema, hemorrhage, or mass effect.

Spondylodiscitis and Spinal Cord Abscess

Although many patients with IE may complain of back pain, the incidence of spondylodiscitis and spinal cord abscess is low [28]. The lumbar region is most commonly involved, and group D streptococcus is the most frequent causative agent [28]. Hematogenous spread in the setting of bacteremia allows bacteria to contaminate the spine and its biological properties determine bone and epidural involvement. Pyogenic spondylodiscitis begins when bacteria reach the metaphyseal vascular arcades, whereas the intervertebral disc is destroyed by the release of proteolytic enzymes. The diagnosis can be confirmed by bone scintigraphy, computed tomography scan, or MRI, which is the most sensitive technique in the acute phase [29]. The occurrence of spondylodiscitis in a patient with IE does not worsen his prognosis, as the outcome depends mainly on the severity of IE [30].

Encephalopathy

Encephalopathy is a relatively common complication of IE that warrants urgent further workup. Ischemic stroke (s), intracranial hemorrhage, cerebral abscess, meningitis, seizures, and systemic complications such as fever, metabolic and electrolyte disturbances, may elicit the encephalopathy [24].

Management of IE Patients with Neurological Complications

Antibiotic Therapy

The guidelines for appropriate antibiotic treatment of infective endocarditis are published by professional societies (European Society of Cardiology (ESC), American Heart Association (AHA) and Society of Thoracic Surgeons (STS)) and updated regularly [31–33].

In cases of native-valve IE due to common microorganisms, the duration of antibiotic treatment ranges from 2 weeks (for uncomplicated IE) to 6weeks (for enterococcus IE). In IE involving a prosthetic valve, the duration of antibiotic therapy is usually 6 weeks, and regimens are similar to those for native-valve IE.

Antiplatelets and Anticoagulants

Initiation of antiplatelet drugs as adjunctive therapy in IE is not recommended. However, maintenance of long-term antiplatelet therapy at the time of development of IE with no bleeding complications may be considered [31]. In the presence of major bleeding, interruption of antiplatelet therapy is recommended [32].

Concerning anticoagulants, there is no evidence to support its use in acute stroke due to IE, so these should be avoided in

the acute phase. However, many patients with IE have indication for permanent anticoagulation, particularly patients with intracardiac thrombus, atrial fibrillation, and mechanical prosthetic valves. In such patients, the potential risks and benefits of antithrombotic therapy must be weighed [11, 31, 32]. According to current recommendations of the American Heart Association (AHA), the discontinuation of all forms of anticoagulation in patients with mechanical valve IE who have experienced a brain embolic event is recommended for at least 2 weeks [31]. The European Society of Cardiology (ESC) recommends that in ischemic stroke without hemorrhage, replacement of oral anticoagulant (anti-vitamin K) therapy by unfractionated or low molecular weight heparin for 1–2 weeks should be considered under close monitoring [32].

In intracranial hemorrhage, interruption of all anticoagulation is recommended by the AHA [32]. In patients with intracranial hemorrhage and a mechanical valve, ESC recommendations state that unfractionated or low molecular weight heparin should be reinitiated as soon as possible following multidisciplinary discussion [32]. The recommendations for management of anticoagulant therapy in IE patients are based on a low level of evidence, and decisions should be made on an individual basis [32].

Thrombolysis and Mechanical Thrombectomy in Acute Ischemic Stroke

Intravenous (IV) thrombolysis is not recommended in cerebral embolic events caused by IE. It has been associated with a high rate of hemorrhagic transformation and therefore treatment has consisted of supportive therapy and intravenous antibiotics [32].

Although successful cases of IV thrombolysis in IE have been reported, the overall outcomes are likely to be poor [34]. In one study, including 222 patients, the rate of intracerebral hemorrhage in IE-related ischemic stroke was 20%, compared with 6.5% in patients without IE [35]. The higher risk of hemorrhagic transformation, the possibility of intracranial mycotic aneurysms, and anticoagulant treatment due to prosthetic valves could be the main reasons for the worse results. The large absolute risk of increase in intracerebral hemorrhage risk probably outweighs the absolute benefit of the thrombolytic treatment.

An alternative treatment for some patients might be endovascular clot retrieval treatment. The value of mechanical thrombectomy in stroke has been demonstrated in clinical trials but, as IE was an exclusion criterion, its safety in acute ischemic stroke secondary to large vessel occlusion from septic emboli remains unknown. The few published case series of mechanical thrombectomy in IE reported recanalization rates and neurological outcomes similar to those described in the general population of stroke patients who are treated with mechanical thrombectomy [36•, 37•, 38, 39]. In a recent review, among 13 case reports of successful mechanical thrombectomy after septic embolization of the middle cerebral artery, the overall outcome was favorable (NIHSS > 3) in nine patients (69%) with no hemorrhagic complications reported in any patient [40•]. However, there is a strong possibility of publication bias. In spite of mechanical thrombectomy being an attractive therapeutic option in ischemic stroke due to infective endocarditis, more evidence is needed to better elucidate which is the best acute therapeutic management in this setting.

Cardiac Surgical Treatment to Prevent Stroke Recurrence

The timing and indications for valvular surgery to prevent systemic embolism remain controversial in patients with IE. Yet, it is recognized that outcomes can be better with early cardiac surgery.

Neurological complications influence both the indication and timing of surgery. In such cases, the risk of cardiac surgery must be weighed against the embolic risk. The decision to operate patients with cerebral infarction should also take into account the risk of hemorrhagic transformation or extension of the infarct due to cardiopulmonary bypass and heparinization [41]. On the other hand, delaying surgery places patients at risk for new septic emboli as well as deterioration of cardiac function due to worsening valvular regurgitation [12•]. Thus, this decision process requires the coordinated effort of a multidisciplinary team, including cardiologists, cardiothoracic surgeons, neurologists, and infectious disease specialists. According to recent data from the International Collaboration on Endocarditis, surgical treatment was indicated in 76% of IE patients. However, it was performed in only 57% of IE patients with stroke, stroke being one of the main reasons for nonsurgical treatment [42].

The current literature on early surgery versus late surgery for patients with IE and neurological injury remains conflicting. In a recent meta-analysis on the surgical timing in IE, the available observational data seems to support delaying surgery by 7–14 days if possible, in IE complicated by ischemic stroke. Patients with hemorrhagic stroke might benefit from delayed surgery, if possible, more than 21 days [43••]. In a multicenter cohort study of 1345 consecutive episodes of IE, the timing of surgery before or after 2 weeks following cerebral infarction did not impact mortality in patients with small brain ischemic lesions. On the other hand, early operation after a moderate or severe stroke was associated with a twofold increase in mortality [5]. Regarding hemorrhagic stroke, mortality was higher when surgery was performed within 4 weeks of the hemorrhagic event compared with later surgery (75% versus 40%). Although greatly feared, hemorrhagic transformation was uncommon (1%) among patients with IE and acute stroke undergoing early valve surgery. It is also worth noting that long-term survival was adversely affected by the presence of preoperative stroke [44•].

According to the current recommendations of the European Society of Cardiology (ESC), after a silent embolism or transient ischemic attack, cardiac surgery, if indicated, should be performed without delay. Valve surgery should 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 (i.e., coma) [29].

The current recommendations of the American Heart Association (AHA), European Society of Cardiology (ESC), and Society of Thoracic Surgeons (STS) are to delay surgery for at least 4 weeks in cases of major ischemic stroke or intracranial hemorrhage [29–31]. In cases of decline in cardiac function, recurrent embolism or failure in antibiotic therapy, and of small brain infarction, STS guidelines state that a delay of less than 4 weeks may be reasonable.

There are no recommendations on the type of valve prostheses in IE patients with cerebral lesions who undergo valve replacement surgery. Some authors prefer biological prostheses in order to avoid the need for postoperative oral anticoagulation [40•].

Concerning the outcomes of valve surgery in patients with mycotic aneurysms, there is also a lack of information. In those cases, the expertise of both neurologists and neurosurgeons should elucidate whether the mycotic aneurysm warrants treatment before open-heart surgery.

Ruptured and Unruptured Mycotic Aneurisms: Conservative Treatment, Endovascular Therapy, or Surgical Approach

There are no high-quality evidence-based recommendations for the treatment of mycotic aneurisms in the setting of IE. Several treatment approaches have been described and used, including conservative treatment with antibiotics, endovascular therapy, microsurgical neck clipping, excision of the aneurysm, and trapping with or without bypass surgery.

Ruptured aneurysms must be immediately secured. Clipping may be technically arduous due to a wide or absent aneurysmal neck and vascular fragility of the affected parent artery and aneurysm wall. Clipping is often obtained with the sacrifice of the parent artery. Significant neurological morbidity may result from these interventions [22].

Endovascular techniques may be safer, providing high occlusion and lower procedure-related complication rates. Aneurysmal coiling can be achieved securely, preserving the patency of the vessel even in distal aneurysms or in those with complex morphology [22]. However, in large case series, most mycotic aneurysms were excluded by parent artery occlusion and only in 24% by aneurysm embolization with vessel preservation [45]. Another option are intracranial stents, with the capacity to simultaneously preserve parent vessel integrity while obliterating the mycotic aneurysm. Their use has been less reported and only for proximally located lesions [46].

The management of unruptured mycotic aneurysms is also not supported by high-quality evidence. Mycotic aneurysms are known to resolve or decrease in size with antimicrobial therapy. Therefore, a conservative approach with antibiotic therapy guided by blood cultures with serial CT or MR angiography follow-up is a reasonable option. Surgical or endovascular treatment is considered if the aneurysm has a large size, enlarges, or fails to reduce in size, despite proper antibiotic therapy.

Management of Brain Abscesses and Spondylodiscitis

The cornerstone of brain abscesses treatment is antibiotherapy. Neurosurgical intervention may be needed for large abscesses or in case of antibiotic failure, in patients with significant mass effect and risk of herniation or hydrocephalus [24].

Concerning treatment of spondylodiscitis, surgical management is the mainstay of treatment, although conservative treatment can be successful in selected patients [29].

Conclusion

Neurological complications of IE are common and can cause significant morbidity and mortality.

The value of combined diagnostic strategies using multimodality imaging—CT, MRI, and DSA—is evolving. In spite of being asymptomatic, nearly half of patients with IE have MRI evidence of cerebral embolization. Valvular surgery plays an important role in the prevention of recurrent stroke, but the optimal timing of surgery is not yet supported by high-quality evidence. While anticoagulation and IV thrombolysis are probably unsafe in the acute phase of ischemic stroke in the context of IE, mechanical thrombectomy can probably be safely used in patients with large vessel occlusion.

As neurological complications of IE may need both medical and surgical treatments, their optimal management needs the participating of a multidisciplinary team including neurologists, cardiologists, cardiothoracic surgeons, neuroradiologists, neurosurgeons, and infectious disease specialists.

Compliance with Ethical Standards

Conflict of Interest José M. Ferro reports grants from Bayer, personal fees from Boehringer Ingelheim, outside the submitted work. Filipa Dourado Sotero, Madalena Rosário, and Ana Catarina Fonseca each declares that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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