Bacterial Endocarditis and Cerebrovascular Disease

Since stroke is a frequent complication of infective endocarditis, physicians should be up-to-date on the latest developments in diagnosis and management.

By Brian Silver, MD

Within the spectrum of cerebrovascular disease, bacterial endocarditis has been the topic of much discussion and interest. Currently, there are many challenges in both diagnosis and management of bacterial endocarditis. This article will review its epidemiology and explore management issues associated with cerebral infarction, intracerebral hemorrhage, and infectious mycotic aneurysms.

INCIDENCE AND IMPACT

The estimated incidence of infective endocarditis (IE), according to age and microorganism in the US, is three to nine cases per million individuals.[1] Additionally, the male to female ratio of those with the disease is roughly 2:1. The highest rates are often observed among patients with prosthetic valves, intracardiac devices, unrepaired congenital heart disease, chronic rheumatic heart diseases, age-related degenerative valve diseases, DM, HIV, IVDA, and hemodialysis.[1]

Despite diagnostic and therapeutic improvements, mortality from IE remains high. In-hospital mortality ranges from 15 to 22 percent, while five-year mortality hovers around 40 percent.[2] Independent predictors of mortality include older age, *S. aureus* infections, health care associated infective endocarditis, and cerebrovascular and embolic events.[2]

Regarding timing, stroke in IE tends to occur most frequently in the early phase of IE.[3] In fact, stroke may be a presenting symptom of IE. Embolic brain infarction, ICH, and mycotic aneurysm are each a minor clinical criteria in the Duke Criteria for Diagnosis of Infective Endocarditis.[3] To qualify as IE, a patient must meet two major criteria (positive blood cultures, evidence of endocardial involvement), or one major plus three minor criteria, or five minor criteria.[3]

The incidence of embolic events in IE is between 10 and 50 percent, and the brain is the most frequent site of symptomatic embolic events, accounting for 65 percent of such events.[4] Moreover, ischemic stroke accounts for approximately 70 percent of cerebrovascular events in patients with bacterial endocarditis who have a stroke. Risk factors for cerebral embolization are *S. aureus* endocarditis, larger vegetation size, greater vegetation mobility, and mitral valve involvement.[4] In an MRI study, 52 percent of patients with IE had ischemic brain lesions, but only 12 percent were symptomatic.[5]

It is worth noting that these ischemic events are cardioembolic in etiology. Histopathological examination of cardiac valve vegetations shows that vegetations are composed of micro-organisms, inflammatory cells, platelets and fibrin. These vegetations are friable, can fracture, and subsequently embolize to the brain.[6]

MANAGEMENT CONSIDERATIONS

When managing endocarditis, physicians must consider a variety of factors. Ahead I will attempt to answer several common questions:

Is my patient's risk of stroke reduced by the antibiotics they are receiving?

Antibiotic therapy is critical in order to reduce the risk of primary and secondary ischemic stroke in bacterial endocarditis. Early antibiotic therapy reduces risk of embolization dramatically—from nearly 4.8 cases per 1,000 patient days in the first week of therapy to less than 1.7 per 1,000 patient days in the second week, with further decreases thereafter.[4] Thus, when IE is suspected or confirmed, antibiotic therapy should be started quickly after blood cultures are drawn. This antibiotic treatment is likely to be empirical at first, then modified according to testing results during the next few days.

Regarding the possibility of second stroke for patients on antibiotics, antimicrobial therapy appears to reduce that. In a prospective incidence cohort study involving 61 tertiary centers with 137 consecutive patients with left-sided endocarditis, approximately 10 percent in this cohort experienced

a stroke. Of note, 52 percent of strokes occurring after initiation of antibiotics occurred in the first week of therapy and 75 percent of all strokes occurred within the first two weeks.[4] Stroke rates fell similarly regardless of the valve involved or the organism. After one week of antimicrobial therapy, however, only 3.1 percent of the cohort experienced a stroke. The day with the single greatest number of events was on "day zero" of antimicrobial therapy. This peak reflects the occurrence of stroke as a common precipitating event for medical attention and hospital admission.

Antibiotic treatment duration should range based on the valve affected and cause of the IE. For native valve IE, treatment ranges from two weeks for IE due to common microorganisms (e.g. uncomplicated IE due to fully PCN susceptible streptococci treated with a beta-lactam antibiotic plus amino-glycoside) to six weeks (e.g. enterococcal IE), whereas with prosthetic valve IE treatment duration should be six weeks.[7] Additionally, it is important to recommend antibiotic regimens before and after an organism is identified.

Does routine anticoagulation reduce my patient's risk of embolic stroke?

Anticoagulation is not recommended as an intervention for stroke prevention in patients with IE. Observational data suggests an increased risk of fatal cerebral hemorrhage, with no reduction in the risk of embolic events for patients with *S. aureus* prosthetic valve IE receiving oral anticoagulant agents.[8-9] In fact, anticoagulant therapy may be an independent risk factor for the occurrence of neurological complications, mostly related to a greater incidence of hemorrhagic events.

In a retrospective analysis of prospectively collected data on a multicenter cohort in 1,345 consecutive episodes of left sided IE, 14 percent of cases had ischemic brain events and four percent had hemorrhages.[8] Anticoagulant therapy was an independent risk factor for neurological complications (HR 1.31). This was particularly related to a greater incidence of hemorrhagic events (HR 2.71).[8]

In another study looking at 637 cases with IE at a hospital between 1975 and 1999, 56 had *S. aureus* IE affecting native valves in 35 patients and prosthetic valves in 21 patients.[9] Of patients with prosthetic valves, 90 percent were taking warfarin and none with native valve. Mortality was higher in the prosthetic valve group (71 percent vs. 37 percent). No patient with native valve IE died due to CNS complications, while 73 percent (11 of 15) with prosthetic valve IE died due to CNS complications. The difference in the distribution of the type of death (stroke vs. other) was also significant. Whereas six of the 21 patients with prosthetic valve had ICH, only one out of 36 patients with native valve IE had ICH. All ICH in prosthetic valve group were detected within 72 hours by CT.[9]

PRACTICAL POINTERS

Nearly half of patients with infective endocarditis have imaging evidence of cerebral embolization, while approximately 15 percent are symptomatic.

Approximately half of patients with infective endocarditis have cerebral microbleeds on heme sensitive sequences. The presence of two or more microbleeds indicates an increased risk of intracerebral hemorrhage.

Mycotic aneurysms may be missed on CTA or MRA, particularly if less than 5mm in diameter. Catheter angiography is the gold standard.

Mycotic aneurysms that are more than 10 mm in diameter, enlarge during antibiotic therapy, or fail to resolve with antibiotic therapy, should be considered for coiling.

For patients who require chronic anticoagulation for a medical condition, the European Society of Cardiology Guidelines recommends oral anticoagulation should be stopped for at least 14 days if possible while antibiotics are being utilized.[7] The guidelines recommend that the oral anticoagulant agent be replaced with heparin for two weeks, in patients already receiving oral anticoagulant therapy, presenting with IE complicated by ischemic, non-hemorrhagic stroke if anticoagulation is absolutely indicated. The guidelines also acknowledge to low level of evidence supporting these recommendations.[7]

Does initiation of an antiplatelet drug reduce my patient's risk of embolic stroke?

Antiplatelet agents are not recommended for patients with IE for the purpose of stroke prevention.[1] One study found no significant decrease in incidence of embolic events in patients with IE who were randomly assigned to receive aspirin 325 mg daily for four weeks.[9] There was a non-significant increase in the rate of cerebral hemorrhage in patients receiving aspirin. In 115 patients over four years, embolic events occurred in 28 percent of patients on ASA and 20 percent of patients on placebo. There was a trend toward a higher incidence of bleeding in the ASA group and development of new intracranial lesions was similar in both groups. Additionally, ASA had no effect on vegetation resolution and valvular dysfunction.[10]

Regarding the continuation of antiplatelet drugs, a retrospective cohort study of IE patients reported that the risk of symptomatic embolism associated with IE was reduced in patients receiving antiplatelet therapy daily before the onset of IE (12 percent versus 28 percent).[11] Thus, it may not be

absolutely necessary to discontinue antiplatelet therapy in those patients with IE without cerebral hemorrhage if they require antiplatelet therapy for another medical condition.

Can I treat a patient with IE who has had an acute ischemic stroke with thrombolytic therapy?

The safety and potential efficacy of IV thrombolysis and IA recanalization approach in IE-related AIS remain unproven. Further research is needed to better elucidate the best urgent therapeutic management in this setting. The currently limited available data suggest that IV tissue plasminogen activator (tPA) is not recommended when IE is suspected as the cause of AIS.[12]

Some patients treated with thrombectomy had hemorrhages, some of which were multifocal. The exact pathogenesis of ICH in these cases remains unknown. Rarely, these events could relate to a mycotic aneurysm. Other potential mechanisms include pyogenic arteritis, micro-abscesses, hemorrhagic transformation of previous ischemic stroke, immune complex mediated arteritis, and inflammation of meningeal vasculature.

As of April 2015, three cases of successful mechanical thrombectomy have been published, but there may be publication bias such that unsuccessful attempts have not been published.

Should my patient's cardiac valve be replaced?

While the rate of early (during antibiotic treatment) valve replacement of repair has increased over the past three decades to 50 percent, its exact role in preventing embolic events remains controversial.[7] The risk of new embolism is highest during the first few days following initiation of antibiotic therapy and rapidly decreases thereafter, particularly beyond two weeks, although some risk persists indefinitely while vegetations remain present. For this reason, the benefits of surgery to prevent embolism are greatest during the first week of antibiotic therapy, when embolic risk peaks.

Valve replacement surgery can be considered in cases of locally uncontrolled infections (e.g., abscess, fistula, enlarging vegetation, or dehiscence of prosthetic valve), as well as in patients with uncontrolled infections and persistent positive blood cultures for more than five to seven days, as well as an infection caused by a multi-drug resistant organism. Surgery should also be considered for the prevention of embolism in a patient with a large vegetation (greater than 10mm in length) after one or more embolic episodes, despite appropriate antimicrobial treatment, especially during the first two weeks of therapy. It may also be acceptable in cases of large vegetations (greater than 15mm in length) without embolism in which the patient also has other predictors of complicated course (e.g., heart failure).

In terms of the appropriate time to have a patient undergo heart valve replacement surgery following a cerebrovascular event, there are several factors to consider. After a TIA or an ischemic stroke (that is not devastating), surgery should not be delayed if the valve must be replaced as long as coma is absent and cerebral hemorrhage has been excluded by CT.[13] If a silent cerebral embolism has occurred and the valve must be replaced, surgery is recommended without delay. If ICH is present, surgery should be delayed for a month. Neurosurgery should be involved in the management decision making as well.[13]

HEMORRHAGIC STROKE

Hemorrhagic stroke accounts for approximately 30 percent of cerebrovascular complications of IE.[14] Hemorrhagic strokes are due to hemorrhagic transformations of brain infarction, primary intracerebral hemorrhages, or ruptures of infectious cerebral mycotic aneurysm.

One study observed microbleeds in 57 percent of 130 patients imaged within seven days of hospital admission for IE.[15] These microbleeds are preferentially distributed in cortical areas,[5] but can occur in deeper brain areas.

The prognostic value of cerebral microbleeds (CMB) was addressed in a study in which the presence of more than two or three lesions was independently associated with the development of intracerebral hemorrhage.[16] In the study, 26 consecutive patients with IE underwent MRI and CMBs were identified in 14 patients (54 percent). Symptomatic ICH was observed in eight patients during a three-month follow-up. The presence and number of CMBs, particularly two or more microbleeds, was an independent predictor of the development of ICH.

Small intracerebral hemorrhages are common in IE. The pathophysiologic process involved in genesis of these microbleeds remains to be elucidated. Cortical localization of microbleeds may reflect a preferential mode of entry of septic material through the blood brain barrier at the corticopial junction. Microbleeds may also be due to a subacute process, either due to an immunologic vasculitis and/or an embolic process in the vasa vasorum. Interruption of all anticoagulation is recommended when symptomatic intracerebral hemorrhage is present.[7]

Unfractionated heparin should be reinstituted as soon as possible in patients with a mechanical valve who require chronic anticoagulation, depending on the evolution of bleeding monitored by serial CT imaging and provided that the patient has remained on antibiotic therapy. Intracranial mycotic aneurysm should be excluded before starting heparin.

INTRACRANIAL MYCOTIC ANEURYSMS

Intracranial mycotic aneurysms (ICMA) are typically distal (e.g., involving segment 2, 3, or 4 of the MCA or PCA), and

in about 25 percent of cases there are more than one. They are typically fusiform in shape but can be saccular, while their prevalence ranges in registry data from two to five percent. Diagnostic criteria that help to differentiate proximal ICMAs from saccular aneurysms have been devised.

Intracranial mycotic aneurysms likely form as a result of arterial wall weakening following septic embolization into the vasa vasorum or the intraluminal space of the artery itself. Registry data may be biased because performance of angiography was determined by the local physician.

Rupture of an ICMA generally occurs during the early phase of IE and can produce subarachnoid hemorrhage, parenchymal hemorrhage, or subarachnoid plus parenchymal hemorrhage. In some patients, especially those with streptococcal IE, the rupture may occur during the latter phase, or even after the end, of antibiotic therapy.

Regarding the detection of ICMA, conventional angiography remains the gold standard for diagnosis of ICMAs because of their frequent distal location within the cerebral arterial tree. CTA and MRA can detect intracranial saccular aneurysms greater than 5mm with good reliability. One study reported that the sensitivity of CTA and MRA was 94 percent and 86 percent respectively for the detection of aneurysms greater than 5mm in diameter or more, but only 57 percent and 35 percent respectively for aneurysms less than 5mm.[17]

As to the question of when to perform an angiography, according to the 2011 Society of Thoracic Surgeons Guidelines, it is "reasonable to reserve catheter angiography for IE patients with evidence of intracranial bleeding or a suggestion of mycotic aneurysm on non-invasive imaging."[18] (Class IIa, Level of evidence C) These statements echo the European Society of Cardiology Guidelines from two years ago, which state that "conventional angiography remains the gold standard and should be performed when non-invasive techniques are negative and suspicion remains."[7]

However, it remains unclear what should raise suspicion and how we define negative noninvasive techniques. It is also still unknown which IE patients remain at highest risk for mycotic aneurysm and in which subset cerebral angiography has the highest yield. In addition, the utility of non-invasive clinical or imaging tests in predicting the presence of mycotic aneurysms in preoperative IE patients is not established.

Concerning the treatment of intracranial mycotic aneurysms, it is worth noting first that unruptured aneurysms may resolve with antibiotic therapy alone. Patients with unruptured aneurysms should receive antibiotics with serial imaging performed to document the resolution of the aneurysm. Endovascular or surgical treatment should be considered if an unruptured aneurysm is very large (e.g., greater than 10mm in length) or if it is not resolving or is enlarging despite treatment with antimicrobials. For ruptured aneurysms, surgical or endovascular intervention should be considered, but the choice between endovascular vs. surgical is complex and should be individualized.[19]

Historically, management of mycotic aneurysms relied on surgery and antibiotics with limited use of endovascular therapy fearing risk of overwhelming infection by introducing a foreign body to an infected area.[20] However, there has been a lack of randomized controlled trials. From a technical standpoint, clipping of a mycotic aneurysm is more difficult than a regular saccular aneurysm due to the friable nature of the aneurysm and the absence of a neck.[20]

SUMMARY

Stroke is a frequent complication of infective endocarditis. Early antibiotic therapy is the cornerstone of treatment to reduce the risk of secondary stroke. Early valve replacement should be considered in those patients who have TIA or ischemic stroke in specific situations. Antibiotic therapy is also the cornerstone of treatment for unruptured mycotic aneurysms, but it may be wise to seek a neurosurgical consultation for ruptured mycotic aneurysms and for unruptured aneurysms that enlarge or do not resolve following completion of antibiotic therapy. ■

Brian Silver, MD is an Associate Professor of Neurology at Alpert Medical School of Brown University and Director of the Comprehensive Stroke Center at Rhode Island Hospital.

1. Hoen B, Duval X. Clinical practice. Infective endocarditis. NEJM 2013; 368: 1425-1433.
2. Thuny F, et al. Management of infective endocarditis: challenges and perspectives. Lancet 2012; 379: 965-975.
3. Li JS, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clinic Infect Dis 2000; 30: 633-638.
4. Dickerman SA, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J 2007; 154: 1086-1094.
5. Duval X, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Annals Intern Med 2010; 152: 497-504.
6. Eiken PW, et al. Surgical pathology of nonbacterial thrombotic endocarditis in 30 patients, 1985-2000. Mayo Clin Proc. 2001 Dec. 76(12): 1204-12.
7. Habib G. et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009; 30: 2369-2413.
8. Garcia-Cabrera E, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation 2013; 127: 2272-2284.
9. Tornos P, et al. Infective endocarditis due to Staphylococcus aureus: deleterious effect of anticoagulant therapy. Arch Int Med 1999; 159: 473-475.
10. Chan KL, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. J Am Coll Cardiol 2003; 42:75-780.
11. Anavekar NS. Clin Infect Dis 2007; 44: 1180-1186.
12. Ong G, et al. Impact of prior antiplatelet therapy on risk of embolism in infective endocarditis. J Neurol 2013; 260; 1339-1342.
13. Rossi M, et al. What is the optimal timing for surgery in infective endocarditis with cerebrovascular complications? Interactive Cardiovasc and Thor Surg 2012; 14; 72-80.
14. Hess A. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. AJNR 2013; 34: 1579-1584.
15. Klein I, et al. Cerebral microbleeds are frequent in infective endocarditis: a case-control study. Stroke 2009; 40: 3461-3465.
16. Okazaki S, et al. Cerebral microbleeds predict impending intracranial hemorrhage in infective endocarditis. Cerebrovasc Dis 2011; 32: 483-488.
17. White PM, et al. Intracranial aneurysms: CT angiography and MR angiography for detection prospective blinded comparison in a large patient cohort. Radiology 2001; 219: 739-749.
18. Byrne JG, et al. Surgical management of endocarditis: the society of thoracic surgeons clinical practice guideline. Ann Thorac Surg 2011; 91: 2012-2019.
19. Corr P, et al. Endocarditis-related cerebral aneurysms: radiologic changes with treatment. AJNR 1995; 16: 745-748.
20. Peters PJ, et al. A dangerous dilemma: management of infectious intracranial aneurysms complicating endocarditis. Lancet Infect Dis 2006; 193: 742-748.