Acta Biomed 2022; Vol. 93, N. 1: e2022203 DOI 10.23750/abm.v93i2.10185

Original article

Predictors, patterns, and outcomes following Infective endocarditis and stroke

Ajay Kumar Mishra[1], Kamal Kant Sahu[1], Benson Mathew Abraham[1], Jennifer Sargent[2], Mark J Kranis[3], Susan V George[4], George Abraham[5]

[1]Resident, Department of Internal Medicine, St Vincent Hospital, Worcester, United States; [2]Department of Internal Medicine, St Vincent Hospital, Worcester, United States; [3]Division of Cardiovascular Medicine, St Vincent Hospital, Worcester, United States; [4]Department of Internal Medicine, St Vincent Hospital, Worcester, United States; [5]Division of Infectious Disease, Department of Internal Medicine, St Vincent Hospital, Worcester, United States

Abstract. Patients with infective endocarditis can have multiple neurological manifestations. Cerebrovascular events (CVE) in patients with IE can be hemorrhagic or embolic. Multiple factors are known to predispose to CVE and increased mortality in patients with IE. In this study, we aimed to describe various outcomes among patients with IE and CVE. We retrospectively analyzed 160 patients with definite IE. Among these, patients with radiological evidence of CVE were included. Clinical, radiological, echocardiographic details were obtained. Outcome studied were the requirement of intensive care unit care, the requirement of mechanical ventilation, prolonged course of antibiotics, prolonged duration of hospital stay, the requirement of surgical intervention, and mortality. In this study, 16 [10%] of patients with IE were identified to have a CVE. The mean age of the patients was 55, and 87.5% of them were male. 25% of patients had prior IE. IE involving left-sided valves were predominant, with the involvement of mitral valve reported in 62.5% of patients. More than half of the patient's had details of magnetic resonance imaging (MRI) of the brain. CVE were mostly ischemic, anterior circulation predominant, multiple, and bilateral. In patients with IE and CVE morbidity including the requirement of ICU care, prolonged antibiotics course, and the requirement of surgical intervention contributed to increased duration of hospital stay. In conclusion, CVE in patients with IE tends to present as multiple infarcts predominantly located over anterior circulation. IE patients with CVE tend to have higher morbidity and mortality. (www.actabiomedica.it)

Key words:

Introduction

Neurological manifestations in patients with infective endocarditis (IE) are diverse. These patients are prone to develop hemorrhagic and embolic events. Septic cerebral embolism is reported in around 40% of patients with IE. (1) IE involving left-sided valves are more prone to develop septic emboli to the brain, and other visceral organs.(2) Multiple patient factors, valvular factors, and microbiological factors predispose to developing of embolic events.(3) Patients with a cerebrovascular event (CVE) in the background of infective endocarditis are known to have higher mortality.(4) In this study, we aimed to describe the various outcomes among patients with IE and cerebrovascular injury (CVI).

Methodology

This single center, retrospective, observational study was conducted among the patients admitted in the Department of Internal Medicine, Infectious Disease, and Cardiology of St. Vincent Hospital,

Worcester. All patients with microbiological and echocardiographic (ECHO) evidence of IE were eligible to be enrolled in the study. As per modified Duke's criteria, only patients with definite IE were enrolled into the study. Eligible patients with infective endocarditis and imaging evidence of CVI between January 2015 to June 2019 [4.5 years] were included in this study. Patients with documented cerebrovascular events and an available neuroimaging were included in the analysis. Patients without neuro-imaging details or sub-optimal imaging were excluded from this study. In patients with IE, neuroimaging [computed tomography or magnetic resonance imaging] was performed in case of worsening sensorium, and the onset of new focal neurological deficits. The initial modality of cardiac imaging was transthoracic echocardiography (TTE). Transesophageal echocardiography (TEE) was obtained in case of a requirement of better characterization of size, site, and numbers of vegetation. TEE was also the initial choice of echocardiography among patients with prosthetic valves, intra-cardiac devices, and prior cardiac surgery.

Following the recruitment of patients, we obtained the details of demographic parameters, clinical features, laboratory parameters, neuroimaging findings, echocardiographic parameters, and the details of treatment. Neuroimaging findings of the stroke that were included are the site, side, size, type, number, and the vascular territories involved by infarcts. The presence of more than one infarct was defined as multiple. ECHO details included were side, valve involved, size, and number of vegetations, and details of valvular complications. Patients with more than one vegetation in ECHO were defined to have multiple vegetations. We obtained details of hospital stay, treatment, worsening clinical status, the requirement of surgical intervention, morbidity, and mortality as an outcome. Patient data were obtained from medical records by trained clinicians. Imaging interpretation was done by trained radiologists. Echocardiographic findings were reported by trained cardiologists. Data were entered in Microsoft excel and was analyzed with a statistical package for social sciences (SPSS version 16). Continuous data were expressed as mean, median, range, and percentage. Institutional review board approval was obtained before initiating the study.

Results

Over four and a half year a total of 160 patients with IE were identified from the medical record. Among these 16 patients had evidence of a cerebrovascular event. The mean age of IE patients presenting with infarct was 55 years. 87.5 % [N=14] of the patients were male. 75% [N=12] of the patients had native valve endocarditis. Risk factors including intravenous drug abuse, prior IE and atrial fibrillation was present in 37.5% [N=6], evidence of local complications was noted in 25% of patients. Left sided IE was documented in 87.5%, and the mitral valve was involved in 62.5% [N=10]. The aortic valve was involved in 37.5% of patients. 50% of patients were reported to have a single vegetation. The most common organism isolated was *Staphylococcus aureus* [68.75%]. Fever and depressed sensorium were present in 62.5% of patients as shown in table 1.

Magnetic resonance imaging of the brain was obtained in 56.2% [N=9] patients. Ischemic infarcts were noted in 87.5% [N=14] of patients. 71.5% [N=10] of these infarcts were multiple, and 43% [N=6] were bilateral. 86% [N=12] of the infarcts were located in the anterior circulation. The commonest site of locations of infarcts was frontal, occipital, parietal and cerebellar region. [Table -2] Other sites involved were front parietal, temporal, and parieto-occipital regions.

Culture conversion was documented in 75% [N=12] of the patients. The median duration for culture conversion was 6 days. The median duration of hospital stay was 8.4 days. The requirement of intensive care unit (ICU) stay, hypotension, and the requirement of mechanical ventilation were reported in 68.7% [N=11], 56.2 [N=9], and 50% [N=8] of patients respectively. 37.5% of patients required surgical intervention, 31.2% required a prolonged course of antibiotics, and 25% required removal of the prosthetic valve. Mortality was reported in 12.5% of patients.

Discussion

Patients with infective endocarditis can have multiple neurological complications including cerebrovascular events, transient ischemic attack, meningitis,

Table 1. Demographic, clinical and laboratory parameters of patients with IE and CVI

Variables	Number: 16, Mean, [SD], (Minimum – Maximum)
Median age	55.25 [18.1] (33-89)
M: F	7: 1 [M: 14, F: 2]
Type of Endocarditis	
Native valve	12 [75%]
Prosthetic valve	5 [31%]
ICD	1 [6%]
Risk Factors	
IVDU	6 [37.5%]
Prior IE	4 [25%]
HTN	6 [37.5%]
DM	4 [25%]
AFIB	2 [12.5%]
CHF	2 [12.5%]
ECHO	
TEE	14 [87.5%]
TTE	2 [12.5%]
Normal EF	13 [81.2%]
Local complications	4 [25%]
Valve involved	
Unilateral	14 [87.5%]
Bilateral	2 [12.5%]
Left sided IE	14 [87.5%]
Right sided IE	3 [18.7%]
Mitral	10 [62.5%]
Aortic	6 [37.5%]
Pulmonary	2 [12.5%]
Tricuspid	1 [6%]
Others	1 [6%]
Vegetations numbers	
Single	8 [50%]
Multiple	7 [43.7%]
Organism	
Staphylococcos aureus	11 [68.7%]
Streptococcos species	2 [12.5%]
Enterococcos	1 [6%]
Clinical presentation	
Fever	10 [62.5%]
Depressed sensorium	10 [62.5%]
Weakness	5 [31%]
Laboratory details	
HB	11.2 [2.03] (8.2 -15.5)
TWBC	12.8 [4.1], (6.4 – 22.6)
Platelet counts	233.5 [112.9] (93 – 560)
Creatinine	1.02 [0.50] (0.57 – 2.48)

Table 2. Patterns of cerebrovascular injury and its outcome in patients with IE

Variables	Number: 16, Mean, [SD], (Minimum – Maximum)
Imaging details	
MRI	9 [56.2%]
CT	7 [43.7%]
Details of CVI	
Ischemic	14 [87.5%]
Hemorrhagic	1 [6%]
Both	1 [6%]
Number of Infarcts	
Multiple	10 [62.5%]
Single	5 [31%]
Laterality	
Bilateral	6 [37.5%]
Right	5 [31%]
Left	4 [25%]
Vascular territory	
Anterior	12 [75%]
Posterior	1 [6%]
Both	2 [12.5%]
Sites of infarcts	
Frontal	8 [50%]
Occipital	8 [50%]
Parietal	7 [43.7%]
Cerebellar	5 [31%]
Frontoparietal	3 [18.7%]
Temporal	2[12.5%]
Parieto-occipital	2 [12.5%]
Others	3 [18.7%]
Outcome	
Culture conversion	12 [75%]
Duration to culture conversion	5.6
Duration of stay	14 [8.4] (5 -31)
ICU admission	11 [68.7%]
Mechanical Ventilation	8 [50%]
Prolonged antibiotics	5 [31%]
Surgical intervention	6 [37.5%]
Removal of device/valve	4 [25%]
Hypotension	9 [56.2%]
Morbidity	11 [68.7%]
Death	2 [12.5%]

brain abscess, encephalopathy, seizure, and mycotic aneurysm.(2) Septic cerebral embolism has been reported in around 40% of patients with infective endocarditis.(4) Among patients with IE risk of ischemic or hemorrhagic stroke is highest starting 4 months before the diagnosis of infective endocarditis, and it continues to be high for 5 months afterward as well.(2,5)

Risk factors

Patients with infective endocarditis are prone to develop hemorrhagic and embolic strokes, with the latter being the commonest.(2,4) Risk factors for developing embolic infarcts are patient factors like older age, presence of atrial fibrillation, prior embolic events, multiple valvular endocarditis, mitral valve vegetation, and larger vegetation.(5-7) Microbiological agents predisposing to higher embolic events are Staphylococcus aureus and Candida.(8-9) Valenzuela et al retrospectively studied 1157 patients of IE. They reported a prevalence of 15.4% [N=178] of non-surgical stroke. Among these patients 78% had an ischemic stroke, 10% had an intraparenchymal hemorrhage, and 8% had a subarachnoid hemorrhage. They also looked for the potential risk factors for developing stroke in IE patients. Risk factors for developing ischemic stroke in their study were prior stroke, staphylococcal infection, mitral vegetation, and valvular abscess. They also reported that the risk factors for hemorrhagic stroke were fungal infection, male gender, and rheumatic heart disease. (4) In another study, Cao et al included 861 patients of infective endocarditis and reported 136 patients developing a stroke. They also reported that higher age, presence of mitral valve vegetation, atrial fibrillation, and fungal infection increased the risk of stroke among patients with infective endocarditis. The odds of in-hospital mortality in this study was 7.7 times higher among patients with IE and stroke. (8) Mitral valve infective endocarditis continues to be the most involved site among patients with IE and stroke. In a study including 147 patients, Cabell et al. reported that mitral valve vegetation, vegetation length, and vegetation area were independent predictors of stroke in patients with IE. (11) Similarly in a meta-analysis of 21 studies, vegetation size of more than 10 mm was a predictor of increased risk of embolism. Among younger patients, the presence of rheumatic heart disease increases the odds of ischemic and hemorrhagic stroke by 5 times. (11-13) Patients in our study also were older, had prior IE, presence of mitral valve involvement, presence of multiple vegetation, and Staphylococcal infection.

Imaging patterns of stroke

The most common site of IE related intracranial embolism is reported to be middle cerebral artery [MCA] territory. In a study including 109 patients with definite or possible infective endocarditis and without any neurological symptoms, screening MRI identified abnormalities in more than 70% of patients. Cerebral micro-bleeds and acute ischemic events were the most common abnormalities and were noted in 57%, and 37% of patients respectively. Authors concluded that the presence of cortical cerebral micro-bleeds and acute small infarcts of varying ages, predominantly located in watershed territories were surrogate imaging markers of infective endocarditis. (14) In another study including 65 patients with septic intracranial embolism, MCA territory was involved in 43% of patients. The most common areas affected were fronto-parietal, and multi-lobar in 20%, and 11% of patient's respectively. (8) Similarly in our study more than 70% of patients had multiple infarcts, located in frontal, occipital, parietal, and cerebellar region. [Figure 1 and figure 2]

Outcome

IE patients with stroke are at a higher risk to have a recurrent stroke. A study including 4236 infective endocarditis patients from the Danish national registry reported a prevalence of 5.6% of stroke during the hospital stay. During 1 year follow-up IE patients with stroke were 3.2 times higher risk of having a recurrence of another stroke as compared to IE patients without stroke. (11)

Among patients with infective endocarditis mortality continues to be as high as 30%. A study of 68 patients with IE and stroke reported a mortality of

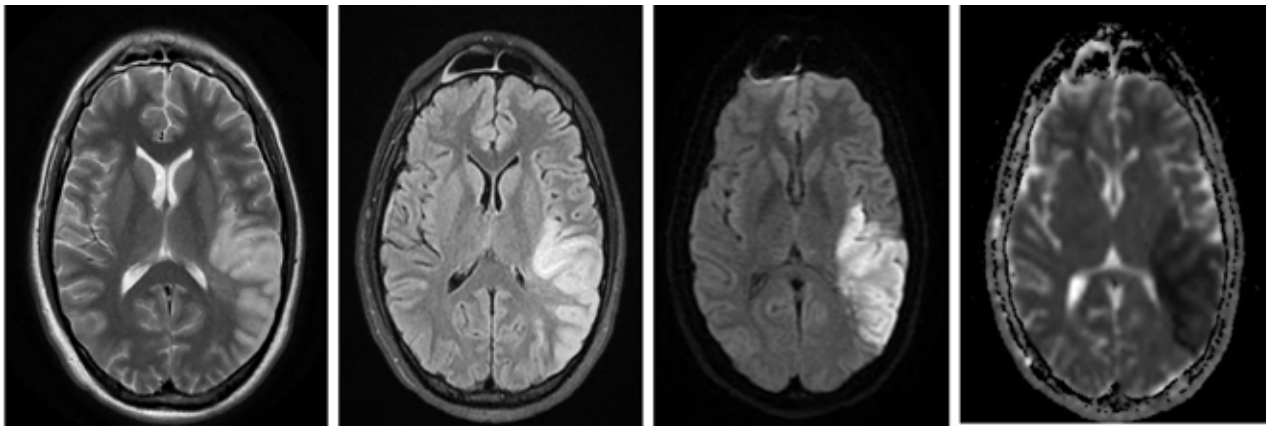

Figure 1. 33-year-old gentleman with right-sided hemiparesis, MRI showing focus of diffusion restriction in left parietal region (arrow, bright on DW and dark on ADC with increased signal of T2W FLAIR).

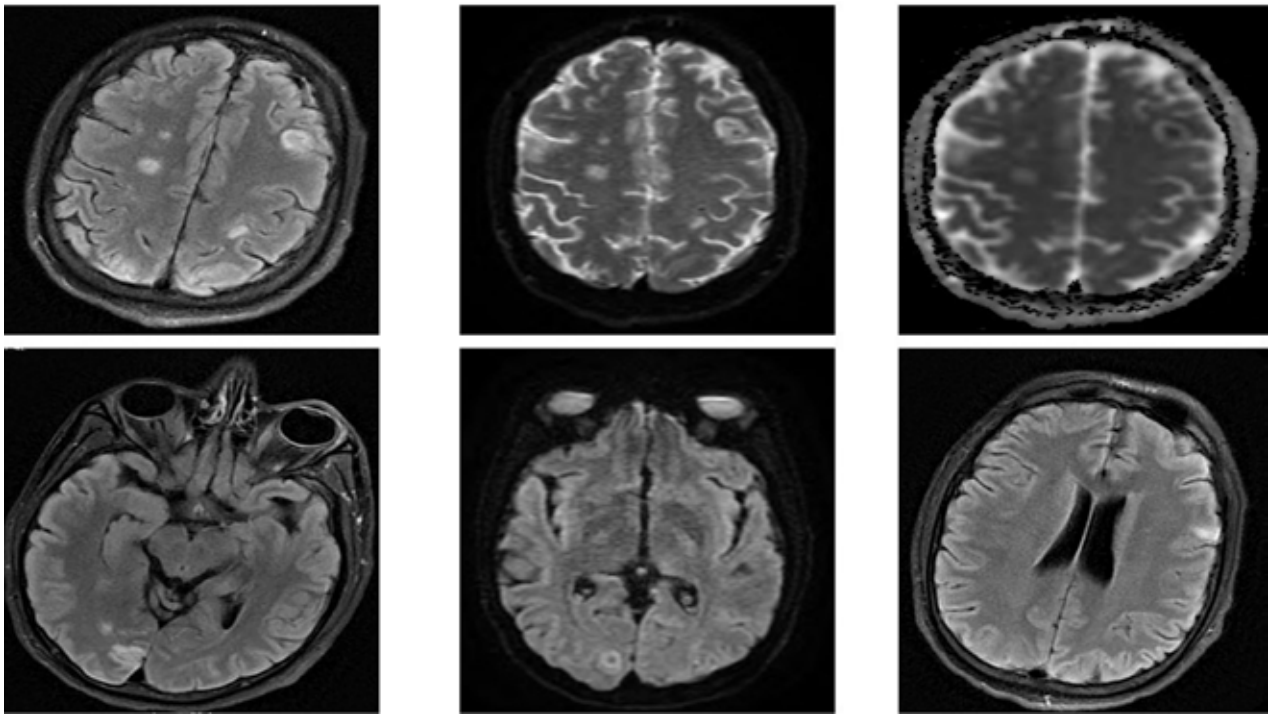

Figure 2. MRI showing multiple infarcts over left frontal, right parietal and right occipital region.

52% at the end of 1 year. (15) Predictors of mortality among patients with IE are age, vegetation size of > 10 mm, Staphylococcus aureus endocarditis, intracardiac abscess, left ventricular ejection fraction of less than 40%, and valvular perforation. (4,6,8,11,16,17) Similarly it has been reported that the odds of in-hospital mortality is higher among patients with IE and stroke. To date studies have only shown that age, vegetation characteristics are predictors of mortality in patients with IE and stroke. Patients with IE and stroke have a 1.7 times higher risk of perioperative mortality and a 1.23-fold higher risk of mortality at the end of 5 years. (11,15) Even though the reported mortality in our study was lesser, morbidity including the requirement of ICU care, mechanical ventilation, prolonged antibiotics course, the requirement of surgical intervention,

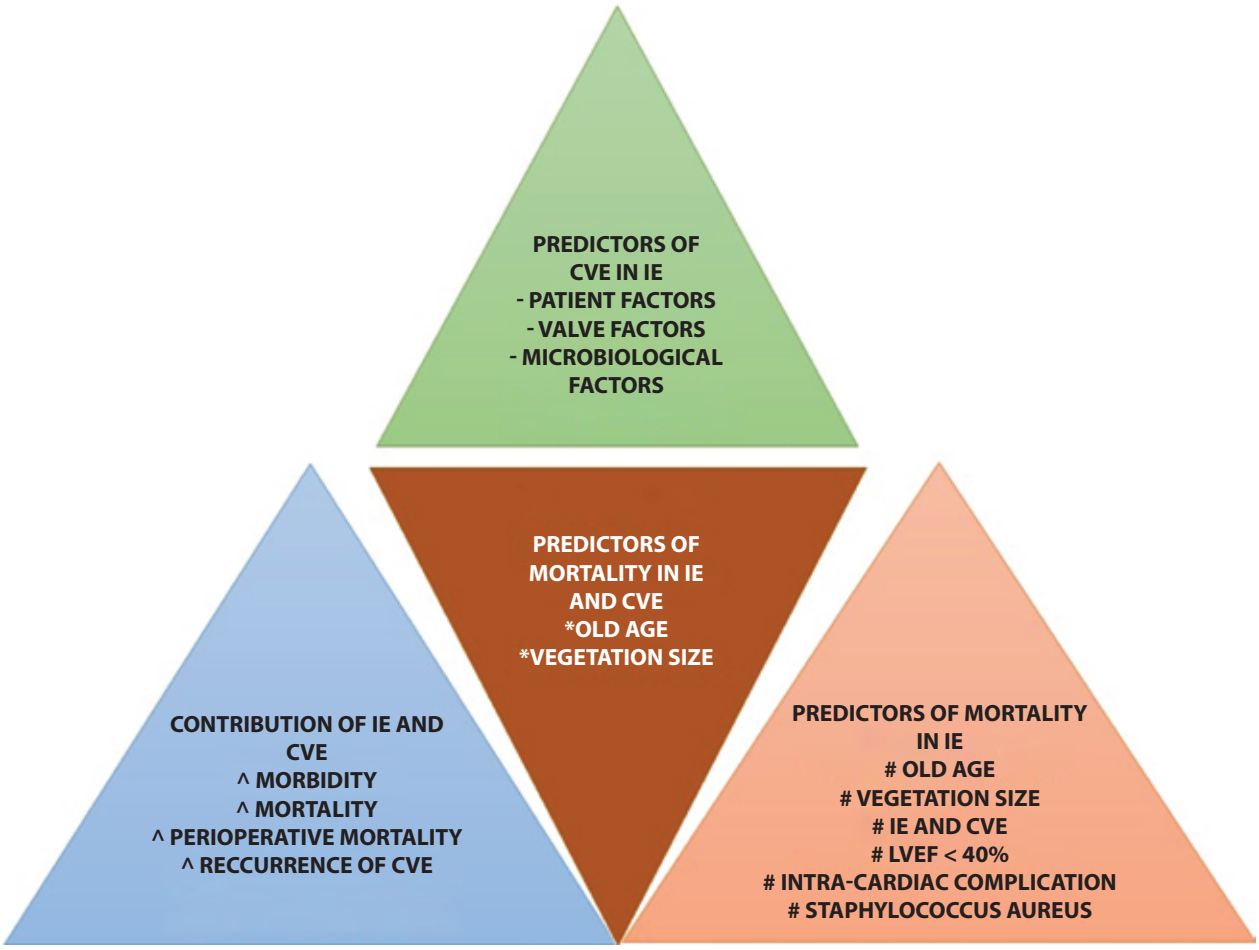

Figure 3. Risk factors, outcome, and the predictors of mortality among patients with CVI and IE.

and removal of medical devices contributed to increased duration of hospital stay. Figure 3 summarizes the risk factors of CVI among patients with IE, the outcome of CVI in patients with IE, and the predictors of mortality among patients with CVI and IE.

Limitations

Higher National Institute of heart stroke score [NIHS] at the presentation in patients with IE and stroke, has been shown to classify, and predict a poor neurological outcome. We did not have details of NIHSS for our patients. (18) Because of the retrospective nature of the study; we did not have details of the MRI brain in all the patients. CT brain might not be able to detect small infarcts, and can characterize dilated venules, Virchow Robin spaces, and artifacts as infarcts. (19) We did not have details of the functional status of these patients at baseline and discharge. Due to the smaller sample size, we were not able to establish any statistical conclusion. The impact of initiation and continuation of appropriate antibiotics, multidisciplinary approach, and timely intervention on patient outcomes were not studied. (20,21) We also did not have follow up details of these patients. The strength of this study was in including patients with definite IE and CVI, and in reporting various morbidities associated with the same.

Conclusion

In summary, CVE in IE is not uncommon. These tend to present as multiple infarcts predominantly

located over MCA circulation. Factors like older age, prior IE, mitral valve involvement, vegetation size, and staphylococcal IE can predispose to CVE in patients with IE. IE patients with neurovascular involvement can have higher mortality and morbidity. Further studies are needed to understand the mechanism and the extent to which these vascular events result in increased morbidity and mortality.

Highlights

Patients with IE prone to develop embolic, hemorrhagic cerebrovascular events, with the former being the commonest.

Patient factors predisposing to embolic events in patients with IE are older age, prior embolic events.

Valvular factors predisposing to embolic events in patients with IE are mitral valve vegetation, and vegetation size.

Staphylococcus aureus IE also predisposes to embolic events in patients with IE.

Among patients with IE infarcts tend to be multiple, predominantly located over anterior circulation, and often bilateral.

Patients with IE and embolic events tend to have higher morbidity and mortality.

References

1. Mishra AK, Sahu KK, Baddam V, Sargent J. Stroke and infective endocarditis [published online ahead of print, 2020 Mar 19]. QJM. 2020;hcaa098. doi:10.1093/qjmed/hcaa098
2. Merkler A.E., Chu S.Y., Lerario M.P., et al: Temporal relationship between infective endocarditis and stroke. Neurology 2015; 85: pp. 512-516
3. Mishra A, Sahu K, Nagabandi S, Benotti J. Infective Endocarditis with mitral leaflet perforation and multiple embolic infarcts [published online ahead of print, 2020 Feb 15]. QJM. 2020;hcaa026. doi:10.1093/qjmed/hcaa026
4. Valenzuela I, Hunter MD, Sundheim K, et al. Clinical risk factors for acute ischaemic and haemorrhagic stroke in patients with infective endocarditis. Intern Med J. 2018;48(9):1072-1080. doi:10.1111/imj.13958
5. Cao G, Bi Q, Cao L. Zhonghua Nei Ke Za Zhi. 2015;54(9):753-757.
6. Mohananey D, Mohadjer A, Pettersson G, et al. Association of Vegetation Size With Embolic Risk in Patients With Infective Endocarditis: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018;178(4):502-510. doi:10.1001/jamainternmed.2017.8653
7. Sahu KK, Mishra AK, Sherif AA, Doshi A, Koirala B. An interesting case of pacemaker endocarditis. Neth Heart J. 2019;27(11):585-586. doi:10.1007/s12471-019-01310-2
8. Cao GF, Liu W, Bi Q. Stroke in Patients with Infective Endocarditis: A 15-Year Single-Center Cohort Study. Eur Neurol. 2018;80(3-4):171-178. doi:10.1159/000495149.
9. Mishra AK, Sahu KK, Lal A, Sujata M, Systemic embolization following fungal infective endocarditis, QJM: An International Journal of Medicine, Volume 113, Issue 3, March 2020, Pages 233–235, https://doi.org/10.1093/qjmed/hcz274.
10. Cabell CH, Pond KK, Peterson GE, et al. The risk of stroke and death in patients with aortic and mitral valve endocarditis. Am Heart J. 2001;142(1):75-80. doi:10.1067/mhj.2001.115790
11. Østergaard L, Andersson NW, Kristensen SL, et al. Risk of stroke subsequent to infective endocarditis: A nationwide study. Am Heart J. 2019;212:144-151. doi:10.1016/j.ahj.2019.03.010.
12. Mishra AK, Sahu KK, Lal A, Menon V. Aortic valve abscess: Staphylococcus epidermidis and infective endocarditis. QJM. 2020;113(3):211-212. doi:10.1093/qjmed/hcz151.
13. Lauridsen TK, Park L, Tong SY, et al. Echocardiographic Findings Predict In-Hospital and 1-Year Mortality in Left-Sided Native Valve Staphylococcus aureus Endocarditis: Analysis From the International Collaboration on Endocarditis-Prospective Echo Cohort Study. Circ Cardiovasc Imaging. 2015;8(7):e003397. doi:10.1161/CIRCIMAGING.114.003397
14. Hess A, Klein I, Iung B, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. *AJNR Am J Neuroradiol*. 2013;34(8):1579-1584. doi:10.3174/ajnr.A3582
15. Anderson DJ, Goldstein LB, Wilkinson WE, et al. Stroke location, characterization, severity, and outcome in mitral vs aortic valve endocarditis. Neurology. 2003;61(10):1341-1346. doi:10.1212/01.wnl.0000094359.47929.e4
16. Derex L, Bonnefoy E, Delahaye F. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol. 2010;257(3):315-321. doi:10.1007/s00415-009-5364-3
17. Rizzi M, Ravasio V, Carobbio A, et al. Predicting the occurrence of embolic events: an analysis of 1456 episodes of infective endocarditis from the Italian Study on Endocarditis (SEI). BMC Infect Dis. 2014;14:230. Published 2014 Apr 29. doi:10.1186/1471-2334-14-230
18. Thuny F, Avierinos J-F, Tribouilloy C, Giorgi R, Casalta J-P, Milandre L, Brahim A, Nadji G, Riberi A, Collart F, Renard S, Raoult D, Habib G. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J. 2007;14:1155–1161. doi: 10.1093/eurheartj/ehm005.
19. Sonneville R, Mourvillier B, Bouadma L, Wolff M. Management of neurological complications of infective

endocarditis in ICU patients. Ann Intensive Care. 2011;14:10. doi: 10.1186/2110-5820-1-10
20. Lee SJ, Oh SS, Lim DS, Na CY, Kim JH. Clinical significance of cerebrovascular complications in patients with acute infective endocarditis: a retrospective analysis of a 12-year single-center experience. BMC Neurol. 2014;14:30. doi: 10.1186/1471-2377-14-30.

Correspondence
Received: 9 July 2020
Accepted: 4 October 2021
Dr. Ajay Kumar Mishra, MD
Department of Internal Medicine
St Vincent Hospital
123 summer street, Worcester, Massachusetts, United States
E-mail: Ajay.Mishra@stvincenthosptial.com
Phone: 5083635000