Characteristics and outcomes of infective endocarditis in South Africa: A retrospective cohort study

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ABSTRACT

Background: Infective endocarditis (IE) remains a disease with significant morbidity and mortality for a predominantly young group of patients in South Africa. There is a paucity of data assessing contemporary outcomes of IE in South Africa, limiting our ability to institute strategies to improve the outcome of patients with IE in South Africa.

Methods: A retrospective cohort of patients with IE was established from healthcare records for the period of 1 January 2017 - 31 December 2018. A profile of clinical, laboratory, microbiologic, echocardiographic, surgical, and morbidity and mortality data was compiled for each patient.

Results: A total of 75 patients with definite IE were included in this study. The mean age was 39.6 years with a male preponderance (68%). Mortality at 6 months (all cause) was 34.7% and embolic complications were common, especially cerebral embolism (21%). Rheumatic heart disease (RHD) was present in 28% of the cohort. A high rate of blood culture negative IE (BCNIE) was present (62.7%). In patients with a positive blood culture, Staphylococcus aureus (43%) and the viridans group of streptococci (32%) were the most common causative organisms.

Conclusion: IE in South Africa remains a disease with a significant mortality rate despite the young age of the patients affected. The high rate of BCNIE is a likely contributor to the associated adverse outcomes. Some of the features of IE in South Africa have evolved to resemble a profile of disease similar to cohorts from high-income countries with a Staphylococcal predominance and a reduction in underlying RHD as predisposing risk factor. SA Heart® 2024;21:218-224

INTRODUCTION

Infective endocarditis (IE) is an infective process of the endocardial surface of the heart, which may involve native valve structures (native valve endocarditis or NVE), prosthetic valves (prosthetic valve endocarditis or PVE) or implanted cardiac devices (device related IE or DRIE).[1-4] In South Africa, IE carries a significant morbidity and mortality with mechanical valve replacement in more than 40% of cases, reported cerebral embolism rates of 12% - 17% and in-hospital and 6-month mortality of up to 25% and 36% respectively.[5,6] IE in South Africa differs from the pattern of disease observed in high-income countries where in-hospital mortality is 18% - 20% and 6-month mortality 20% - 25%; but similar regarding rates of surgical management (40% - 50%) and embolic complications, particularly cerebral embolism (15% - 20%).[2,7-11]

Infective endocarditis (IE) in high-income countries is predominantly a disease of older patients with normal valves or degenerative valve disease, caused by Staphylococcus aureus and other hospital acquired organisms.[4,12] In contrast, IE in South Africa has been reported to be a disease of predominantly young patients without significant co-morbidities, commonly associated with underlying rheumatic heart disease (RHD) and caused by the viridans group of streptococci.[5]

Previously low rates of Staphylococcus aureus associated IE were reported in South Africa and this led to many local empirical protocols not including specific antimicrobial therapy to target Staphylococcus aureus, an example being the empiric use of ampicillin / penicillin G with gentamicin as standard therapy.[5] Recent reports have shown a more equal distribution with similar rates of Staphylococcus aureus and viridans group of streptococci reported in patients with IE.[6,13] Similar to cohorts from high-income countries, Staphylococcus aureus is the most common cause of right sided IE in South Africa and associated with intravenous drug use.[6,14]

The clinical features of IE have evolved in both low- and middle-income as well as high-income countries. The so-called "classical" features of IE, such as Osler nodes, Janeway lesions and Roth spots, are now rarely encountered in both low- and middle-income as well as high-income countries.[7,15] Clubbing, fever and anaemia with the presence of a regurgitant murmur remains the most common clinical features of IE in both low- and middle as well as high-income countries.[3,5]

We aimed to determine the current morbidity and mortality rates of IE in the Western Cape region of South Africa. In addition, we aimed to describe the clinical features, predisposing heart diseases and common causative organisms associated with IE in a retrospective cohort of patients with IE.

METHODS

Tygerberg Hospital (TBH) is a tertiary referral hospital for a network of 17 hospitals in Cape Town, South Africa, and serves a population of approximately 2.4 million people.[16] All patients presenting to this network of hospitals with suspected IE are referred to TBH.[17] Patients with possible IE were identified by reviewing the echocardiographic database of the Division of Cardiology at Tygerberg Hospital as well as the minutes of the weekly Heart Team meetings for the period January 2017 - December 2018.

The EchoPAC system (GE) is an internal network database of all echocardiograms (transthoracic and transoesophageal) performed by the Division of Cardiology at TBH. All transthoracic echocardiograms were obtained using a standard echocardiography machine (GE, Milwaukee, USA) with a 2- to 3.6MHz transducer probe (GE 3S/4S/5S) and performed by qualified health care professionals according to current guidelines.[18,19] Patient records are identifiable by name, surname, date of birth and a unique hospital number assigned to each patient upon entry into the health care system. This database was reviewed searching for patients either referred for suspected IE as well as all patients whose report mentioned possible vegetation(s) present on imaging.

The Heart Team consists of clinicians from both the Division of Cardiology and the Division of Cardiothoracic Surgery. Meetings are routinely held on a weekly basis. All patients that would potentially require surgery are discussed and reviewed, decisions being documented in minutes of each meeting. The minutes for the time period January 2017 - December 2018 was reviewed and all patients with IE were included.

All patients with suspected IE between 1 January 2017 - December 2018 were identified. Clinical notes, laboratory results, echocardiography images and surgical reports were reviewed and patients with definite or possible IE were included.[20]

Demographic, clinical, laboratory investigation, echocardiographic, surgical and outcome data were collected for all included patients. Demographic data recorded included age, sex and income status categorisation. Clinical data collected was aimed at determining the predisposing conditions (RHD, other history of valvular heart disease, intravenous drug use, previous valve surgery / replacement, history of congenital heart disease), co-morbid diagnoses, general cardiovascular risk factors and specific data such as human immunodeficiency virus (HIV) infection status. All clinical findings were captured including heart rate, blood pressure, measured temperature, presence of clubbing as well as all minor criteria described in the Duke criteria. Laboratory investigations captured included white cell count, haemoglobin concentration, creatinine, C-reactive protein (CRP), complement fraction 3 and 4 (C3 and C4), rheumatoid factor as well as auto-immune serological test results collected during the initial work-up. Echocardiographic data collected included whether TTE or TEE or both were performed, underlying valve characteristics, measurements of vegetations (linear length, circumference, mobility and sites of attachment), peri-annular extension if present and degree of valvular destruction. Surgical data was reviewed to establish the indication for surgery (haemodynamic instability, embolic phenomenon or inability to gain source control), which surgical technique was utilised (valve repair, valve reconstruction or valve replacement), what the calculated EuroSCORE II was and how many days elapsed between diagnosis and surgery. Outcome data collected was sought to confirm whether patients survived to discharge, survival to 6 months, degree of dyspnoea (as measured by the NYHA system) and whether they developed recurrence of IE.

STATISTICAL ANALYSIS

Statistical analysis was done on SPSS v27 for Windows. Descriptive statistics were calculated, nominal data was compared via cross tabulation and Chi-square tests, parametric data was compared using independent-sample T-tests (Cohen's d) and non-parametric data was compared using independent-samples T-test (Mann-Whitney U or Kruskal-Wallis 1-way ANOVA). Where possible, regression modelling was performed on nominal variables for measured outcomes.

ETHICAL CONSIDERATIONS

This study was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University (ref S19/10/234) and performed in accordance with the Helsinki Declaration of 1975 (updated in 2013). Waiver of individual consent was obtained from HREC to include data from patient records in this retrospective cohort.

RESULTS

A total of 75 patients were included (Figure 1). The baseline characteristics are summarised in Table I. The mean age was 39.6 years with a male predominance (68%). Thirty-five patients (46.7%) met modified Duke Criteria for definite IE, all the rest having criteria for possible IE. HIV infection was present in 21.5% of patients with a mean absolute CD4 count of 442 cells/µl. The majority of people living with human immuno-deficiency virus (PLHIV) (10/14; 71.4%) were on combination antiretroviral therapy (c-ART). Five patients (6.7%) volunteered a history of intravenous drug use (IVDU).

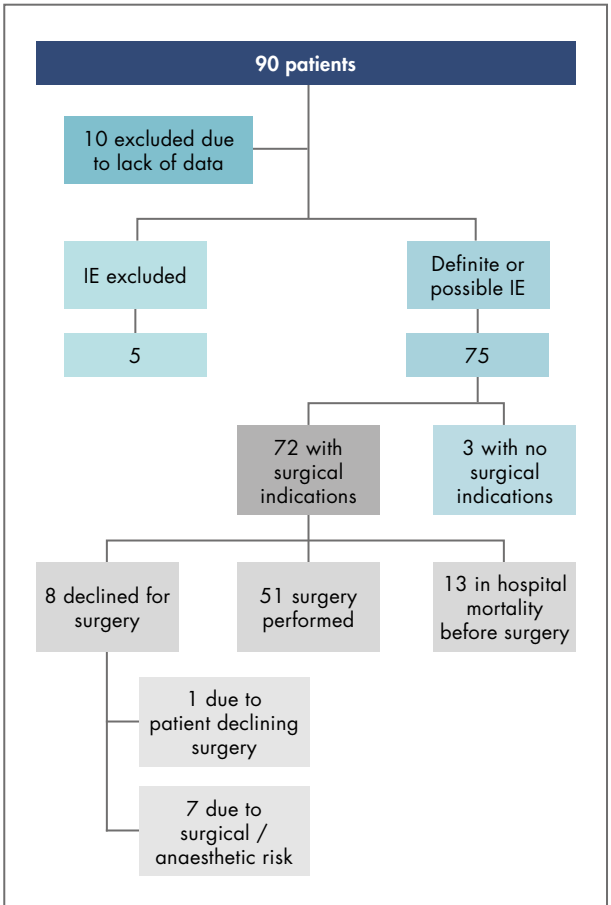

FIGURE 1: Schematic of case selection.

The clinical findings on examination are summarised in Table II. An audible murmur (96%), documented fever >38.3°C (56%), pallor (56%) and clubbing (32/75 or 42.7%) were the most frequently detected findings on examination. Cerebral embolism was the most common embolic complication, present in 16/75 (21%).

Laboratory investigations are summarised in Table III. An elevated CRP was present in 71/75 (94.7%) and a white cell count (WCC) above 11x109 cells/L in 25/75 (33.3%). C3 levels were less than 0.9g/L in 20/65 (30.8%) and C4 less than 0.1g/L in 9/65 (13.8%). Rheumatoid factor was elevated above 10IU/mL in 30/56 (53.6%).

Blood cultures were negative (BCNIE) in 47 of the 75 (62.7%) patients. In patients with positive blood cultures (BCPIE), Staphylococcus aureus was the most common causative organism (12/28; 42.9%) followed by the viridans group of streptococci (9/28; 32.1%). Other organisms identified by blood culture are shown in Figure 2.

Echocardiographic features of vegetations are listed in Table IV. Vegetations were, on average, large with mean vegetation length of 13.7mm on the aortic valve, 14mm on the mitral valve and 18.4mm on the tricuspid valve. Echocardiographic features of underlying rheumatic heart disease were present in 28% of patients.

TABLE I: Baseline characteristics.

	n=75 (%)
Age in years	
Mean (SD)	39.6 (12.3)
Male	51 (68.0)
Income status	
H0-1 (R0-70000 p.a.)	64 (85.3)
H2-4 (R>70000 p.a.)	11 (14.7)
Rheumatic heart disease	
History	15 (20.0)
Echocardiographic evidence	21 (28.0)
IVDU	5 (6.7)
HIV	
PLHIV	14 (18.7)
Unknown	10 (13.3)
On c-ART	10 (13.3)
Previous cardiac surgery	10 (13.3)
Cigarette smoking	27 (36.0)
Hypertension	15 (20.0)
Diabetes	3 (4.0)

SD: standard deviation, IVDU: intravenous drug user, HIV: human immunodeficiency virus, c-ART: combination antiretroviral therapy.

TABLE II: Clinical features.

	n=75 (%)
Dyspnoea present	68 (90.7)
Grade I	2 (2.7)
Grade II	13 (17.3)
Grade III	26 (34.7)
Grade IV	27 (36.0)
Night sweats	25 (33.3)
Weight loss	29 (38.7)
History of valvular heart disease	24 (32.0)
History of congenital heart disease	3 (4.0)
Fever (>38.3˚C)	42 (56.0)
Audible murmur	72 (96.0)
Pallor	42 (56.0)
Clubbing	32 (42.7)
Embolic / vascular phenomenon	
Stroke	16 (21.3)
Septic emboli	6 (8.0)
Major arterial emboli	1 (1.3)
Immunological phenomenon	
Splinter haemorrhages	18 (24.0)
Splenomegaly	6 (8.0)
Janeway lesions	2 (2.7)
Glomerulonephritis*	14 (18.7)
Features of severe AR	29 (38.7)
Features of severe MR	42 (56.0)
Features of severe TR	9 (12.0)
Left heart failure	37 (49.3)
Right heart failure	5 (6.7)
Biventricular failure	16 (21.3)

**Glomerulonephritis based on microscopic haematuria with / without acute kidney injury. Data on presence of haematuria only available in 20 patients. All patients that had microscopic haematuria detected had an elevated creatinine. AR: aortic regurgitation, MR: mitral regurgitation, TR: tricuspid regurgitation.*

Morbidity, mortality rates and surgical characteristics are summarised in Table V. The all-cause mortality rate at 6 months was 34.7%. There was a statistically significant difference in 6-month mortality between patients with an indication for surgery undergoing surgery when compared to patients with an indication for surgery who did not undergo surgery (21.6% vs. 71.4%; p<0.01).

Predictors of mortality at 6 months included failure to undergo surgery when indicated (OR 8.1; p=0.02), left ventricular dysfunction (OR 3.1; p=0.07) and EuroSCORE II more than 12% (OR 4.7; p=0.02) (Table VI).[21]

BCPIE as well as increasing vegetation length in millimetres on the aortic valve were associated with an increased risk for cerebral embolism (Table VII).

TABLE III: Laboratory investigations.

White cell count	<4x10⁹/L	0/75
	4-11x10⁹/L	50/75
	>11x10⁹/L	25/75
Haemoglobin	<10g/dL	31/75
	10-12g/dL	28/75
	>12g/dL	16/75
C-reactive protein	>10mg/L	71/75
Estimated glomerular filtration rate*	>90mL/min/1.73m²	42/75
	61-90mL/min/1.73m²	15/75
	30-60mL/min/1.73m²	15/75
	<30mL/min/1.73m²	3/75
Complement fraction 3	<0.9g/L	20/65
Complement fraction 4	<0.1g/L	9/65
Rheumatoid factor	Positive (>10IU/mL)	30/56
Anti-nuclear antibody	Positive (>1:40)	3/22
Anti-nuclear cytoplasmic antibody	Positive	1/4
Urine dipstick	Haematuria	31/49
	Proteinuria	16/49

**eGFR calculated using CKD-EPI formula; all patients categorised as "not African-American".*

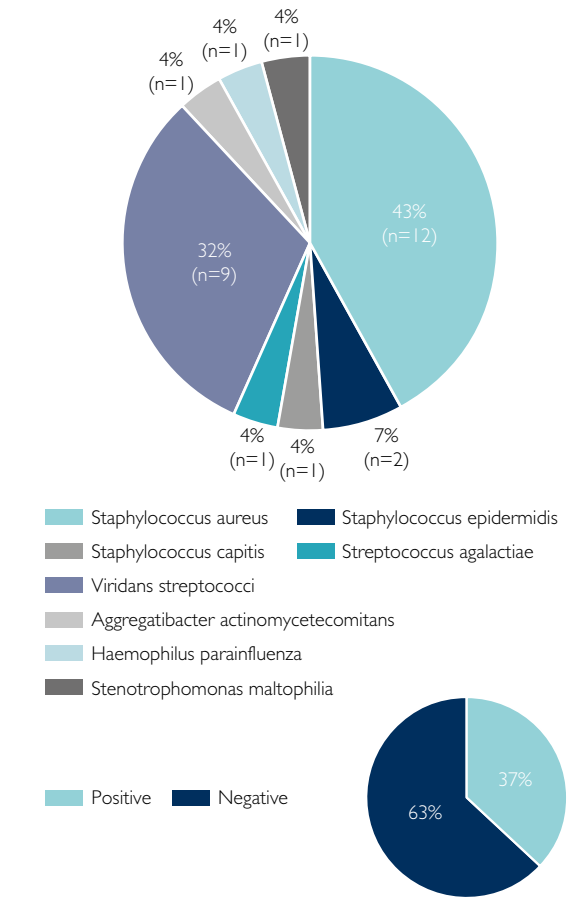

FIGURE 1: Blood culture results.

TABLE IV: Echocardiographic findings.

	n=75 (%)
Total vegetations*	47 (62.7)
Involved valve(s)	
Aortic valve	26 (34.7)
Mitral valve	31 (41.3)
Tricuspid valve	5 (6.7)
Aortic and mitral	8 (10.7)
Aortic and tricuspid	2 (2.7)
Mitral and tricuspid	2 (2.7)
Aortic valve vegetations	36 (48.0)
Mean size linear (SD)	13.7 (6.2)
Mean size circumferential (SD)	34.5 (15.4)
Mitral valve vegetations	41 (54.7)
Mean size linear in mm (SD)	14 (6.6)
Mean size circumferential in mm (SD)	38.6 (16.5)
Tricuspid valve vegetations	9 (12.0)
Mean size linear (SD)	18.4 (6.7)
Mean size circumferential (SD)	46.8 (15.8)

**Forty-seven patients had mobile valvular vegetations, 1 being a windsock deformity of the anterior mitral valve leaflet with submittal aneurysm due to Mycobacterium tuberculosis.*
SD: standard deviation, mm: millimeters.

TABLE V: Surgical characteristics.

	n=51 Surgery indicated, performed (%)	n=21 Surgery indicated, not performed (%)	p
Procedure			
Mechanical valve	34 (66.7)		
Tissue valve	7 (13.7)		
Valve repair	7 (13.7)		
Valve reconstruction*	3 (5.9)		
ICU stay in days (SD)	6.8 (9.9)		
Days from diagnosis to surgery (SD)	42.3 (37.8)		
EuroSCORE II			
Mean (SD)	7.7 (9.6)	15.9 (17.3)	0.01
RHD	15 (29.4)	4 (19.0)	0.36
IVDU	1 (2.0)	4 (19.0)	0.01
Blood culture positive	17 (33.3)	10 (47.6)	0.26
In hospital mortality	4 (7.8)	13 (61.9)	<0.01
Days to in hospital mortality from diagnosis (SD)	45.5 (26.8)	28.9 (17.3)	<0.01
Six 6-month mortality	11 (21.6)	14 (66.7)	<0.01

**Reconstruction defined as use of saphenous vein reconstruction or pericardial patch on mitral valve.*
ICU: intensive care unit, SD: standard deviation, RHD: rheumatic heart disease, IVDU: intravenous drug user. EuroSCORE II.[21]

TABLE VI: Predictors of 6-month mortality.

	OR	95% CI	p
Surgery indicated, not performed	8.1	2.1-30.6	0.02
EuroSCORE II >12%	4.7	1.3-17.8	0.02
Left heart failure	3.1	0.8-12.5	0.07
Weight loss*	1.9	0.6-6.6	0.27

**Variable kept in model due to interaction with subgroup not undergoing surgery – not reaching statistical significance (p=0.16).*

TABLE VII: Factors associated with stroke.

	OR	p
BCPIE	12.3	<0.01
BCPIE – Streptococcus	6.6	0.01
BCPIE – Staphylococcus	2.1	0.15
AV vegetation >10mm in linear length	2.4	0.12
MV vegetation >10mm in linear length	0.12	0.73
TV vegetation >10mm in linear length	0.64	0.43

BCPIE: Blood culture positive infective endocarditis, AV: aortic valve, mm: millimetres, MV: mitral valve, TV: tricuspid valve.

DISCUSSION

The 6-month mortality rate associated with IE (34.7%) recorded in this retrospective study remains higher than published data from high-income countries and similar to previous reports from South Africa.[5,11] In addition, embolic events and cerebral embolism in particular (21.3%) remain a significant contributor to the mortality and morbidity rates associated with IE. The high mortality rate is unexpected given the young age of patients and the low rate of associated comorbidities.

The 6-month mortality rate observed in our cohort (34.7%), is remarkably similar to the 35.6% mortality rate reported 20 years ago, despite advances in diagnostic and treatment strategies.[5] Compared to previous data from our institution, this cohort has a higher rate of PLHIV, PVE and patients reporting intravenous drug use.[5] Although retroviral disease is not considered as a predictor of adverse outcomes, PVE and intravenous drug use associated IE have been validated as predictors of worse outcomes.[22]

We identified various factors associated with mortality at 6 months. In this study failure to undergo surgery when indicated, a EuroSCORE II of more than 12% and left ventricular dysfunction (left ventricular ejection fraction <50%) were associated with 6-month mortality (Table VI).

Mortality at 6 months was significantly lower in patients with a surgical indication who underwent surgical treatment compared to mortality in patients in whom surgery was indicated, but did not undergo surgery (21.6% vs. 66.7%; p<0.01). Failure to undergo surgery when indicated, may be a contributing factor to high mortality rate observed. The group with surgical indications who underwent surgery had a mean EuroSCORE II value of 7.7% which correlated with the observed in-hospital mortality (7.8%).

The majority of patients that underwent surgery had a mechanical valve replacement due to the young age of patients, the prevalence of RHD and the significant valvular destruction observed at presentation. Although there has been a decrease in the prevalence of RHD compared to a previous cohort, a significant proportion of patients (28%) had underlying RHD.[5,14] The decrease in proportion of patients with underlying RHD in this cohort may be due to the change in bacteriological profile as screening studies do not suggest a decrease in the prevalence of subclinical RHD.[23] These subclinical cases may however not progress to severe lesions due to better screening and subsequent prophylactic antibiotic use. It may also reflect the relative increase in other predisposing conditions for the development of IE, such as intravenous drug use and prosthetic valve use.

Cerebral embolism was the most common embolic phenomenon and occurred in 21.3% of patients, which is similar to the reported rates from developed world cohorts in high-income countries.(.[7,11] It has been demonstrated that the presence of large vegetations (>10mm) is an independent risk factor for early cerebral embolism as well as mortality due to IE.[13,23] In this cohort large vegetations (>10mm) was not statistically predictive of cerebral embolism, this is likely due to this study being underpowered. Patients with BCPIE, especially IE caused by the viridans group of streptococci, were associated with an increased risk for cerebral embolism. It should be noted that the average vegetation size in the 9 patients with viridans group streptococcal infections was 17mm and 12.2mm when involving the AV and the MV, respectively. It is therefore possible that it was in fact vegetation size that contributed to cerebral embolism, rather than the specific organism causing infection. These vegetations were not statistically different in size compared to patients with BCPIE with non-streptococcal organisms (p=0.80 and 0.54 for AV and MV respectively) (Table VI).

Staphylococcus aureus was the most common organism detected, in contrast to previous reports identifying the viridans group of streptococci as the most common cause of IE in South Africa.[5] The organism detection rate in our cohort was lower than reported in cohorts from high-income countries, but similar to previously published data from South Africa with a BCNIE rate of 62.7%.[5,14] Even with the addition of serological and surgical specimen analysis, a causative organism could only be detected in 41.3% of patients. It should be noted that no set protocol for organism detection was employed and additional tests were performed on the discretion of the managing physician. The high rates of BCNIE in South Africa has been attributed to antibiotic use prior to blood culture sampling, although a recent publication from an ongoing prospective cohort study at our centre has demonstrated that non-culturable organisms, such as the Bartonella quintana, are an important cause of BCNIE.[24] Although high rates of BCNIE have been associated with worse outcomes, we did not detect a difference when comparing 6 month mortality in patients with BCPIE and BCNIE (37% vs. 31%; p=0.6).

The common clinical features observed in our cohort were similar to previous reports from South Africa and high-income countries.(.[5,14] The most common symptom on presentation was dyspnoea (90.7%), with fever, pallor, and clubbing the most common clinical signs of IE detected. Osler nodes, Janeway lesions, and Roth spots were rarely detected, although still incorporated in the modified Duke / ESC 2015 clinical criteria.[2,15]

LIMITATIONS

This was a retrospective study exposed to the usual limitations associated with it, such as inclusion bias and incomplete data availability. Ten potential cases were excluded due to incomplete data (11.1% or 10/90).

CONCLUSION

The profile of IE in South Africa has evolved to more closely resemble that observed in high income countries with Staphylococcal predominance and a reduction in underlying RHD, the driver for this reduction is not readily apparent. In many other respects it has remained unchanged over the past 2 decades, affecting a younger, otherwise healthy patient population with a high mortality rate and significant morbidity. Cerebral embolism remains the most frequently occurring embolic complication and is common. BCNIE remains a common entity, making directed treatment decisions and compilation of local organism profiles difficult.

Conflict of interest: none declared.

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