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A retrospective epidemiologic study to define risk factors, microbiology, and clinical outcomes of infective endocarditis in a large tertiary-care teaching hospital

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Abstract

Objective: This study aims to define risk factors as well as their association with microbiology and clinical outcomes in a large US infective endocarditis population.

Methods: Hospital records were searched for appropriate infective endocarditis–related ICD codes from 16 July 2007 to 13 August 2015. A total of 363 cases were retrospectively identified that met definite Modified Duke Criteria for infective endocarditis and were analyzed by age group, causative organism, and associated risk factors for use of valvular surgical intervention, 30/90/180-day mortality after admission, and embolic phenomena.

Results: Chronic hemodialysis was the most common risk factor (26.7% of cases). Of all age groups, those aged 78+ years had the lowest 30-day mortality but those aged 58–77 years had the highest mortality ($p = 0.039$). *Staphylococcus aureus* was the most prevalent causative organism. Those aged 78–97 years were more likely to have *enterococcal* infective endocarditis than those aged 18–27 years ($p = 0.0144$). Chronic hemodialysis associated infective endocarditis was more likely to be caused by coagulase-negative *staphylococcus* ($p = 0.0121$) and have a higher 30-day mortality ($p = 0.141$) than intravenous drug use associated infective endocarditis. Intravenous drug use and chronic hemodialysis were similarly likely to be caused by *S. aureus*. Intravenous drug use associated infective endocarditis was more likely to be caused by viridans group *streptococci* ($p = 0.0001$). Fungal infective endocarditis was most likely to embolize. Chronic hemodialysis patients were less likely to undergo valvular surgery ($p = 0.001$) and those with chronic hemodialysis who did had lower mortality than those only managed medically that did not reach statistical significance ($p = 0.2991$). Infective endocarditis caused by coagulase-negative *staphylococci* had the greatest 30-day mortality at 31.3% but did not reach statistical significance over all other causative organisms ($p = 0.060$).

Conclusion: In our infective endocarditis population, *S. aureus* is the predominant causative organism. Chronic hemodialysis is the most common risk factor present in infective endocarditis populations and has greater association with coagulase-negative *staphylococci* and 30-day mortality. Intravenous drug use had the lowest mortality among risk factors with a similar proportion of *S. aureus* infective endocarditis compared to chronic hemodialysis but a higher proportion of viridans group *streptococci* infective endocarditis cases. Further study will need to be performed on prevention and treatment of infective endocarditis in chronic hemodialysis patients.

Keywords

Infective endocarditis, epidemiology, outcomes, hemodialysis, microbiology, risk factor, mortality

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Introduction

Changes in the epidemiology of infective endocarditis (IE) have been happening over the past several decades. As a disease first recognized in 1885,[1] only a couple advances have been made that have reduced mortality associated with IE. The discovery and utilization of penicillin reduced mortality

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by 30%, and the institution of surgical options dropped it further to as low as 10% in the 1960s.[2] Currently, the mortality of IE is reported between 14% and 37%.[3–7] Developments over the past several decades have created a changing epidemiology for the disease. Successful treatment of *streptococcal* pharyngitis has lowered the incidence of rheumatic heart disease and subsequent subacute IE caused by viridans group *streptococci* (VGS).[7,8] The rise in intravenous drug use (IVDU) in the United States has made *Staphylococcus aureus* a major causative organism for IE in the United States.[5,9] Worldwide increases in *enterococcal* IE have also been documented.[9,10] Higher risk for IE is now being found in patients who are elderly,[3,5,7,9,11,12] chronically ill,[6] have prosthetic valves,[11] or go through invasive procedures.[10]

Within the past couple of decades, there has been a worldwide increase in IE caused by *S. aureus*.[3,6,9–11,13,14] Chronic hemodialysis (CHD) mimics the intermittent venous access seen in IVDU and could possibly contribute to this rise, particularly in the United States where there is a large population with end-stage renal disease (ESRD) and many opt for CHD over peritoneal dialysis.[15] Additionally, IE has been recognized as a complication of CHD since at least 1969,[16] but only recently are we recognizing it as a rising risk factor.[6,17] There is a reported higher risk of IE caused by *staphylococcal* species in those undergoing CHD over the general population, particularly with an increase in methicillin-resistant species.[6,18–23] CHD-associated IE has also been shown to have greater mortality and complications than non-CHD-associated IE.[18,21,22]

There have been few large population-based studies performed in the United States[5–8] with only two distinct populations found in our search of the literature. Of these, only one addresses IE in the past decade.[5] This study aims to determine the prevalence of literature-reported developing risk factors in our IE population and compare their associated outcomes. By independently analyzing the epidemiology of IE in the Hampton Roads, Virginia area, we determined the risk factors that are most prevalent in our IE population. By reviewing each risk factor's associated microbiology and clinical outcomes, we hope to determine associations with 30-day mortality.

Materials and methods

Population

This study was approved by the Institutional Review Board at Eastern Virginia Medical School for retrospective study of patient electronic medical records (EMR). The EMR from Sentara Norfolk General Hospital (SNGH) and Sentara Heart Hospital (SHH), both located on the same premises, was used to identify potential admissions for active cases of IE. The Sentara Healthcare system services a population of over 2 million and has an encatchment area that spans from central Virginia to the coast, then expands both north into the Eastern Shore and south into North Carolina. SNGH and SHH make up this system's large tertiary-care referral center. Norfolk is primarily an inner-city population with referrals from rural and suburban areas. The US Census has the city of Norfolk estimated at 245,115 people with 44.3% non-Hispanic White, 43.1% African American, 6.6% Hispanic, and 3.3% Asian. Approximately 48.7% of IE cases at SNGH and SHH were referred from outside hospitals. As with many inner-city populations, there is a high prevalence of IVDU and HIV infection in this population.

Data collection and analysis

In this study, we aimed to identify most prevalent risk factors in our IE population and their relationship with microbiology and 30-day mortality. Primary endpoint was defined as 30-day mortality after admission. Secondary endpoints included 90/180-day mortality after admission and valvular surgical intervention. Embolic phenomena were used as a secondary endpoint when analyzing causative organisms and age groups.

We retrospectively identified potential adult (aged 18+ years) patient admissions with active IE through a search of ICD9 codes 421.0–421.9, 391.1, 424.90–99, 017.90–96, 074.22, 098.84, 115.04, 115.14, 036.42, 112.81, and 093.20–4, from when the EMR first went live on 16 July 2007 to 13 August 2015. Each admission was characterized based on Modified Duke Criteria, and only those that met definite criteria for IE were included in the study. Cases seen at our facility a second time within 6 months of a prior admission for definite IE with the same causative organism were excluded from analysis. Cases with multiple possible causative organisms, or multiple equally identified organisms, were also excluded from analysis.

Patient records were examined for pertinent information including age, culture results and susceptibilities, serology, echocardiography, risk factors, embolic phenomena, valvular surgical intervention, and 30/90/180-day mortality after admission. Echocardiography was reviewed as well as microbiology data related to blood cultures, other site cultures, and serology. Mortality was determined by documentation of death in the EMR. Embolic phenomena were looked for in each patient record through imaging and symptoms reported by providers and radiology in the patient record. Janeway and other skin lesions were excluded as embolic phenomena due to lack of consistent skin-finding documentation on physical examination. Each chart was then reviewed for data within 1 year of the identified admission. Data were analyzed in three ways: by age group, by risk factor association, and by causative organism.

For analysis by age group, all cases of definite IE were divided into groups for each 20-year interval starting from age 18 years, with the creation of four possible age groups: 18–37 years, 38–57 years, 58–77 years, and 78–97 years. There were no patients >97 years old identified. Each age group was then reviewed for 30/90/180-day mortality after admission, surgical intervention, embolic phenomena, and causative organism. Odds ratios (ORs) were calculated for

comparative groups and 95% confidence intervals (CIs) were determined. Chi-square was calculated for categorical values and significance was defined as $p \leq 0.05$.

For analysis by risk factor, risk factors studied were CHD, history of IVDU, other long-term cardiovascular (CV) access, presence of a prosthetic valve, other intracardiac device (ICD), known valvular or structural heart disease not already included above, immunocompromised state, and poor dentition. If the case was associated with more than one risk factor, it was grouped under each association. Immunocompromised conditions were defined as HIV infection, use of immune-suppressants for transplant rejection, and active non-skin cancer or chemotherapy. Those with HIV were analyzed for CD4 count closest to admission and for appropriate highly active antiretroviral therapy (HAART). Other ICDs included both mechanical implants and non-autologous grafts. These risk factor groups were then reviewed for 30/90/180-day mortality after admission, surgical intervention, mean age, and causative organism. ORs were calculated for comparative groups and 95% CIs were determined. Chi-square calculations were used for categorical values with frequencies of <5 for >20% of values not calculated per appropriateness criteria. Analysis of variance (ANOVA) was used for analyzing multiple quantitative values. We chose ANOVA over multiple linear regressions since the data could not be assumed to have a normal distribution in residual errors and some categories had too few data points to determine the lack of multicollinearity or the data being homoscedasticity. Significance was defined as $p \leq 0.05$.

For analysis by causative organism, all cases of definite IE were divided into groups based on culture results and susceptibilities, as well as serology. The organism that fulfilled major microbiological Modified Duke's Criteria was identified as the causative organism. If major criteria were not fulfilled, then results that met minor criteria were reviewed for causative organism. This classification was then compared to treatment regimens to confirm agreement with provider determination of causative organism. Each causative organism group was then evaluated for 30/90/180-day mortality after admission, mean age, and embolic phenomena. ORs were calculated for comparative groups and 95% CIs were determined. Chi-square calculations were used for categorical values with frequencies of <5 for >20% of values not calculated per appropriateness criteria. ANOVA was used for analyzing multiple quantitative values. We chose ANOVA over multiple linear regressions since the data could not be assumed to have a normal distribution in residual errors and some categories had too few data points to determine the lack of multicollinearity or the data being homoscedasticity. Significance was defined as $p \leq 0.05$.

Results

A total of 492 potential cases were identified through the above ICD9 codes with 363 that met definite criteria for IE and the rest meeting possible criteria for IE. Of these 363 cases, 20 were excluded due to being a second admission seen for recurrent IE or a polymicrobial episode leaving a total of 343 cases. The mortality for all cases of definite IE was 20.7%, 26.2%, and 29.2%, respectively, at 30, 90, and 180 days after admission. The number of patients who experienced embolic phenomena is shown in Table 1. CHD was the most common risk factor, associated with 91 (26.5%) cases. The number of cases associated with each studied risk factor is shown in Table 2. There were 22 cases associated with an immunocompromised state with only 7 associated with HIV (1.9% of all definite IE cases). Of these 7 HIV-associated cases, 2 had CD4 <200 with both on appropriate HAART, 3 with CD4 between 200 and 500 with two on appropriate HAART, and 2 with CD4 >500 that were not on appropriate HAART. A total of 87 (25.4%) underwent valvular surgery. There was a total of 256 (74.6%) involving a native valve, 63 (18.4%) involving a prosthetic valve, and 27 (7.9%) involving a device. Mean, median, mode, and standard deviation of age for all 343 cases of definite IE analyzed were 56.7, 57, 63, and 14.8, respectively, with ages ranging from 20 to 90.

Outcomes by age group

Valvular surgery, emboli, microbiology, and mortality analysis by age group is shown in Table 1. Those aged 78–97 years had a lower 30-day mortality than those aged 58–77 years (OR = 0.3, 95% CI = 0.08–0.97, p = 0.0451). Those aged 38–57 years were also less likely to experience 30-day mortality than those aged 58–77 years (OR = 0.5, 95% CI = 0.27–0.89, p = 0.0191). Those aged 78+ years were least likely to experience 30-day mortality with those aged 58–77 years most likely to experience 30-day mortality ($\chi^2 = 8.35$, p = 0.0393). Those aged 78+ years were least likely to experience mortality at 90 and 180 days as well (Table 1). Those aged 38–57 years were more likely to undergo valvular surgery than those aged 58–77 years (OR = 3.0, 95% CI = 1.71–5.22, p = 0.0001) and those aged 78–97 years (OR = 19.1, 95% CI = 2.52–143.87, p = 0.0043). Those aged 38–57 years were also most likely to undergo valvular surgery ($\chi^2 = 26.16$, p = 0.00001).

Those aged 38–57 years were more likely to experience embolic phenomena compared to those aged 78–97 years (OR = 2.4, 95% CI = 0.94–6.35, p = 0.0670) and those aged 58–77 years (OR = 1.6, 95% CI = 0.98–2.75, p = 0.0578) although results fell short of statistical significance. They were also similarly likely to experience embolic phenomena as those aged 18–37 years (OR = 1.4, 95% CI = 0.63–3.04, p = 0.4156). Of patients who experienced embolic phenomena, those aged 38–57 years had lower 30-day mortality than those aged 58–77 years (OR = 0.3, 95% CI = 0.11–1.06, p = 0.0641) with results not quite reaching significance. They also had similar 30-day embolic mortality as those aged 18–37 years (OR = 0.6, 95% CI = 0.10–3.46, p = 0.5679) and those aged 78–97 years (OR = 0.7, 95% CI = 0.07–6.72, p = 0.7308).

Table 1. Trends by age group.

	Total	18–37 years	38–57 years	58–77 years	78–97 years	p-value
Total cases	343	37	138	137	31	
30-day mortality	71 (20.7%)	8 (21.6%)	22 (15.9%)	38 (27.7%)	3 (9.7%)	0.039
90-day mortality	90 (26.2%)	8 (21.6%)	29 (21.0%)	49 (35.8%)	4 (12.9%)	0.009
180-day mortality	100 (29.2%)	10 (27.0%)	32 (23.2%)	53 (38.2%)	5 (16.1%)	0.012
Valve surgery	87 (25.4%)	8 (21.6%)	54 (39.1%)	24 (18.1%)	1 (3.2%)	<0.001
Embolic phenomena	104 (29.5%)	11 (29.7%)	51 (37.0%)	36 (26.3%)	6 (19.4%)	0.127
Brain	56 (16.3%)	5 (13.5%)	32 (23.2%)	15 (10.9%)	4 (12.9%)	0.043
Pulmonary	22 (6.4%)	4 (10.8%)	9 (6.5%)	7 (5.1%)	2 (6.3%)	–
Abdominal organs	20 (5.8%)	–	12 (8.7%)	8 (5.8%)	–	–
Other location	30 (8.7%)	3 (8.1%)	10 (7.2%)	17 (12.4%)	–	–
30-day mortality	19 (18.3%)	2 (18.2%)	6 (11.8%)	10 (27.8%)	1 (16.7%)	–
Causative organism						
S. aureus	125 (36.4%)	19 (51.4%)	53 (38.4%)	45 (32.8%)	8 (25.8%)	0.109
MRSA	60 (17.5%)	5 (13.5%)	30 (21.7%)	22 (16.1%)	3 (9.7%)	0.303
CoNS	48 (14.0%)	4 (10.8%)	14 (10.1%)	24 (17.5%)	6 (19.4%)	0.244
MR	23 (6.7%)	1 (2.7%)	7 (5.1%)	13 (9.5%)	2 (6.3%)	–
Enterococcus	42 (12.2%)	2 (5.4%)	13 (9.4%)	19 (13.9%)	8 (25.8%)	0.041
VGS	54 (15.7%)	3 (8.1%)	25 (18.1%)	23 (16.7%)	3 (9.7%)	–
Other strep	31 (9.0%)	3 (8.1%)	17 (12.3%)	9 (6.6%)	2 (6.3%)	–
Other bacteria	26 (7.6%)	3 (8.1%)	11 (8.0%)	9 (6.6%)	3 (9.7%)	–
Serology positive	4 (1.2%)	1 (2.7%)	–	3 (2.2%)	–	–
Fungal	7 (2.0%)	3 (8.1%)	2 (1.5%)	2 (1.5%)	–	–
Valve type affected						
Native	256 (74.6%)	27 (73.0%)	106 (76.8%)	95 (69.3%)	22 (71.0%)	0.572
Prosthetic	63 (18.4%)	6 (16.2%)	22 (15.9%)	30 (21.9%)	2 (6.5%)	0.193
Device	27 (7.9%)	3 (8.1%)	7 (5.1%)	7 (5.1%)	7 (22.6%)	0.004

MRSA: methicillin-resistant *Staphylococcus aureus*; CoNS: coagulase-negative *Staphylococci*; MR: methicillin resistant; VGS: viridans group *streptococci*. Percent of total are in parentheses with exception of embolic 30-day mortality which is a percent of embolic phenomena for that age group. Emboli are classified by location.

S. aureus was the most prevalent causative organism in all cases of definite IE. Those aged 78+ years were less likely to have *S. aureus* IE (OR = 0.3, 95% CI = 0.12–0.92, p = 0.0348) but more likely to have *enterococcal* IE than those aged 18–37 years (OR = 6.1, 95% CI = 1.19–31.27, p = 0.0305). Those aged 78+ years were also similarly likely to have coagulase-negative *staphylococcus* (CoNS) IE than those aged 18–37 years (OR = 2.0, 95% CI = 0.50–7.77, p = 0.3276). There is a general decreasing trend of *S. aureus* IE and an increasing trend in CoNS and *enterococcal* IE as age groups got older. Viridans group *streptococcal* (VGS) IE was most prevalent in 38–57 years of age but was not significantly higher than the group with the least VGS IE, those aged 18–37 years (OR = 2.5, 95% CI = 0.71–8.82, p = 0.1519).

Outcomes by risk factor

Mortality, valvular surgical intervention, and causative organism analysis by risk factor is shown in Table 2. χ^2 analysis for all risk factors' primary and secondary endpoints only showed significance for 180-day mortality and undergoing valvular surgery (Table 2). However, cases associated with CHD had a higher 30-day mortality rate than IVDU-associated cases (OR = 12.5, 95% CI = 1.62–96.33, p = 0.0153). Only one IVDU case showed 30-day mortality and was also on CHD. Patients with IVDU also had a statistically significant lower 30-day mortality than patients with a prosthetic valve (OR = 0.1, 95% CI = 0.01–0.74, p = 0.0242), valvular/structural cardiac disease (OR = 0.1, 95% CI = 0.01–0.98, p = 0.0480), and immunocompromised state (OR = 0.1, 95% CI = 0.01–0.95, p = 0.0453). They also had lower 30-day mortality that almost reached statistical significance compared to those with other ICDs (OR = 0.1, 95% CI = 0.02–1.06, p = 0.0570), other types of CV access (OR = 0.1, 95% CI = 0.01–1.68, p = 0.1199), poor dentition (OR = 0.1, 95% CI = 0.02–1.33, p = 0.0874), and history of IE (OR = 0.1, 95% CI = 0.02–1.09, p = 0.0602).

Those with other ICD and CHD were least likely to undergo valvular surgery, while those with poor dentition were most likely to undergo valvular surgery ($\chi^2 = 27.34$, p = 0.0006). The 30-day mortality of those undergoing valvular surgery for each risk factor is shown in Table 2. When comparing mortality to those in the same risk factor group who did not undergo valvular surgery, all groups failed to reach significance.

CHD-associated IE was similarly likely to be caused by *S. aureus* as IVDU-associated IE (OR = 1.2, 95% CI = 0.52–2.53,

Table 2. Risk factor association with mortality, age, valvular surgery, and causative organism.

	CHD	IVDU	CV	PV	ICD	V/S	Hx IE	Dental	IMC	p-value
Total cases	91	34	11	78	70	44	48	29	23	
30-day mortality	25 (27.5%)	1 (2.9%)	2 (18.2%)	19 (24.4%)	13 (18.6%)	9 (20.5%)	9 (18.8%)	5 (17.2%)	5 (21.7%)	0.242
90-day mortality	29 (31.9%)	3 (8.8%)	2 (18.2%)	23 (29.5%)	18 (25.7%)	10 (22.7%)	11 (23.0%)	7 (24.1%)	5 (21.7%)	0.389
180-day mortality	35 (38.5%)	3 (8.8%)	2 (18.2%)	24 (31.0%)	20 (28.6%)	12 (27.3%)	13 (27.1%)	8 (27.6%)	5 (21.7%)	0.140
Valve surgery	14 (15.4%)	11 (32.4%)	3 (27.3%)	18 (23.1%)	6 (8.6%)	14 (31.8%)	18 (37.5%)	12 (41.4%)	3 (13.0%)	0.001
30-day surgical mortality	2 (14.2%)	–	–	4 (22.2%)	2 (33.3%)	4 (28.6%)	2 (11.1%)	1 (8.3%)	–	
Mean age	55	46.5	52	59	65.5	53	50	55	57	<0.001
Age standard deviation	12.8	12.9	14.7	13.2	15.0	17.7	11.4	10.0	15.3	
Age range	27–83	20–68	22–71	28–83	29–89	20–86	28–67	25–67	26–84	
Causative organism										
S. aureus	46 (50.5%)	16 (47.1%)	5 (45.5%)	27 (34.6%)	33 (47.1%)	12 (27.3%)	10 (20.8%)	7 (24.1%)	5 (21.7%)	0.005
MRSA	28 (30.8%)	9 (26.5%)	4 (36.4%)	9 (11.5%)	12 (17.1%)	6 (13.6%)	8 (16.7%)	6 (20.7%)	2 (8.7%)	0.034
CoNS	25 (27.5%)	–	2 (18.2%)	15 (19.2%)	10 (14.3%)	6 (13.6%)	2 (4.2%)	3 (10.3%)	6 (26.1%)	0.003
MR	9 (9.9%)	–	2 (18.2%)	4 (5.1%)	7 (10.0%)	2 (4.5%)	–	1 (3.4%)	4 (17.4%)	–
Enterococcus	8 (8.8%)	2 (5.9%)	2 (18.2%)	10 (12.8%)	10 (14.3%)	3 (6.8%)	6 (12.5%)	3 (10.3%)	5 (21.7%)	0.615
VGS	2 (2.2%)	10 (29.4%)	–	7 (9.0%)	7 (10.0%)	14 (31.8%)	4 (8.3%)	9 (31.0%)	4 (17.4%)	<0.001
Other *streptococci*	–	2 (5.9%)	1 (7.7%)	8 (10.3%)	3 (4.3%)	1 (2.3%)	2 (4.2%)	4 (13.8%)	–	–
Other bacteria	5 (5.5%)	1 (2.9%)	1 (9.1%)	8 (10.3%)	5 (7.1%)	4 (9.1%)	5 (10.4%)	1 (3.4%)	–	–
Fungal	1 (1.1%)	2 (5.9%)	2 (18.2%)	1 (1.3%)	1 (1.4%)	–	2 (4.2%)	–	–	–
Serology positive	–	–	–	–	–	2 (4.5%)	1 (2.1%)	1 (3.4%)	1 (4.3%)	–
Valve type affected										
Native	74 (81.3%)	28 (82.4%)	7 (63.6%)	20 (25.6%)	37 (52.9%)	20 (45.5%)	26 (54.2%)	26 (90.0%)	15 (65.2%)	<0.001
Prosthetic	12 (13.2%)	5 (14.7%)	–	54 (69.2%)	3 (4.3%)	1 (2.3%)	19 (39.6%)	5 (17.2%)	2 (8.7%)	<0.001
Device	7 (7.7%)	2 (5.9%)	2 (18.2%)	4 (5.1%)	23 (32.9%)	2 (4.5%)	4 (8.3%)	–	2 (8.7%)	–

CHD: chronic hemodialysis; IVDU: intravenous drug use; CV: cardiovascular access; PV: prosthetic valve; ICD: intracardiac device; V/S: native valvular/structural disease; Hx IE: history of infective endocarditis; dental: poor dentition; IMC: immunocompromised; MRSA: methicillin-resistant *staphylococcus aureus*; CoNS: coagulase-negative *Staphylococci*; MR: methicillin-resistant; VGS: viridans group *streptococci*.

p=0.7284) but was more likely to be caused by CoNS (OR=26.5, 95% CI=1.56–447.88, p=0.0232). IVDU-associated IE was more likely than CHD-associated IE to be caused by VGS (OR=18.5, 95% CI=3.80–90.36, p=0.0003). IE associated with valvular/structural cardiac disease was also more likely to be caused by VGS than CHD-associated IE (OR=20.8, 95% CI=4.46–96.71, p=0.0001).

Outcomes by causative organism

Mortality, valvular surgical intervention, and embolic outcomes by causative organism are shown in Table 3. VGS had a lower 30-day mortality than *S. aureus* (OR=0.3, 95% CI=0.07–0.80, p=0.0179) and CoNS (OR=0.2, 95% CI=0.05–0.58, p=0.0041), but only near significant lower 30-day mortality than other *streptococci* (OR=0.3, 95% CI=0.07–1.03, p=0.0550) and *enterococcus* (OR=0.4, 95% CI=0.11–1.47, p=0.1679). The likelihood of undergoing valvular surgery was greatest in IE caused by fungus and other *streptococci* ($\chi^2=20.24$, p=0.0025). VGS IE was more likely to have valvular surgery than *S. aureus* (OR=3.2, 95% CI= 1.48–6.81, p=0.0020) as well as CoNS (OR=2.2, 95% CI=0.86–5.43, p=0.0993) although the latter failed to reach significance. By raw numbers, cases with fungal IE were most likely to embolize than IE caused by other organisms with "other bacteria" being least likely to embolize ($\chi^2=18.93$, p=0.0043).

Discussion

In our population, CHD was the most common risk factor found in all definite IE cases. CHD patients had the highest 30-day mortality and were also more likely to be infected by any *staphylococcal* species. Similarly, these findings are also seen in the IVDU population with the exception that IVDU patients were more likely to have VGS IE rather than CoNS IE compared to CHD patients. IVDU-associated IE had the lowest 30-day mortality. This may be explained by IVDU patients' better immune status and younger mean age than CHD patients, possibly allowing them greater survival and the ability to clear bacteremia by less virulent skin flora. The higher incidence of VGS IE in the IVDU population is likely due to the practice of cleaning needles with saliva and subsequently introducing oral flora into the CV system with drug injection. Additionally, it has been discussed in prior reviews and studies that technique for accessing arteriovenous dialysis fistulas predisposes to bacteremia.[24] However, one study used mupirocin gel prophylaxis in CHD patient that had a history of local or systemic infection and showed no difference between access methods.[25] In this case, the use of prophylactic antibiotic creams/gels may show benefit in reducing IE burden in CHD patients through reduction of colonization and introduction of skin flora into the bloodstream. This is important as our study shows the majority of causative organisms in CHD-associated IE are likely skin flora. With the high mortality in CHD-associated IE, this could help improve overall mortality from IE.

S. aureus was also the most common causative organism associated with the majority of risk factors and concurs with the current literature supporting and increase in *S. aureus* IE.[3,6,9–11,13,14] CoNS had the highest 30-day mortality of all causative organisms at 32.0%. This is likely due to this infection occurring in those with more compromised immune systems which includes CHD patients. VGS had the lowest mortality which may be due to its association with two risk factors with lower average ages and possibly healthier immune status (IVDU and native valvular/structural heart disease) as well as more bactericidal antibiotic options. Fungal IE was most likely to undergo valvular surgery and had the greatest risk of embolization, both of which are likely related. Fungal IE may have a higher risk of embolization as fungi tend to form larger colonies that have greater potential to detach and enter the bloodstream. Embolization would then take a piece of friable valve with it, creating a greater need for emergent surgery. Additionally, this could also cause a rule-in bias as fungal IE cases that did not embolize may not have fulfilled one of the minor criteria to subsequently qualify as definite IE.

Our study showed a similar 30-day mortality to that reported in the literature at 20.7%. Those aged 58–77 years had the highest mortality. While age and comorbidities likely accounted for higher mortality, it is interesting to note that those aged 78–97 years had the lowest mortality (p=0.0393). This differs from prior findings in the literature that found that age >65 years was an independent predictor of mortality in IE.[26] This difference in our population could be due to several reasons. One is that those living past 78 years may not have suffered the comorbidities of those in next youngest age group, such as CHD due to ESRD. It also could be an age-related general decrease in immune status predisposed them to more infections by organisms not as likely to affect younger populations that we have better antibiotic coverage for. This was shown by having the highest likelihood *enterococcal* IE (p=0.0406) along with their lower likelihood of *S. aureus* IE than those aged 18–37 years (p=0.0305). Those aged 78–97 years were also less likely to undergo valvular surgery which concurs with previous literature findings.[26] This is likely due to both their age not being suitable for non-lifesaving surgery and the causative organism's lower virulence reducing need for surgery due to less valvular destruction.

There was no distinct trend of increasing or decreasing frequency of embolic phenomena or embolic 30-day mortality among age groups. However, those aged 38–57 years were most likely to experience embolic phenomena to the brain. They also had more embolic phenomena in general, which was close to significance at p=0.1268. It is unclear as to why this age group experienced the most embolic phenomena.

Most emboli located to the brain. The reason is likely two-fold. First, providers are more likely to take neurologic

Table 3. Outcomes by causative organism.

	S. aureus		CoNS		*Streptococcus*					
	All	MR	All	MR	ETC	VGS	Other strep	Other bacteria	Fungal	p-value
Total cases	125	60	48	23	42	54	31	26	7	
30-day mortality	29 (23.2%)	13 (21.7%)	15 (31.3%)	7 (30.4%)	7 (16.7%)	4 (7.4%)	7 (22.6%)	5 (19.2%)	–	0.060
90-day mortality	34 (27.2%)	17 (28.3%)	19 (39.6%)	8 (34.8%)	7 (16.7%)	7 (13.0%)	8 (25.8%)	7 (26.9%)	–	0.030
180-day mortality	40 (32.0%)	21 (35.0%)	19 (39.6%)	8 (34.8%)	9 (21.4%)	7 (13.0%)	8 (25.8%)	7 (26.9%)	–	0.029
Valve surgery	17 (13.6%)	6 (10.0%)	9 (18.8%)	5 (21.7%)	7 (16.7%)	18 (33.3%)	14 (45.2%)	6 (23.1%)	3 (42.9%)	0.003
Mean age	55	55.5	61	63	62.5	56.5	53	53.5	38	0.002
Age standard deviation	15.3	14.7	14.5	13.3	15.7	11.5	12.2	16.3	14.8	
Age range	20–89	20–89	27–83	27–83	28–90	33–88	32–81	22–86	22–65	
Embolic phenomena	37 (29.6%)	18 (30.0%)	14 (29.2%)	6 (26.1%)	9 (21.4%)	21 (38.9%)	12 (38.7%)	3 (11.5%)	6 (86.7%)	0.004
Brain	21 (56.8%)	10 (55.6%)	8 (57.1%)	2 (33.3%)	4 (44.4%)	10 (47.6%)	9 (75.0%)	1 (33.3%)	1 (16.7%)	0.215
Pulmonary	12 (32.4%)	5 (27.8%)	1 (7.1%)	1 (16.7%)	2 (22.2%)	6 (28.6%)	–	–	2 (33.3%)	–
Renal/spleen	4 (10.8%)	2 (11.1%)	4 (28.6%)	2 (33.3%)	6 (66.7%)	5 (23.8%)	–	–	1 (16.7%)	–
Other locations	11 (29.7%)	4 (22.2%)	5 (35.7%)	2 (33.3%)	–	4 (23.8%)	4 (33.3%)	2 (66.7%)	2 (33.3%)	–
Valve type affected										
Native	96 (76.8%)	49 (81.7%)	34 (70.8%)	17 (73.9%)	30 (71.4%)	44 (81.5%)	24 (77.4%)	14 (53.8%)	3 (42.9%)	0.073
Prosthetic	19 (15.2%)	7 (11.7%)	10 (20.8%)	3 (13.0%)	9 (21.4%	8 (14.8%)	5 (16.1%)	8 (30.8%)	1 (14.3%)	0.591
Device	12 (9.6%)	5 (8.3%)	4 (8.3%)	3 (13.0%)	3 (7.1%)	2 (3.8%)	1(3.2%)	4 (15.4$)	2 (28.6%)	–

CoNS: coagulase-negative *staphylococci*; MR: methicillin resistant; ETC: *enterococcus*.
Other *streptococci* are shown in the column as a subset of *streptococcus*. Percents of total are in parentheses with exception of percent of embolic phenomena that is a percent of the embolic phenomena per causative organism.

symptoms more seriously, from altered mental status to classic stroke symptoms, and be more inclined to order brain imaging. This can possibly identify infarcts that may or may not explain the patient's symptoms. Second, the arteries to the brain make up some of the first branches of the aorta, with their upward direction being more of a straight-shot than the lateral branches going to the upper extremities.

Those with poor dentition did understandably have higher rates of VGS, although *S. aureus* was still the most common causative organism. This is likely due to poor dentition in our study being discovered by imaging rather than signs or symptoms, giving a bias toward dental abscesses which may be more associated with *S. aureus*. Those with other valvular/structural cardiac disease had a higher prevalence of VGS IE than those with CHD, likely due to the same mechanism that predisposes those with rheumatic heart disease to develop subacute IE caused by VGS. Immunocompromised patients had a relative increase in *enterococcal* and CoNS IE, similar to those aged 78+ years and likely also due to being more susceptible to less virulent organisms. Despite the large HIV population in the area, less than 2% of cases were associated with HIV which does not appear to be an important risk factor given the various CD4 levels and use of HAART. Presence of any foreign material in the heart was also a major risk factor which stands to reason as artificial surfaces are ideal for bacterial colonization.

Patients on CHD and with ICDs were least likely to undergo valvular surgery. This is likely related to CHD patients' ESRD both decreasing their immune status and making them poor surgical candidates. Some CHD patients may also die before they are able to receive surgical intervention. Those with other ICDs likely only needed removal of the ICD which likely acted as the nidus of infection. Even though it did not reach significance, those with CHD who underwent valvular surgery had a lower mortality rate than those that did not (OR = 0.43, 95% CI = 0.09–2.09, p = 0.2991). In our hospital, CHD is often a condition that prevents a patient from being a surgical candidate as many studies show increased mortality in CHD patients undergoing valvular surgery for IE versus non-CHD patients.[21,27] However, one study found that of patients with CHD-associated IE, those who underwent valvular surgery had a 15% lower in-hospital mortality compared to those treated only medically.[28] Another study reported that valvular surgical intervention was an independent predictor of survival in CHD-associated IE patients on logistic regression.[29] Our study population for CHD-associated IE undergoing valvular surgery was too small to draw conclusions from. But as surgical technique and anesthesia improve to minimize risks of surgery, we may need to reconsider valvular surgery in CHD patients who have indications for non-emergent surgical intervention. Surgical mortality outcomes per risk factor versus those who did not undergo valvular surgery did not reach significance in any of the risk factor groups. This is likely due to small patient population size of those undergoing valvular surgery for each risk factor.

Our study can be prone to error due to underreporting of symptoms and physical findings by both patients and physicians. Additionally, our mortality may be underreported as documentation in the patient file was needed to confirm mortality, although this only mattered in outpatient mortality outside our medical system which was only questionable in a handful of cases. IVDU association may be underreported in our study as well due to their dependence on patient memory and openness as well as detail in provider reporting. As a retrospective cohort study, this study is unable to prove causation for the outcomes studied and all aspects may not be generalizable outside our Hampton Roads, VA population. Additionally, some statistical analysis by risk factor and causative organism could not be calculated due to small frequency in these multiple populations that were inappropriate to analyze by χ^2 (e.g. device-associated IE).

Conclusion

In our population, the most common risk factor for endocarditis was CHD followed by prosthetic valve, other ICDs, and history of IE. CHD-associated IE had higher 30-day mortality than IVDU-associated IE. Those undergoing CHD or who had other ICDs were least likely to undergo valvular surgery. CHD and IVDU-associated IE both were most likely to be caused by *S. aureus*, but IVDU was more likely to be associated with VGS, while CHD was more likely to be associated with CoNS. IVDU-associated IE had the lowest mean patient age. Patients aged 58–77 years had the highest 30-day mortality, while those aged 78–97 years had the lowest mortality. Older age groups were less likely to undergo valvular surgery than younger age groups. Those aged 38–57 years were most likely to experience embolic phenomena to the brain. Those aged 78–97 years were more likely to have *enterococcal* IE and less likely to have *S. aureus* IE. Fungal IE was the most likely to embolize but least likely to experience mortality. CoNS IE had the highest mortality.

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