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Article

Microbiology of Infective Endocarditis in United States Veterans — Association Between Causative Organism and Short- and Long-Term Outcomes

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Abstract

Background: Previous studies have elucidated the relationship between causative organism and outcomes in infective endocarditis, however this relationship has not been studies in United States Veterans. The aim of this manuscript is to evaluate the association between causative organism and short-term and long-term outcomes in United States (US) Veterans with infective endocarditis (IE) requiring surgical management between 2010–2020. **Methods**: We analyzed 489 patients with surgically treated IE from the Veterans Affairs (VA) Surgical Quality Improvement Program and the VA Informatics and Computing Infrastructure databases. Patients were divided into groups using causative organism identified from blood or intraoperative cultures – Staphylococcus, Streptococcus, Gram-negative rods, Enterococcus, Polymicrobial, and Unknown/Culture Negative. Other identified organisms were excluded from analysis. Cox proportional hazard models were used to calculate risk for stroke/transient ischemic attack (TIA), myocardial infarction (MI), and death based on group. The models were adjusted for covariates using backward elimination. Continuous variables were compared using ANOVA or Kruskal-Wallis H tests, and categorical variables were compared using Chi square tests. **Results**: Mean follow-up was 4.0 ± 6.3 years. Gram negative rods (GNRs) were associated with greater risk of long-term mortality (adjusted hazard ratios (aHR) 2.15, 95% CI: 1.20–3.86, $p = 0.01$). Enterococcus was associated with long-term risk of MI (aHR 2.05, 95% CI: 1.07–3.94, $p = 0.03$). Resistant organisms, such as methicillin-resistant staphylococcus aureus, were associated with long-term risk of MI (aHR 2.51, 95% CI: 1.14–5.45, $p = 0.02$). Polymicrobial infections were associated with greater risk of perioperative complications, including prolonged mechanical ventilation (48 hrs) (aHR 1.76, 95% CI: 1.05–2.97, $p = 0.034$), tracheostomy (aHR 5.64, 95% CI: 2.35–13.55, $p < 0.001$), and prolonged ICU stay (5 days) (aHR 1.39, 95% CI: 1.01–1.91, $p = 0.043$). **Conclusions**: In US Veterans, polymicrobial infections had notably worse perioperative outcomes but similar long-term outcomes in comparison to monomicrobial infections. GNR infections were associated with increased long-term mortality. Enterococcus and resistant organisms were associated with increased long-term risk of MI. Polymicrobial infections were associated with greater risk of perioperative complications, including prolonged mechanical ventilation, tracheostomy, and prolonged ICU stay.

Keywords

infective endocarditis; causative organisms; veterans affairs; veterans health administration

Introduction

Despite advancements in medical and surgical treatments, infective endocarditis (IE) remains associated with high morbidity and mortality [1–3]. In the US, there is an incidence of between 3–10 cases of IE per 100,000 adults, and rates of IE-related hospitalizations increased from 34,488 per 100,000 adults in 2003 to 54,405 per 100,000 adults in 2016 [4]. Evidence has demonstrated that patients benefit greatly from a collaborative approach, which allows for coordination of multiple experts, including cardiologists, cardiac surgeons, infectious disease practitioners, radiologists, neurologists, and congenital heart disease specialists [2]. This multidisciplinary strategy facilitates patient-centered care for a set of diseases that vary widely with respect to origins of infection, valves affected, patient comorbidities, the nature of any pre-existing cardiac conditions, and the microorganisms involved. Cardiac surgery is required in more than half of patients with IE and is usually indicated when IE is already advanced [2], although indications for early surgical intervention can include heart failure, persistent infection, abscess, heart block, infection with highly resistant organisms, or recurrent emboli.

The microbiology of IE is a central piece to patient prognosis and treatment, though a complicated one. Identification of responsible pathogens is important not only for treatment selection in individual patients, but also for our understanding of how specific microorganisms may contribute to patient complications and outcomes. While viridans group streptococcus species were historically the most common set of pathogens identified in these illnesses, staphylococcus species (specifically S. aureus), have become the predominant pathogens worldwide over the last two decades [2,5,6]. Contributing factors include a large increase in injection drug usage [7,8], an increase in implantable cardiac devices and the broadening of their use [9], an increase in other indwelling devices in healthcare (i.e., central venous catheters) [8], and ergo a resulting overall increase in healthcare-related infections [10,11]. While staphylococcal and streptococcal species comprise the majority of identified organisms, gram negative rods (GNRs), enterococcus, polymicrobial infections, fungal species, and culture-negative cases have also been regularly identified [3,12–14].

US veterans are a distinct population that warrants special consideration. The US Veteran healthcare system delivers care to over 9.6 million individuals with overall poorer health status and more medical comorbidities than civilians, with unique healthcare needs related to their time serving [15–17]. While previous research has demonstrated associations between particular sets of organisms and patient outcomes in IE [18–20], the comparative impact of these pathogens on short and long term US Veteran morbidity and mortality remains unclear.

Thus, in this study, we aimed to investigate the association between causative organism and short-term and long-term outcomes in US Veterans with IE requiring surgical management.

Materials and Methods

Study Population

Records were obtained via the Veterans Affairs (VA) Surgical Quality Improvement Program (VASQIP) and the Corporate Data Warehouse (CDW) via the VA Informatics and Computing Infrastructure (VINCI). These databases prospectively collect preoperative, intraoperative, postoperative, and outcomes data on all patients who undergo cardiac surgery at any of 43 VA cardiac surgery centers in the United States [21,22], and external studies have demonstrated consistent reliability of the data [21,23].

For this study, institutional review board approval was obtained from the Washington DC VA Medical Center and a waiver of informed consent was obtained (IRB number 1584919, approval renewed 10/19/2022). Using standard international classification of disease (ICD) codes for infective endocarditis and standard current procedures terminology (CPT) codes for repair or replacement of aortic, mitral, tricuspid, and pulmonic valves, we identified patients who underwent surgical management of infective endocarditis between January 1 2010 and December 31 2020. Culture data and surgical pathology records were queried from VINCI; either blood culture at the time of surgery or culture of the surgical specimen was used to identify the culprit organism for each patient. Patient demographic information, including past medical history and co-morbid medical conditions, were obtained through VINCI and VASQIP. Patients with both native valve and prosthetic valve endocarditis were included in the study population. Patients were divided into six groups using causative organism identified from blood or intraoperative cultures – Staphylococcus, Streptococcus, Gram-negative rods (GNRs), Enterococcus, Polymicrobial, and Unknown/Culture Negative. Patients with fungal endocarditis were excluded due to the sample size being too small to perform any meaningful statistical analysis. Due to small sample size, no planned direct comparisons of organisms between native and prosthetic valve endocarditis were completed. Follow-up data was retrieved from outpatient records within VINCI. Patient demographics, operative variables, culture data, perioperative outcomes, and long-term myocardial infarction (MI), stroke or transient ischemic attack (TIA), and death were recorded using data contained within VINCI as well as operative reports. Date of death was determined via the VINCI database, which is linked with Veterans Health Administration vital status files, Social Security Administration, Center for Medicare and Medicaid Services, and the National Cemetery Administration. Follow-up was completed through May 10, 2022, and is reported as median and interquartile range (IQR).

Statistical Analysis

Preoperative demographics, patient characteristics, clinical comorbidities, 30-day outcomes, 1-year outcomes, and long-term outcomes were compared between cohorts at the univariable level. Continuous variables were compared with ANOVA or Kruskal-Wallis H with Bonferroni *post hoc* tests. Categorical variables were compared using Chi square tests. Cox proportional hazard models were used to calculate risk of death, MI, and stroke or TIA between groups. All multivariable models implemented a backward stepwise selection procedure of covariates triangulated with a purposeful selection approach using stay criteria of $\alpha = 0.1$. Comparisons of demographics, patient characteristics, and clinical comorbidities resulting in a p-value < 0.20 were considered potential confounding covariates and were adjusted for in multivariable analysis to better elucidate the independent effect of operative intervention on outcomes of interest. Confounding covariates for adjustment included: weight (kg), age, body mass index (BMI), American So-

Table 1. Patient characteristics for veterans undergoing surgical intervention for IE.

	Staph spp	Strep spp	GNRs	Enterococcus	Polymicrobial	Culture negative	*p*
	(n = 109)	n = 102)	(n = 30)	(n = 88)	(n = 63)	(n = 97)	
Age (y)	57.9 ± 11[abc]	63.0 ± 10[a]	63.9 ± 6	63.73 ± 12[b]	63.3 ± 10[c]	60.3 ± 11	<0.001
Sex (% male)	97.2	99.0	96.7	98.9	95.2	99.0	0.510
BMI	33.0 ± 10[a]	28.9 ± 7[a]	27.9 ± 6	30.9 ± 10	29.8 ± 8	30.1 ± 9	0.011
CAD n (%)							0.390
Mild	14 (20.3)	13 (19.1)	4 (25.0)	13 (22.4)	9 (20.9)	9 (13.8)	
Moderate/severe	13 (11.9)	8 (7.8)	1 (3.3)	10 (11.4)	11 (17.5)	9 (13.8)	
Prior AV replacement n (%)	8 (7.3)	4 (3.9)	3 (10.0)	5 (5.7)	7 (11.1)	4 (4.1)	0.372
Prior MV replacement n (%)	2 (1.8)	1 (1.0)	1 (3.3)	1 (1.1)	1 (1.6)	2 (2.1)	0.896
Prior MV repair n (%)	1 (0.9)	1 (1.0)	1 (3.3)	0	1 (1.6)	0	0.349
Prior TV repair n (%)	0	0	0	0	1 (1.6)	0	0.190
Preoperative sepsis n (%)	28 (25.7)	17 (16.7)	13 (43.3)	17 (19.3)	20 (31.7)	7 (7.2)	<0.001
Cerebrovascular disease n (%)							0.333
TIA	1 (0.9)	4 (3.9)	0	5 (5.7)	1 (1.6)	0	
Stroke	22 (20.2)	19 (18.6)	7 (23.3)	17 (19.3)	16 (25.4)	23 (23.7)	
Class III or IV Heart Failure n (%)	60 (55.0)	63 (61.8)	14 (46.7)	56 (63.6)	36 (57.1)	53 (54.6)	0.528
Smoking status n (%)							0.326
Never smoker	30 (27.5)	16 (15.7)	8 (26.7)	20 (22.7)	13 (20.6)	26 (26.8)	
<14 days	31 (28.4)	33 (32.4)	5 (16.7)	16 (18.2)	14 (22.2)	20 (20.6)	
14 days–3 months	10 (9.2)	4 (3.9)	2 (6.7)	8 (9.1)	4 (6.3)	7 (7.2)	
>3 months	38 (34.9)	49 (48.0)	15 (50.0)	44 (50.0)	32 (50.8)	44 (45.4)	
Hypertension n (%)	89 (81.7)	76 (74.5)	23 (76.7)	78 (88.6)	47 (74.6)	79 (81.4)	0.172
Diabetes n (%)	42 (38.5)	27 (26.5)	15 (50.0)	38 (43.2)	23. (36.5)	28 (28.9)	0.051
Oral medications	37 (33.9)	22 (21.6)	12 (40.0)	28 (31.8)	18 (28.6)	23 (23.7)	0.187
Insulin	29 (26.6)	18 (17.6)	11 (36.7)	19 (21.6)	16 (25.4)	16 (16.5)	0.142
Total ADL dependence n (%)	12 (11.0)	7 (6.9)	5 (16.7)	10 (11.4)	9 (14.3)	6 (6.2)	0.332
Hx illicit drug use n (%)	16 (14.7)	9 (8.8)	4 (13.3)	9 (10.2)	11 (17.5)	8 (8.2)	0.395

Univariate comparisons reported. Superscripts to indicate results of post-hoc analyses. Significance (*p*) as follows. Age: a = 0.007, b = 0.002, c = 0.017. BMI: a = 0.013.

Abbreviations: ADL, activities of daily living; AV, aortic valve; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GNRs, gram negative rods; IE, infective endocarditis; MV, mitral valve; spp, species; TIA, transient ischemic attack; TV, tricuspid valve.

ciety of Anesthesiologists (ASA) classification, presence of cardiomegaly, cerebrovascular disease (CVD), presence of Class III or IV heart failure, renal failure, chronic obstructive pulmonary disease (COPD), moderate to severe coronary artery disease (CAD), current smoking status, diabetes mellitus, functional status (FST), hypertension, peripheral vascular disease, prior heart surgery history, prior MI, sex, race, and pre-operative intra-aortic balloon pump (IABP). Adjusted hazard ratios (aHR) are reported for long-term outcomes along with 95% CI. *p*-values < 0.05 using two sided tests were considered statistically significant. All statistical analyses were performed using SPSS software version 29 (IBM SPSS Statistics for Windows, Version 29, IBM Corp, Armonk, NY, USA).

Results

Patient Demographics

We identified 501 patients who underwent surgery for IE, of whom 12 were excluded due to sample size for their causative organism being too small for statistical analysis, leaving 489 patients in the cohort. Groups varied in respect to age [$F(5,483) = 4.61$, $p < 0.001$], and BMI [$F(5,483) = 3.03$, $p = 0.011$]. The GNR group had a higher rate of preoperative sepsis [adjusted X2 (5, N = 489) = 19.2, $p < 0.002$]. Detailed patient demographics and characteristics for each group are presented in Table 1.

Table 2. Operative details for veterans undergoing surgical intervention for IE.

	Staph spp (n = 109)	Strep spp (n = 102)	GNRs (n = 30)	Enterococcus (n = 88)	Polymicrobial (n = 63)	Culture negative (n = 97)	*p*
# Valves involved n (%)							0.760
0	6 (5.5)	2 (2.0)	1 (3.3)	3 (3.4)	2 (3.2)	6 (6.2)	
1	84 (77.1)	77 (75.5)	20 (66.7)	66 (75.0)	49 (77.8)	70 (72.2)	
2	19 (17.4)	21 (20.6)	8 (26.7)	17 (19.3)	10 (15.9)	21 (21.6)	
3	0	2 (2.0)	1 (3.3)	2 (2.3)	2 (3.2)	0	
MV replace (%)	40 (36.7)	34 (33.3)	9 (30.0)	23 (26.1)	18 (28.6)	38 (39.2)	0.429
MV repair (%)	8 (7.3)	8 (7.8)	5 (16.7)	8 (9.1)	3 (4.8)	8 (8.2)	0.539
AV replace (%)	59 (54.1)	74 (72.5)	17 (56.7)	67 (76.1)	47 (74.6)	58 (59.8)	0.003
AV repair (%)	1 (0.9)	0	2 (6.7)	0	0	0	0.013
PV replace (%)	0	1 (1.0)	0	1(1.1)	0	1 (1.0)	0.846
TV repair (%)	9 (8.3)	5 (4.9)	4 (13.3)	4 (4.5)	3 (3.2)	6 (6.2)	0.396
TV replace (%)	7 (6.4)	3 (2.9)	2 (6.7)	3 (3.4)	5 (7.9)	1 (1.0)	0.233
Multivalve operation (%)	19 (17.4)	23 (22.5)	9 (30.0)	19 (21.6)	12 (19.0)	21 (21.6)	0.757
Multivalve and CABG (%)	0	2 (2.0)	0	1 (1.1)	1 (1.6)	0	0.479
Prosthetic IE with any valve (%)	8 (7.3)	4 (3.9)	4 (13.3)	3 (3.4)	6 (9.5)	6 (6.2)	0.305
Prosthetic AV IE (%)	7 (6.4)	3 (2.9)	3 (10.0)	2 (2.3)	5 (7.9)	4 (4.1)	0.333
Prosthetic MV IE (%)	1 (0.9)	1 (1.0)	1 (3.3)	1 (1.1)	0	2 (2.1)	0.808
Prosthetic TV IE (%)	0	0	0	0	1 (1.6)	0	0.190
CABG (%)	14 (12.8)	12 (11.8)	1 (3.3)	13 (14.8)	10 (15.9)	11 (11.3)	0.614

Abbreviations: AV, aortic valve; CABG, coronary artery bypass graft; IE, infective endocarditis; MV, mitral valve; PV, pulmonic valve; TV, tricuspid valve.

Table 3. Perioperative outcomes for veterans undergoing surgical intervention for IE.

	Staph spp (n = 109)	Strep spp (n = 102)	GNRs (n = 30)	Enterococcus (n = 88)	Polymicrobial (n = 63)	Culture negative (n = 97)	*p*
Operative mortality (%)	3 (5.1)	2 (3.4)	3 (17.6)	4 (10.5)	4 (12.1)	2 (3.7)	0.183
Prolonged ventilation (%)	15 (13.8)	14 (13.7)	7 (23.3)	18 (20.5)	19 (30.2)	10 (10.3)	0.016
Reintubated w/in 30 d (%)	5 (4.8)	4 (4.0)	4 (13.8)	6 (7.1)	5 (8.5)	5 (5.3)	0.431
Tracheostomy (%)	2 (1.9)	1 (1.0)	3 (10.0)	4 (4.8)	9 (15.0)	2 (2.2)	<0.001
ICU stay (d)	8.8 ± 11	6.9 ± 4	13.4 ± 16	8.1 ± 8	13 ± 15	5.9 ± 6	<0.001
Hospital stay (d)	16.1 ± 13	14.7 ± 10	24.0 ± 19	16.6 ± 20	24.6 ± 26	12.0 ± 8	<0.001

Operative Characteristics and Perioperative Outcomes: Univariate Comparisons

Groups varied in respect to proportion of cases that included aortic valve repair [X2 (5, N = 489) = 20.4, p = 0.013] and replacement [X2 (5, N = 489) = 17.7, p = 0.003]. Univariate analyses of additional operative details are shown in Table 2.

The polymicrobial group had a higher rate of postoperative tracheostomy than the other groups [X2 (5, N = 489) = 23.37, $p < 0.001$; *post hoc* $p = 0.018$].

The polymicrobial group had longer postoperative ICU LOS (13 days) than the Staphylococcus (9 days, $p < .001$), Streptococcus (7 days, $p = 0.006$), Enterococcus (8 days, $p = 0.009$), and Culture Negative (6 days, $p < 0.001$) groups, though not the GNR group. [H(5) = 29.11, $p < 0.001$]. The Culture Negative group had the shortest ICU LOS when compared to all other groups (Staph p = 0.024, Strep $p = 0.004$, GNR $p = 0.009$, Enterococcus p = 0.005). Additional *post hoc* pairwise comparisons were not significant (Table 3). The Culture Negative group also had the shortest postoperative hospital LOS at 12 days (H(5) = 18.78, $p = 0.002$) when compared with each of the other groups [Staph: 16 days, $p = 0.007$, Strep: 15 days, p = 0.021, GNR: 24 days, $p < 0.001$, Enterococcus: 17 days, $p = 0.011$, Polymicrobial: 25 days, $p = 0.001$]. The GNR group also had a longer LOS than the Strep group (p = 0.040). Additional *post hoc* pairwise comparisons were not significant (Table 3).

Groups also varied with respect to mortality at 1 year postoperatively [X2 (5, N = 489) = 13.85, $p = 0.017$]. There were no differences among groups in incidence of MI, stroke, or mortality at 30 days postoperatively. There were no group differences in MI or stroke rates at 1 year postoperatively (Table 4).

Table 4. Short term outcomes for veterans undergoing surgical intervention for IE.

	Staph spp (n = 109)	Strep spp (n = 102)	GNRs (n = 30)	Enterococcus (n = 88)	Polymicrobial (n = 63)	Culture negative (n = 97)	*p*
MI 30 d (%)	6 (5.5)	10 (9.8)	1 (3.3)	10 (11.4)	3 (4.8)	4 (4.1)	0.256
Stroke 30 d (%)	8 (7.3)	7 (6.9)	2 (6.7)	9 (10.2)	1 (1.6)	8 (8.2)	0.494
Mortality 30 d (%)	5 (4.6)	2 (2.0)	1 (3.3)	4 (4.5)	5 (7.9)	5 (5.2)	0.641
MI 1 y (%)	9 (8.3)	11 (10.8)	2 (6.7)	12 (13.6)	4 (6.3)	4 (4.1)	0.260
Stroke 1 y (%)	12 (11.0)	10 (9.8)	4 (13.3)	12 (13.6)	2 (3.2)	8 (8.2)	0.363
Mortality 1 y (%)	14 (12.8)	5 (4.9)	8 (26.7)	16 (18.2)	12 (19.0)	13 (13.4)	0.017

Cox-Proportional Hazards Models

Median follow-up for the entire cohort was 3.7 years (IQR 1.3–6.9 years). After adjusting for significant covariates, GNRs were associated with greater risk of long-term mortality (aHR 2.15, 95% CI: 1.20–3.86, $p = 0.01$) (Table 5). Enterococcus (aHR 2.05, 95% CI: 1.07–3.94, $p = 0.03$) and resistant organisms, such as methicillin-resistant staphylococcus aureus (aHR 2.51, 95% CI: 1.14–5.45, $p = 0.02$), were both associated with long-term risk of MI (Table 5). Polymicrobial infections were associated with greater risk of perioperative complications, including prolonged mechanical ventilation (48 hrs) (aHR 1.76, 95% CI: 1.05–2.97, $p = 0.034$), tracheostomy (aHR 5.64, 95% CI: 2.35–13.55, $p < 0.001$), and prolonged ICU stay (≥5 days) (aHR 1.39, 95% CI: 1.01–1.91, $p = 0.043$).

Infective organism was not predictive of long-term stroke/TIA occurrence. Significant predictors of long-term risk, MI, mortality, and composite outcomes are demonstrated in Table 5.

Discussion

The microbiology of IE is a critical factor in IE patient prognosis and treatment. While undergoing surgery independently predicts improved outcomes for IE patients [3,18,19], individual pathogens themselves also have a large influence on patient prognosis [3,20]. The comparative impact of these pathogens on short- and long-term patient morbidity and mortality in the US Veteran population remains unclear. Our present study found that GNRs were associated with greater risk of long-term mortality, that Enterococcus and resistant organisms were associated with long-term risk of MI, and that Polymicrobial infections were associated with greater risk of perioperative complications. Though prosthetic valve IE historically carries a worse prognosis than native valve IE [24], we did not identify this as an independent predictor of morbidity or mortality. The lack of this finding in the current study may reflect small sample size, as only 44 patients (9.0%) in our cohort had a history of prior valve replacement.

The development of IE requires the setting of a damaged or altered cardiac valve and simultaneous bacteremia by an organism that is capable of colonizing this altered surface [25]. Damage can be caused by any number of events, including rheumatic disease, catheters, repeated intravenous drug use, or elective cardiac procedures. Therefore, there are innumerable combinations of etiologies and organisms resulting in this relatively rare illness. Methods of adherence, formation of biofilms, circulating immune complexes, pathological antibodies– each factor has the potential to dramatically impact the severity of a patient's illness and response to treatment [25,26]. Certain patient characteristics have also been associated with worsened outcomes, including age, gender, comorbidities, previous valve damage, and whether the valve is native or prosthetic [27].

While the present study did not identify staphylococcal infection as an independent predictor of mortality or worsened perioperative outcomes, multiple other studies have demonstrated an association between Staphylococcus and decreased survival, as well as higher rates of vascular complications, sepsis, embolic events, and stroke [14,19,25–29]. Some of this may be due to the local tissue destruction and enhanced coagulopathy seen with S. aureus endocarditis, mediated by the secretion of proteases which degrade collagen and affect partial plasma thromboplastin and plasma thrombin times [28]. However, these effects are also seen with other staphylococcal species, and data have shown similar overall outcomes for patients with coagulase negative staphylococcal IE and those with S. aureus IE [29]. Staphylococcus has also been associated with increased likelihood of stroke [26,30]. It has demonstrated high levels of antimicrobial resistance [26], making it particularly challenging to treat effectively.

Streptococcus spp are also frequently identified in IE cases, and multiple groups have demonstrated that streptococcus independently predicts improved survival for patients [23,25,31]. In one study of over 86 thousand patients, Becher *et al.* [32] showed that streptococcal infection was independently associated with decreased mortality when compared to culture negative IE, while staphylococcus and GNRs were both associated with increased mortality. In another study of over 6200 patients, Sunder *et al.* [33] demonstrated that infection with streptococcus/enterococcus species was independently associated with improved patient survival at one year, while infection

Table 5. Predictors of long-term outcomes in veterans undergoing surgical intervention for IE.

Long-term mortality			
	aHR	95% CI	*p*
CAD (moderate/severe)	1.85	1.27–2.71	0.002
Weight (l bs)	1.00	1.00–1.00	0.19
Heart failure (class III–IV)	1.37	1.04–1.82	0.027
Diabetes mellitus (insulin-dependent)	1.86	1.36–2.56	<0.001
Renal failure	1.49	0.90–2.48	0.125
Total dependence for ADLs	1.53	1.02–2.29	0.039
Hypertension	1.46	0.98–2.15	0.061
History of illicit drug use	1.51	0.98–2.34	0.065
Mitral valve replaced	0.51	0.32–0.81	0.004
Any mitral valve operation	2.66	1.70–4.16	<0.001
Prosthetic aortic valve involvement	1.66	0.92–3.00	0.096
Staphylococcus	1.39	0.91–2.14	0.128
GNRs	2.15	1.20–3.86	0.01
Enterococcus	1.56	0.99–2.47	0.058
Polymicrobial	1.60	0.98–2.60	0.058
Culture negative	1.38	0.88–2.16	0.164
Long-term MI			
	aHR	95% CI	*p*
Resistant organism	2.51	1.14–5.49	0.022
Concomitant CABG	2.37	1.29–4.35	0.005
Pre-operative sepsis	1.82	1.03–3.23	0.041
Streptococcus	1.83	0.95–3.54	0.072
Enterococcus	2.05	1.07–3.94	0.031
Long-term stroke			
	aHR	95% CI	*p*
History of CVD/TIA/Stroke	2.442	1.88–3.18	<0.001

Abbreviations: ADL, activity of daily living; CABG, coronary artery bypass graft; CAD, coronary artery disease; GNRs, gram negative rods; IE, infective endocarditis; MI, myocardial infarction.

with staphylococcus was associated at worsened mortality both during initial hospitalization and at one year.

Enterococci are the third leading cause of IE and account for about 10% of cases in non-intravenous drug users [26]. Among enterococcal species, E. faecalis plays a predominant role in IE and bacteremia, producing almost 90% of enterococcal IE [34], and E. faecium is also isolated relatively frequently among enterococcus cases [26]. When compared to other pathogens, enterococcal IE has been associated with older patients with multiple chronic comorbidities, the presence of prosthetic valves, and nosocomial acquisition [35–38]. Many factors have been identified which contribute to its virulence, including Asc10, glycoproteins, and pili, among others [39]. These species also can demonstrate high-levels of resistance to multiple antimicrobial regimens (including aminoglycosides, ampicillin and vancomycin) [34]. With respect to mortality, enterococcus is associated with increased survival when compared to staphylococcus, but decreased survival when compared to streptococcus [37]. One study of left-sided IE by Martínez-Marcos *et al*. [38] found that in-hospital mortality was 32.9% for enterococcal IE, 9.3% for viridans group streptococci, and 48.6% for S. aureus cases (enterococci *vs*. VGS, $p < 0.0001$; enterococci *vs*. S. aureus, $p = 0.02$).

Other organisms, including GNRs, fungal spp, and polymicrobial IE, are less commonly identified. IE caused by the HACEK GNRs (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella spp) accounts for about 5–10% of community-acquired native valve IE in patients who are not intravenous drug users [26]. In one case-control study by Ambrosioni *et al*. [13], IE second to HACEK organisms demonstrated a lower 1 year mortality risk when compared to viridans group strep cases. However, IE caused by non-HACEK GNRs is rare, is primarily caused by E. coli and pseudomonas species, and is associated with a high mortality rate [14,40]. Fungal spp are even less frequently identified, though they have also been associated with worsened prognosis when compared to Streptococcus and Enterococcus [14]. One study by Limonta *et al*. [41] specifically looked at IE caused by 'unusual organisms', that is, species not in the staphylococcal, streptococcal, or enterococcal families. Of 471 cases, 9.8% were due to these 'unusual' species, with a predominance of anaerobes, yeast, and GNRs. As compared with IE related to staphylococci, streptococci, or enterococci, these cases were associated with longer duration of fever and nosocomial acquisition, though no differences in hospital mortality were observed [41].

A small but notable number of IE cases are also caused by polymicrobial infections. These infections have previously been associated with a high mortality rate [42,43]. The incidence of polymicrobial IE has been increasing in recent years, especially amongst intravenous drug users [42]. However, it can be a difficult group of infections to study, in part due to the high variability of species involved. In one study by García-Granja *et al*. [44], 5.9% of 1011 cases were determined to be polymicrobial, though this was not associated with any differences in in-hospital mortality.

While "culture negative" IE is often treated as a single entity in analyses, the truth is much less convenient. Culture-negative IE may result from the use of antibiotics before blood cultures are obtained, infection with highly fastidious bacteria or fungi, or the presence of uncommon pathogens which do not grow in routine culture media [3,26]. This poses a challenge to patients and their providers, who then must treat this highly morbid illness without specific guidance on how best to treat it. The number of these cases is shrinking, however. Some groups, like Fournier *et al*. [45] and Wang *et al*. [46], have found that the use of PCR assays or Sanger sequencing significantly increases their diagnostic efficiency in these cases, identifying pathogens including staphylococcus and streptococcus, brucella and legionella, candida and aspergillus, and mycoplasma and bartonella [3,45,46].

Given the relative infrequency of IE and the large number of causative organisms and populations at risk, identifying the predictive value of each of these factors is a difficult task. There remains a need for large, multi-institutional studies in order to dissect these elements from one another.

Limitations

This study is subject to the inherent limitations of retrospective database research, including the inability to demonstrate causality. Though the data within the database is collected prospectively, the retrospective nature of the study limits the extent to which variables can be controlled and the conclusions that can be drawn. As noted in Table 1, our cohort populations had several differences in chronic medical conditions that are known risk factors for major morbidity, which may have affected our results despite best efforts to implement multivariable statistical controls. Additionally, as it is true for all the studies performed within the VA system, most included patients are male, potentially limiting the generalizability of the results.

Our study is also limited by several absent post-operative data points. For example, we lack data on post-operative use of anticoagulation which could have affected certain outcomes (i.e., stroke).

There is potential for selection bias in our study, as it included data only from patients who eventually received some type of major surgical intervention, excluding those who either may not have been offered surgery secondary to high risk or those who died before a planned operation could be performed.

Conclusions

In US Veterans, polymicrobial infections had notably worse perioperative outcomes but similar long-term outcomes in comparison to monomicrobial infections. GNR infections were associated with increased long-term mortality. Enterococcus and resistant organisms were associated with increased long-term risk of MI. Polymicrobial infections were associated with greater risk of perioperative complications, including prolonged mechanical ventilation, tracheostomy, and prolonged ICU stay. Pre-operative sepsis was strongly associated with worse perioperative, 30-day, and one-year outcomes.

Availability of Data and Materials

Datasets used and/or analyzed for this study are available from the corresponding author upon appropriate request.

Author Contributions

Conception and design: JD, JA, GT. Administrative support: All authors. Provision of study materials or patients: JD, AP. Collection and assembly of data: JD, AP, SH. Data analysis and interpretation: all authors. Manuscript writing: all authors. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

For this study, institutional review board approval was obtained from the Washington DC VA Medical Center and a waiver of informed consent was obtained (IRB number 1584919, approval renewed 10/19/2022).

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Conflict of Interest

The authors declare no conflict of interest. GT is a member of the editorial board of this journal. GT declares that he was not involved in the processing of this article and has no access to information regarding its processing.

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