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Colonization with Multidrug-resistant Organisms in Patients with Ventricular Assist Devices

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Abstract

Infection is a leading cause of morbidity and mortality in patients with ventricular assist devices (VAD). The impact of colonization with multidrug-resistant organisms (MDRO) on outcomes in this cohort is unknown. Patients on VAD support from July 2008 to September 2018 at a single site were evaluated for MDRO colonization after implantation. MDROs included methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species, and extended-spectrum beta-lactamase producing gram-negative bacteria. 378 patients with 433 VADs were included. 42.6% (n = 161) of patients were colonized with an MDRO throughout the duration of VAD support. Eighty-two VAD infections occurred, 74.4% (n = 61) of whom were MDRO colonized before infection. MDRO colonization was associated with an increased risk of a subsequent VAD infection (hazard ratio 3.704, $p < 0.001$). MDRO colonization is common after VAD implantation and is associated with future VAD infections. Further study is needed to determine best management strategies for VAD recipients with MDRO colonization given this increased risk.

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Keywords

ventricular assist device; infection; multidrug-resistant organism; colonization

Ventricular assist devices (VAD) can be implanted as a bridge to heart transplantation (BTT) or as destination therapy in patients with end stage heart failure. Although the mean duration of VAD support is 20 months, patients can remain on VAD support for >10 years.¹ The percutaneous exit site of the device driveline predisposes patients to infection, an important cause of morbidity and mortality in this patient population. Longer duration with a VAD is a well-established risk factor the development of infection. By 48 months, post VAD implantation over half of patients have had a device-related infection, and approximately 8% of all VAD deaths are attributable to major infection.¹ When infection occurs, it is difficult to manage as patients often require long-term systemic antibiotics and at times entire device exchanges are required.

An important growing epidemiologic threat is the rise of multidrug-resistant organisms (MDRO). Few studies have evaluated the impact of MDROs as causative pathogens in VAD patients. Previously reported incidence rates of infection have ranged from 5.1% to 31.6%; however, many of these studies were limited by varying definitions of VAD infection, a low prevalence of continuous-flow VADs, small samples sizes, and inconsistent MDRO reporting.^{2–10} In addition to causing infection, a significant consideration is the presence of MDRO colonization. In the solid organ transplant (SOT) population, MDRO colonization pretransplant has been shown to increase the risk of true infection posttransplant, and outcomes in patients colonized with resistant pathogens are worse.^{11–13} Furthermore, decolonization in SOT patients has proved successful in improving both clinical outcomes and cost-effectiveness.^{14,15} To our knowledge, only one prior study has assessed MDRO colonization in the VAD population and showed higher rates of subsequent infection-related death. However, this study evaluated only a single VAD type implanted as destination therapy and included a small patient population, limiting external validity.¹⁶ In this retrospective cohort, we characterize the incidence, risk factors, and clinical outcomes of VAD patients with MDRO colonization over a 10-year period.

Materials and Methods

Patients and Procedures

All patients 18 years of age or older with VADs implanted at Northwestern Memorial Hospital in Chicago, IL, between July 2008 and September 2018 were included in the study. Second generation VADs (axial-flow) implanted included the HeartMate II (Thoratec Corp, Pleasanton, CA). Third generation VADs (centrifugal flow) implanted included the HeartMate 3 (Abbott, Chicago, IL), HeartWare (Medtronic, Minneapolis, MN), and in select patients, the VentrAssist (Ventricor Ltd., Brisbane, AU). Patients with pulsatile VADs, isolated right-sided VADs, or biventricular VADs were excluded. Perioperative surgical infection prophylaxis from July 2008 through June 2013 was vancomycin, rifampin, ciprofloxacin, and fluconazole, and from June 2013 through September 2018 was vancomycin and cefuroxime. Following VAD implantation, dressing changes were

performed three times weekly by caregivers with 2% chlorhexidine gluconate cleansing and use of a SorbaView SHIELD (Centurion MP, Williamston, MI) over the driveline exit site. If patients developed contact dermatitis or allergies to chlorhexidine gluconate, povidone-iodine was substituted as the primary agent for cleansing. In a select minority of patients, changes to the above strategy included a BIOPATCH Protective Disk (Ethicon, Somerville, NJ) applied to the exit site, a 72-hour dressing instead of a 24-hour dressing, and self-dressing changes in lieu of caregiver changes.

Classification of MDROs included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* or *Enterococcus faecium* (VRE), or gram-negative bacteria possessing an extended-spectrum beta-lactamase (ESBL) producing enzyme. Colonization was determined by either positive nasal or rectal screening culture or clinical specimen with an MDRO identified. Rectal VRE culture screening was performed on admission and discharge from the intensive care units (ICU). MRSA nasal culture screening was obtained on ICU admission only. ESBL rectal culture screening was performed on ICU admission only until November 2013. MDRO colonization was coded as positive on a per-patient as opposed to a per-VAD basis.

Patient Consent Statement

As all data were obtained retrospectively, a waiver of patient consent was obtained and this study was approved by the Northwestern Memorial Hospital Institutional Review Board.

Outcomes

The primary outcome was development of a VAD-related or VAD-specific infection among patients who had evidence of MDRO colonization *versus* those who did not show evidence of exposure. VAD-specific and VAD-related infections were characterized according to 2013 International Society for Heart and Lung Transplantation definitions.¹⁷ Non-VAD infections such as pneumonias or urinary tract infections were not assessed. Outcomes were evaluated according to patient and not by VAD number.

Statistical Analysis

Data collection was performed by review of electronic medical records and our center's durable VAD database for demographics, details regarding type of device, signs and symptoms of infection, laboratory parameters, microbiologic data, radiographic findings, surgical, and histopathologic results. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, and continuous variables with a Student's two sample *t*-test or Mann-Whitney *U* test. Kaplan-Meier survival analysis with log-rank test was used to compare the difference of time to infection between groups. Cox proportional-hazards regression was used to assess the primary outcome of time to infection. Adjusted Cox proportional-hazards regression was used to account for covariates (age, gender, heart failure etiology, VAD generation) between groups. A competing risk analysis using the cumulative incidence function by Fine and Gray was used to account for the possible competing events in a secondary analysis of patient postimplantation survival, heart transplantation, and VAD explantation. Time to event was measured to the point of VAD removal, whether by death, transplant, or removal for other reasons. Time to event was censored at the time

of loss to follow up, and if a patient had a VAD at the end time of data collection, this time point was censored to August 31, 2018. Proportional-hazard assumptions for MDRO colonization in the competing events analysis were not satisfied, therefore, analysis through the first 1000 days after VAD implantation were stratified by MDRO colonization. If a patient had at least one VAD exchange, the most recently implanted VAD was utilized for survival time analysis. A two-sided p value of <0.05 was deemed significant. Correction for multiple hypothesis testing was not performed. All analyses were performed using IBM SPSS Statistics version 25.0 and SAS Enterprise Guide version 8.1 (SAS Institute, Cary, NC).

Results

Patient Characteristics

A total of 378 patients with 433 VADs met inclusion criteria and were included in the study. Mean age was 55.0 (± 13.5) years, 77.5% ($n = 293$) were male, and 58.5% ($n = 221$) were white. Predominating diagnosis was nonischemic cardiomyopathy (NICM) (58.7%, $n = 222$) with a goal of bridge to transplantation in 54.0% ($n = 204$) of patients. Three hundred thirty patients (87.3%) had New York Heart Association functional class IV symptoms at the time of VAD implant. Intra-aortic balloon pumps, extracorporeal membrane oxygenation (ECMO), and Impella (ABIOMED, Danvers, MA) devices bridged 44, 6, and 12 patients, respectively, to VAD. Total VADs used included 6 patients with the VentrAssist, 161 patients with the HeartMate II, 28 patients with the HeartMate 3, and 238 patients with the HeartWare HVAD. Median duration of VAD support was 277 days (interquartile range [IQR] 120–618 days) with a minimum of 1 day and a maximum of 2759 days. Patients with second generation VADs had a median duration of support of 375 days (IQR 135.5–757.5 days), compared with 258 days (IQR 107.75–541 days) for patients with third generation VADs ($p = 0.047$). Full baseline characteristics according to colonization status are outlined in Table 1. Groups were well-balanced with the exception of VAD generation where a higher percentage of third generation VADs were seen in the non-MDRO colonized group ($n = 151$, 69.6%) compared with the MDRO-colonized group ($n = 96$, 59.6%, $p = 0.049$). Fifty-five VAD exchanges occurred in 43 patients, 10 (18.2%) in 7 patients (16.3%) due to infection.

Comparison of Second and Third Generation VADs

MDRO colonization was seen more frequently in second generation VADs ($n = 65$, 49.6%) when compared with third generation VADs ($n = 96$, 38.9%); however, longer times on VAD support were seen in second generation VAD patients compared with third generation VADs as outlined earlier. Time to infection was less in MDRO-colonized patients when performing sensitivity analyses according to VAD generation and was consistent across both second and third generation VADs (Figure, Supplemental Digital Content 1, <http://links.lww.com/ASAIO/A765>). All patients with MDRO colonization had a median duration of VAD support of 316 days (IQR 135–722 days) compared with noncolonized patients with a median VAD duration of 245 days (IQR 104.75–577 days, $p = 0.278$). One hundred sixty-one patients (42.6%) were colonized with any MDRO as defined in Table 2. Forty-six patients (12.2%) were MRSA-colonized, 137 patients (36.2%) were VRE-colonized, and 39 patients (10.3%) were ESBL-colonized. Forty-six patients (12.2%) were colonized with

multiple organisms, not necessarily concurrently, throughout the duration of VAD support. Patients with second generation VADs were more likely to have VRE colonization than third generation VADs ($n = 62$, 47.3% vs. $n = 75$, 30.4%, $p = 0.002$). MDRO colonization was observed in higher frequencies in VADs implanted before the June 2013 change in antimicrobial prophylaxis (52.2%, $n = 69$ vs. 37.4%, $n = 92$, $p = 0.005$), while VAD infections were seen in lower frequencies (15.9%, $n = 21$ vs. 24.8%, $n = 61$, $p = 0.046$) (Table, Supplemental Digital Content 1, <http://links.lww.com/ASAIO/A765>).

Development of VAD Infection

MDRO colonization was associated with less time to developing a VAD-specific or VAD-related infection (Log-rank $p < 0.001$, Figure 1). Of the 81 patients who developed a VAD-specific or VAD-related infection, 61 patients (75.3%) were MDRO colonized, and 16 had true infections secondary to a colonized MDRO (26.2%). All were colonized with >1 MDRO. Length of index hospitalization during VAD implantation was longer in colonized patients compared with noncolonized patients (27.0 vs. 18.5 days, $p = 0.001$).

Of the 81 patients who developed a VAD infection, 40.7% ($n = 33$) had pump infections, 16.0% ($n = 13$) had pocket infections, 46.9% ($n = 38$) had driveline infections, and 17.3% ($n = 14$) had >1 type of infection. Pump infections were more common in MDRO-colonized patients compared with non-MDRO colonized patients (49.2%, $n = 30$ patients vs. 15.0%, $n = 3$, $p = 0.007$), while the reverse was true for driveline infections (39.3%, $n = 24$ vs. 70.0%, $n = 14$, $p = 0.017$). There was no difference found in patients with pocket infections or in those with multiple types of infections.

Univariable and multivariable Cox proportional-hazard regressions were performed with results outlined in Table 3. On multivariable analysis accounting for covariates of age, sex, diagnosis, and VAD generation, there was a significant effect between MDRO colonization and time to development of a VAD infection (HR 3.704, 95% CI 2.222–6.173, $p < 0.001$). This result was similar when performing a sensitivity analysis excluding patients with VAD exchanges (Table, Supplemental Digital Content 2, <http://links.lww.com/ASAIO/A765>).

Mortality, Transplantation, and VAD Explantation

The overall mortality was not assessed due to violation of proportional-hazard assumption; however, a survival analysis stratified by MDRO colonization was performed when evaluating mortality up to 1000 days. Stratified cumulative incidence function is shown in Figure, Supplemental Digital Content 2, <http://links.lww.com/ASAIO/A765>, with cumulative incidence rates noted in Table, Supplemental Digital Content 3, <http://links.lww.com/ASAIO/A765>.

Discussion

In this retrospective cohort study, we determined the epidemiology of MDRO colonization and its effect on clinical outcomes in a VAD cohort over a 10-year period. We found a high prevalence of MDRO colonization in this VAD population; almost half of patients were colonized with at least one MDRO throughout the duration of VAD support. Moreover, we showed that MDRO colonization is a risk factor for future VAD infection.

We found a significant association between MDRO colonization and the subsequent development of a VAD-related or VAD-specific infection. This was true regardless of causative pathogen; however, MDRO colonization portended later infection with that same MDRO. To our knowledge, only one prior study has characterized the epidemiology of MDRO colonization in this population and colonization rates were similar to our study at 34.1%.¹⁶ These colonization rates are significantly higher than those published in SOT recipients and likely reflect the long-term nature of a prosthetic device with a cutaneous exit site that poses a risk for bacterial inoculation. It has previously been shown that longer duration of VAD support leads to a higher frequency of infection, and our finding of this correlation to MDRO colonization warrants study to assess this exposure to the temporal association of infection as colonization may be the first step in this pathway.¹

As total VAD time may be an important risk factor for acquiring MDRO colonization, reducing late-onset colonization represents an attractive, targeted intervention. Our observation of MDRO colonization being more frequently seen in patients with second generation devices compared with third generation devices may be due to overall longer durations of VAD use and supports this hypothesis. Prior studies have shown type of VAD complication is highly dependent on time post implantation; the majority of VAD-specific infections occur beyond 90 days in contrast to VAD-related or non-VAD infections.¹⁸

Surprisingly, we found significantly higher rates of VRE colonization when compared with MRSA. *Staphylococcus aureus* is the most common causative organism for true VAD infection, presumably due to the cutaneous driveline exit site, and colonization was expected to follow this trend. It is possible the high rates of VRE colonization in patients may be secondary to the universal implementation of vancomycin as perioperative prophylaxis at our institution regardless of MRSA colonization status. Our comparatively low rates of MRSA colonization after VAD implantation may argue against universal use of vancomycin at the time of VAD implantation, although MRSA screening was performed in lesser frequency than for VRE at our institution. One recent meta-analysis found no difference in rates of LVAD-specific infections when institutions used multidrug compared with single-drug surgical infection prophylaxis, highlighting the need for further insight into optimal perioperative protocols.¹⁹ Interestingly, we observed higher frequencies of MDRO colonization and lower frequencies of VAD infections in VADs implanted before the June 2013 transition from vancomycin, levofloxacin, rifampin, and fluconazole perioperative antimicrobial prophylaxis to vancomycin and cefuroxime, possibly reflective of the broader spectrum antibiotic use in the earlier cohort.

It is possible MDRO colonization is a consequence of, rather than a cause for, poor clinical outcomes and is reflective of a sicker cohort with more healthcare exposures. Colonized patients had longer hospital stays and more total VAD days, known risk factors for MDRO colonization.^{20,21} As a consequence, they may have been at higher risk for acquiring MDRO colonization and this may account for patients colonized with one organism but becoming infected with a different organism at a later time period. We also found patients who were MDRO colonized were more likely to have pump infections and less likely to have driveline infections when compared with non-MDRO-colonized patients, possibly reflective of a sicker group with more hospitalization and ICU stays. While MDRO colonization

represents a potential screening tool as a predictor for complication in select patients, this pathophysiology requires further study.

There are a number of limitations to this study. The retrospective and single-center nature of the cohort limit generalizability, although this study represents the one of the largest single-center cohorts with multiple types and generations of VADs. MRSA and ESBL colonization rates are likely underestimated owing to our institutional screening policies of culturing VRE rectal swabs on admission to, and discharge from, the ICU while MRSA and ESBL cultures are obtained only on ICU admission and clinical indication. There is also selection bias, as sicker patients with more ICU admissions would have greater opportunity for screening. Additionally, regular ESBL screening stopped midway through the study period; however, a sensitivity analysis excluding ESBL colonization yielded nearly identical results. This study also assessed only three forms of bacteria classified as MDROs; however, others seen at our facility such as carbapenem-resistant *Acinetobacter baumannii*, multidrug-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Enterobacteriaceae* warrant consideration in future evaluations. We did not obtain MDRO colonization status over time, and the temporal dynamics of MDRO acquisition in our cohort is unknown; colonization status in initial VAD courses in those with exchanges is also unknown. Finally, certain biases may have impacted results, most notably misclassification bias; providers may have defined infection differently and a noted guideline change on infection classification occurred in 2013.¹⁷

There was an association between MDRO colonization and the subsequent development of a VAD infection in this cohort; however, further research is needed to clarify pathogenesis and causality. Strategies such as targeted decolonization, dedicated antimicrobial stewardship teams, active surveillance, and enhanced hospital infection control programs warrant study in the VAD population and have potential to greatly improve outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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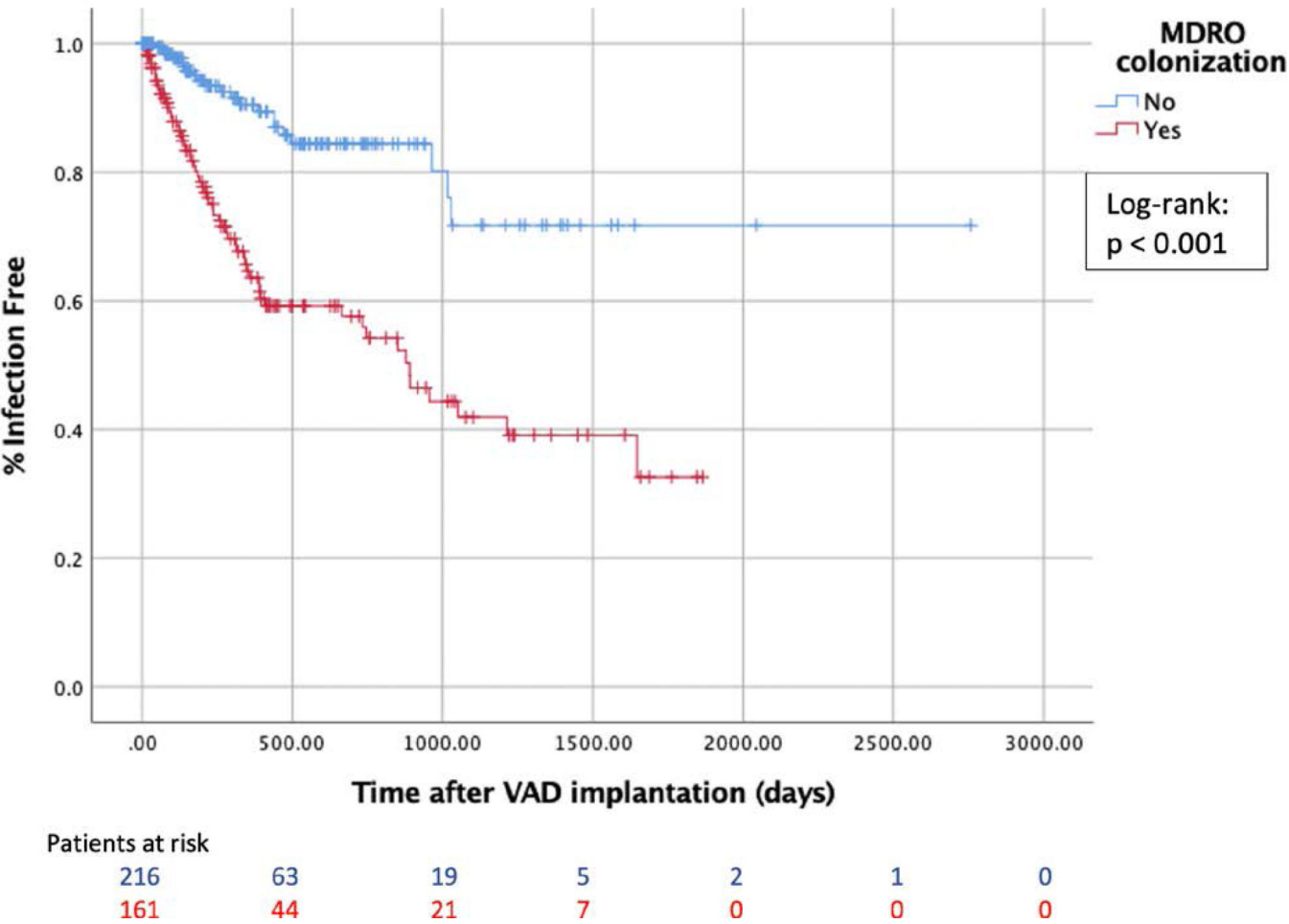


Figure 1. Time to infection Kaplan-Meier curve according to MDRO-colonized status. Percentage of patients free from infection plotted against time in days since date of VAD implantation according to MDRO colonization status. Cases are censored at explantation regardless of cause. Log-rank between colonization groups $p < 0.001$. MDRO, multidrug-resistant organisms; VAD, ventricular assist devices.

Table 1.

Demographic and Clinical Characteristics

Characteristic	Total Cohort (n = 378)	No MDRO Colonization (n = 217)	MDRO Colonization (n = 161)	p
Age (years)	55.0 (±13.5)	54.4 (±13.1)	55.8 (±14.0)	0.301
Sex				0.804
Male	293 (77.5%)	167 (77.0%)	126 (78.2%)	
Female	85 (22.5%)	50 (23.0%)	35 (21.7%)	
Race				0.776
White	221 (58.5%)	125 (57.6%)	96 (59.6%)	
Black	101 (26.7%)	60 (27.6%)	41 (25.5%)	
Hispanic	36 (9.5%)	23 (10.6%)	13 (8.1%)	
Asian	14 (3.7%)	7 (3.2%)	7 (4.3%)	
Other	5 (1.3%)	2 (0.9%)	3 (1.9%)	
Disease				0.525
NICM	222 (58.7%)	131 (60.4%)	91 (56.5%)	
ICM	154 (40.7%)	85 (39.2%)	69 (42.9%)	
Goal therapy				0.602
BTT	204 (54.0%)	120 (55.3%)	84 (52.2%)	
DT	174 (46.0%)	97 (44.7%)	77 (47.8%)	
NYHA class				0.739
IV	330 (87.3%)	190 (87.6%)	140 (87.0%)	
III	23 (6.1%)	15 (6.9%)	8 (5.0%)	
II	3 (0.7%)	2 (0.9%)	1 (0.6%)	
Bridge device				0.310
IABP	44 (11.6%)	28 (12.9%)	16 (9.9%)	
ECMO	6 (1.6%)	4 (1.8%)	2 (1.2%)	
Impella	12 (3.2%)	11 (5.1%)	1 (0.6%)	
Other	4 (1.1%)	3 (1.4%)	1 (0.6%)	
VAD generation				0.049
Second	131 (34.7%)	66 (30.4%)	65 (40.4%)	
Third	247 (65.3%)	151 (69.6%)	96 (59.6%)	

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Characteristic	Total Cohort (n = 378)	No MDRO Colonization (n = 217)	MDRO Colonization (n = 161)	p
VAD time (days)	277 (120–618)	245 (104.75–577)	316 (135–722)	0.278

BTT, bridge to transplant; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICM, ischemic cardiomyopathy; MDRO, multidrug-resistant organisms; NICM, nonischemic cardiomyopathy; VAD, ventricular assist devices.

Table 2.

MDRO Colonization Demographics

	All	Second Generation (n = 131)	Third Generation (n = 247)	p
Total	161 (42.6%)	65 (49.6%)	96 (38.9%)	0.049
MRSA	46 (12.2%)	16 (12.2%)	30 (12.1%)	1.000
VRE	137 (36.2%)	62 (47.3%)	75 (30.4%)	0.002
ESBL	39 (10.3%)	11 (8.4%)	28 (11.3%)	0.478
Multiple	46 (12.2%)	17 (13.0%)	29 (11.7%)	0.743

ESBL, extended-spectrum beta-lactamase; MDRO, multidrug-resistant organisms; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus faecalis* or *Enterococcus faecium*.

Table 3.

Adjusted and Unadjusted Cox Proportional-hazard Regression

Variable	Univariable Infection HR (95% CI)	p	Multivariable Infection HR (95% CI)	p
Age	1.014 (1.000–1.029)	0.047	1.016 (1.000–1.033)	0.045
Sex (M)	0.540 (0.330–0.885)	0.014	0.597 (0.359–0.992)	0.047
Diagnosis (ICM)	1.040 (0.666–1.623)	0.894	1.427 (0.862–2.358)	0.167
VAD generation (3)	1.282 (0.806–2.037)	0.293	1.376 (0.855–2.212)	0.188
MDRO colonization	3.759 (2.268–6.250)	0.001	3.704 (2.222–6.173)	0.001

HR, hazard ratio; M, male (compared with female); ICM, ischemic cardiomyopathy (compared with nonischemic cardiomyopathy); 3, third generation VAD (compared with second generation VAD); VAD, ventricular assist devices.