Clinical Investigation

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Multidrug-Resistant Organism Infections

in Patients with Left Ventricular Assist Devices

Left ventricular assist devices improve survival prospects in patients with end-stage heart failure; however, infection complicates up to 59% of implantation cases. How many of these infections are caused by multidrug-resistant organisms is unknown. We sought to identify the incidence, risk factors, and outcomes of multidrug-resistant organism infection in patients who have left ventricular assist devices.

We retrospectively evaluated the incidence of multidrug-resistant organisms and the independent risk factors associated with them in 57 patients who had permanent left ventricular assist devices implanted at our institution from May 2007 through October 2011. Outcomes included death, transplantation, device explantation, number of subsequent hospital admissions, and number of subsequent admissions related to infection. Infections were categorized in accordance with criteria from the Infectious Diseases Council of the International Society for Heart and Lung Transplantation.

Multidrug-resistant organism infections developed in 18 of 57 patients (31.6%)—a high incidence. We found 3 independent risk factors: therapeutic goal (destination therapy vs bridging), P=0.01; body mass index, P=0.04; and exposed velour at driveline exit sites, P=0.004. We found no significant differences in mortality, transplantation, or device explantation rates; however, there was a statistically significant increase in postimplantation hospital admissions in patients with multidrug-resistant organism infection. To our knowledge, this is the first report in the medical literature concerning multidrug-resistant organism infection in patients who have permanent left ventricular assist devices. ***(Tex Heart Inst J 2015;42(6):522-7)***

Heart failure is a chronic disease state with substantial morbidity and mortality rates.[1] End-stage heart failure is characterized by worsening symptoms despite optimal medical management, and heart transplantation is the definitive treatment. However, rates of heart failure are increasing, whereas the number of organs available for transplantation is static.[2] Therefore, mechanical support for the failing heart, especially ventricular assist devices (VADs), has attracted strong interest. Left VAD (LVAD) implantation imparts higher survival rates in end-stage heart failure than does optimal medical management.[3-6] Although LVADs are potentially life-saving, implantation sequelae include right ventricular failure, thromboembolism, bleeding, and infection. Investigators have reported infection rates of 18% to 59% in patients with LVADs, and mortality rates estimated at 70% for infections such as VAD-related mediastinitis and endocarditis.[3,7-9] Depending on the site of the infection, treatment can range from simple wound care to device explantation.[7,10] Multidrug-resistant organisms (MDROs) are increasingly prevalent and are associated with substantial morbidity and mortality rates.[11-13]

Patients with LVADs are at greater risk for MDRO infection because of their exposure during medical procedures and their generally longer lifespans after implantation. To our knowledge, no data have been published about the incidence of MDRO infections in patients who have LVADs. Our primary objective in this study was to determine that incidence, and our secondary objective was to evaluate outcomes and risk factors in MDRO infection.

Patients and Methods

Our retrospective cohort study included patients whose permanent LVADs had been implanted at Emory University Hospital from May 2007 through October 2011. The Emory institutional review board approved the study. Baseline data collected from

the VAD database included demographic details; device type—either the HeartMate® II Left Ventricular Assist System (Thoratec Corporation; Pleasanton, Calif) or the HeartWare® Ventricular Assist System (HeartWare Inc.; Framingham, Mass); indication for implantation; burial or exposure of the velour at driveline exit sites; hospital and intensive care unit days before implantation and before the development of an MDRO; class, number, and duration of antibiotics administered before implantation; the presence or absence of preimplantation diabetes mellitus; and preimplantation albumin and prealbumin values. Infection-related data included infection type (VAD-specific, VAD-related, or non-VAD-related, and MDRO or non-MDRO), organism type, and each infection's antibiotic susceptibility. All infections were recorded; however, organisms were counted only once per patient. Patients were considered to be uninfected if they had never had an infection or if they had had an infection before but not after implantation.

The primary endpoint was the incidence of MDRO infections in VAD patients, defined as the new occurrence of an MDRO infection after LVAD implantation. Secondary endpoints were outcomes (death, transplantation, device removal, number of subsequent hospital admissions, and number of subsequent hospital admissions related to infection) and risk factors for the development of MDRO infection.

Outcome Definitions

Infections were identified by means of culture-positive documentation in the electronic medical records. We defined infections as MDRO if they were resistant to 2 or more classes of antibiotics. Definitions of infection type were obtained from the Infectious Diseases Council of the International Society for Heart and Lung Transplantation.[8] We defined VAD-specific infections as infection of the VAD hardware, driveline, or pocket tissue. We defined VAD-related infections as those related to the presence of the VAD but not directly involving the hardware or the containing body tissue; examples included endocarditis, catheter-associated bloodstream infection, and mediastinitis. We defined non-VAD-related infections as those occurring independently of the VAD, such as pneumonia, urinary tract infections, and *Clostridium difficile*. Urinary tract infections were not included as infections unless they had specifically been treated with antibiotics. We defined infection-related hospital admissions as those admissions for which infection had been recorded as the primary indication for hospitalization.

Statistical Analysis

For descriptive analysis, all patients were classified after LVAD implantation according to whether they had a non-MDRO infection, an MDRO infection, or neither. To compare the distributions of predictors across these groups, 2-sample t tests and χ^2 tests were used for numerical and categorical variables, respectively. Variables that were significant at the $\alpha = 0.20$ level were considered for further multivariable regression analysis, a conservative approach to determining which predictors were independently associated with MDRO. Because 4 of the 57 patients underwent more than one LVAD implantation, a repeated-measures generalized linear model was constructed to account for the correlation of responses. An iterative backwards-elimination strategy was used, whereby the least significant of the candidate variables were sequentially removed but were later tested for the confounding effect. The final regression model contained all variables that were significant at the $\alpha = 0.05$ level and any confounders that were identified. All analyses were performed with use of SAS version 9.3 (SAS Institute Inc.; Cary, NC). Appropriate tests were selected on the basis of normality. No adjustments for multiple tests were performed. A P value <0.05 was considered statistically significant.

Results

Table I shows the baseline characteristics of the patients. In total, 61 LVADs were implanted in 57 patients (4 of whom underwent reimplantation). Their mean age at implantation was 49.5 ± 13.5 years; 70.5% of recipients were men. HeartMate II devices were more often implanted than HeartWare (in 52 patients; 85.2%), and destination therapy was the chief indication for LVAD implantation (26 patients; 42.6%). Significant differences for development of an MDRO were as follows: therapeutic goal (destination therapy vs bridging), $P = 0.001$; body mass index (BMI), $P = 0.04$; and velour exposure at driveline exit sites, $P = 0.004$.

Overall, 27 patients (47.4%) developed an infection. Eighteen of the 57 patients (31.6%) had an MDRO infection. Table II shows descriptions of infections by group. In patients who had MDROs, more infections were VAD-specific (10 MDRO vs 6 non-MDRO, $P = 0.001$) or VAD-related (7 MDRO vs 3 non-MDRO, $P = 0.003$) than in patients who had no MDRO. Table III shows all the organisms found in the study population; the most prevalent MDRO was *Staphylococcus aureus*.

Figure 1 shows the time to development of an MDRO infection. In the Kaplan-Meier analysis, patients were censored upon development of the first MDRO; however, subsequent MDROs were recorded and included in the final analyses. The mean time to development of a new MDRO was 174 ± 37 days.

Outcomes

Table IV shows the patients' outcomes. Hospital admissions, including those related to infection, were sig-

TABLE I. Baseline Characteristics of the Study Patients

Variable	All Implants (n=61)	Uninfected (n=34)	Non-MDRO Infection (n=9)	MDRO Infection (n=18)	*P* Value
Male	43 (70.5)	22 (64.7)	6 (66.7)	15 (83.3)	0.36
Age (yr)	49.5 ± 13.5	48 ± 12.8	46.9 ± 12.1	53.6 ± 15.2	0.31
Device	—	—	—	—	0.4
HeartMate II	52 (85.2)	28 (82.4)	7 (77.8)	17 (94.4)	—
HeartWare	9 (14.8)	6 (17.6)	2 (22.2)	1 (5.6)	—
Therapy goal	—	—	—	—	0.001
Destination therapy	26 (42.6)	13 (38.2)	4 (44.4)	9 (50)	—
Bridge to transplantation	20 (32.8)	18 (52.9)	1 (11.1)	1 (5.6)	—
Bridge to candidacy	15 (24.6)	3 (8.8)	4 (44.4)	8 (44.4)	—
Weight (kg)	88.3 ± 23.8	83 ± 19.9	97.4 ± 35.8	93.6 ± 22.4	0.15
Body mass index (kg/m^2)	28.4 ± 6.8	26.4 ± 5.5	30.3 ± 9.4	31 ± 6.9	0.04*
Velour exposed	28 (45.9)	10 (29.4)	4 (44.4)	14 (77.8)	0.004
Antibiotic days before VAD	12.2 ± 12.4	13.4 ± 12.9	10.2 ± 14.1	10.8 ± 10.6	0.69
Antibiotics before VAD (n)	2.61 ± 1.86	2.76 ± 1.81	2.22 ± 1.86	2.5 ± 2.04	0.72
ICU days before VAD	20.8 ± 18.8	23.6 ± 18.1	11.3 ± 4.9	20.3 ± 23	0.22
Hospital days before VAD	46.3 ± 34.2	44.7 ± 30.7	36.6 ± 35.2	54.2 ± 40	0.42
Diabetes mellitus	28 (45.9)	14 (41.2)	5 (55.6)	9 (50)	0.68
Albumin (mg/dL)	3.03 ± 0.58	2.88 ± 0.6	3.31 ± 0.56	3.2 ± 0.5	0.051
Albumin <3.5 mg/dL	13 (21.3)	6 (17.7)	4 (44.4)	3 (16.7)	0.18
Prealbumin (mg/dL)	16.2 ± 6.8	16.1 ± 7.1	14.8 ± 7.2	16.8 ± 6.4	0.83
Prealbumin <17 mg/dL	22 (36.1)	13 (38.2)	3 (33.3)	8 (44.4)	0.91

ICU = intensive care unit; MDRO = multidrug-resistant organism; VAD = ventricular assist device

*Difference between non-MDRO and MDRO infection groups

Data are presented as mean ± SD or as number and percentage. $P < 0.05$ was considered statistically significant.

TABLE II. Incidence of MDROs by Infection Type

Infection Type*	All Implants (n=61)	Uninfected** (n=34)	Non-MDRO Infection (n=9)	MDRO Infection (n=18)	*P* Value
VAD-specific	16 (26.2)	0	6 (66.7)	10 (55.6)	<0.001
VAD-related	11 (18)	1 (2.9)	3 (33.3)	7 (38.9)	0.003
Non-VAD-related	25 (41)	12 (35.3)	3 (33.3)	10 (55.6)	0.32

MDRO = multidrug-resistant organism; VAD = ventricular assist device

*Patients potentially had all 3 infection types.
**Never infected, or had an infection before but not after implantation.

Data are presented as number and percentage. $P < 0.05$ was considered statistically significant.

nificantly more numerous in patients with infections ($P < 0.001$). No other variable was statistically significant.

Discussion

In this retrospective, single-center study, we found an MDRO infection rate of 31.6% in patients who had undergone LVAD implantation. To our knowledge, these are the first such data reported in the medical literature. We found an overall incidence of infection of 47%, similar to that reported in previous studies.[3,7,9,14,15]

Left ventricular assist device implantations are increasing in number because of increasing rates of heart failure and the shortage of donor hearts for transplanta-

TABLE III. Frequency of the Infectious Organisms

Organism	Frequency Overall*	Frequency as MDRO**
Methicillin-resistant *Staphylococcus aureus*	7	7
Pseudomonas aeruginosa	5	5
Coagulase-negative *Staphylococcus* spp.	6	4
Escherichia coli	9	4
Klebsiella pneumoniae	6	4
Enterobacter cloacae	3	3
Serratia marcescens	3	3
Nonhemolytic *Streptococcus* spp.	2	2
Enterobacter aerogenes	3	2
Klebsiella oxytoca	2	1
Methicillin-susceptible *Staphylococcus aureus*	8	1
Corynebacterium jeikeium	1	1
Proteus mirabilis	2	1
Aeromonas spp.	1	1
Streptococcus mitis/oralis	1	1
Providencia stuartii	1	1
Enterococcus faecalis	4	0
Streptococcus sanguinis	1	0
Acinetobacter baumannii	1	0
Stenotrophomonas maltophilia	2	0
Gram-negative rod (not further identified)	1	0
Streptococcus anginosus	1	0
Corynebacterium pseudodiphtheriticum	1	0

MDRO = multidrug-resistant organism

*Each occurrence of infection per organism, MDRO and non-MDRO, counted once per patient

**Each MDRO organism counted once per patient

tion. As LVAD technology and medical therapy improve, patients with LVADs are living longer and are at greater risk of developing infection.[16]

The baseline characteristics of our patients are similar to those of LVAD patients in other retrospective reviews, with the exception of the indication for LVAD implantation.[13,17] Destination therapy was the indication in 42.6% of our patients—more than the 34% of patients in the INTERMACS database who were given an LVAD for that indication.[16] Previous investigators have also reported lower percentages of destination-therapy patients than we did.[9] Destination therapy is typically reserved for patients with contraindications to heart transplantation,[3,18] such as age >70 years, cancer with an elevated risk of recurrence, BMI >30 kg/m^2, diabetes mellitus with end-organ damage, and active tobacco use or substance abuse.[19] Therefore, it is possible that patients in destination-therapy cohorts are in poorer overall health than are patients who are bridged.[18]

The infective MDROs that we identified most frequently were methicillin-resistant *S. aureus* and *Pseudo-*

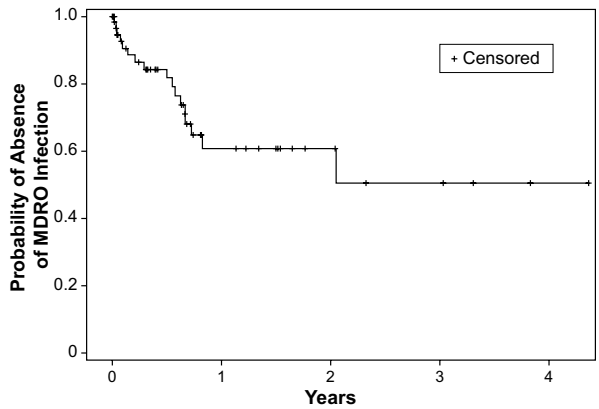

Fig. 1 *Kaplan-Meier curve shows time to development of a multidrug-resistant organism (MDRO). Patients were censored upon development of their first MDRO.*

TABLE IV. Outcomes in Patients with Left Ventricular Assist Devices

Variable	All Implants (n=61)	Uninfected (n=34)	Non-MDRO Infection (n=9)	MDRO Infection (n=18)	*P* Value
Death	25 (41)	13 (38.2)	5 (55.6)	7 (38.9)	0.63
Device explantation	13 (21.3)	8 (23.5)	2 (22.2)	3 (16.7)	0.85
Heart transplantation	9 (14.8)	6 (17.6)	2 (22.2)	1 (5.6)	0.4
Hospital admission (n)	2.7 ± 3.2	1.82 ± 1.99	2.33 ± 2.12	4.67 ± 4.64	<0.001*
Infection-related admission (n)	0.85 ± 1.66	0.12 ± 0.33	1.44 ± 1.81	1.94 ± 2.34	<0.001

MDRO = multidrug-resistant organism

*Difference between MDRO and uninfected groups

Data are presented as mean ± SD or as number and percentage. $P < 0.05$ was considered statistically significant.

monas aeruginosa. In type and frequency, the organisms in our study population were similar to those reported in other LVAD-infection studies.[9,16]

We found an independent increase in MDRO incidence in patients whose drivelines were tunneled in such a way that some of the velour covering protruded from the exit site, rather than being entirely inside the patient with only silicone-elastic exposed at the exit site. Exposed velour has been associated with an increased risk of infection.[20] At our institution, velour was left exposed until April 2010—after which time it was buried, to decrease risk of infection. Several risk factors contributing to death and morbidity in LVAD patients have been proposed, including obesity, poor nutritional status, and comorbid diabetes mellitus.[13,21] However, of these, only BMI was a statistically significant predictor of MDRO infection in our study, specifically in our uninfected and infected groups.

As might be expected, we found a significant increase in hospital admissions in MDRO-infected patients. Although poor outcomes have been associated with infections in patients with VAD implants, we did not find a statistically significant increase in deaths, transplantation, device explantation, or overall hospital admissions in relation to the occurrence of an MDRO infection.[9,22] Our study might have been underpowered to detect these differences.

Limitations of the Study

Our study has several limitations. We had a relatively small patient population, and the patients had a greater likelihood of undergoing implantation for destination therapy than did LVAD-implant patients overall. Destination therapy typically signifies poorer health, a possible confounding factor. In this retrospective chart analysis, infection was defined as culture-positive documentation; clinical indicators of infection were not considered. In addition, care that patients might have received at other institutions was not part of our data. However, most patients received most of their care at Emory University Hospital after their implantation and were closely monitored in the Emory VAD clinic. Records of care that was delivered in other institutions were typically forwarded to the Emory VAD clinic and were screened for infection-related events.

Conclusion

We found a 31.6% incidence of MDRO infection in patients who had undergone LVAD implantation—to our knowledge, the first such data to be reported. Therapeutic goal, BMI, and exposed velour were independent risk factors for the development of MDRO infection. Our MDRO patients had more hospital admissions caused by infection and therefore more total hospital admissions. A larger study, perhaps prospective, is warranted to evaluate additional MDRO risk factors and outcomes.

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