

Management and Outcome of Left Ventricular Assist Device Infections in Patients Undergoing Cardiac Transplantation

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Background. Postoperative management of patients undergoing cardiac transplantation with an infected left ventricular assist device (LVAD) is unclear.

Methods. We retrospectively screened all adults with an LVAD who underwent cardiac transplantation at our institution from 2010 through 2018. We selected all cases of LVAD-specific and LVAD-related infections who were receiving antimicrobial therapy as initial treatment course or chronic suppression at the time of cardiac transplantation. Non-LVAD infections, superficial driveline-infection, or concurrent use of right ventricular assist device or extracorporeal membrane oxygenation device were excluded.

Results. A total of 54 cases met study criteria with 18 of 54 (33.6%) classified as LVAD-specific or related infections and 36 of 54 (66.6%) as noninfected. Cases of LVAD infection had a higher median Charlson Comorbidity Index score at the time of transplantation compared with noninfected cases ($P = .005$). Of the 18 cases of infection, 13 of 18 (72.2%) were classified as LVAD-specific and 5 of 18 (27.8%) were classified as LVAD-related. Nine of 13 (69.2%) cases had proven LVAD-specific infections. Antimicrobial therapy was extended posttransplant to treat preceding LVAD-specific infection in all 9 cases (9 of 13, 69.2%) with a median duration of 14 days (interquartile range, 14–28). After LVAD removal, antimicrobial treatment was not continued for preceding LVAD-related infections.

Conclusions. Patients with an LVAD-specific infection were treated with 2 weeks of pathogen-directed therapy postheart transplant without any relapses. For those without LVAD-specific infection or uncomplicated LVAD-related bacteremia who had completed antimicrobial therapy pretransplant, antibiotics were discontinued after standard perioperative prophylaxis and no relapses were observed.

Keywords. heart transplant; left ventricular device infections; management; outcomes.

Cardiac transplantation remains the definitive treatment for an ever-increasing number of patients who progress to end-stage heart failure [1, 2]. However, with the shortage of donor hearts, the number of left ventricular assist device (LVAD) implantations, either as a bridge to transplantation (BTT) or destination therapy (DT) has exponentially increased. Due to recent advances in LVAD technology [3–5], patients' survival rates, functional status, and quality of life have significantly improved [6]. Nonetheless, infection of these devices, with reported rates

of up to 30% [7–11], could impact long-term survival, transplant candidacy, and predispose to other serious complications.

Similar to cardiac implantable electronic device (CIED) infections [12], LVAD infections may present as a local infection, involving the driveline or pocket, or as an endovascular infection, the latter arising as a result of hematogenous seeding from a distant site [7, 13, 14]. In contrast to the management of CIED infections, where complete device removal is recommended for infection cure [12], this approach in LVAD infections is reserved for severe or intractable cases [15]. Consequently, treatment of LVAD infections is primarily directed at suppressing rather than curing device infection. A common treatment strategy involves LVAD retention, prolonged antimicrobial therapy, and local debridement, if applicable and feasible. Antimicrobial therapy is thus continued indefinitely (chronic suppression) in patients receiving DT or until cardiac transplantation in those on BTT, once the infected device is removed.

Although survival of patients with LVAD infection preceding cardiac transplantation has been evaluated previously [16–18], management recommendations for the period after removal of

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an infected device are lacking. If inadequately treated, LVAD infections can add to posttransplant morbidity, mortality, and length of hospital stay. However, unnecessary antibiotic exposure in cardiac transplant recipients as an extension of pretransplant LVAD infection may result in the development of opportunistic infections, antimicrobial resistance, drug interactions, and other drug adverse events. We thus aimed to delineate the clinical presentation, management, and outcomes of patients undergoing cardiac transplantation with preceding LVAD infection at our institution.

METHODS

We retrospectively screened all adult patients (≥ 18 years of age) who underwent heart transplantation at our institution from January 1, 2010 through December 31, 2018 to include

those bridged to transplantation with a continuous-flow (CF) LVAD. We used a modified version of definitions proposed by the International Society for Heart and Lung Transplantation (ISHLT) (Table 1) [13]. We included all cases of LVAD-specific and LVAD-related infections who were receiving antimicrobial therapy as suppression or initial course of treatment before cardiac transplantation. Regardless of the source, cases of bloodstream infection (BSI) were defined as “complicated,” if there were persistently positive blood cultures at 96 hours or evidence of metastatic infection, such as vertebral osteomyelitis.

Episodes of non-LVAD infections (Table 1) that did not result in BSI were omitted from the analysis. Patients were excluded if (1) they had a superficial driveline infection that was successfully treated, (2) they had a concurrent right ventricular assist device, or (3) they required extracorporeal membrane oxygenation device support. Patients on CF-LVAD as a BTT, without

Table 1. Study Definitions of LVAD Infections

Category	Definition	Number of Study Cases
LVAD specific-infection ^a	Pump and/or cannula infections	2
	Pocket infections	2
	Percutaneous driveline infection	
	Deep infection	5
	Superficial infection ^a	
	>2 LVAD components	4
LVAD related-infection	Infective endocarditis	0
	BSI	
	CVC Present	
	BSI presumed LVAD-related	4
	BSI presumed CVC-related	
	No CVC Present	
	BSI LVAD-related	
	BSI non-LVAD-related	
	Mediastinitis	
	LVAD-Related	
Sternal wound infection SSI-organ space		
Pocket infection		
Non-LVAD related	1	
Other causes of mediastinitis		
Non-LVAD infection	Lower respiratory tract infection	N/I
	Cholecystitis	
	<i>Clostridioides difficile</i> infection	
	Urinary tract infection	
Cured LVAD infection	Cases of successfully treated LVAD-infection, with no clinical, laboratory, or radiographic findings suggestive of infection at the time of transplantation	4
Not clinically infected	Absence of clinical, laboratory, or radiographic findings consistent with LVAD infection	36
Proven LVAD infections ^b	(1) Positive microbiology for typical causative organism identified from intraoperative cultures	
	(2) Histologic or operative findings suggestive of infection	
	(3) Imaging data consistent with infection	
	(4) Local inflammatory signs or systemic symptoms and/or positive blood cultures for typical organism with no alternative source.	

Abbreviations: BS, bloodstream; BSI, BS infection; CVC, central venous catheter; LVAD, left ventricular assist device; N/I, not included; SSI, surgical site infection.

NOTE: Definitions adapted according to the International Society for Heart and Lung Transplantation (ISHLT) guidelines [12].

^aExcluded from analysis: cured superficial percutaneous driveline infection.

^bRefer to Tables 3–6 of ISHLT guidelines [12].

documented LVAD-specific or LVAD-related infectious complications, were included as a comparison group.

Demographic, comorbid conditions, transplant, and device data of infected and noninfected LVAD cases were extracted from electronic health records. For cases of LVAD infection, clinical presentation, imaging, laboratory, and microbiology data were analyzed to ensure fulfillment of ISHLT criteria infection definitions.

Management indicated at the time of diagnosis for each case of LVAD-infection, including choice of antimicrobial agent, route, duration, surgical debridement, and/or device exchange if performed, was documented. On the day of the cardiac transplant procedure, recorded systemic symptoms, vital signs, physical examination, laboratory, and microbiologic data were analyzed to identify patients with sepsis (for definition, see footnote of Table 2). Operative findings at the time of LVAD removal and cardiac transplant, the number of specimens collected from infected device and tissues, microbial results, and organism(s) identified from cultures and histopathology were collected. Once the device was explanted, LVAD-specific infections were confirmed per ISHLT criteria (Table 1).

Relapse was defined as a posttransplant infection involving tissues adjacent to the former LVAD sites (driveline, pump-pocket), whereas recurrent BSI was defined as BSI due to the same organism and susceptibility pattern identified during index episode, after hospital dismissal. Outcomes analyzed included length of hospital stay and overall survival rate at 5 years between LVAD-infected and noninfected cases.

The χ^2 test and Wilcoxon rank-sum test were used for comparison of categorical variables and continuous data, respectively. Overall posttransplant survival between cases of LVAD infection and noninfected cases was calculated using Kaplan-Meier methodology and Cox proportional hazards models. Statistical tests were 2-tailed with $P < .05$ considered statistically significant. Analyses were performed using JMP software (Cary, NC). All patients consented to use their medical records for research purposes, and the Mayo Clinic Institutional Review Board approved the study.

RESULTS

Demographic, Clinical, Transplant, and Device Features of Left Ventricular Assist Device (LVAD)-Infection Versus Noninfected LVAD Cases

Figure 1 illustrates the patient flow diagram. Overall, 292 patients underwent cardiac transplantation during the study period, 77 of 292 (26.3%) of whom had a CF-LVAD as a BTT. After applying the study criteria, 54 cases were included in the final analysis. Of these, 18 of 54 (33.6%) were classified as LVAD-specific or related infections and 36 of 54 (66.6%) were classified as noninfected. There were no significant differences in demographic, transplant, or device characteristics between groups (Table 2). However, cases of LVAD-infection had a higher prevalence of diabetes mellitus (72.2% vs 16.6, $P < .001$), hypertension (66.6% vs 25%, $P = .003$), and median Charlson comorbidity index score at the time of transplantation (5 [IQR, 3–8] vs 3 [IQR, 2–4]; $P = .005$). The median durations of LVAD support for infected and noninfected cases

Table 2. Demographic Characteristics, Comorbidities, Cardiac Transplant, and Device-Related Features of Patients With LVAD as a Bridge to Transplantation

Variable	LVAD-Infected Cases (n = 18)	Noninfected LVAD Cases (n = 36)	P Value
Demographic Data and Comorbidities			
Age, years median (IQR)	48 (42.7–62.2)	55 (48–63)	.3826
Male	14 (77.7%)	30 (83.3%)	.6203
White	17 (94.4%)	36 (100%)	.1534
Body mass index median (IQR)	30.7 (24.4–34.2)	29.3 (25–34)	.8544
Charlson comorbidity index median (IQR)	5 (3–8)	3 (2–4)	.005
Diabetes mellitus	13 (72.2%)	6 (16.6%)	<.001
Hypertension	12 (66.6%)	9 (25%)	.0031
Chronic kidney disease	13 (72.2%)	27 (75%)	.8262
Device Characteristics			
Device type Heartmate II Heartware	14 (77.8%)	30 (88.2%)	--
Other	4 (22.2%)	3 (8.8%)	
	–	1 (2.9%)	
Duration of LVAD support, days median (IQR)	593 (294.2–1428)	490 (311.2–801.2)	.5089
Transplant Characteristics			
Simultaneous cardiac and kidney transplant	4 (22.2%)	4 (11.1%)	.2786
Modified immunosuppression induction protocol	1 (0.5%) ^a	0	--

Abbreviations: IQR, interquartile range; LVAD, left ventricular assist device.

Bold text indicates values that are statistically significant.

^aA single patient received reduced dose of thymoglobulin due to history of infection.

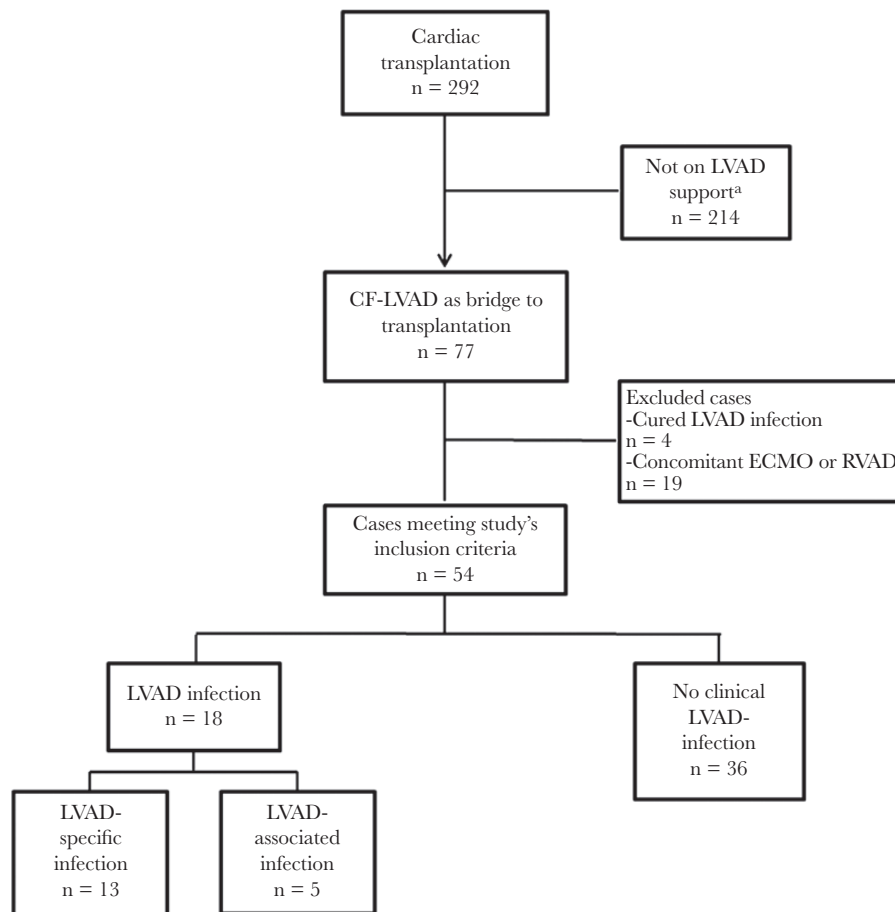


Figure 1. Patient flow diagram. CF, continuous flow; ECMO, extracorporeal membrane oxygenation device; LVAD, left ventricular assist device; RVAD, right ventricular assist device;

were similar (593 [IQR, 294.2–1428] vs 490 [IQR, 311.2–801.2] days). Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) was only documented in few patients from both groups; however, most patients were classified as INTERMACS II in the LVAD-infected cases (3 of 10) and as INTERMACS I (3 of 9) and IV (3 of 9) in the noninfected cases.

Pretransplant Diagnosis and Management of Left Ventricular Assist Device-Infection Cases

Left Ventricular Assist Device (LVAD)-Specific Versus LVAD-Related Clinical presentation and management of all LVAD infection cases before cardiac transplantation are shown in [Table 3](#) and [Supplementary Table S1](#). Regardless of the classification scheme, most cases of LVAD infection developed within the first 2 years after LVAD implantation. Of the 18 cases of infection, 13 of 18 (72.2%) were classified as LVAD-specific and 5 of 18 (27.8%) were classified as LVAD-related. Among LVAD-specific infections, driveline infections were the most common type (5, 38.4%), followed by pump or pocket infection (4, 22.2%) and those involving more than 1 LVAD site (4, 22.2%). A total of 7 of 13 (53.8%) had concomitant BSI, although none

of these met study criteria for complicated infection. The majority of LVAD-specific cases were caused by Gram-positive organisms (7 of 13), followed by polymicrobial infections with Gram-positive/Gram-negative organisms (5 of 13) and 1 case of fungal infection. In contrast, most LVAD-related infections were categorized as presumed LVAD-related BSI (4 of 5, 80%), all due to Gram-positive cocci, and none were deemed complicated. The remaining case was classified as non-LVAD-related mediastinitis.

After the diagnosis of LVAD infection, all patients received pathogen-directed antimicrobial therapy. In addition, a total of 6 of 13 (46.1%) LVAD-specific infections and 1 of 5 (20%) LVAD-related infections required surgical debridement; however, in all cases, the LVAD-device was retained. Before transplant, among patients with documented BSI, including those with LVAD-related (4 of 5, 80%) and LVAD-specific infections (7 of 13, 53.8%), patients achieved blood culture clearance on antimicrobial therapy. Median duration of antimicrobial therapy from diagnosis to time of transplantation was 217 (IQR, 125.5–364.5) and 132 (IQR, 53.5–628.5) days for cases of LVAD-specific and LVAD-related infections, respectively.

Table 3. Clinical Presentation and Management of 18 Cases of LVAD Infection Before Cardiac Transplantation

Variable	LVAD-Specific Infection (n = 13)	LVAD-Related Infection (n = 5)
Infection Management Pretransplantation		
Time from implantation to index infection, days median (IQR)	519 (263.5–1669.5)	704 (380.5–1212.5)
Surgical debridement ^a	6 (46.1%)	1 (20%)
Antimicrobial therapy before transplantation, days median (IQR)	217 (125.5–364.5)	132 (53.5–628.5)
Oral route of antimicrobial therapy	9 (69.2%)	5 (100%)
Adverse events reported on chronic suppression	1 (7.6%)	1 (20%)
Features at the Time of Cardiac Transplantation		
Sepsis ^b	0	0
Erythema, purulent drainage or tenderness at the driveline site	6 (33.3%)	---
Positive blood cultures ^c	2/13 (14.2%)	0/2 (0)

Abbreviations: IQR, interquartile range; LVAD, left ventricular assist device.

^aSurgical management included the following: LVAD debridement in 6 patients with LVAD-specific infection and infected-hematoma evacuation in 1 patient with LVAD-related mediastinitis.

^bDefined as the presence of ≥ 2 systemic inflammatory signs of infection (defined as temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 , respiratory rate >20 , white blood cell count of $12\,000/\text{mm}^3$, $<4000/\text{mm}^3$, or $>10\%$ bands) and suspected or present source of infection.

^cBlood cultures were only obtained in 13 patients with LVAD-specific infection and in 2 patients with LVAD-related infection.

Day of Transplantation

On the day of transplantation, 1 patient was receiving active antimicrobial therapy, whereas the remaining cases were on chronic antimicrobial suppression (17 of 18, 94.4%). At the time of cardiac transplantation, no patients were deemed septic. Blood cultures were obtained before or at the time of cardiac transplantation in all patients with LVAD-specific infection and 2 patients with LVAD-related infection. Two cases of LVAD-specific infection had positive blood cultures with the same organism identified at index infection despite previously having achieved negative blood cultures. All patients received standard immunosuppression per transplant protocol, except for 1 case in which thymoglobulin induction was deferred due to a history of infection. Standard perioperative prophylaxis, in addition to coverage of pathogens detected with LVAD-infection, was administered in all patients.

Peri- and Posttransplant Features of Left Ventricular Assist Device-Specific Infections

Intraoperative device and tissue specimens were obtained in 11 of 13 (83.3%) cases, 8 of 11 of which (66.6%) had an organism identified. In addition, operative findings consistent with infection were reported in 6 of 13 patients (46.1%), all cases of driveline and pocket infection. Histopathology of infected tissue, however, was not submitted in these cases. A total of 9 of 13 (69.2%) cases were deemed proven LVAD-specific infections. Antimicrobial therapy was extended to treat preceding LVAD infection in all 9 cases (9 of 13, 69.2%). The median duration of posttransplant antimicrobial therapy was 14 days (IQR, 14–28). Three cases of pocket-infection required further surgical debridement during the same hospital stay before chest closure and received 28 days (2 cases) and 180 days (1 case)

of pathogen-directed therapy. The latter was a case of LVAD-pocket infection with *Candida glabrata* complicated by mediastinitis and empyema in the posttransplant period. The patient required multiple surgical debridements and a treatment course for 6 months followed by chronic antimicrobial suppression. The median length of hospital stay in this group was 23 days (IQR, 15.5–31) (Table 4).

Peri- and Posttransplant Features Left Ventricular Assist Device-Related Infections

No cases of LVAD-related infection had intraoperative cultures collected or specimens submitted for histopathology evaluation other than the explanted heart. Intraoperative reports had no findings suggestive of infection in these 5 cases. After LVAD removal, antimicrobial treatment was not continued for preceding LVAD-related infection. The median length of hospital stay was longer than in cases of LVAD-specific infection (74.5 days [IQR, 30.2–176.5] vs 23 days [IQR, 15.5–31]) (Table 4).

Noninfected Left Ventricular Assist Device Cases

None of the noninfected LVAD cases had incidental operative findings consistent with infection. Therefore, intraoperative cultures were not obtained in these cases.

Outcomes

Four patients (22%) in the LVAD infection group and 7 of 36 (19.4%) of the noninfected cases developed infectious complications (other than LVAD) during the same hospitalization, mainly nosocomial pneumonia. Length of hospital stay was not significantly different between the 2 groups (25 days [IQR, 18–36] vs 55 days [IQR, 12.5–149]; $P = .277$). None of the patients in the LVAD-infection group experienced infection relapse after hospital dismissal. Survival to transplantation was

Table 4. Peri- and Posttransplant Features of the 18 Patients With LVAD Infection

Variable	LVAD-Specific Infection (n = 13)	LVAD-Related Infection (n = 5)
Intraoperative Features at the Time of Transplantation		
Operative report consistent with infection or positive histopathology if available	6 (46.1%)	0
Positive microbial cultures from device or tissues	8/11 (60%)	N/A
Proven infections ^a	8/12 (66.6%)	--
Peri- and Posttransplant Features		
Standard induction immunosuppression reduced due to infection	1/13 (7.6%)	0
Pathogen-directed antimicrobial therapy extended for LVAD infection	9 (75%)	0
Total days of antimicrobial therapy indicated for LVAD infection, days median, IQR	14 (14–28)	--
Need for subsequent surgical debridement after LVAD removal and transplant	3/13 (25%)	0
Infection relapse	0	0
Length of hospital stay, days	23 (15.5–31)	74.5 (30.2–176.5)

Abbreviations: IQR, interquartile range; LVAD, left ventricular assist device; N/A, not available.

^aSee Table 1 for definitions.

similar between groups (94.4% vs 91.6%, $P = .713$). There was no significant difference in the overall 5-year posttransplant survival observed between infected and noninfected groups (Figure 2).

DISCUSSION

Optimal postoperative management of patients with LVAD infections undergoing cardiac transplantation is unclear and therefore a critical analysis of this topic is warranted. In our study, patients with proven LVAD-specific infection at the time of heart transplant and device removal received antimicrobial therapy for a median duration of 14 days (IQR, 14–28) after transplant (treatment was prolonged in 3 cases that required repeated surgical debridement). None of these patients

had relapsing infection involving the tissues adjacent to the former LVAD sites. However, 1 patient with fungal mediastinitis received chronic antimicrobial suppressive therapy posttransplant. In contrast, for patients in whom LVAD-specific infection was not confirmed, antimicrobial therapy was discontinued after standard perioperative prophylaxis, and none developed relapse. Finally, cases of uncomplicated LVAD-related BSI who completed antimicrobial therapy before transplantation and achieved negative blood cultures were not continued on antimicrobial therapy. None of these patients had recurrence of BSI due to the same organism identified during index episode, after cardiac transplantation.

An earlier investigation [18] of LVAD infections, reported approximately 2 decades ago, exemplifies substantial changes

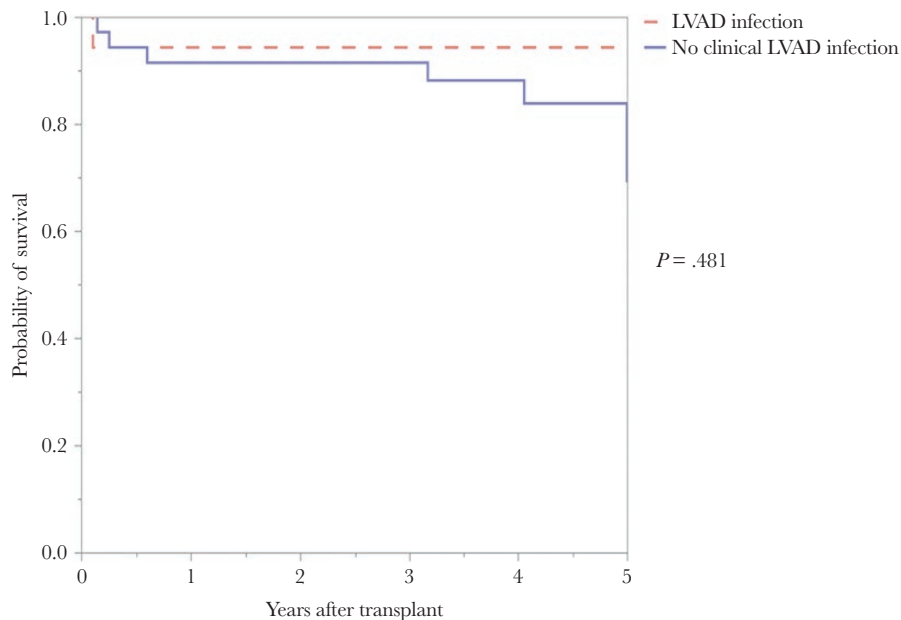


Figure 2. Kaplan-Meier survival analysis between left ventricular assist device (LVAD) infected and noninfected LVAD cases.

that have occurred in practice over time. In this study, 8 patients with an active LVAD infection underwent heart transplantation, 5 of them had driveline infections, and the remaining 3 had intravascular infections. All of these 8 patients had positive blood cultures documented within 1 week of transplantation. Posttransplant, antimicrobial therapy was continued for cases of driveline and intravascular infection for 4 and 6 weeks, respectively. In comparison, the majority (16 of 18, 88.8%) of patients in our study had negative blood cultures before undergoing transplantation, and shorter antibiotic courses posttransplant (and LVAD removal) were not associated with infection relapse. Moreover, antimicrobial therapy was not continued in cases of BSI who had completed a treatment course before heart transplant and LVAD removal. Of note, all BSI cases in our study cohort were deemed uncomplicated, whereas the former study did not clarify this important aspect. Hematogenous seeding of microorganisms at distant sites typically warrants longer courses of therapy.

Posttransplant survival of a patient with pretransplant LVAD infection has been explored in several recent studies. Similar to our study findings, no significant difference was observed when compared with cases without an LVAD infection [19]. Therefore, active or suppressed LVAD infection should not dissuade or delay patients and physicians from proceeding with heart transplantation if an organ becomes available.

Uncontrolled LVAD infection or sepsis at the time of transplant can have a negative impact on posttransplant survival. In

a study by Schulman et al [17], patients who had sepsis due to LVAD infection at the time of heart transplant were less likely to survive, compared with those without a history of LVAD infection. In our study cohort, although signs of active infection were present in one third of the patients and 2 cases had positive blood cultures on the day of transplant, none were deemed septic.

Another critical outcome evaluated in our study was the length of hospital stay, which was also not significantly impacted by LVAD infection, even though some patients required subsequent surgical debridements resulting in delayed chest closure. In contrast, an earlier investigation [17] reported a prolonged length of hospital stay, particularly in those with driveline and pocket site involvement. However, posttransplant survival among infected and noninfected cases was not statistically different.

Our study has several limitations. First, the retrospective nature of the analysis and the limited number of patients prevented us from providing conclusive statements. Larger studies are needed to validate our observations, specifically as it pertains to recommendations on antimicrobial duration. Besides, some LVAD-infection syndromes were not represented in our cohort. Furthermore, the decision to treat or not was based mainly on microbiologic data and gross inspection at the time of the procedure, which can certainly be subjective. Prolonged antimicrobial therapy before transplant may have affected yield of intraoperative cultures. The histopathologic examination was

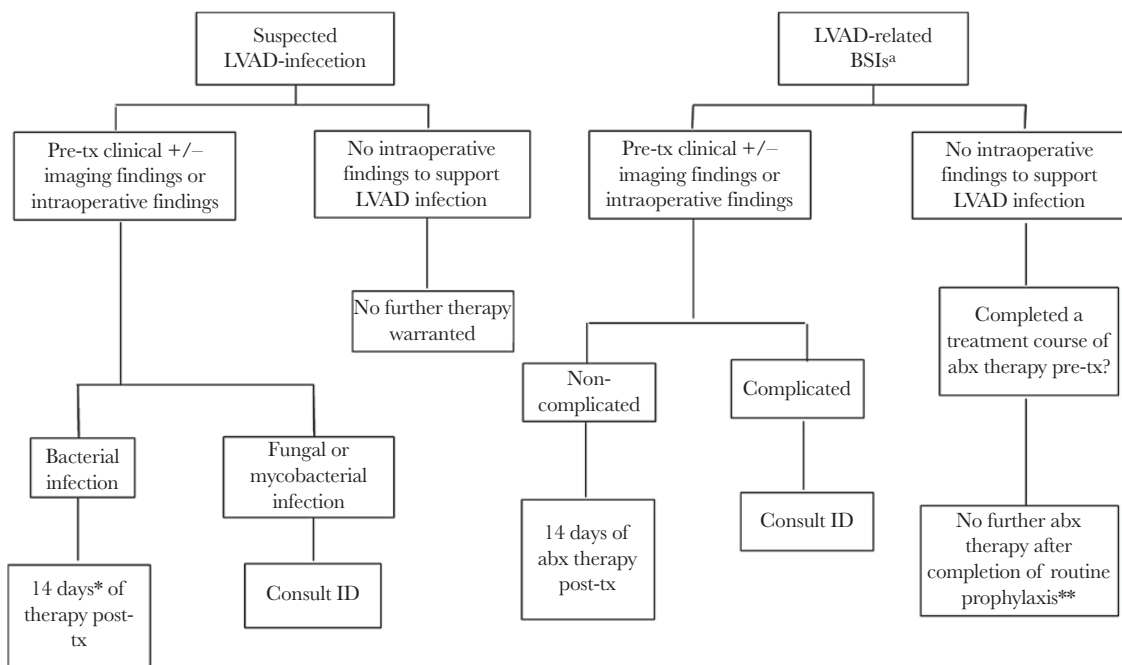


Figure 3. Management of suspected left ventricular assist device (LVAD) infection at the time of heart transplant. *, Longer if complications such as mediastinitis or need for further debridement. **, Duration of routine perioperative prophylaxis at our institution is 48 hours posttransplant. ^aIf bloodstream infection (BSI) with fungal or mycobacterial organisms, consult Infectious Diseases (ID). abx, antibiotic; tx, transplant.

rarely obtained, which does not align with the recommendations by the ISHLT to confirm an infection diagnosis.

Some patients received antimicrobial therapy (duration of 7–14 days) for indications other than LVAD infection (mainly for cases of pneumonia), which may have targeted causative organisms for previous LVAD infection as well. Furthermore, use of trimethoprim/sulfamethoxazole, indicated for prevention of toxoplasmosis or pneumocystis infections, could have cured soft tissue infections (at explanted driveline or pump pocket site) caused by susceptible organisms. Despite these limitations, our study provides valuable insights into the management of LVAD infections after heart transplant.

Implications for Clinical Practice

Based on our study observations, we suggest that patients with proven LVAD-specific infections, based on imaging or intraoperative findings, may be treated with up to 2 weeks of pathogen-directed therapy after heart transplant (Figure 3). However, a longer course of therapy may be needed if complications such as mediastinitis are present and patients undergo repeated surgical debridement. Infectious Diseases service should be consulted to guide antimicrobial therapy for mycobacterial or fungal infections. Finally, for patients who complete treatment course for BSI before transplant and have negative blood cultures and intraoperative findings, further antimicrobial therapy after heart transplant and LVAD removal may not be necessary.

CONCLUSIONS

In this single-center study, patients with known LVAD-specific infection at the time of heart transplant were managed with a median of 14 days of antimicrobial therapy after transplant with no relapses. In cases without LVAD-specific infection or uncomplicated LVAD-related BSI, who completed therapy for BSI and achieved negative blood cultures pretransplant, antibiotics were discontinued after standard perioperative prophylaxis and none experienced recurrent BSI. Larger, multicenter studies with comparator groups are needed to validate these observations.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Potential conflicts of interest. M. R. S. reports receiving funds from Medtronic for prior research unrelated to this study and unrelated honoraria/consulting fees from Medtronic, Spectranetics, Boston Scientific, and

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