2018

Outcomes and predictors of early infection after heart transplantation

Kendall C. Shultes

Jerrica E. Shuster

Scott Micek

Justin M. Vader

Keki Balsara

See next page for additional authors

Authors

Kendall C. Shultes, Jerrica E. Shuster, Scott Micek, Justin M. Vader, Keki Balsara, Akinobu Itoh, and Bethany R. Tellor

Outcomes and Predictors of Early Infection after Heart Transplantation

Kendall C. Shultes,[1] Jerrica E. Shuster,[2] Scott Micek,[3] Justin M. Vader,[4]
Keki Balsara,[5] Akinobu Itoh,[6] and Bethany R. Tellor[2]

Abstract

Background: Limited data exist on the incidence and outcome of early infection after orthotopic heart transplantation (OHT). The purpose of this study was to describe characteristics and outcomes of OHT recipients with an early infection and to identify predictors of such infections.

Methods: This retrospective, single-center study included patients greater than 18 years of age who underwent OHT from February 2009 to May 2014 and had an infection within 30 days of transplantation. Patient demographics, clinical variables, and outcomes were collected. Multivariable logistic regression was performed to identify independent predictors of infection.

Results: Of the 172 eligible OHT recipients, 51 (29.7%) had an early infection. The median time to diagnosis was five days, with gram-negative organisms being slightly more common (58.2%). No differences in mortality rate, rejection, or re-admission were found between the groups. Longer durations of mechanical ventilation and lengths of stay were found in the infection group (p < 0.001). Patients with an early infection also had a higher incidence of mechanical circulatory support, history of drive-line infection, longer duration of mechanical ventilation, continuous renal replacement therapy (CRRT), and delayed chest closure (p < 0.05 for all). Pre-OHT left-ventricular assist device (adjusted odds ratio [AOR] 2.53; 95% confidence interval [CI] 1.015–6.286; p < 0.046), pre-OHT extracorporeal membrane oxygenation (AOR 14.10; 95% CI 1.38–150.5; p = 0.026) and post-OHT CRRT (AOR 3.98; 95% CI 1.67–9.52; p = 0.002) were found to be independent risk factors for an early infection. A total of 90% of the available susceptibility panels for the gram-negative isolates (26/29) were resistant to the standard peri-operative cephalosporin given.

Conclusions: Prior mechanical circulatory support and the acute need for CRRT may predispose OHT patients to an infection early in the post-operative period. Evaluation of peri-operative antimicrobial prophylaxis, based on an individual center's resistance panels, may be warranted.

Keywords: infection; left ventricular assist device; orthotopic heart transplantation

S
INCE THE FIRST HEART TRANSPLANTATION in 1967, the procedure has grown worldwide to a total of 120,991 adult recipients as of June 2016 [1]. With advances in immunosuppression regimens and surgical technique, the overall risk of rejection and survival have improved [2,3]. However, infectious complications remain and may influence survival, rejection, and re-admission rates.

According to the Scientific Registry of Transplant Recipients (SRTR) and Organ Procurement and Transplantation Network (OPTN) Annual Data Report in 2015, infection was the most common cause of death (2.3% of the series) at one year after OHT [2]. Infection within the first month post-OHT has demonstrated even higher mortality rates (13%–60%) in some studies [4,5]. Bacterial infections continue to be the most common type of severe infections [4,6–9], with gram-positive organisms being the primary infecting pathogens [6]. Interest in β-lactamase-producing Enterobacteriaceae and fungal infections in this patient population also has emerged recently [10–12].

---

[1]Belmont University College of Pharmacy, Nashville, Tennessee.
[2]Department of Pharmacy, Barnes-Jewish Hospital, St. Louis, Missouri.
[3]St. Louis College of Pharmacy, St. Louis, Missouri.
[4]Department of Medicine, Division of Cardiology, Washington University in St. Louis, St. Louis, Missouri.
[5]Department of Cardiac Surgery, Section of Surgical Sciences, Vanderbilt University Medical Center, Nashville, Tennessee.
[6]Department of Surgery, Division of Cardiothoracic Surgery, Washington University in St. Louis, St. Louis, Missouri.

Although the incidence and type of infection post-OHT have been reported [1,2,4,5], the characteristics of patients who develop infection in the early transplant period have not been described well. Descriptions of the organisms cultured, sites of infection, and risk factors contributing to these early infections are lacking. Additionally, the impact of early infection on clinical outcomes is unclear. The purpose of this study was to describe the characteristics and outcomes of OHT recipients with an infection identified within 30 days of transplantation. Secondary objectives were identifying factors associated with an early infection.

Patients and Methods

This retrospective, single-center cohort study was performed at Barnes-Jewish Hospital, a 1,315-bed tertiary-care academic medical center that is the affiliated teaching hospital for Washington University School of Medicine in St. Louis. The Washington University School of Medicine Human Research Protection Office and the Protocol Review and Monitoring Committee approved this study.

The Barnes-Jewish Hospital medical informatics system was queried to identify OHT recipients who were admitted between February 2009 and May 2014. To be included in the early-infection cohort, OHT recipients had to be at least 18 years of age, have a positive culture with one or more organism(s), and meet the specified definition of infection within 30 days post-transplant. Exclusion criteria included death within 48 hours of transplant, missing data in the medical chart, transplant performed at an outside hospital, or active infection requiring intravenous antibiotics at the time of transplantation.

Electronic medical records were searched to identify demographic data, immunosuppressive and antimicrobial regimens received, site of positive culture(s), organism(s) cultured, and time to first positive culture. Baseline comorbidities were identified via the International Classification of Disease 9th revision codes [13,14]. Hospital and intensive care unit (ICU) length of stay (LOS), rejection occurrence, re-admission dates, and mortality data also were collected.

Definitions

All documented infections were confirmed on the basis of clinical signs and symptoms of infection in correlation with a positive culture and an infectious disease consultation when applicable. Pneumonia was defined as the presence of new or worsening radiographic pulmonary infiltrates along with clinical findings suggesting infection (leukocytosis, fever, purulent sputum) in addition to growth of organism(s) in cultures obtained through sputum or tracheal aspirate, with hospital-acquired pneumonia (HAP) occurring 48 hours or more after admission and ventilator-associated pneumonia (VAP) occurring 48 hours or more after endotracheal intubation. Nosocomial tracheobronchitis was defined when clinical findings suggested a pulmonary infection with a positive respiratory culture without a new lung infiltrate [4,15]. Urinary tract infection (UTI) was diagnosed in patients without an indwelling urethral catheter when documentation of pyuria or bacteremia in addition to a positive urine culture ($>10^5$ colony-forming units [CFU]/mL) was found [4]. In patients with indwelling urethral catheters, $\geq 10^5$ CFU/mL of one or more bacterial species in a urine specimen

had to be noted [16]. Blood stream infection (BSI) was defined as one or more organisms isolated from at least two consecutive blood cultures. In cases involving micro-organisms of doubtful significance (e.g., *Bacillus* spp., coagulase-negative *Staphylococcus* spp.), clinically relevant episodes were noted only if evidence of clinical infection was present in addition to an infectious disease consultation diagnosis.

Multi-drug resistance (MDR) for *Staphylococcus aureus*, *Enterococcus* spp., Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. were defined according to standardized terminology [17]. Our institution's microbiology laboratory reports susceptibility results of AmpC-stable β-lactamases as well as non-β-lactam agents for *Enterobacter* spp., *Serratia* spp., and *Citrobacter freundii*. Default resistance to AmpC-labile agents (ceftriaxone, aztreonam, piperacillin/tazobactam) is reported for the aforementioned bacterial isolates, as at our center, 85% have inducible AmpC resistance and 11% have stable high-level AmpC expression [18].

Appropriate antimicrobial therapy was defined as an initially prescribed regimen with activity against the identified pathogen based on *in vitro* susceptibility testing and administration within 24 hours of culture. Acute cellular rejection (ACR) was defined as a biopsy specimen post-OHT displaying Grade $\geq 2R/3a$ rejection [19].

Standard process of care

Peri-operative prophylaxis for OHT recipients includes vancomycin and cefazolin intra-operatively, continued for 24 hours after chest closure. Heart transplant recipients at our institution do not receive routine surveillance cultures in the intra-operative or post-operative periods. Cultures are obtained only when there is clinical evidence suggestive of infection that may warrant treatment. Clinical evidence of infection prompting an infectious work-up include fever, leukocytosis, hypotension, and diagnostic imaging or other hemodynamic measures suggestive of sepsis. Infectious disease consultations generally are obtained on all transplant recipients. The current immunosuppression protocol at Barnes-Jewish Hospital is methylprednisolone intra-operatively followed by mycophenolate mofetil (MMF), tacrolimus, and methylprednisolone immediately post-operatively. Patients who received induction therapy from February 1, 2009 to August 2010 received anti-thymocyte globulin and those operated on from August 2010 to May 2014 received basiliximab because of a change in institution protocol. Patients received induction unless considered at high risk for infection; i.e., on suppressive antibiotics prior to transplantation.

Statistical analysis

Statistical analysis was completed using SPSS software, version 22.0 (SPSS, Inc., Chicago, IL). Continuous data were analyzed using the Student's *t*-test for parametric data and the Mann-Whitney U test for nonparametric data. Categorical data were analyzed with the χ^2 or the Fisher exact test. A p value <0.05 was considered significant. Backwards stepwise logistic regression was utilized to identify risk factors independently associated with an early infection. Variables significant at a p value ≤ 0.1 in the univariable analyses were

entered in the stepwise multivariable logistic regression model.

Results

A total of 185 OHTs were performed during the study period. Thirteen patients were excluded, leaving 172 patients for analysis. Early infection criteria were met in 51 patients (29.7%) (Fig. 1). The majority of the patients were Caucasian males, younger than 65 years, with an idiopathic cardiomyopathy diagnosis. A significantly higher percent of patients in the early infection cohort received extracorporeal membrane oxygenation (ECMO) before OHT (11.8% vs. 0.8%; p = 0.003), were left-ventricular assist device (LVAD) explants (66.7% vs. 30.6%; <0.001), and had histories of driveline infection (23.5% vs. 10.7%; p = 0.035) (Table 1). When further analyzed by type of infection, no differences in demographic data were found.

No difference in induction therapy was noted between the early-infection and no early-infection cohorts. The primary agent utilized was basiliximab in both groups. All patients received maintenance therapy with tacrolimus, MMF, and steroids per protocol. Patients in the infection cohort had a higher incidence of continuous renal replacement therapy (CRRT) after OHT, delayed chest closure, ECMO after OHT, and a longer duration of mechanical ventilation (p < 0.05) (Table 2).

Early infection cohort

The median temperature at the time of infection diagnosis was 37.3°C (interquartile range [IQR] 36.6–37.9°C). Of note, 24 patients (47%) were on CRRT at the time of their infection diagnosis, potentially masking the presence of a fever. The median white blood cell (WBC) count at the time of infection diagnosis was $23 \times 10^3/mm^3$ (IQR $17.5–28.7 \times 10^3/mm^3$). The majority of patients (78.4%) were receiving at least one vasopressor. The median time to infection diagnosis was five days (IQR 2.1–8.7 d).

A total of 67 organisms were identified in the 51 patients with an early infection (Table 3). The most prevalent organisms were gram-negative bacteria (n = 39; 58.2%) with fewer gram-positive organisms (n = 20; 29.9%). The most

common organisms were *Staphylococcus* spp., *Enterobacter* spp., and *Escherichia coli*. Twenty-four MDR pathogens (47%) were identified (20 gram-negative, two methicillin-resistant *S. aureus*, two vancomycin-resistant Enterococci).

The most prevalent infection was pneumonia (n = 24; 47%; 19 VAP, five HAP) followed by BSI (n = 0; 19.6%) and UTI (n = 7; 13.7%). Other infections were ventricular-assist device (VAD) pocket (n = 3; 5.8%), tracheobronchitis (n = 2; 3.9%), *Clostridium difficile* diarrhea (n = 2), and mediastinitis, groin seroma, pericarditis, and pacemaker (n = 1 each; 2.0%). Of the 24 pneumonia episodes, the organisms most often isolated were gram-negative species with a median time to infection of 4.3 days. Of note, patients with pneumonia had a longer median mechanical ventilation duration of 9.5 (IQR 5.4–15.7) days compared with 2.8 (IQR 0.7–5.1) days in the patients with other sites of infection (p < 0.001). Additionally, the median mechanical ventilation duration for patients with pneumonia was significantly longer than for the non-infected group (9.5 vs. 1.8 days; IQR 0.8–3.6 days; p < 0.0001). The most common BSI organisms were *Serratia marcescens* (n = 3; 30%) and *Enterobacter cloacae* (n = 2; 20%) with a median time to infection of 5.3 days. *Escherichia coli* and *Pseudomonas aeruginosa* (n = 2; 28.6% each) were the most common UTI organisms with a median time to infection of nine days. The median duration of mechanical ventilation prior to a diagnosis of a non-respiratory infection was four days. This was not significantly different from those with a respiratory infection.

Antimicrobial therapy

Standard peri-operative antimicrobial prophylaxis was administered to 75% of patients who sustained an early infection when patient allergies or previous culture history did not cause divergence. The remaining 25% received broader coverage with linezolid in the case of vancomycin intolerance and aztreonam or meropenem for cephalosporin intolerance. Of the 33 patients with gram-negative isolates, 29 (88%) had susceptibility panels available for assessment. Notably, a total of 26 (90%) of the available susceptibility panels for the gram-negative isolates, which included *Citrobacter freundii*, *Enterobacter* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp., *Pseudomonas aeruginosa*, and *Serratia marcescens*, showed resistance to cefazolin. The median time to
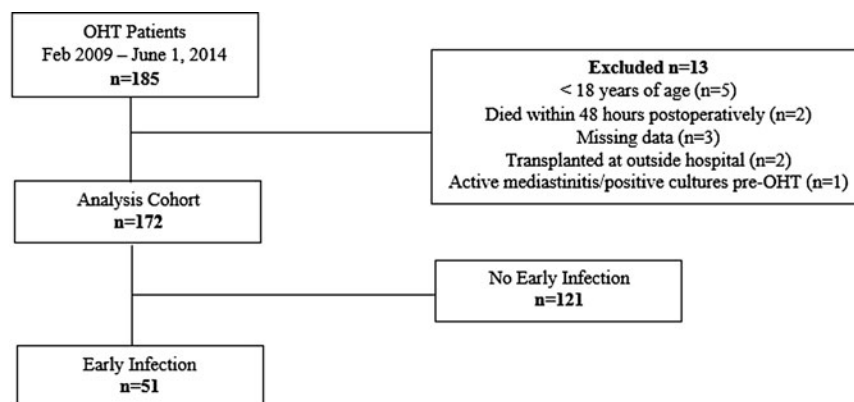

FIG. 1. Adult orthotopic heart transplant (OHT) recipients from Barnes-Jewish Hospital were assessed for study inclusion. Based on the inclusion criteria, 172 patients were eligible for analysis, with 51 patients meeting the criteria for early infection.

TABLE 1. BASELINE CHARACTERISTICS OF EARLY INFECTION COHORT VS. NO EARLY INFECTION COHORT[a]

Variable	Early infection (n=51)		No early infection (n=121)		p
Race					0.284
Caucasian	35	(68.6)	96	(79.3)	
African American	16	(31.4)	23	(19.0)	
Asian	0		1	(0.8)	
Native American	0		1	(0.8)	
Age (y)[b]	53.9	(45–63)	54.4	(48–62)	0.873
≥65	9	(17.6)	18	(14.9)	0.648
Male sex	37	(72.5)	79	(65.3)	0.353
Body Mass Index (kg/m^2)[b]	28.4	(24.2–32.4)	27.6	(22.8–30.9)	0.289
≥35	8	(15.7)	16	(13.2)	0.670
Reason for orthotopic heart transplantation					0.157
Idiopathic	30	(58.8)	64	(52.9)	
Ischemic cardiomyopathy	12	(23.5)	41	(33.9)	
Valvular	5	(9.8)	3	(2.5)	
Restrictive	2	(3.9)	3	(2.5)	
Hypertrophic	2	(3.9)	5	(4.1)	
Graft dysfunction	0		5	(4.1)	
Co-morbidities					
Coronary artery disease	23	(45.1)	55	(45.5)	0.966
Diabetes mellitus	27	(52.9)	55	(45.5)	0.369
Chronic obstructive pulmonary disease	8	(15.7)	19	(15.7)	0.998
Asthma	4	(7.8)	8	(6.6)	0.751
Prior ECMO during same hospitalization	6	(11.8)	1	(0.8)	0.003
Left-ventricular assist device (LVAD) explants	34	(66.7)	37	(30.6)	<0.001
History of LVAD DL infection	12	(23.5)	13	(10.7)	0.035
Duration of antibiotic for DL infection (d)[b]	233.5	(153.5–705.25)	227	(81–503.5)	0.320

[a]All values presented as n (%) unless otherwise noted.
[b]Values presented as median (interquartile range).
DL = drive line; ECMO: extracorporeal membrane oxygenation.

positive culture in this group was 1.5 days. Overall, inappropriate antimicrobial treatment was noted in 12 patients (24%).

Outcomes

No differences in the mortality rate at 30 days or one year were found. The median time to death was shorter in the infection cohort although not significantly so (41.6 vs. 470 days; p = 0.23). Three patients in the early infection group died prior to hospital discharge as a result of sepsis (n = 2) or primary graft dysfunction (PGD) (n = 1). One pa-

tient in the no-infection group died of PGD. Rejection rates were similar in the two groups. Patients with an early infection had a longer ICU and hospital LOS (p < 0.001). No differences in 30-day re-admission rate were found (Table 4).

Risk Factors for Early Infection

The following variables in the univariable analyses with a p value <0.1 were entered in a backwards stepwise logistical regression analysis: LVAD (with and without drive-line infection), ECMO (pre- and post-OHT), delayed chest closure, and CRRT. This analysis revealed that that pre-OHT LVAD

TABLE 2. POST-OHT PROCESS-OF-CARE VARIABLES[a]

Variable	Early infection (n=51)		No early infection (n=121)		p
Induction therapy					
None	16	(31.4)	34	(28.1)	
Basiliximab	28	(54.9)	68	(56.2)	0.889
Anti-thymocyte globulin	7	(13.7)	19	(15.7)	
CRRT	29	(56.9)	18	(14.9)	<0.001
Delayed chest closure	32	(62.7)	31	(25.6)	<0.001
ECMO	9	(17.6)	3	(2.5)	<0.001
Mechanical ventilation duration (d)[b]	5.27	(2.56–11.7)	1.68	(0.8–3.39)	<0.001

[a]All values presented as n (%) unless otherwise noted.
[b]Values presented as median (interquartile range).
CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation.

TABLE 3. ORGANISMS ISOLATED[a]

Gram negative 39 (58.2%)		Fungi 6 (9.0%)	
Enterobacter cloacae	9	Candida spp.	3
Escherichia coli	7	C. albicans	2
Klebsiella pneumonia	5	C. tropicalis	1
Serratia marcesens	5	Aspergillus fumigatus	1
Pseudomonas	4	Aspergillus niger	1
aeruginosa		Yeast (unspecified)	1
Haemophilus influenza	2		
Stenotrophomonas	2	Anaerobes 2 (3.0%)	
maltophilia		Clostridium difficile	2
Acinetobacter	1		
calcoaceticus-			
baumannii			
Citrobacter freundii	1		
Enterobacter sp	1		
Moraxella catarrhalis	1		
Prevotella oris	1		
Gram positive 20 (29.9%)			
Staphylococcus spp.	11		
S. aureus	8		
S. epidermidis	2		
S. lugdunensis	1		
Beta-hemolytic	1		
Streptococcus Group G			
Beta-hemolytic	1		
Streptococcus Group F			
Beta-hemolytic	1		
Streptococcus Group C			
Brevibacterium spp.	1		
Coryneform bacteria	1		
Enterococcus faecium	2		
Other Enterococcus spp.	1		
Cocci (no speciation)	1		

[a]Sixteen patients (31.4%) had polymicrobial cultures.

(AOR 2.53; 95% CI 1.015–6.286; p<0.046), pre-OHT ECMO (AOR 14.1; 95% CI 1.38–150.5; p=0.026), and post-OHT CRRT (AOR 3.98; 95% CI 1.67–9.52; p=0.002) were independent risk factors for an early infection (Table 5). Further analysis assessing the impact of a prior LVAD on the development of an infection was performed. No significant differences in the number of pneumonia, BSI, UTI, or wound infections were found in patients with and without a LVAD.

Discussion

This study provides insight into the characteristics of OHT recipients with an early infection. The incidence of early infection found in this study (29.7%) is lower than that in previous reports of infection within 30 days of heart transplantation (48.6%), likely due to the requirement of a positive culture for inclusion in our study [7]. Although gram-positive bacteria have been the primary cause of infections in this patient population historically, one study assessing more than 600 heart transplant recipients noted a *P. aeruginosa* infection rate as high as 43%, with the most common site of infection being the lungs (35%) [4]. Similarly, gram-negative organisms comprised the majority of the isolates in our study (58.2%), with the lungs being the most prevalent site of infection. Gram-positive infection still was prevalent (30%) followed by fungal infection (9%). Significantly, MDR pathogens were present in 47% of patients. Extended-spectrum ESBL-producing gram-negative organisms have been reported in 2.2% of heart transplant recipients [12], whereas we noted two ESBL infections (3.9%).

The median time to early infection was less than a week in our study, with lung infections prevailing at a median of five days and blood cultures at a median of 1.5 days. In fact, all patients but one met the infection criteria within 14 days of transplant, suggesting this is the most critical time period to prevent post-OHT infection. Montoya et al. [4] report median times for infectious episodes to be 28 days for mediastinal incisions, 48 days for bacteremia, and 65 days for pneumonia. The differences may be attributable to the large percentage of pre-OHT mechanical circulatory support in our study, as the infection risks in this patient population are well known.

Our mortality rate in the early post-transplantation period was less than 5% and was not different at one year, similar to the findings in other published reports [2,8]. Although the difference was not statistically significant, it should be recognized that the 30-day mortality rate was 4% in the infection cohort and 0.8% in the no-infection cohort. The likelihood of a Type II error in testing this difference is high. In addition, rejection and re-admission were similar in the two groups. Mechanical ventilation duration and LOS were longer in the infection cohort; however, it remains unknown whether this was a consequence of or a risk factor for infection. It is intuitive to think that patients with pneumonia will require longer mechanical ventilation. Likewise, patients with any

TABLE 4. OUTCOMES OF EARLY INFECTION COHORT VS. NO EARLY INFECTION COHORT[a]

Variable	Early infection (n=51)	No early infection (n=121)	p
Death			
Median time to death (days)[b]	41.6 (13.9–736.6)	470.3 (192.3–801.5)	0.230
At 1 y	3 (5.9)	6 (5.0)	0.726
At 30 d	2 (3.9)	1 (0.8)	0.210
Rejection <60 d	8 (15.7)	17 (14.0)	0.781
Post-OHT intensive care unit length of stay (d)[b]	14.2 (6.8– 21.2)	5.6 (3.9– 7.9)	<0.001
Post-OHT hospital length of stay (d) [b]	29.8 (17.7– 19.5)	14.7 (11.7– 19.5)	<0.001
30-d re-admission	17 (33.3)	42 (34.7)	0.862
Infection	7 (41.1)	13 (31.0)	
Other	10 (58.8)	29 (69.0)	

[a]All values presented as n (%) unless otherwise noted.
[b]Values presented as median (interquartile range).
OHT=orthotopic heart transplantation.

TABLE 5. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS
FOR PREDICTORS OF EARLY INFECTION

Variable	AOR (95% CI)	p
Pre-OHT LVAD	2.53 (1.015–6.286)	0.046
Pre-OHT LVAD with drive-line infection	1.16 (0.377–3.54)	0.799
Pre-OHT ECMO	14.40 (1.38–150.50)	0.026
Post-OHT ECMO	3.05 (0.587–15.80)	0.185
Post-OHT delayed chest closure	1.69 (0.697–4.09)	0.246
Post-OHT CRRT	3.98 (1.670–9.52)	0.002

Hosmer-Lemes p = 0.99.

AOR = adjusted odds ratio; CI = confidence interval; CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; LVAD = left-ventricular assist device; OHT = orthotopic heart transplantation.

infection may have a longer LOS, with the assumption that they have a greater severity of illness requiring longer treatment and monitoring. Regardless, we were unable to establish causality between these important factors.

Predictors of an early infection in our study included the use of mechanical circulatory support and the need for acute CRRT. Induction immunosuppression, renal replacement therapy, delayed chest closure, and the use of ECMO have been associated with a possible increase in the risk of fungal infections in OHT recipients [11,12]. However, these studies were small and do not addresses whether these factors place patients at risk for other bacterial infections [10,11,21] Previous LVAD-related infections have been noted to put patients at risk for more invasive infections after OHT, with continuous antimicrobial treatment before, during, and after transplantation being associated with fewer relapses [20]. In our study, more patients in the infection group had histories of drive-line infections, but this did not remain a predictor of infection by logistic regression analysis. This finding may suggest that the presence of an LVAD alone (with or without a previous infection) is a risk factor for post-OHT infection. Although delayed chest closure did not remain a predictor of infection in our study, it is worth noting that fungal infections occurred in only three of these patients, whereas gram-negative infections (72%) prevailed. The three patients with delayed chest closure who developed a fungal BSI (within 10–16 days) were all LVAD explants, with one receiving chronic suppressive antibiotics for a median of 80 weeks. Although this may be important, because of the limited number of fungal infections and study design limitations, we are unable to make definitive recommendations on anti-fungal prophylaxis. However, known risk factors for fungal infection, such as long-term receipt of antibiotics [22], should be considered when deciding on prophylaxis in this patient population. Regarding routine antibiotic prophylaxis, it is worth noting that in our study, 90% of the susceptibility panels for the gram-negative isolates showed resistance to our standard intra-operative and peri-operative prophylaxis cephalosporin, cefazolin. Accordingly, the median time to positive culture in this group experiencing resistance was less than two days. A broader-spectrum cephalosporin with adequate in vitro activity against the most common organisms cultured, such as cefepime, may be warranted in the early transplant period in these high-risk populations. Non-cephalosporin alternatives such as carbapenems

may be appropriate at centers with higher rates of ESBL-producing organisms. Likewise, centers with lower rates of AmpC-producing organisms may desire to use β-lactamase–inhibiting agents, such as piperacillin/tazobactam.

There are several limitations of this study. This was a retrospective cohort investigation and suffers from the potential biases inherent to this design. The interpretation of positive culture significance, therapeutic management, and patient outcome depends on the accuracy of the documentation. Additionally, patients treated for culture-negative sepsis or suspected clinical infections were not included. The majority of the positive cultures were identified during the patient's stay in the ICU, and the incidence and impact of an early positive culture outside of an ICU remains unknown. Furthermore, the frequency and timing of any previously treated infections was not assessed. It remains unknown if prior infections, outside of chronic drive-line infections, increased the risk of post-OHT infection in this study. In addition, the impact of nasogastric tube application and receipt of enteral nutrition on the occurrence of pneumonia infections could not be assessed. Finally, as this study was conducted at a single institution, the results may not be applicable to other institutions.

In conclusion, this study has provided additional descriptions of the OHT patient population with an infection in the early post-operative period. Gram-negative organisms accounted for the majority of isolates, with most common sites of infection being the lungs and blood. Although no statistically significant differences in overall mortality, rejection, or re-admission rates were seen, a longer LOS and duration of mechanical ventilation were found in patients with an early infection. The relative difference in the 30-day mortality rate may support a modified approach to preventing infection in higher-risk patients. Previous mechanical support and the need for acute CRRT may place heart transplant recipients at risk for an early infection. Evaluation of peri-operative antimicrobial prophylaxis duration and selection based on an individual center's resistance panels may be warranted in these patients.

Author Disclosure Statement

No competing financial interests exist.

References

1. Lund LH, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-First Official Adult Heart Transplant Report – 2014; Focus Theme: Retransplantation. J Heart Lung Trans 2014;3:996–1008.
2. Colvin M, Smith JM, Skeans MA, et al. OPTN/SRTR 2015 Annual Data Report: Heart. Am J Transplant 2017;17:286–356.
3. George JF, Pamboukian SV, Tallaj JA, et al. Balancing rejection and infection with respect to age, race, and gender: Clues acquired from 17 years of cardiac transplantation data. J Heart Lung Trans 2010;29:966–972.
4. Montoya JG, Giraldo LF, Efron B, et al. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis 2001;33:629–640.
5. Hsu RB, Chang CI, Fang CT, et al. Bloodstream infection in heart transplant recipients: 12 year-experience at a university hospital in Taiwan. Eur J Cardio-Thorac Surg 2011; 40:1362–1367.

6. Haddad F, Deuse T, Pham M, et al. Changing trends in infectious disease in heart transplantation. J Heart Lung Trans 2010;29:306–315.

7. Sanchez-Lazaro IJ, Almenar L, Blanes M, et al. Timing, etiology, and location of first infection in first year after heart transplantation. Transplant Proc 2010;42:3017–3019.

8. Van De Beek D, Kremers WK, Del Pozo JL, et al. Effect of infectious disease on outcome after heart transplantation. Mayo Clin Proc 2008;83:304–308.

9. Rostad CA, Wehrheim K, Kirklin JK, et al. Bacterial infections following pediatric heart transplantation: Epidemiology, risk factors, and outcomes. J Heart Lung Transplant 2017;36:996–1003.

10. Rabin AS, Givertz MM, Couper GS, et al. Risk factors for invasive fungal disease in heart transplant recipients. J Heart Lung Transplant. 2015;34:227–232.

11. Tissot F, Pascual M, Hullin R, et al. Impact of targeted antifungal prophylaxis in heart transplant recipients at high risk for early invasive fungal infection. Transplantation 2014;97:1192–1197.

12. Bui KT, Mehta S, Khu TH, et al. Extended spectrum β-lactamase-producing Enterobacteriaceae infection in heart and lung transplant recipients and in mechanical circulatory support recipients. Transplantation 2014;97:590–594.

13. International Classification of Diseases, Ninth Revision (ICD-9). Rockville, MD: National Center for Health Statistics. *Available at*: https://www.cdc.gov/nchs/icd/icd9.htm Accessed August 31, 2017.

14. HCUP Overview. Healthcare Cost and Utilization Project (HCUP). July 2017. Rockville, MD: Agency for Healthcare Research and Quality. *Available at*: www.hcup-us.ahrq.gov/overview.jsp Accessed August 31, 2017.

15. American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA). Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016; 63:e61–e111.

16. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America (IDSA). Clin Infect Dis 2010;50:625–663.

17. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–281.

18. Dunne WM, Hardin DJ. Use of several inducer and substrate antibiotic combinations in a disk approximation assay format to screen for ampC induction in patient isolates of *Pseudomonas aeruginosa*, *Enterobacter* spp., *Citrobacter* spp., and *Serratia* spp. J Clin Microbiol 2005;43:5945–5949.

19. Costanzo MR, Dipchand A, Startling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914–956.

20. Simon D, Fischer S, Grossman A, et al. Left ventricular assist device-related infection: Treatment and outcome. Clin Infect Dis 2005;40:1108–1115.

21. Uribe LG, Cortés JA, Granados CE, Montoya JG. Antifungal prophylaxis following heart transplantation: systematic review. Mycoses 2014;57:429–436.

22. Pappas PG, Kauffman CA, Andes D, et al.; Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;48:503–535.

Address correspondence to:
Dr. Kendall C. Shultes
Belmont University
College of Pharmacy
1900 Belmont Boulevard
Nashville, TN 37212-3757

E-mail: kcshultes06@gmail.com