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REVIEW ARTICLE

In Full Flow: Left Ventricular Assist Device Infections in the Modern Era

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With the rising prevalence of heart disease in the United States, there is increasing reliance on durable mechanical circulatory support (MCS) to treat patients with end-stage heart failure. Left ventricular assist devices (LVADs), the most common form of durable MCS, are implanted mechanical pumps that connect to an external power source through a transcutaneous driveline. First-generation LVADs were bulky, pulsatile pumps that were frequently complicated by infection. Second-generation LVADs have an improved design, though infection remains a common and serious complication due to the inherent nature of implanted MCS. Infections can affect any component of the LVAD, with driveline infections being the most common. LVAD infections carry significant morbidity and mortality for LVAD patients. Therefore, it is paramount for the multidisciplinary team of clinicians caring for these patients to be familiar with this complication. We review the epidemiology, prevention, diagnosis, treatment, and outcomes of LVAD infections.

Keywords. cardiac device infection; driveline infection; left ventricular assist device.

Heart failure affects 6.5 million adults in the United States. Definitive therapy with heart transplantation, however, is limited by donor availability and recipient candidacy, with only 3551 patients receiving heart transplants in 2019. Alternatively, durable mechanical circulatory support (MCS) is rapidly evolving (Figure 1) [1] and increasingly used as bridge to transplantation or as permanent destination therapy. Left ventricular assist devices (LVADs), the most common form of durable MCS, are implantable pumps that offload a failing left ventricle. LVADs connect to an external power source through a subcutaneously tunneled cable called a driveline, which typically exits the skin in the abdominal wall. The driveline exit site requires an overlying sterile dressing that is managed by the patient with routine dressing changes, thereby providing a portal of entry to the external environment. Bulky first-generation LVADs required the formation of a pump pocket in the peritoneal cavity and used pulsatile flow through bioprosthetic valves to emulate the heart's contractility. These pulsatile-flow LVADs had limited durability and a 52% 1-year survival [2] and are rarely used today. Second-generation LVADs aimed to reduce complications by simplifying the pump's components and transitioning from pulsatile to continuous flow with either axial or centrifugal pumps. The HeartMate II LVAD is the most encountered second-generation LVAD. Third-generation LVADs employ centrifugal flow and eliminate the use of metal bearings by using a magnetically suspended rotor. The HeartWare Ventricular Assist Device and the HeartMate III LVAD are the 2 third-generation devices currently approved for treatment of adults with heart failure in the United States (Figure 2).

With major advances in MCS technology over the last decade, survival after continuous-flow LVAD has consistently improved, currently at 81% at 1 year [1]. However, infection remains the most common LVAD complication, contributing to major morbidity and mortality post-LVAD. One in 6 patients will develop an LVAD-related infection within the first year postimplant [1], a rate that rises with duration of support. Infection is currently responsible for 7% [3] of all LVAD-related deaths in the first year and for 15% of LVAD deaths thereafter. Patients are being increasingly referred to infectious disease specialists, and management of LVAD infectious complications using a multidisciplinary approach is paramount. The purpose of this review is to further outline the epidemiology, prevention, diagnosis, and treatment of LVAD-related infections to raise awareness of an increasingly common clinical encounter for the infectious disease specialist.

Epidemiology and Risk Factors

Wide variability in LVAD infection definitions and institutional practices has limited the study of the epidemiology of LVAD infections. The most widely used definition of LVAD infection is "any infection that occurs in the presence of a VAD," set by

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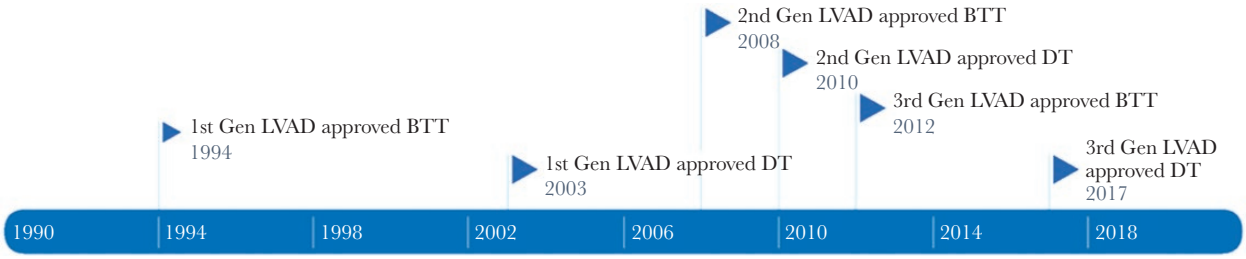

Generation	Details	Examples
First	Pulsatile flow through bioprosthetic valves; pump pocket in the peritoneal cavity	HeartMate XVE Novacor
Second	Continuous flow with either axial or centrifugal pumps; smaller pump with simplified components	HeartMate II (HMII, axial pump) VentrAssist (centrifugal pump)
Third	Magnetically suspended centrifugal rotor eliminates metal bearings	HeartWare (HVAD) HeartMate 3 (HM3)

Figure 1. Left ventricular assist device approval timeline. Each generation LVAD device is described, with examples of the devices most used, now or previously, in the United States. Abbreviations: BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device.

the International Society for Heart and Lung Transplantation (ISHLT). For pulsatile-flow devices, LVAD-related infection affected 42%–64% of patients [4] and resulted in 38% of all LVAD-related deaths [5]. Since the implementation of continuous-flow LVADs, infections occur in 19%–39% of recipients [6–9] and result in >10% of LVAD-related deaths. The higher frequency of infections in destination therapy as compared with bridge-to-transplant LVADs [6] suggests that incidence increases with longer LVAD support duration. Today, continuous-flow LVADs are almost exclusively used, and this review will henceforth focus on continuous-flow LVADs, which will be referred to as LVADs, unless pulsatile flow is otherwise specified.

LVAD infections may occur when an organism ascends the driveline, spreads hematogenously, or is directly inoculated at the time of implantation. Infections may occur at any component of the LVAD, with varying rate of infection risk across components (Figure 3) [4, 6–14]. Driveline infections (DLIs) are the most frequent LVAD infection overall and typically occur >30 days postimplantation, as do pump pocket infections (PPIs). Internal component and bloodstream infections are less frequent but most commonly occur in the immediate postoperative period (<30 days postimplantation). In the immediate postoperative period, LVAD recipients are particularly susceptible to hospital-acquired non-VAD infections, with respiratory, urinary tract, and *Clostridium difficile* infections outnumbering VAD-related infections [15].

Overall, DLIs affect 12%–35% of patients [6, 7, 13, 14]. The risk of DLI increases with duration of support and is not affected by location of the driveline exit site [16]. PPI occurs in 2%–10% of patients [6–8]. PPIs occurring in the first 30 days are likely caused by direct inoculation during the surgery, whereas later PPIs are usually an extension of precedent DLIs [7]. The pump pocket is a poorly vascularized space, and PPIs are more resistant to conservative management than DLIs. Modern LVADs require a much smaller pump pocket, and centrifugal pumps have eliminated the need for a pump pocket altogether.

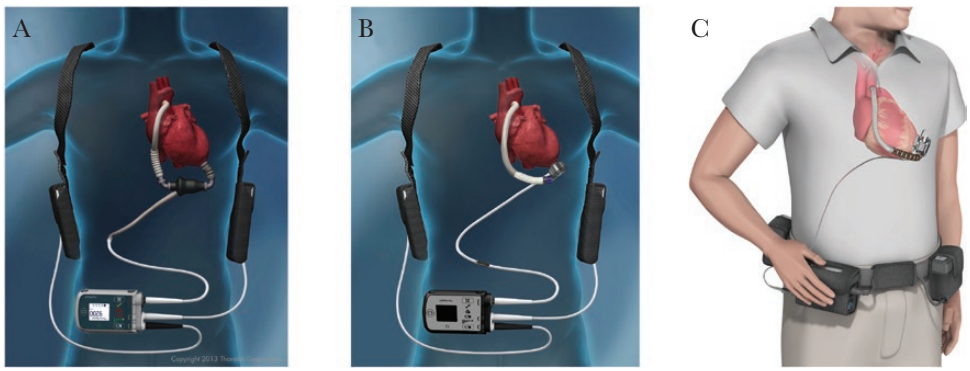

Figure 2. Most frequently encountered LVADs currently in use in the United States: (A) HeartMate II, (B) HeartMate III, and (C) HeartWare HVAD. Images of HeartMate 2 and HeartMate 3 are reproduced with permission from Abbott. Image of HeartWare is reproduced with permission from Medtronic, Inc.

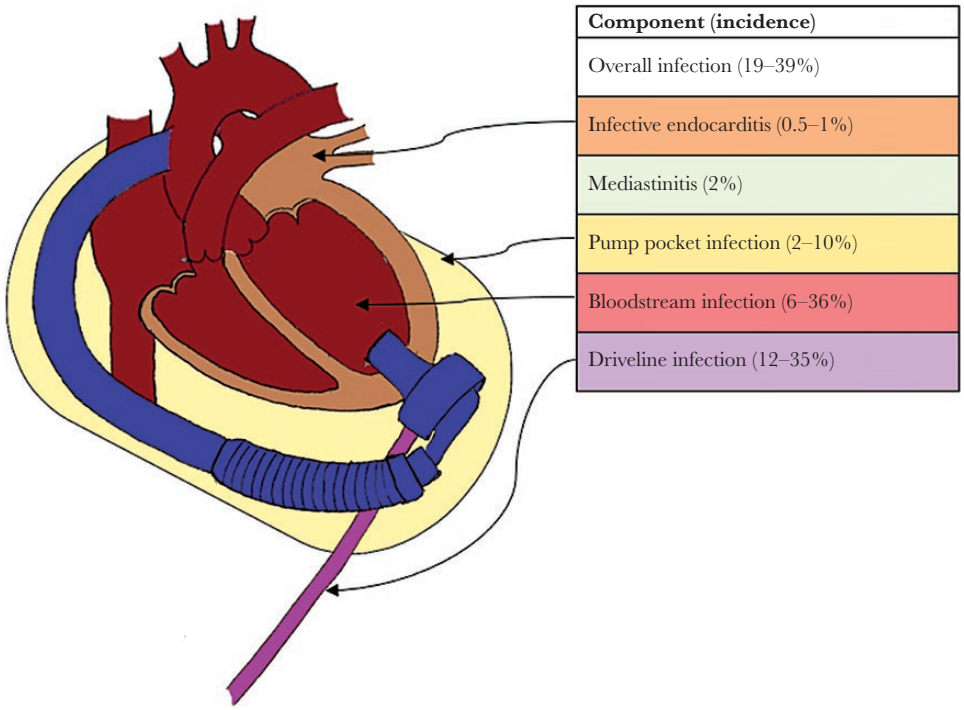

Figure 3. Potential infection sources in a patient with heart failure and left ventricular assist device, with component and range of reported infection incidence indicated.

Pump and central cannula infections and infective endocarditis are very rare (<1%) but are often fatal. The incidence of bloodstream infection (BSI) varies among studies, though BSI rates are lower in more recent publications as compared with older data, suggesting that this rate is decreasing [5, 17, 18]. Finally, mediastinitis affects 2% of LVAD patients, typically in the immediate postoperative period, with mortality as high as 53% [19].

Numerous studies have identified predisposing factors for LVAD infection. Elevated body mass index (BMI) is the most commonly cited independent predictor of infection [20, 21] followed by history of trauma to the driveline site [22], young age [12] (possibly due to increased risk of trauma to the driveline), and duration of LVAD therapy [13, 22]. Several studies have found implantation year to be a driver of infection [23] and survival [24], again suggesting that experience and advancements have improved outcomes over time. There are conflicting data regarding the association of LVAD infections and diabetes, renal disease, history of depression, vitamin D deficiency, and low albumin (as a surrogate for malnutrition). Gender and race do not appear to impact the rate of LVAD infections [25]. Predictors of fungal infections are much less studied; the use of parenteral nutrition, which is associated with fungal infections in other patient populations, may have been a risk factor in first-generation LVADs [26]. Finally, LVADs seem to alter host immunobiology and in turn may affect predisposition and response to infection [27].

Microbiology

The most common pathogens in LVAD infections are skin flora (often dismissed as colonizing flora or contaminants in other patient populations) and enteric bacteria. The most common pathogen in LVAD infections is *Staphylococcus aureus* (14%–56%), either methicillin-sensitive *S. aureus* (8%–43%), methicillin-resistant *S. aureus* (4%–30%), or unspecified. This is followed by coagulase-negative *Staphylococcus* (7%–56%), *Pseudomonas aeruginosa* (3%–28%), *Enterococcus* (5%–29%), and other gram-negative rods such as *Escherichia coli*, *Enterobacteriaceae*, and *Klebsiella* species. The incidence of infection by each organism varies by infection site (detailed in Table 1) [6, 7, 9, 11, 14, 23, 26, 28, 29]. Notably, polymicrobial infections are identified in over half of cases. Multidrug-resistant organisms are common in LVAD infections; patients with multidrug-resistant bacteria may have higher readmission rates but no significant difference in mortality or transplantation rates [30].

Fungal LVAD infections are less common [26, 29] but have significantly worse outcomes. Fungal infections occurred in 16%–33% of pulsatile-flow LVADs [31, 32] but affect only 2%–8% of newer-generation LVADs [7, 26, 29] likely due to a combination of improved surgical technique, advances in pump design, and implementation of perioperative antifungal prophylaxis [32, 33], though the utility of the latter has been

Table 1. Frequency of Bacterial (A) and Fungal (B) Pathogens in LVAD Infections as Percentage of Bacterial and Fungal Infections, Respectively

A, Reported Frequency of Bacterial Organisms Among Patients With Bacterial LVAD Infections				
Bacterial Pathogen	Reported Frequency, %			
	DLI	PPI	IE	BSI
Staphylococcus aureus	10–43	8–22	20–25	33
MSSA	4–30	11–25	8–21	0
MRSA	44–56	21	0	14
Unspecified				
Coagulase-negative *Staphylococcus*	7–29	17–50	21–40	33–56
Enterococci	5–15	11–26	8–29	8–17
Corynebacterium	2–14	2	8–20	0
Pseudomonas aeruginosa	4–28	3–25	17–20	3
Klebsiella species	2–13	5–7	7–8	5
Escherichia coli	1–4	5–11	0	0

B, Reported Frequency of Fungal Organisms Among Patients With Fungal LVAD Infections	
Fungal Pathogen	Reported Frequency, %
Candida albicans	28–45
C. glabrata	14–23
C. kruseii	14–19
Other *Candida* species	13
Aspergillus species	28

Data are listed as a range between the lowest and highest reported frequencies per pathogen [6, 7, 9, 11, 14, 23, 26, 28, 29].

Abbreviations: BSI, bloodstream infection; DLI, driveline infection; IE, infective endocarditis; LVAD, left ventricular assist device; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PPI, pump pocket infection.

questioned in the continuous-flow era. Fungemia in pulsatile-flow LVAD recipients was associated with a 71%–91% mortality rate [26, 34]. LVAD-related aspergillosis is particularly fatal, whereas some *Candida* spp. infections have been successfully treated [29, 34].

Prevention

Understanding the multifaceted strategies for preventing LVAD infections is important for infectious disease specialists, who play a fundamental role in preventing nosocomial infections and in choosing prophylactic regimens. Technological improvements have reduced infection rates, as newer LVADs have thinner drivelines and are substantially smaller, eliminating the need for an infection-prone pump pocket [35]. Improvement in surgical technique has substantially contributed to decreased infection rates [36]. For example, complete implantation of the driveline velour reduced DLIs by up to 50% [37], and increased tunneling of the driveline decreased LVAD infections by up to 86% [38]. Study of the efficacy of different antimicrobials is limited by the variability in prophylactic regimens, the selection of which should consider institutional resistance profiles and antimicrobial risk profiles. Generally, these include a beta-lactam and/or vancomycin (depending on the institutional prevalence of methicillin-resistant *S. aureus*) for gram-positive organisms, a cephalosporin and/or quinolone for gram-negative pathogens [14], and fluconazole for fungal prophylaxis [39]. A survey found that 43% of centers use a 4-drug regimen (3 antibiotics + fluconazole), 24% use a 3-drug regimen (3 antibiotics or 2 antibiotics + fluconazole), 24% use a 2-antibiotic regimen, and 9% use vancomycin only [40]. A single-center retrospective review found no differences in 1-year mortality or infection rates between single-drug and multidrug antibiotic prophylaxis for continuous-flow devices [41]. No significant differences in rate of infection have been demonstrated when comparing perioperative prophylaxis alone to lifelong prophylaxis [42]. Similarly, extended antifungal prophylaxis does not seem to improve outcomes, significantly increases cost, and can induce drug resistance and precipitate a shift toward more aggressive fungal species [43]. Therefore, some centers advocate for limiting systemic fungal prophylaxis to the immediate perioperative period, whereas others have eliminated it altogether [33]. Our institution uses single-drug prophylaxis with cefazolin, with the addition of vancomycin in patients colonized with methicillin-resistant *S. aureus*, for the 24-hour perioperative period when the risk of bacteremia and device seeding are greatest.

Infection prevention is fundamental in the outpatient setting as well, as the majority of LVAD infections occur months after implantation. Driveline trauma provides a portal of entry for infection, and the use of an anchoring device to secure the driveline reduces the risk of infection by minimizing shearing of the tissue barrier at the driveline exit site [44]. Appropriate driveline care, such as scrubbing with chlorhexidine during dressing changes, is critical in preventing infections. Topical antibiotic prophylaxis may also reduce infections [45] at the risk of perpetuating resistance and is therefore not standard practice. Daily vs every-few-days dressing changes have comparable infection rates [46], and weekly dressing changes, extrapolated from Joint Commission requirements for central

line care, are now standard [47]. The choice of cleaning agent is also important: Chlorhexidine is preferred due to lower rates of DLI as compared with povidone-iodine solution (10.3% vs 60.0%) [48]. Attempts to reduce the incidence of *Pseudomonas aeruginosa* by prohibiting conventional showering to preserve dressing integrity did not find any difference in outcomes [49].

Diagnosis

Patients with LVAD infections may present with inflammation and drainage at the driveline site, systemic signs of infection, or septic physiology that may be reflected in hemodynamic changes in LVAD parameters on device interrogation. The ISHLT categorizes infections as VAD-specific (DLI, PPI, and cannula infection) and VAD-related (endocarditis, bloodstream infection, and mediastinitis) [10, 50]. They further subdivide DLIs into superficial and deep infections. Superficial DLIs spare the fascia and muscle layers, whereas deep DLIs involve these deeper tissues and are more frequently associated with fever or systemic signs of infection. Diagnostic criteria vary by infection site but generally require microbiology data, histologic features, and clinical or radiologic evidence of infection [10]. Blood cultures are essential in ruling out a bloodstream infection, and superficial driveline cultures should be sent in cases of purulent drainage. A white blood cell count should be obtained for all patients, and chest radiography and urine studies may be indicated based on symptoms in patients with VAD-related infections. When internal component infection or endocarditis is suspected, 4 sets of blood cultures and visualization with transesophageal echocardiography are preferable [15].

Several radiologic studies play a role in LVAD infection diagnosis. Ultrasonography may be used to identify a superficial fluid collection or abscess around the driveline. Computerized tomography (CT) can identify superficial or deeper driveline involvement. The sensitivity and specificity of CT imaging for diagnosing LVAD infection are poorly established due to the lack of a comparative gold standard; however, some key features concerning for infection on CT imaging include abscess formation and fat stranding. Indolent bacterial organisms, including coagulase-negative *Staphylococcus* and *Corynebacterium* species, may not cause CT changes and therefore result in false-negative imaging. Recently, positron emission tomography (PET) has emerged as one of the most sensitive and specific imaging modalities for the detection of LVAD infections, outperforming both conventional CT [51] and leukocyte-labeled scintigraphy [52]. The sensitivity and specificity of combined PET/CT may be as high as 90%–95% and 67%–71%, respectively [52, 53], though their availability, cost, radiation exposure, and the rate of false-positive images due to inflammation from recent surgical procedures preclude routine use.

Treatment

In 2017, the ISHLT released guidelines for MCS infection management (Table 2) [50]. Intravenous antibiotics should be used for patients with superficial DLIs with evidence of systemic illness or as initial therapy for any infection other than superficial DLI. The choice of empiric antimicrobial remains institution-dependent, typically covering skin flora and enteric bacteria based on local susceptibility patterns; however, therapy should be based on cultures and susceptibility data when feasible. As many as two-thirds of LVAD infection pathogens are multidrug-resistant, and these patients have higher rates of hospitalization and increased length of stay [30]. Furthermore, many LVAD pathogens produce biofilm, which increases virulence, eases migration along the driveline [54], provides physical protection from the host immune response, and facilitates the transfer of antibiotic resistance genes. Biofilm-producing organisms are therefore harder to eradicate and more likely to cause chronic infections. Therefore, the current recommendation for 2 weeks of intravenous or oral antibiotic therapy for superficial infections (affecting soft tissue outside the fascia and muscle layers) may overestimate clearance rates due to the lack of a radiographic or microbiologic test of cure. In fact, up to 50% of patients with DLI without bacteremia relapse if long-term antimicrobial suppression is not used [55], and intractable infections may more than double mortality when compared with patients whose infections cleared (67% vs 29%) [56]. Some authors have therefore recommended extending antibiotics up to and for a few weeks following heart transplantation [15]. In patients with destination therapy LVADs, the decision to pursue oral antibiotic suppressive therapy, either lifelong in destination therapy LVADs or until transplantation in bridge-to-transplant LVADs, requires careful consideration of the risks of relapse vs the negative impact of prolonged antibiotic use. Relapse risk assessment should include whether relapse has previously occurred, the organism's potential for biofilm formation, radiographic imaging to determine the extent and location of the hardware compromised by infection, and whether debridement was performed. Extended antibiotic therapy places these patients at risk of antibiotic drug resistance, secondary infections, antibiotic toxicity/side effects, and *Clostridium difficile* infection [15]. When a biofilm-producing pathogen is suspected, it may be reasonable to consider additional treatment with antibiofilm antibiotics like rifampin, which have shown benefit when used in other biofilm-related infections [57]. Notably, rifampin is a potent inducer of the CYP3A4 system, and therefore increases warfarin metabolism, often requiring higher doses of warfarin to maintain a therapeutic INR, which is of utmost importance to prevent pump thrombosis in LVAD patients. Documenting exam findings with photographs of the driveline site is often helpful in monitoring treatment. Eradication of fungal LVAD infections is particularly challenging and relies on guidelines for fungal endocarditis treatment, including combined therapy with multiple antifungal agents [33].

Deeper or recurrent infections should prompt consultation for surgical debridement. In most devices, the driveline and

Table 2. Summary of ISHLT 2017 Recommendations for the Medical and Surgical Management of LVAD Infections [50]

	Infection	Medical Management	Surgical Management
LVAD-specific	Superficial DLI	IV/PO antibiotics for 2 weeks or until infection resolves	None
	Deep DLI/PPI	IV antibiotics for 6–8 weeks or until infection resolves followed by long-term PO suppression	Surgical debridement with or without wound vacuum; new driveline exit site may be required
	Pump, cannula, or Bacteremia	IV antibiotics until after heart transplant or an extended course followed by PO suppression (destination therapy); ID consult is advised	Surgical drainage, debridement, or explant may be required; urgent device replacement should be considered in bridge to transplant to prevent end-organ damage that may preclude heart transplant
LVAD-related	Bacteremia	Duration of antibiotics depends on the source, organism, and clearance, at least 2 weeks from first negative blood cultures	
	Bacterial mediastinitis	Antibiotics for at least 6–8 weeks from last surgical debridement	Surgical debridement is often indicated
	Infective endocarditis	Same as for pump and cannula infection	Surgical intervention may be required

Abbreviations: BSI, bloodstream infection; DLI, driveline infection; ID, infectious disease; IE, infective endocarditis; IV, intravenous; LVAD, left ventricular assist device; PO, oral; PPI, pump pocket infection.

pump form a single unit, and isolated driveline exchange is not possible. However, the new HeartMate3 features a modular driveline that may be exchanged to cure difficult-to-treat infections, though experience with this device is still limited. Device exchange is rarely performed, as it requires removal of the entire LVAD (inflow cannula, motor, outflow graft, and driveline) and the ability to temporarily provide cardiac support to allow recovery from infection before either device replacement or heart transplantation. Heart transplant candidates can gain a higher waitlist status priority based on the presence and severity of LVAD infection. Heart transplantation is often curative of LVAD infection, and these patients have similar long-term outcomes as patients without a history of LVAD infection [58]. Cardiovascular implantable electronic devices (CIEDs) such as defibrillators and pacemakers are commonly left in place after LVAD implantation but may serve as infectious foci. The incidence of CIED infection following LVAD infection is not well studied; however, CIED removal is generally recommended in cases of primary CIED infection due to the high mortality rate [59]. Some centers have successfully utilized alternative therapies such as platelet gel, a thrombin-enriched platelet coagulum, for the prevention [60] and treatment of resistant infections [61]. The recent success of bacteriophage therapy as adjunctive treatment with antibiotics for a patient with mediastinitis and bacteremia suggests that this may be a promising treatment option in cases of severe infection in patients not eligible for heart transplantation [62].

Outcomes

The presence of hardware, production of biofilm by common pathogens, and possible immune dysregulations of LVAD patients are some of the factors complicating the successful treatment of LVAD infection. As many as one-third of patients with driveline infection may fail initial therapy [63], with similar rates of recurrence in the subgroup who undergo device exchange [64]. Patients with driveline infections are at risk for worsening infection—as many as 87.5% of PPIs [65], and up to half of BSIs are due to preceding DLIs [66].

There is contradicting evidence regarding the impact of LVAD infections on mortality. The majority of studies examining LVAD infections as a whole found no overall impact on mortality or post-transplant survival [6, 58, 67]; however, certain subtypes of LVAD infections, such as BSI and endocarditis—and in some studies even DLI and PPI—may be associated with increased mortality [8, 22, 68]. Furthermore, BSI in LVAD patients is associated with an up to 8-fold increase in the incidence of stroke, with greatest stroke risk immediately after the onset of bacteremia [69, 70]. There is a particularly notable risk of hemorrhagic stroke, up to 20-fold higher than in patients without bacteremia, partly due to the elevated risk of conversion of thromboembolic stroke in the setting of anticoagulation. LVAD infections may preclude a patient from undergoing transplant, and some studies have shown that LVAD patients with BSI have a lower rate of undergoing transplantation (31.8% vs 81.1%; $P = .01$) [71]. The impact of LVAD infection on mortality persists long after heart transplantation (47.5% vs 27.8% 10-year survival) [72]. Interestingly, there is a higher rate of post-transplant infections in LVAD patients with and without known pretransplant DLIs as compared with non-LVAD patients who undergo transplantation [73, 74] possibly due to activation of occult pretransplant infections in the setting of post-transplant immunosuppression. This should be considered when choosing postoperative antibiotic prophylaxis for patients with a history of LVAD infection who undergo cardiac transplantation.

Additionally, LVAD-related infections result in increased health care utilization, with an incremental increase in implantation cost of $37 721 for patients who develop LVAD infections [75]. LVAD-related infections increase hospital length of stay and are the leading cause for readmission in LVAD patients [76].

CONCLUSIONS

The rising prevalence of heart failure and limited ability to transplant patients have resulted in increased use of mechanical circulatory support, namely LVADs, and have increased the duration of LVAD support. LVAD-related infection is the most common complication of long-term LVAD support. The LVAD driveline remains exposed to the external environment and is consequently the most common site of LVAD infection. Typical pathogens are gram-positive skin flora and enteric gram-negative organisms. Device and driveline modifications have likely helped reduce rates of infection, though increasing experience and knowledge-sharing have undoubtedly played a significant role as well. LVAD-related infections increase health care costs and utilization and may increase mortality. Recent publication of large society guidelines, such as those by the ISHLT, aim to improve outcomes in LVAD infections, though complete standardization in practice is challenging given the variability in pathogens across institutions. Management of these patients requires a multidisciplinary coordinated effort between cardiologists, cardiothoracic surgeons, LVAD nurse coordinators, and infectious disease specialists with involvement from patients and caregivers. Ongoing clinical and research efforts are needed to further elucidate the most effective methods for prevention and treatment of infection in this rapidly expanding high-risk population.

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