

Left ventricular assist device driveline infections: recent advances and future goals

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Abstract: Left ventricular assist devices (LVADs) have revolutionized the treatment of advanced heart failure, but infection remains a substantial risk. LVAD driveline infections (DLIs) are the most common type of LVAD-associated infection (LVADI). In the past several years we have expanded our understanding of DLI epidemiology, standardized the definition of LVADIs, improved infection rates through changes in implantation techniques, and investigated potential new modalities for DLI diagnosis. However, significant challenges remain for optimizing DLI prevention and treatment. These challenges include standardizing and improving both empiric and targeted antimicrobial therapy, expanding our understanding of effective driveline exit site dressings and topical therapies, and defining the patient population that benefits from device exchange and transplant. Additionally, in an era of expanding antibiotic resistance we need to continue investigating novel, non-antibiotic therapies for prevention and treatment of DLIs.

Keywords: Device-related infection; left ventricular assist devices (LVADs); driveline infections (DLIs); biofilm

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Introduction

Left ventricular assist devices (LVADs) have revolutionized the treatment of advanced heart failure, but infection remains a substantial risk. Although LVAD technology continues to advance rapidly, all current devices still require an external power source with energy supplied via a tunneled percutaneous driveline. Driveline infections (DLIs) are the most common type of LVAD-associated infection (LVADI). DLIs occur frequently because the driveline exit site creates a conduit for entry of bacteria and the prosthetic material of the driveline creates an ideal environment for the formation of bacterial biofilms (1). DLI, along with gastrointestinal bleeding (GIB) and stroke, are the leading causes of unplanned readmission for patients with LVADs, with a median direct hospital cost of more than \$7,000 per readmission (2).

The prevalence of LVAD complications, including infection, is increasing as use of LVADs has expanded from short-term use as a bridge to transplantation (BTT) to also

include long-term destination therapy (DT) in patients who are not eligible for transplant (3). Several recent reviews and retrospective studies have outlined the epidemiology and broad treatment approach for LVADIs (1,4-7). This review will focus on recent advances and persisting knowledge gaps related to diagnosis, specific treatments, and prevention of DLIs in adults.

Definitions and rates of infection

Definitions

In 2011, the International Society for Heart and Lung Transplantation (ISHLT) proposed consensus guidelines for the definition of LVADIs. Within the ISHLT definition, LVAD DLIs can be divided into deep and superficial infections. Both infections involve the soft tissue surrounding the driveline exit site and are accompanied by erythema, increase in temperature around the site, and purulent drainage. Deep infections also include the fascia

and muscle layers (8). Since the exact extent of infection can often only be determined during surgical exploration, the distinction between superficial and deep infection is of limited utility in clinical care. Additionally, differentiating DLI from pump pocket infection, which is infection involving the body cavity that holds the LVAD pump, can also be difficult in the absence of surgical investigation.

Rates of infection

Incidence and prevalence of DLIs vary greatly between studies depending on the population evaluated and definitions used. In their 2011 review, Pereda and Conte note a range in DLI incidence of 14-48% in a sample of studies published from 2004 to 2010 (1). One difficulty in defining the epidemiology of DLIs has been the small sample size of most studies. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) allows for evaluation of larger patient cohorts involving multiple institutions. Using INTERMACS, Goldstein *et al.* evaluated 2,006 LVAD recipients who had a continuous-flow LVAD implanted from June 2006 to September 2010 and found a 19% prevalence of DLI 12 months after implantation (6).

More recent studies have attempted to go beyond incidence rates and evaluate risk factors for DLI, including age. Advanced age does not appear to be a risk factor for DLI with a recent study showing no difference in infection rates in patients over and under age 65 (9). However, younger age was actually found to be the only risk factor for DLI in a multivariate analysis by Goldstein *et al.* This finding is thought to be due to higher activity rates, and therefore increased risk for driveline exit site trauma, in the younger population (6). Trauma has previously been identified as a risk factor for subsequent DLI (10).

Diagnosis

Diagnosis of a DLI usually occurs when the patient, caregiver, or provider notes erythema, warmth, or purulent drainage around the driveline exit site. However, determining whether the infection is limited to the driveline exit site or involves deeper structures is difficult. There are no specific guidelines for the use of imaging to assess the extent of infection after diagnosis of a DLI. Ultrasound can detect fluid pockets but otherwise gives little information about whether structures are infected. Additionally, computed tomography (CT) is of limited utility given the

artifact caused by the device (11).

Due to the limitations of standard imaging techniques, more advanced imaging options have been considered for evaluation of DLIs. One case series found that gallium single photon emission tomography-CT (SPECT-CT) may elucidate the extent of LVAD structures involved after diagnosis of DLI and help to inform decisions related to need for device exchange (11). However, it should be noted that previous publications have questioned the sensitivity of this imaging modality since inflamed but uninfected tissue might be misidentified as infection (3). Positron emission tomography (PET)-CT is also undergoing investigation as an imaging modality for LVADI and was useful in identifying infection of LVAD components and response to therapy (12,13). PET-CT may also reveal unsuspected distant sites of infection such as paravertebral abscess (12). Given the prolonged bacteremia that often accompanies DLIs, especially with pathogens such as *Staphylococcus aureus* or *Pseudomonas aeruginosa*, evaluation for metastatic sites of infection can be crucial.

Pathogens

The pathogens involved in cases of LVAD DLI are predominantly skin organisms, including *S. aureus*, coagulase negative staphylococci and *Corynebacterium spp.* However, *P. aeruginosa* and Enterobacteriaceae are also frequently isolated, with *Candida* found as a less frequent pathogen (14). Nienaber *et al.* evaluated pathogens implicated in local infections (which included DLI, pump pocket infections, cardiovascular implantable electronic device pocket infections, and mediastinitis without bloodstream infection) and found that the most common pathogens isolated were Gram-positive cocci (44.8%) and Gram-negative rods (24.1%) (4).

Polymicrobial infections are also common and may involve multi-drug resistant organisms. In one published case of a progressive polymicrobial infection with methicillin resistant *S. aureus* (MRSA) and an extended spectrum beta lactamase *Erwinia*, the patient was eventually treated with pump exchange with no recurrence of infection after 1 year (15). As our understanding of DLI evolution progresses, it is becoming apparent that polymicrobial infections often occur due to superinfection of an existing infected driveline site while a patient remains on suppressive therapy for the initial pathogen. In these cases, *P. aeruginosa* is one of the most common secondary pathogens (16).

Additionally, it is often difficult to distinguish commensal

skin organisms from true pathogens. In a recent example, a *Staphylococcus epidermidis* DLI was initially suspected, but allergy to an e-polytetrafluoroethylene membrane used during surgery was ultimately identified as the likely cause of the patient's purulent fluid collections (17).

Pathogenesis

The LVAD driveline provides an ideal surface for the formation of biofilms due to its high surface area, and biofilm formation has been well demonstrated in a murine model of staphylococcal DLI (18). Biofilms are also thought to be involved in the pathogenesis of DLIs due to other biofilm-forming organisms such as *P. aeruginosa*, *Candida spp.*, and *Enterococcus spp.*

Biofilms occur when bacteria adhere to a surface and form microcolonies embedded in an extracellular polymeric substance known as matrix. In this environment, the actual organisms may account for as little as 10% of the biomass of the biofilm, with the remainder of the biofilm biomass comprised of matrix. The composition of the matrix varies from species to species and can protect the bacterial cells from the host's immune system and prevent penetration of antibiotics (19). These factors make antibiotic selection particularly important in the treatment of DLIs.

Treatment

Guidelines

No comprehensive guidelines for treatment of LVADIs exist to date, though general guidelines for treatment duration proposed by Nienaber *et al.* suggest 2-4 weeks of antimicrobial therapy with or without surgical debridement for DLI. Suppressive antibiotics are not suggested for isolated DLI but should be considered if pump pocket infection is suspected (4). Current guidelines do not address choice of empiric or targeted antimicrobial therapy for LVAD DLIs.

Empiric therapy

For any suspected DLI, a culture of the site should be obtained and empiric therapy started while awaiting results. The best empiric therapy for DLIs has not been established. For early localized infection, oral antibiotics are often used (4). There is no standard definition for early localized infection, but it is generally described as drainage

or inflammation around the driveline exit site without systemic symptoms or concern for underlying abscess. The current recommended empiric antibiotic choice for these early infections at the University of Minnesota is doxycycline 100 mg BID for 14 days with antibiotic choice adjusted as needed based on culture results. Another published regimen includes ciprofloxacin 500 mg BID and doxycycline 100 mg PO BID for 10 days (20). For more extensive local infections or when systemic symptoms are present, patients are admitted to the hospital for monitoring, imaging, and broad-spectrum antibiotics while awaiting culture results.

Targeted therapy

When the pathogen(s) responsible for a DLI are identified, empiric antibiotics can be changed to targeted therapy. However, multiple options are often available and antibiotic choice is currently guided by reports of anecdotal success rather than rigorous evidence. For example, several oral antibiotics might be chosen for a superficial MRSA DLI and an equal number of choices exist if intravenous therapy is used. While the potential benefits of certain antibiotic choices can be extrapolated from literature pertaining to other biofilm-related infections, such as osteoarticular infections with retained hardware, significant differences exist between the surfaces involved in those infections and the driveline exit site (21). Despite the growing base of literature around LVADIs, specific guidance for antibiotic choice is currently lacking.

This absence of evidence is particularly perplexing when rifampin is considered as part of a treatment regimen. Rifampin is a bactericidal antibiotic that can penetrate and eradicate biofilms (22). It can be used only as adjunctive therapy with another antibiotic due to potential for development of resistance, but it demonstrates synergy with many common antibiotics making it an appealing addition to therapy for DLIs (23). However, rifampin interacts with warfarin and causes significant INR instability leading to complications such as GIB and CVA (23). To date, neither the bleeding risks nor the potential treatment benefits of rifampin have been studied in patients with LVADIs. However, it is known that infection is a risk factor for GIB in patients with LVADs (24). Additionally, persistent bloodstream infection in patients with LVADs has been associated with all-cause CVA (25). Therefore, defining the risk and benefits of rifampin use in this population is especially important.

Suppressive therapy

Suppressive antimicrobial therapy in LVADs is often used in cases of extensive or recurrent infection. In fact, Nienaber *et al.* found that 35% of patients with local infections received suppressive oral antimicrobials (4). However, the risks and benefits of suppression remain unclear. In one oft-cited small study, 5/16 (31%) of patients treated with chronic antimicrobials experienced clinical failure. The study could not draw any firm conclusions due to the small sample size (26). Therefore, evidence to date is insufficient to guide therapy choices.

Device exchange

Device exchange can be used to achieve source control in otherwise intractable DLIs, and 0.6-11% of device exchanges are performed for infection. While one study showed that 6.5% of patients who undergo pump exchange die within 30 days, another showed no difference in mortality between the exchange and non-exchange group (27,28). A recent case series and review of the literature found that data remain limited regarding successful approaches and outcomes for device exchange due to the differences in pathogens, patient characteristics, and approach to management among published cases (29). While device exchange should remain a consideration for difficult infections, larger studies of patients undergoing exchange would help to guide which patients should be offered device exchange, the utility of interventions such as antibiotic impregnated beads, and the ideal use of antibiotics after the procedure.

Similarly, transplant can be used to cure DLIs. In a 2015 study of patients with active DLI at the time of transplant there was no difference found in length of hospital stay, infections, or mortality after 30 months (30). The safety of transplant in patients with poorly controlled infections is unclear, though there are reported cases of good outcomes in these settings (31).

Alternative therapies

The frequent failure of traditional antibiotics to control DLIs has resulted in renewed interest in alternative therapies. Many of the proposed treatment modalities are those currently used in chronic wound management. Some, such as medical grade honey and topical antibiotics are used despite lack of evidence for efficacy in this patient group.

Others are currently under investigation. Ultraviolet B (UVB) radiation has been used in chronic wound therapy but not at the driveline exit site due to concerns about effects of UVB on driveline materials. A recent *in vitro* pilot study suggested that UVB therapy may change the elasticity of the HeartMate II driveline materials but that this change may not be detrimental, which is encouraging as a future avenue of investigation (32). Investigations of UVB as well as other alternative therapies are valuable since these therapies often avoid complications such as antibiotic resistance, medication interactions, and *Clostridium difficile* infection that can occur with ongoing use of traditional antibiotics.

Prevention

Implantation method and device type

Infection rates may differ between VAD device types, although this has not been shown definitively. A single retrospective observational study of patients receiving an LVAD as BTT by Haglund *et al.* demonstrated a 17% readmission rate for DLI among HeartMate II recipients *vs.* a 2% readmission rate for HeartWare HVAD recipients (P=0.03). However, the small sample size (n=81) and the retrospective study design suggest that further investigation is needed to confirm these findings (20). Another recent study showed a DLI rate of 0.25 events per patient-year for the HeartWare HVAD (33). One potential advantage of the HVAD is its smaller driveline diameter since a smaller diameter is thought to be associated with lower infection rates (1,33).

There are ongoing efforts to optimize driveline implantation techniques with the goal of decreasing DLIs (34-36). One promising study by Dean *et al.* compared DLI rates in patients with the Dacron velour portion of the HeartMate II driveline either partially exposed (control group) or entirely implanted under the skin (silicone-skin interface group). Their results showed 1 year DLI prevalence rates of 9% in the silicone-skin interface group *vs.* 23% in the control group (37). However, the ideal length of non-Dacron coated silicone to internalize remains unclear (38).

Nutrition

Nutrition has also emerged as a possible predictor of DLI requiring admission. In a study by Imamura *et al.*, serum albumin concentration and low body mass index at hospital discharge after LVAD implantation both independently

predicted readmission due to DLI. Based on these findings, the authors developed a scoring system that risk-stratifies patients as low, intermediate, or high risk for DLI requiring admission based on these two parameters. While this study was limited by its design as a single center retrospective study, these findings suggest that optimizing nutrition for patients with recently implanted devices may help to prevent admission due to DLI (39).

Driveline dressings

Typically, the driveline exit site is cleansed with an antiseptic agent such as chlorhexidine, hydrogen peroxide, or povidone-iodine and dressed in a sterile fashion either daily or weekly. The site is then usually stabilized with a driveline securement device. There is currently no standard protocol for changing driveline dressings, although an effort is being made to evaluate the convenience and efficacy of ready-made dressing kits (40). A small 2015 study showed no difference between daily and weekly dressing changes in a prospective trial, but the study was significantly limited because patients were only followed for 30 days after hospital discharge (41).

In another recent study, driveline exit sites were dressed with octenidine with or without the addition of merbromin in a non-blinded study. Over 2 years the merbromin group had no patients with DLI *vs.* 11.8% of patients in the standard group developing infections (42). This study suggests that we would benefit from closer evaluation of driveline exit site maintenance and alternative dressing strategies as an easy and effective method to reduce or prevent DLIs.

Conclusions

Our understanding of LVAD DLI epidemiology and evolution has improved in recent years. Additionally, initial strides have been taken to optimize LVAD implantation techniques and adjust driveline exit site maintenance as methods for DLI prevention. However, further studies are urgently needed to define evidence-based treatment of these infections including choice of biofilm-active antibiotic regimens, necessity of device exchange, and utility of suppressive antibiotics.

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