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Chapter 3

LEFT VENTRICULAR ASSIST DEVICE INFECTIONS: A PRACTICAL APPROACH

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ABSTRACT

Left ventricular assist devices (LVADs) have become a standard treatment modality for the management of end-stage heart failure, either as a bridge to cardiac transplantation or as destination therapy. Infection is a

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frequent complication in up to one-third of LVAD recipients. Although the epidemiology of LVAD infections has been well-described, strategies for prevention, diagnosis, and management of these infectious complications remain controversial and vary among institutions. The goals of this review are to provide the infectious diseases practitioner with a brief introduction to the general anatomy and physiology of an LVAD, pre-implantation infectious disease management guidance, and an understanding of the epidemiology and pathophysiology of LVAD infections. We address methods for the diagnosis and characterization of these infections and suggest medical and surgical approaches for management.

Keywords: LVAD infection, left ventricular assist device infection, driveline infection

AN INTRODUCTION TO THE LVAD FOR THE INFECTIOUS DISEASES CLINICIAN

The left ventricular assist device, or LVAD, was approved by the United States Food and Drug Administration in 1994 as a bridge to cardiac transplantation [1], and various models have been shown to improve 24-month survival [2], 6-minute walk [3], and heart failure class [4]. Typical indications include ischemic cardiomyopathy (usually due to coronary artery disease and/or a history of myocardial infarction), nonischemic cardiomyopathies (such as postpartum, chemotherapy-induced, Chagas disease, familial, or idiopathic), and intractable arrhythmias refractory to other therapies [5]. These patients are also typically maximized on medical therapy, and may require continuous infusions of inotropes, intra-aortic balloon pumps, or possibly extracorporeal circulatory support devices.

Candidates for an LVAD typically have an advanced heart failure class (New York Heart Association class III or IV) with a low ejection fraction, and are anticipated to have high 1-2 year mortality. Patients who are candidates for an orthotopic heart transplant (OHT) but who are too ill to survive until transplantation may receive an LVAD as a bridge to transplant (BTT). Those who have irreversible exclusions from an OHT, which may be due to medical comorbidities (e.g., malignancy, cirrhosis, pulmonary

hypertension) or other issues may be considered for destination therapy (DT). Those with a potentially reversible condition, such as kidney disease, obesity, or deconditioning may receive an LVAD as a bridge to decision (BTD).

The most common models in use in the United States are the HeartWare HVAD [6], the Thoratec HeartMate II (HMII) [3], and the Thoratec HeartMate 3 (HM3) [7, 8]. All devices are comprised of an inflow cannula implanted into the apex of the left ventricle, a centrifugal (HVAD/HM 3) or an axial-flow pump (HM II), and an outflow graft anastomosed to the ascending aorta (Figures 1a, 1b). Power is provided from a portable battery and controller via a driveline tunneled through the abdominal wall (Figure 1c). This driveline provides the major portal of entry for many LVAD-associated infections. The proximal portion of the driveline is coated with a velour surface to promote integration into the subcutaneous tissues, whereas the distal portion exiting through the abdominal wall is covered in silicone.

INFECTIOUS DISEASES SCREENING BEFORE LVAD IMPLANTATION

In our institution, patients who are candidates for LVADs receive the same evaluation as those being evaluated for OHT, since a patient's candidacy for an OHT may go back and forth from DT to BTT. Our evaluation is mostly protocol-driven and based on published guidelines [9]. The potential recipient is tested for HIV, hepatitis B and C, herpes simplex viruses 1 and 2, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, toxoplasmosis, syphilis, and tuberculosis. Immunity to measles, mumps, and rubella is also checked to determine whether the patient needs a booster vaccination. Latent tuberculosis is typically treated as per published guidelines [10].

The infectious diseases consultant is most helpful in obtaining a detailed history of exposure and travel. This may reveal risk factors for latent endemic mycoses (such as those caused by *Histoplasma*, *Blastomyces*, and

Coccidioides) and parasites (especially *Strongyloides*, and also *Trypanosoma cruzi* in recipients from endemic areas). The presence of pets at home may reveal risk factors for zoonotic infections, should the patient ultimately receive an OHT, such as *Salmonella* in the case of reptiles or amphibians at home, or *Cryptococcus* in the case of psitaccine birds [11].

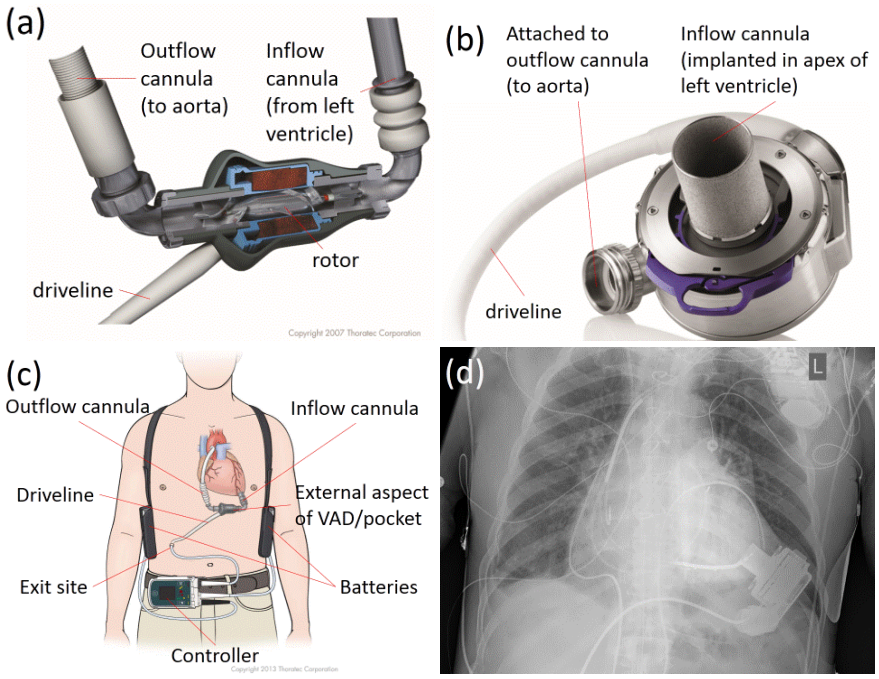

Figure 1. (a) Cutaway view of the HeartMate II LVAD (b) The HeartMate 3 LVAD (c) Schematic of LVAD as worn by a patient. Images provided courtesy of St. Jude Medical, Inc., with labels added by the authors. (d) Chest X-ray of a patient with a HeartMate 3 LVAD.

It is important that serology for hepatitis C be checked prior to LVAD implantation, since there have been a number of reports of the LVAD resulting in a false-positive hepatitis C antibody [12-15]. The mechanism in most studies appears to be isolated reactivity to the hepatitis C protein NS4 (5-1-1p/c100p). The patients typically revert to seronegative after LVAD

explantation at the time of heart transplant. As a result, we often check the hepatitis C viral load immediately before LVAD explant and OHT, especially if considering a donor with a past history of cleared hepatitis C.

The pre-implantation vaccination evaluation is conducted both to make sure that a cardiac patient is appropriately vaccinated, and also to anticipate a possible OHT. Per guidelines [16], vaccination typically includes 13-valent pneumococcal conjugate vaccine, 23-valent pneumococcal polysaccharide vaccine, influenza, varicella zoster when indicated, tetanus-diphtheria-acellular pertussis (Tdap), measles-mumps-rubella (MMR) when indicated, human papilloma virus (HPV) when indicated, and the hepatitis B series so that the patient may receive an OHT from a donor exposed to hepatitis B.

Summary

Infectious diseases screening and vaccination for candidates for LVAD or OHT should be algorithmic and based on published guidelines; consultation with an infectious diseases specialist may provide additional guidance. Hepatitis C screening should be performed before LVAD implantation, since the LVAD may cause a false-positive serology.

PRE-IMPLANTATION ANTIBIOTICS AND PREVENTION OF INFECTION

Pre-Operative Antibiotics

Antimicrobial prophylaxis for LVAD implantation is not standardized, and the optimal regimen has not been determined. Evaluation of regimens has been hampered in large part by the lack of standardized definitions of infections in patients with LVADs. In 2011, a working group for the

International Society for Heart and Lung Transplantation (ISHLT) published criteria for definitions of infections [17]. ISHLT 2013 guidelines for mechanical circulatory support recommend broad-spectrum gram-positive and gram-negative antimicrobial coverage not to extend beyond 24 to 48 hours postoperatively [18]. A comprehensive review of antibiotic prophylaxis regimens, published in 2012 and which acknowledged the lack of standardized definitions of infection, examined 373 papers [19]. The studies varied in antibiotic choice, timing, duration, and follow-up, as well as in type of device. It found that the ten best-evidence papers generally favored the use of vancomycin, a cephalosporin, beta-lactam, and fluoroquinolone, with the option of additional fluconazole and mupirocin, with duration of prophylaxis ranging from 48 to 72 hours. The authors recommended that a beta-lactam be used, with vancomycin at institutions where the risk of MRSA is determined to be high, along with topical mupirocin and a systemic antifungal agent, unspecified, all to be started prior to device implantation and to be continued for an unspecified period of time post-operatively.

At our institution, the antimicrobial prophylaxis regimen is based on that used in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial: vancomycin, levofloxacin, rifampin, and fluconazole, started immediately preoperatively and continued for 48 hours postoperatively [20]. We have adapted this to include ciprofloxacin rather than levofloxacin, and vancomycin is continued until all chest tubes have been removed. Although there is no data supporting the extension of vancomycin prophylaxis, we have infrequently observed adverse effects or the development of vancomycin-resistant organisms; however, we do change to other regimens with gram-positive coverage (e.g., tetracyclines) or stop antibiotics whenever adverse effects become a concern.

It is worth noting the pharmacologic profile of fluoroquinolones, including QT interval prolongation and the elevated risk of ventricular arrhythmias (including ventricular tachycardia and torsades de pointes) when co-administered with other QT-interval prolonging agents such as

amiodarone, and inhibition of warfarin metabolism. Fluconazole and rifampin drug interactions are often of similar concern. Alternative agents are used as necessary due to drug allergy, drug interactions, or other contraindications.

Local Care

In addition to antimicrobial prophylaxis, a number of procedural approaches to decrease the risk of infection have been reviewed. Studies suggest that leaving the entire driveline velour portion below the skin, in the subcutaneous tunnel, resulting in a silicone-skin interface at the exit site, may reduce the risk of infection [21, 22]. The practice of keeping the LVAD exit site dry while bathing by avoiding conventional showering may reduce the risk for *Pseudomonas* exit site infections [23]. Chlorhexidine gluconate (CHG) has been recommended by LVAD manufacturers for driveline exit site antisepsis. A comparison of driveline exit site infections among patients receiving CHG and those receiving povidine-iodine (PVP-I) due to intolerance of CHG (either anaphylaxis or driveline exit site skin irritation) showed that a patients with driveline exit site infections were more likely to have CHG intolerance compared to those without driveline infection site infection [24]. Infections were more likely to be caused by *S. aureus* in the CHG-intolerant patients and by *Stenotrophomonas* and *Acinetobacter* in the CHG-tolerant patients. The contributions of local effects of CHG and PVP-I on skin and on the driveline, skin irritation, and antimicrobial actions of the two agents were unclear. Dressing change frequency (daily, three times a week, weekly) did not seem to affect driveline infection [25]. In one study, prolongation of prophylactic antibiotics (levofloxacin plus doxycycline) compared to sterile dressing changes with CHG topical antisepsis showed no significant difference in the incidence of driveline infections [26]. Finally, other factors, such as shearing forces at the driveline site from trauma, are a probable risk factor for driveline exit site infection of which patients should be made aware.

Summary

Antimicrobial prophylaxis before implantation of an LVAD should cover gram-positive organisms, gram-negative organisms, and fungi, and be brief in duration. Attention should be paid to interactions with cardiac medications. Tunneling the entire velour-coated portion of the driveline and local antisepsis may reduce later infections.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF LVAD INFECTIONS

The ISHLT definitions of infections in LVAD recipients are based on pathophysiologic equivalents in infections involving prosthetic devices such as cardiac prosthetic valves, intravascular catheters, and prosthetic joints [17]. Their definitions have been divided into three categories: VAD-specific infections (VSI), VAD-related infections (VRI), and non-VAD infections. VSI include infections of the pump, cannula, or pocket, and both superficial and deep percutaneous driveline infections. VRI include infective endocarditis, bloodstream infections either with or without a central venous catheter present, and mediastinitis related or unrelated to the VAD. Non-VAD infections include lower respiratory tract infections, cholecystitis, *Clostridium difficile* infection, and urinary tract infection. These definitions should allow studies to analyze risk factors, incidence, epidemiology, and outcome of infections, as well as to define management among patients with LVADs.

The spectrum of pathogens causing LVAD-related infections is broad, but gram-positive organisms tend to predominate [27-30]. Percutaneous driveline infections are among the most common infections in LVAD recipients. Gordon et al. [27] prospectively reviewed 86 patients who received HeartMate II devices, of whom 22% developed 34 VAD-related infections at a median of 68 days. Staphylococci were the most common

pathogen (47%) but gram-negative bacteria caused 33% of infections. Interestingly, a history of depression and elevated baseline serum creatinine were independent predictors of VAD infections, but the use of prior devices such as intraaortic balloon pumps, mechanical ventilation, and prior antibiotic usage were not. Koval et al. [28] also noted that up to 40% of VSI (driveline, pocket, pump/cannula) were caused by *S. aureus* and coagulase-negative staphylococci. In a 2013 study, Nienaber et al. [29] found that for driveline infections, the microbiology consisted of *S. aureus* (45%), S. *epidermidis* (7%), *Enterococcus* (2%), and *Corynebacterium* (2%). *P. aeruginosa* was implicated in up to 28%, *Serratia* in 9%, *Enterobacter* in 2%, and *Klebsiella* in 2%. *Candida* species were occasionally reported to be the cause of driveline infections. Coagulase-negative staphylococci and *S. aureus* accounted for most pocket infections and bloodstream infections. They noted that 13-17% of all bloodstream infections were caused by fungi (*C. albicans, C. krusei, C. glabrata*, and *Aspergillus* spp.). Similar results were noted in a 2017 study by Simeon et al. [30], who also noted that alcoholism, diabetes, and immunosuppression were important co-morbidities.

Interestingly, a recent review by one author (unpublished, D. Lerman), showed that 28 of 74 LVAD recipients (24%) who subsequently underwent OHT had VSI, of which 71% were caused by gram-negative bacteria. Of those with VSI, superficial driveline infections were the most common (14.9%), followed by pocket infection (6.8%). This may reflect the ability of patients with gram-negative LVAD infections to survive to transplant.

Summary

The risk factors for LVAD-related infections are not well-defined but may include depression, renal failure, and diabetes. The driveline is the most common site of infection. Approximately half of the infections are caused by gram-positive organisms, one-quarter by gram-negative organisms, and the remaining quarter by fungi and anaerobes.

DIAGNOSIS OF LVAD INFECTIONS

Clinical Presentation

The initial clinical presentation of an LVAD infection may involve warmth, erythema, tenderness or induration of the abdominal wall along the driveline, or over an abdominal wall collection (Figure 2a). The patient may not be febrile if the infection is limited in extent. The wound swab from purulent drainage from a driveline exit site or other abdominal wound is often sufficient to make the initial diagnosis of infection, although the full extent of infection may not be immediately evident. Blood cultures in febrile patients may demonstrate the presence of bacteremia, which may affect subsequent management.

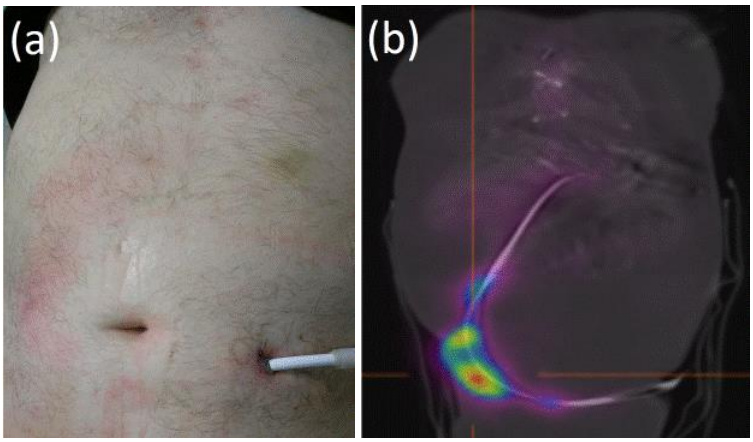

Figure 2. (a) Patient with driveline infection; note erythema tracking along abdominal wall. (b) Gallium-67 single-photon emission computed tomography (Ga SPECT-CT) of the same patient confirming the presence of infection limited to the driveline.

Imaging Studies

The precise extent of infection may not necessarily be evident on exam. There are few effective imaging modalities and no standardized guidelines

for the use of imaging studies in the diagnosis of LVAD-associated infections. Although there is a retrospective study demonstrating the utility of computed axial tomography (CT) [31], in our experience CT is often limited by artifact from the device itself, especially if there is no large collection. Magnetic resonance imaging is contraindicated due to the metallic components of the LVAD. Ultrasonography is useful in detecting collections in the abdominal wall and those around the LVAD pump residing in the pre-peritoneal pocket, although it cannot definitively ascertain the presence of infection within a fluid collection around the LVAD.

On the other hand, nuclear medicine studies appear to be a viable option for localizing and determining the extent of a device related infection (DRI), and various modalities have been employed, including fluorine-18 deoxyglucose positron emission tomography (FDG-PET) scans [32-35], (99m)Tc-labeled leukocyte single-photon emission computed tomography (SPECT-CT) [36], indium-111-labeled leukocyte SPECT-CT [37]. In these case series, the studies contributed to decision-making 60-85% of the time.

Our institution has previously published a series of three patients with four different DRIs in which gallium-67 (Ga) SPECT-CT was used to confirm the presence and document the extent of infection, and compared to findings in three patients with suspected LVAD infection with negative results [38]. Figure 2b shows a representative image demonstrating an infection limited to the driveline.

Ga SPECT-CT has advantages over other nuclear scans because it can be carried out as a single injection, since it does not require the additional steps of extracting, radiolabeling, and injecting labeled leukocytes. Also, in the United States, Ga SPECT-CT is approved for the diagnosis of infections, while FDG PET-CT is not. Our exploratory study highlighted the utility of this nuclear imaging modality as a useful tool to describe the anatomic extent of DRIs. As a consequence, in our institution Ga SPECT-CT has become the *de facto* standard modality in determining the presence and anatomical extent of LVAD DRIs. We are currently conducting a study to further characterize our experiences and determine the clinical impact of the use of Ga SPECT-CT in the management of LVAD DRIs.

Role in Transplant Listing

An infected LVAD may affect the patient's status on the OHT waiting list by increasing the priority for an available organ. In the United States, the definition of pump-related local or systemic infection employed by the Organ Procurement and Transplantation Network and the United Network of Organ Sharing to obtain a status 1A exception [39] involves at least one of the following:

1) Erythema, warmth, and pain along the driveline with either leukocytosis, or a 50 percent increase in white blood cell count from the last recorded white blood cell count, and:
    a) Positive bacterial or fungal cultures from the driveline exit site; or
    b) A culture-positive fluid collection between the exit site and the device
2) Surgical debridement of the driveline with positive cultures from sites between the exit site and the device
3) Positive culture of material from the pump pocket of an implanted device
4) Bacteremia with the same organism that recurs within 4 weeks following treatment with an antibiotic regimen to which the pathogen is susceptible.

Patients who do not precisely fit these criteria may often be considered for a status 1A exception. We propose that future definitions for infection may also include criteria based on radiographic or nuclear medicine studies consistent with infection.

Summary

The clinical presentation of an LVAD infection may involve signs and symptoms of inflammation related to the driveline, purulent drainage from

the abdomen, and fevers. Although CT and ultrasound may be useful to image large collections, determination of the extent of infection with CT may be limited by artifact. PET scans and nuclear imaging provide functional studies to more precisely determine the extent of infection, of which our standard modality is Ga SPECT-CT. Patients with documented LVAD infections may receive a higher priority for OHT.

MEDICAL MANAGEMENT STRATEGIES

The approach to medical management of device infections is based upon guidelines developed for the care of patients with infections of prosthetic valves, joints and cardiac implantable electronic devices that cannot be safely removed without significant morbidity and mortality. The following discussion incorporates those treatment guidelines in addition to the American Society of Transplantation LVAD infection treatment guidelines [28].

Superficial Driveline Infections

The driveline is the lifeline of the ventricular assist device (VAD). The driveline is connected to the pump, tunneled through the abdominal wall, and exits the skin and is connected to the controller, which in turn is connected to a power source (Figure 1c). The driveline is coated with a velour material that helps facilitate integration or the adherence of skin and subcutaneous tissues to the driveline. A break in this area of integration can lead to the development of a driveline infection (DLI). Driveline infections tend to occur late and risks of infection are cumulative over time. Patients, no longer trapped by symptoms of heart failure, are able to spend less time homebound. Unless tightly secured, any slipping or falling of the battery source or controller can lead to pulling of the driveline and a break in the integration, which is critical in keeping out microorganisms, and can lead to infection [28, 29].

Driveline infections are classified as superficial or deep infections. Superficial infections are localized and do not involve deeper tissues such as fascia and muscle [17]. These patients do not have systemic signs of infection or objective measures of inflammation such as elevated white blood cell count (WBC) or C-reactive protein (CRP). In order to appropriately treat, cultures of exit site drainage should be obtained. Surveillance blood cultures should be performed as a positive result would not only assist in the identification of the pathogen but suggest a deeper infection.

Given that gram-positive and gram-negative bacteria cause approximately three-quarters of infections (see section on epidemiology above), empiric antibiotics are aimed at these microorganisms [29]. In addition, knowledge of the patient's previous infections, including microbial colonization and a history of MRSA infection, as well as hospital resistance patterns are important in choosing an empiric regimen [28]. Imaging such as Ga SPECT-CT and ultrasound may assist in ruling out a deeper infection (see section on diagnosis above). Oral antibiotics with good tissue penetration (such as fluoroquinolones for gram negative bacteria and trimethoprim/sulfamethoxazole for staphylococci) are usually adequate for superficial percutaneous driveline infections; duration is dependent on clinical response (cessation of drainage, erythema, and reintegration), but should usually be at least two weeks. Highly adherent organisms such as *S. aureus*, *S. lugdunensis*, *Pseudomonas* and *Candida spp.* are difficult to eradicate even in a superficial infection due to biofilm production, and have a high likelihood of progressing to deep infection. Often these patients may need prolonged treatment and antibiotic suppression until transplantation in those who are candidates, or lifelong in the case of those patients with destination therapy (DT) [40, 41].

Deep Driveline

Deep driveline infections involve fascial and muscle layers [17] and will often require surgery (see section below on surgical management) as an

adjunct to antimicrobial therapy [42]. Patients usually have significant drainage, and may develop fever in addition to pain along the course of the driveline and exit site. Cultures of exit site and blood should be obtained. Given the severity of infection, patients should be admitted to the hospital for the initiation of intravenous antibiotics pending culture results. Imaging studies should be performed to determine the extent of infection and identify any drainable focus. Source control with adequate debridement and appropriate antibiotics is critical to eradicate or control the infection. The patient should undergo echocardiography to assess pump function and the presence of vegetations and thrombi [29]. Cure of these infections is difficult, even with antibiotics and surgery, but has been reported. Antibiotic administration often continues until the time of transplantation or, in the case of patients who are DT, lifelong. Our approach is to give 4-6 weeks of intravenous therapy, followed by oral suppressive therapy when possible, which is paramount in preventing relapse. Patients with multidrug resistant organisms may require long-term intravenous therapy.

LVAD Pocket Infections

It is important to understand the anatomical location of the LVAD. The pocket is defined as the space in which the device rests (Figure 1c). The pocket of the first and second generation assist devices, such as the Heartmate XVE and HeartMate II are preperitoneal, whereas the newer devices are intrapericardial. Infection of the pocket is usually an ascending infection, and often presents with drainage from the exit site; however, the infection of the pocket can also be secondary to bacteremia with seeding of the pocket, or due to inoculation at the time of surgery. Patients with pocket infections usually have symptoms such as drainage, fever and pain [17, 28]. Depending on the virulence of the organism, these patients can appear ill. Occasionally these infections can develop slowly, and some patients, especially those without fever or exit site drainage, can present with left upper quadrant, flank, or intercostal pain mimicking an abdominal or musculoskeletal process. In patients with a suspected pocket infection, blood

cultures should be obtained and empiric intravenous antibiotics administered pending blood and wound culture results. Imaging studies may suggest an area to drain or the need for surgical debridement and echocardiography should be performed to look for pump/cannula infection and endocarditis. An aspirate or deep culture done at the time of debridement should be sent for culture for bacterial and fungal pathogens. Patients with pocket infection should receive intravenous antibiotics and may require debridement and pocket revision to control the process. Cure of pocket infection is rare even with surgical revision, and most individuals require antibiotics until explant whether due to transplant or recovery. Patients who have a device for destination therapy require lifelong antibiotics [17, 28]. Otherwise, duration of intravenous antibiotics is typically 6 or more weeks. If the infection is well-controlled and the isolate is susceptible, an oral antibiotic can be used for suppression. Given the connection between the pocket and mediastinum it is important to continue intravenous antibiotics for a prolonged course after transplantation to prevent deeper infection in the setting of immunosuppression, frequently 6 weeks or more.

Management of Bloodstream Infections

Bacteremia or fungemia in a patient with a LVAD may reflect an LVAD infection; however, they may also be due to non-device related process such as pneumonia or urinary tract infection [17]. Infections caused by central venous catheter, hemodialysis catheters, pacemaker, and defibrillators can occur and can be difficult to distinguish from a LVAD specific infection. Management depends upon the source and the organism involved.

In patients with a bloodstream infection, a search for the source should be performed. Urinalysis, urine cultures, and a chest X-ray should be obtained. Patients with abdominal complaints suggestive of cholecystitis, nephrolithiasis and diverticular disease should undergo appropriate studies. Unless a clear alternate source is identified, all central lines, hemodialysis catheters and intravenous catheters should be removed [43] to prevent seeding of the LVAD and repeat blood cultures performed. When a

cardiovascular electronic device (pacemaker or AICD) is present, transesophageal echocardiography is recommended to evaluate leads and heart valves [41].

Patients with a clear source of infection can receive a finite course of antibiotics if the infection is not LVAD related, and if they rapidly clear blood cultures, have no evidence of thrombus, vegetation, or suppurative process. Because of its ability to adhere to devices, *S. aureus*, when present in the blood, is of particular concern as rates of device infection (whether permanent pacemaker or defibrillator) can run as high as 45% [41], and removal of the device or long term catheter should be performed regardless of the presence of vegetation or thrombi. LVAD patients with a bloodstream infection that is difficult to eradicate despite optimal antibiotic treatment and removal of cardiovascular electronic device or central venous catheter should be considered for suppressive therapy until explant [41].

LVAD Endocarditis

LVAD endocarditis or device-related pump or cannula infection is suggested by persistently positive blood cultures without any other clear source, or positive blood cultures despite removal of other potential sources such as central venous catheters and cardiovascular devices [17, 28]. Patients usually have fever, elevated white blood cell count and C-reactive protein, and may have other manifestations of endocarditis, such as glomerulonephritis, Osler's nodes, Roth spots, and splinter hemorrhages. The function of the device itself may be impaired and patients may have signs of pump thrombus and hemolysis. To establish the diagnosis of VAD endocarditis, multiple blood cultures should be obtained. A transesophageal echocardiogram should be performed to rule out native or prosthetic valvular disease, cardiac abscess, and cannula dehiscence [17, 28, 29]. Nuclear medicine studies such as Ga SPECT-CT may demonstrate focal enhancement at the cannula site.

Treatment of endocarditis depends on the organism involved; however, the same principle applies. Patients with LVAD endocarditis are approached

similarly to those with prosthetic valve endocarditis [44] or prosthetic joint infection [45] who cannot undergo surgery, i.e., a prolonged course of intravenous antibiotics followed by suppressive therapy. Organisms such as coagulase-negative staphylococci or *S. aureus* are initially treated with vancomycin, pending susceptibility testing. The addition of an aminoglycoside and rifampin for staphylococci can be difficult in these patients as chronic kidney disease is often present, and the patient may be on warfarin to prevent thrombosis. Fungal LVAD infection should be considered in those patients with persistent fevers despite antibacterial treatment. Fungal pump infections (usually *Candida* species) cause significant morbidity and mortality, with a mortality rate approaching 30% [46]. The only curative measure for device-related endocarditis is transplantation. LVAD exchange [47, 48] is a modality of last resort, as it is associated with high morbidity and can be reinfected at the time of exchange. At the time of explant, cultures should be obtained. A prolonged course (6 or more weeks) of antimicrobials is necessary after LVAD endocarditis to minimize infectious complications.

Summary

Much of the approach to these patients is based upon knowledge derived from the approach to prosthetic valve and joint infections, in which surgical intervention or revision is contraindicated. Understanding the nature of the organism causing disease, extent of infection, and the anatomy and device structure and function, will provide the necessary background to care for these patients.

SURGICAL MANAGEMENT STRATEGIES

Surgical management of LVAD infections requires a combination of clinical acumen in conjunction with appropriate diagnostic evaluation in order to develop the optimal approach to these complex clinical scenarios. Topkara et al. describe 60% of their LVAD, driveline or pump-related,

infections as requiring surgical intervention [49]. Classic surgical principles with regards to the treatment of an infected foreign body include drainage and debridement of infected tissue and removal of the foreign body. However, in the case of LVADs, the foreign body is life-sustaining and complete removal is unacceptable, except in rare cases where a patient has concomitant cardiac recovery. Therefore, a surgical armamentarium for the treatment of patients with device-related infections is essential.

Localized Driveline Infection

The simplest surgical intervention for an isolated abscess associated with a driveline infection is incision and drainage. A thorough clinical exam and investigation utilizing imaging modalities previously described must be performed in order to confirm that the process is localized to the subcutaneous tissue. Clinical findings indicative of an isolated process include a well-circumscribed area of induration, erythema, or fluctuance without extension along the driveline tract or purulent drainage from the driveline exit site. In our experience, a localized process is rare. The surgeon must be careful not to undertreat and leave active infection behind. Figure 3 shows two images from an abdominal CT scan from a patient whose driveline infection was successfully controlled with local drainage, velour stripping of the driveline, and vacuum-assisted closure (VAC) to facilitate wound healing.

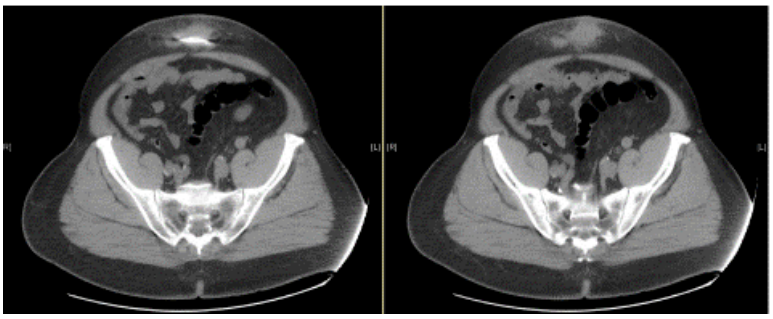

Figure 3. CT scan of the abdomen without contrast that depicts an infraumbilical abscess localized to the driveline.

Complex Driveline Infection

More commonly, patients present with a complex driveline infection. Standard surgical principles apply with regards to wide drainage and removal of infected tissue. However, the patient will typically be left with a large incision traversing across 2 or 3 quadrants of the abdomen with an exposed driveline. A variety of techniques have been described to treat complex driveline infections with two basic concepts in mind: 1) remove the driveline from the infected field and 2) surround the driveline with healthy, vascularized tissue.

In our experience, the driveline tract on index implantation is created utilizing a counter incision in the right lateral abdomen and driveline exit site out of the left lower quadrant. When a patient presents with an infection of the driveline, an incision along the length of the driveline is made. Subcutaneous tissue and muscle is divided down to the level of the driveline and exposed velour is removed. The extent of the incision can only be determined intraoperatively where all necrotic tissue is debrided until healthy, uninfected tissue is encountered. Exposed driveline is then painted with povidone-iodine, the controller is disconnected, the driveline connector is covered with a piece of sterile glove that is secured with a tie, and retunneled utilizing a chest tube tunneling clamp. Meticulous hemostasis of the exposed driveline tract is critical and may be challenging because the tissue is inflamed and hypervascular from active infection, in addition to the patient being on anticoagulation and antiplatelet therapy for their device. A VAC device is placed 24-72 hours after surgery when the wound is deemed hemostatic.

Other surgical techniques have been described. Pieri et al. published a case series of 13 patients who underwent an omental wrap of their driveline with translocation of the driveline via an intraperitoneal tunnel [50]. Interestingly, ½–inch tubing from a cardiopulmonary circuit was used for passage of the driveline through the tunnel in an attempt to maintain sterility [50]. Trachtenberg et al. describe application of antimicrobial beads to the wound after resection of infected tissue [42]. The soft tissue defect was subsequently covered with adjacent rectus muscle. In all surgical techniques

described, the underlying principle is to remove infected tissue and surround the driveline with healthy tissue.

Pump Exchange

Infection of the pump and pump pocket is a considerably morbid complication of continued device support with approximately 5-6% of LVAD recipients developing this complication [29, 49]. In patients who successfully have a device exchange for infection, a 40% rate of recurrent infection persists. Interestingly, this is similar to the 38% rate of recurrence for all patients undergoing any surgical treatment for a device-related infection [51]. Despite complete removal of the infected pump, a new device is being reimplanted in a less than sterile field and outcomes are unpredictable. In a case series of 4 patients undergoing pump exchange for infection, Levy et al. describe 1 patient who eventually underwent heart transplant with postoperative infectious complications, 1 patient who died, and 2 patients without recurrent infection [47].

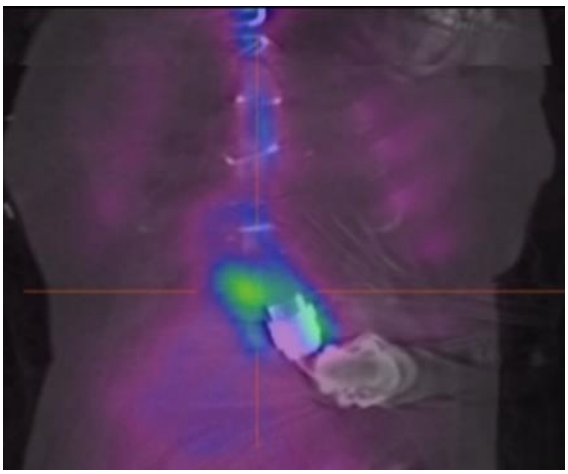

Figure 4. Ga SPECT-CT demonstrating infection limited to the proximal portion of the outflow tract of a HeartMate II LVAD. This allowed for a graft-to-graft anastomosis, and preservation of the distal anastomosis to the aorta.

Pump exchange may be performed through a subcostal approach or through a sternotomy if removal of the inflow cannula or portion of the outflow graft is indicated. In a case where only the proximal outflow graft exhibited evidence of infection on Ga SPECT-CT (Figure 4), we performed a pump exchange and partial outflow graft resection with a graft-to-graft anastomosis to avoid revision of the outflow graft anastomosis to the aorta. The latter demonstrates the utility of nuclear imaging for surgical planning. An additional approach to device exchange for infection involves a lateral thoracotomy approach which has been described in 6 patients, five of which had a device-related infection, where a HeartMate II or HVAD was exchanged for a HeartMate 3 [48]. Other surgical maneuvers have been described to preserve a device in the setting of a pump infection. Shafii et al. describe a successful case of LVAD salvage without device exchange by relocating the pump to an intraperitoneal space with omental flap transposition occupying the infected, extraperitoneal space [52].

Mediastinitis

Mediastinitis is a diagnosis predominantly seen in the perioperative period. Significant morbidity and a 53% mortality rate has been described [53]. Salvage procedures to save the patient include reopening of the sternum, debridement, and lavage. A staged closure with VAC device and subsequent omental transposition to cover the mediastinum has been successful [53, 54]. An aggressive surgical approach for source control is essential and a prolonged and complicated hospitalization can be expected.

OUTCOMES AFTER LVAD INFECTION

The impact of LVAD-related infections on patient outcomes is a subject of continued research effort, since the numbers are small and the data are occasionally conflicting. However, the main differences in outcomes are

seen between those who survive to LVAD explantation and OHT, versus those who do not.

Although it would be intuitive to think that infection should result in worse outcomes in LVAD patients, many of the studies of infectious outcomes in LVAD patients did not carefully distinguish between all-cause sepsis in LVAD patients versus DRIs. For instance, the REMATCH trial found that LVAD patients with sepsis were found to have significantly lower survival, with survival rates of 60% vs 39% at 1 year and 38% vs 8% at 2 years in non-septic vs septic patients [20]; however, the fraction of patients who became septic during the trial was relatively high, 52% at two years. However, percutaneous site or pocket infection did not affect survival. Similarly, the ADVANCE BTT trial also found that there was a trend towards reduced survival in septic LVAD recipients compared to patients who remained free of sepsis [55] and that there was no negative impact on survival in patients with driveline exit-site infections. Shulman et al. also found that LVAD patients with sepsis were less likely to be bridged to transplant [56].

In a more rigorous multi-center study in which investigators carefully determined the presence of LVAD infection in 33 patients, Gordon and colleagues [27] found that patients with LVAD infections had overall worse 12-month outcomes: infected patients had a 32.3% mortality, with 34.3% proceeding to OHT, whereas uninfected patients had a 22.7% mortality, with 38.7% proceeding to OHT. A comparable single-center study by Koval et al. describes a significant increase in one-year mortality in patients with driveline infections when compared to uninfected controls, with a 50% mortality due to sepsis [57].

For those patients with LVAD-specific infections who receive transplants, the literature is less clear on the effects on post-OHT outcomes. Several analyses have found that driveline, pocket or pump pocket infections have no impact on post-transplant survival for follow-up times of six months to three years [56, 58-61]. Regarding the role of post-OHT immuno-suppression after LVAD infection, in 57 driveline infections, no increased post-transplant infection risk was observed in patients receiving anti-thymocyte globulin for immunosuppression [62].

The converse finding, that LVAD infection predicts worse post-OHT outcomes, was found in other studies. An analysis by Thoratec to evaluate the impact of LVAD support time and other variables on post-transplant survival found a trend for slightly lower survival at 1 year in patients with percutaneous lead infections during LVAD support who underwent transplant [63]. Healy et al. found that patients with LVADs who were listed 1A for infection had higher 1-year and 10-year post-transplant mortality, when compared with those listed 1A for other indications such as thromboembolism, malfunction, arrhythmia, and other indications [64]. Shulman et al. also found that driveline infections predicted post-transplant infections in the former driveline or pocket site, and increased length of stay following transplant [56]. Regarding other post-OHT outcomes, a study of 74 LVAD patients referenced above did not show an increase in post-OHT mortality due to infection, but it did suggest that the presence of pneumonia or urinary tract infection among LVAD recipients prior to transplant appeared to confer an increased risk for rejection post-OHT [61].

Summary

The overall conclusions that can be drawn from these studies suggest that LVAD infections do negatively affect survival, but for those patients who survive to explantation and OHT, post-transplant outcomes are favorable. LVAD infection is therefore not a contraindication to tramsplant, but may provide an impetus for infected patients to proceed to OHT if they are candidates.

CONCLUSION

The LVAD plays a pivotal role in the care for heart failure patients. Although patients with LVADs have to make major life changes, these devices can be lifesaving, especially those with anticipated long waits for transplant. Infections play a major role in the morbidity and mortality in

these patients and the infectious disease consultant plays a pivotal role in the care of these patients, both before and after implantation. With a thorough medical and surgical approach at the time a LVAD infection is identified, patients with infection who proceed to transplantation can have a successful outcome similar to those patients without infection.

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Publications from the Last 3 Years:

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Honors: Castle Connolly Top Doctor, New York Metropolitan Area, 2017, 2018

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