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Ventricular assist device-related infections and solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract

The Infectious Diseases Community of Practice of the American Society of Transplantation has published evidenced-based guidelines on the prevention and management of infectious complications in SOT recipients since 2004. This updated guideline reviews the epidemiology of ventricular assist device (VAD) infections and provides recommendations for the management and prevention of these infections. Almost one half of those awaiting heart transplantation are supported with VADs. Despite advances in device technologies, VAD infections commonly complicate mechanical circulatory support and remain typified by common components and anatomic locations. These infections have important implications for transplant candidates, most notably increased wait-list mortality. Strategic management of these infections is crucial for successful transplantation. Coincidentally, explantation of all VAD components at the time of transplantation is often the definitive cure for the device-associated infection. Highlighted in this updated guideline is the reported success of transplantation in patients with a variety of pre-existing VAD infections and guidance on post-transplant management strategies.

KEYWORDS

bacteremia, device infection, driveline infection, ventricular assist device

1 | INTRODUCTION

An implantable ventricular assist device (VAD) is a mechanical pump that provides circulatory support by augmenting the ability of a failing heart to deliver appropriate blood flow. VAD therapy is well established for the management of patients with refractory heart failure. Compared to medical therapy alone, these devices improve survival, functional status, and quality of life.[1-4] VADs may be implanted to support either the right ventricle (RVAD) or the left ventricle (LVAD), or both; the vast majority today is LVAD.[5]

Initial VADs were pulsatile pumps, intended to mimic the natural function of the heart. Continuous flow pumps, introduced in 2004, have demonstrated improved survival and now represent >95% of pumps in use.[2,5,6] Most publications reporting outcomes for continuous flow VADs are with the HeartMate II (Abbott) device, approved by the FDA in 2008 (Figure 1A).[7] Newer devices include the HeartWare HVAD (Medtronic; approved in 2012)[8] and the HeartMate 3 (Abbott; approved in 2017)[9] (Figure 1B) both designed with a centrifugal pump intended to reduce hemorrhagic and thrombotic complications. These pumps are smaller, are implanted directly into the pericardium (avoiding the preperitoneal pump pocket of HeartMate II), and have drivelines of smaller caliber and longer durability.

Since the advent of continuous flow pumps, the average time that patients live with device support has increased from 126 to 348 days, and survival is now >80% at 1 year and >70% at 2 years.[1,2,5,6,10,11]

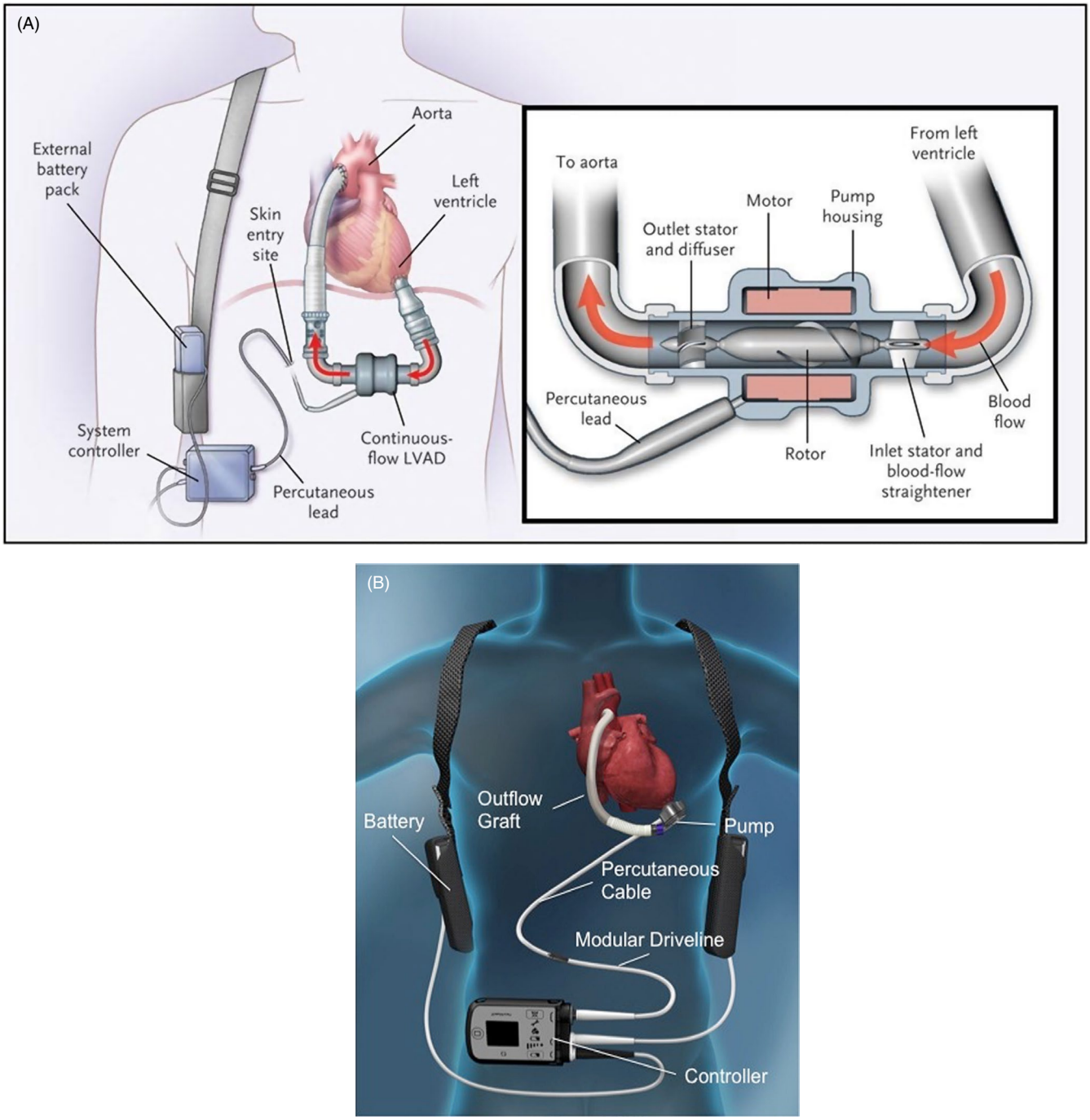

FIGURE 1 A, Components of the HeartMate II (Abbott) continuous flow LVAD. Reproduced with permission from [1]. Copyright 2007 Massachusetts Medical Society. All rights reserved. B, Components of the HeartMate 3 (Abbott) continuous flow centrifugal pump LVAD. Reproduced with permission. MR Mehra, MD, FACC, FESC, FHFSA, FRCP

Currently, over 40% of device implantations are considered destination therapy (DT) for heart failure, while 57% of VADs are placed in those listed or under evaluation for heart transplantation (HT).[5] Ultimately, over 40% of HT recipients are supported with an LVAD prior to transplantation.[12]

Infection remains one of the most common complications of VAD therapy and contributes to mortality on the transplant waitlist.[13] However, those with infection can often be transplanted with excellent post-transplant outcomes.[13,14] Management strategies for VAD infections have advanced mostly based on clinical experience. This guideline reviews current data in the field and recommended approaches to VAD infections.

2 | EPIDEMIOLOGY AND RISK FACTORS

Infection is a leading complication following VAD implantation, occurring in up to 60% of recipients, and a frequent cause of hospital

readmissions.[1-6,15-19] By adapting accepted definitions of infection such as infective endocarditis, catheter-related bloodstream infections, cardiovascular device infections, and intra-abdominal infections, the ISHLT introduced working standardized definitions for infections in patients with VADs in 2011.[20] Such definitions are intended to create consistency in language of infection reporting and guide diagnostic criteria in clinical practice. Although not validated in prospective clinical studies, these definitions have largely been adopted by clinicians and researchers in the field. Infections are classified as VAD-specific, VAD-related, or non-VAD (Table 1). VAD-specific infections may involve any component of the device, including the percutaneous driveline, the pump pocket, and the pump and/or cannula; coexistent infection at multiple sites is common.[20] The percutaneous driveline is quite vulnerable to infection at the exit site, particularly when the skin seal is lost due to traction injury of the driveline. The entire device, but especially the driveline, is susceptible to biofilm formation from infecting organisms and, thus, infection is nearly impossible to completely eradicate without device removal.[11,21,22] A portion of the driveline has a polyester velour surface to promote tissue ingrowth and biointegration of the driveline with host tissues, but this velour also promotes biofilm formation.[24] Indeed, studies have demonstrated higher rates of driveline exit site (DLES) infections when the velour as opposed to the silicone surface of the driveline interfaces with the exit site.[25,26]

Ventricular assist device-related infections occur as a complication of the surgical procedure or VAD-specific infection. These infections include mediastinitis (which may coexist with a pocket infection for intrathoracic pumps)and bloodstream infections (which can result from intravascular catheter-related infections or complicate VAD-specific infections). In the International Registry of Mechanically Assisted Circulatory Support (IMACS), which includes patients supported with VADs or total artificial hearts, over 85% of reported bloodstream infections were unrelated to a device infection and were attributed to other sites of infections such as intravascular catheters, the lower respiratory tract, the urinary tract, and the gastrointestinal tract.[27] With pump and/or cannula infections, infective endocarditis, defined by modified Duke's criteria, is a frequent coexisting feature; valvular VAD-related endocarditis is distinguished by the presence of vegetation on a native valve.[20]

Pathogens that are commonly implicated in device component infections are listed in Table 2. The majority of device infections are caused by bacteria. Fungal infections, typically caused by *Candida*

TABLE 1 Spectrum of infections in patients support with VADs[20]

Category and type of infection	Additional characterization of infection
VAD-specific infections	
Pump pocket and/or cannula infections	
Pocket infections	
Driveline exit site infections	Superficial vs deep driveline infection
VAD-related infections	
Bloodstream infections	VAD infection-related
	Intravascular catheter-related
	Non-VAD-related (eg, secondary to urinary tract infection)
Infective endocarditis	VAD-related (secondary to pump and/or cannula infection)
	Valvular VAD-related (native valve vegetation present)
Mediastinitis	Coexists with sternal wound infection or pocket infection if VAD has an intrathoracic pump
	Non-VAD infection if secondary to another cause such as esophageal perforation
Non-VAD infections	
Lower respiratory tract infections	
Urinary tract infections	
Clostridium difficile infections	
Cholecystitis	

Note. VAD, ventricular assist device.

TABLE 2 Distribution of pathogens in ventricular assist device-specific infections[11,28,30,37,39,66]

Site of infection	Pathogen	Distribution (%)
Driveline	*Staphylococcus aureus*	28-44
	Pseudomonas aeruginosa	10-50
	Enteric gram-negative bacteria	13-30
	Coagulase negative staphylococci	7-20
	Enterococcus spp.	0-15
	Corynebacterium spp.	0-15
	Candida spp.	0-8
	Proteus spp.	0-5
Pocket	Coagulase negative staphylococci	15-40
	S aureus	20-30
	Enterococcus spp.	20-24
	Enteric gram-negative bacteria	5-25
	P aeruginosa	5-19
	Candida spp.	10
Pump/cannula	Coagulase negative staphylococci	20-40
	S aureus	20
	P aeruginosa	8-20
	Corynebacterium spp.	8-20
	Enteric gram-negative bacteria	0-15
	Enterococcus spp.	0-30

spp., were reported in up to 20% of cases from the 1990s and early 2000s and were more frequently associated with VAD-related bloodstream infections than in more recent eras.[27,28] They have been associated with high mortality, though more recent outcome data would be of great interest.[28]

Finally, in the early postoperative period after VAD implantation, patients are at risk for non-VAD, hospital-acquired, infections such as pneumonia, urinary tract infections, and *Clostridium difficile* infection. Such infections account for the largest category of VAD infections and, especially if complicated by bacteremia, can result in seeding of the VAD itself.

Since the availability of continuous flow pumps in 2004, infection rates and infection-related mortality have declined.[5,10,29] This has largely been attributed to improvements in the pumps, but data indicate that clinical experience with patient selection and management strategies are more closely associated with reduced infection rates overall.[30] Even so, infection remains a leading adverse event after VAD implantation with newer generation pumps.[5,31,32] Infection-related mortality, attributed to nosocomial sepsis events and bloodstream infections, is greatest in the early postimplant period, but infection is a chief cause of death throughout the duration of VAD support.[5,32,33] Death rates have fallen from 25% in the early years of support to 7.7%, another indication of improved management.[4,34,35]

The type and site of infection varies with timing after device implantation. Sepsis events, including bloodstream infections, and non-VAD infections account for the majority of infections occurring within 30 days of implantation.[35,36] Non-VAD infections predominate from 31 to 90 days postimplantation, although device-specific infections may be seen. Pump pocket and, especially, driveline infections continue to occur in the period beyond 90 days and likely account for the rise in bacteremic events during this late period (Figure 2).[11,30,33,36,37]

In addition to the inherent morbidity and mortality related to infectious complications of VAD implantation, emerging data indicate VAD-related bloodstream infections are associated with both ischemic and hemorrhagic stroke.[29,40,41] Infection-associated cerebrovascular accidents tend to occur in the later postimplantation period, with *Staphylococcus aureus* and *Pseudomonas aeruginosa* being frequently encountered[13,29] pathogens in this setting.[41,42] The postulated pathophysiology, confirmed in a small number of patients at the time of neurosurgical intervention, is cerebral mycotic angiopathy with subsequent vascular rupture.[41,42]

Predictors for specific infections vary widely (Table 3). Associated risks for early severe sepsis or bacteremia following VAD implantation include older patient age,[27,30] higher heart failure risk score,[27,30] baseline chronic kidney disease or hemodialysis,[27] higher BMI,[27] frailty,[27] previous cardiac surgery,[27] and intra-aortic balloon support prior to VAD implantation.[30] Factors implicated in DLES and other VAD-specific infections include patient characteristics such as increased duration of device support,[11,38,39,43,44] older age,[44] age <50 years,[26,45] lower cardiac index,[30] higher heart failure score,[38] and longer duration of mechanical ventilation,[44] and surgical and driveline management factors such as DLES on the right side of abdomen,[26] DLES with velour interface material,[25,26] use of driveline anchoring suture,[26] and DLES trauma.[43] Patient comorbidities associated with overall infection risk include infection prior to VAD implantation,[13,37] alcohol use,[13] no hemodialysis,[13] diabetes mellitus,[29,37] and poor nutritional status.[4] Finally, total parenteral nutrition is an important association with development of VAD-specific fungal infections.[28]

There is compelling evidence that cellular and immune system dysfunction occurs following VAD implantation[46,47]; however, many of these observations occurred during the pulsatile pump era, and it is unknown whether these phenomena contribute to overall infection risk after VAD implantation or HT. One study demonstrated that pretransplant VAD was associated with post-transplant

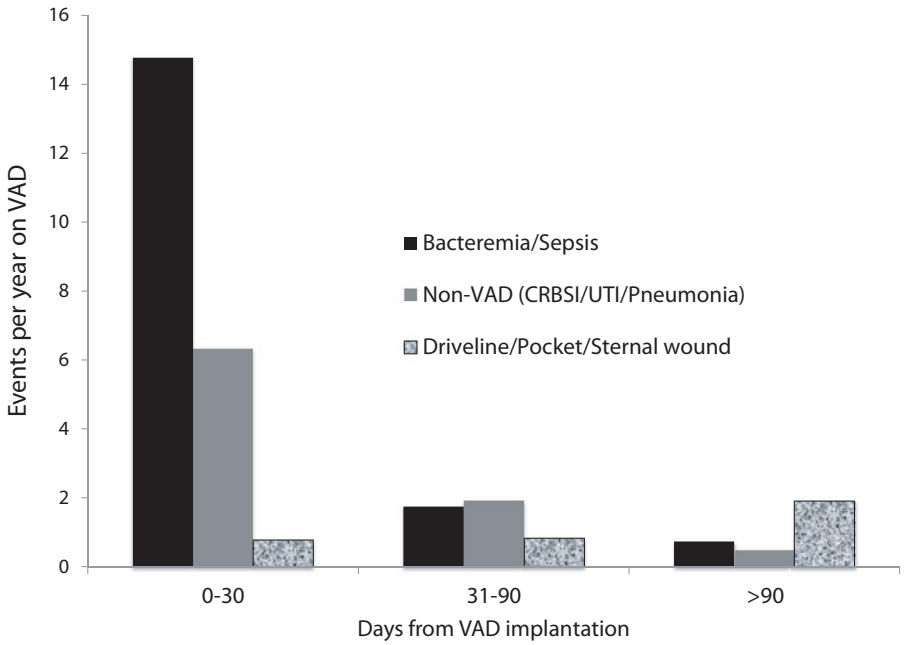

FIGURE 2 Timing and type of infection with continuous flow VAD. Adapted from Schaffer et al.[30] CRBSI, catheter-related bloodstream infection; UTI urinary tract infection; VAD, ventricular assist device

TABLE 3 Patient-, surgical-, and driveline-related predictors of infection in patients with VAD support

Site of infection	Patient characteristics	Surgical and driveline management technique
Overall infection risk	Prior cardiac surgery Infection prior to VAD implantation[13,37] Alcohol use[13] No hemodialysis[13] Higher BMI[29] Diabetes mellitus[29] Malnutrition[4]	
Sepsis/Bloodstream infection	Older age[27,30] Frailty[27] IABP prior to VAD implantation[30] Previous cardiac surgery[27] Chronic renal disease and hemodialysis[27] Higher heart failure score[27,30] Higher BMI[27]	
DLES and other VAD-specific infections	Longer duration of VAD support[11,38,39,43,44] Older age[44] Younger age[26,45] Lower cardiac index[30] Higher heart failure score[38] Longer duration of mechanical ventilation[44]	DLES on right side of abdomen[26] Velour interface material[25,26] Use of driveline anchoring suture[26] Trauma (traction injury) at DLES[43]
Fungal infection	Total parenteral nutrition[28]	

Note. DLES, driveline exit site; IABP, intra-aortic balloon pump; VAD, ventricular assist device.

infection-related mortality, potentially indicating a residual immunologic effect related to the VAD.[51] In a recent small study of VAD patients, senescent T-cell subsets, such as TMRA CD8+ and CD4+ PD1 + CD57+ lymphocytes, were predictors of infection.[52] This is an area that requires further study.

Although limited to small case series and reports, mechanical circulatory support with VAD appears to be a feasible strategy for both DT and as a bridge to transplantation (BTT) in patients with controlled HIV infection.[53,54] In these reports, infection risk and outcomes do not appear increased compared with the general LVAD population.

Because there are no randomized controlled trials related to VAD infections, recommendations are based on observational studies and expert opinion. It is generally recommended that composite risk for overall patient outcome be assessed on a case by case basis prior to VAD implantation with particular attention to recognized risk factors.

3 | DIAGNOSIS

In general, patients with VADs may not present with classic signs of infection. When infection is suspected, a standardized diagnostic approach is recommended that captures VAD-specific, VAD-related, and non-VAD infections.[20] The evaluation typically includes a white blood cell count, basic chemistries, chest radiography, at least two sets of blood cultures, urinalysis, and urine culture. If a central venous catheter or PICC is present, a culture from that line should be obtained coincident with at least one peripheral blood culture.

3.1 | Driveline infections

Driveline infections are most commonly superficial affecting the DLES and surrounding area but may evolve into or present coincidently with deep infection involving the fascial and muscle layers. Diagnosis of both types of infection can be problematic. The driveline should be inspected visually under sterile conditions and palpated along the driveline tract away from the cutaneous exit site. Noting evidence of trauma to the driveline or loss of tissue seal with exposure of the velour component of the driveline may increase the suspicion for driveline infection.[25,26] While at times the driveline appears overtly infected, with purulent discharge and/or surrounding cellulitis (Figure 3A), often infection is more difficult to recognize, with wound dehiscence or serous discharge as the only indications. Conversely, in the absence of infection, surrounding skin erythema may be due to other factors, such as trauma from the driveline or adverse reactions to topical antiseptic agents (Figure 3B). Even with infection, systemic signs, such as fever, leukocytosis, or elevated inflammatory markers, may not be present.[11]

Drivelines can become secondarily infected after an initial infecting event.[39] This can occur during prolonged antimicrobial therapy for the initial infection. While the initial infection may be gram-positive in origin, these secondary infections are more often caused by gram-negative bacteria with propensity to develop antibiotic resistance over time. Secondary infections with gram-negative organisms may also predispose to deeper driveline infection.[39]

If purulent drainage is present, a sterile aspirate from the exit site should be obtained for bacterial and fungal culture. If an aspirate is not feasible due to low quantity of material, a sterile swab may be used. Repeating cultures in the setting of ongoing or apparent

TABLE 4 Treatment for VAD-specific and VAD-related infections

	Antibiotic strategy	Surgical and adjunctive strategies
VAD-specific infection		
Superficial driveline	Oral or intravenous antibiotics • Directed to pathogen when able • ≥2 wk duration • Can consider stopping if resolved	Ensure driveline immobilization Optimize driveline hygiene Monitor for relapse, secondary infection
Deep driveline	Intravenous antibiotics • If sepsis, empiric coverage for *Pseudomonas* sp. and MRSA • Directed to pathogen when able • 2-8 wk depending on time to source control and if coincident bloodstream infection • Oral suppressive antibiotics expected	Surgical debridement of abscess(es) Externalization of driveline Wound care, including possible wound VAC Reinsertion of driveline in new tract may be of benefit In limited situations, completed device exchange can be considered
Pump pocket	Intravenous antibiotics • If sepsis, empiric coverage for *Pseudomonas* sp. and MRSA • Directed to pathogen when able • 4-8 wk depending on time to source control and if coincident bloodstream infection • Oral suppressive antibiotics expected	Drainage of abscess, at least for culture Surgical debridement if size and position favorable or if recurrent. Possible wound VAC Transplant with device explant is ideal surgical strategy In limited situations, completed device exchange can be considered
Pump/cannula	Intravenous antibiotics • If sepsis, empiric coverage for *Pseudomonas* spp. and MRSA • Directed to pathogen when able • Prolonged duration(≥6 wk) • Suppressive antibiotics (may be iv) expected	Transplant with device explant is ideal surgical strategy In limited situations, completed device exchange can be considered
VAD-related infection		
Bloodstream infection	Intravenous antibiotics • If sepsis, empiric coverage for *Pseudomonas* spp. and MRSA • Directed to pathogen when able ≥2 wk duration depending on organism and evidence for removable source (central venous catheter)	Central venous catheter removal if present Additional management strategies depend on source (eg, refer to VAD-specific infection recommendations)
Mediastinitis	Intravenous antibiotics • If sepsis, empiric coverage for *Pseudomonas* sp. and MRSA • Directed to pathogen when able • 4-8 wk depending on time to source control and if coincident bloodstream infection • Oral suppressive antibiotics expected	Surgical debridement Wound care, including possible wound VAC

Note. VAC, vacuum-assisted closure; VAD, ventricular assist device.

recurrent infection are important since organisms can evolve over time after initial infection.[39]

Imaging with ultrasound or computed tomography (CT) is recommended when deep driveline infection or abscess along the driveline tract is suspected, though artifact from the pump hardware may limit the utility of CT.[56] Leukocyte SPECT/CT imaging may be more sensitive than CT at detecting anatomic location and extent of infection along the driveline cable and near the pump pocket.[57] However, this testing may not be uniformly available. In a small prospective comparative trial of VAD-specific, VAD-related, and non-VAD infections, ^{18}F-FDG PET/CT outperformed leukocyte-labeled scintigraphy in identifying site of infection, with PET/CT demonstrating 95.2% sensitivity and 66.7% specificity.[58]

3.2 | Pocket infections

Ventricular assist device pocket infections may arise from direct extension of a primary driveline infection or may develop due to inoculation at the time of surgery or thereafter, in a manner similar to that seen with other implanted devices such as pacemakers. While infections may develop slowly, systemic signs often emerge. Coincident bloodstream infection may emerge and indicate the involved pathogen.

Imaging with ultrasound or CT may be helpful in suggesting the diagnosis. Leukocyte SPECT/CT imaging may be more sensitive than CT at identifying a deeper infection but is not commonly used,[57] and PET/CT may have utility.[58] Ultrasound or CT-guided aspiration of fluid for gram stain and culture is recommended particularly if an organism has not yet been identified.

3.3 | Cannula/pump infections

Infection of the internal portions of the pump or cannula, also called VAD endocarditis, presents in a manner similar to prosthetic valve endocarditis, with persistent bacteremia and fever. In addition, these infections may be associated with internal VAD thrombosis, obstruction, and dysfunction.

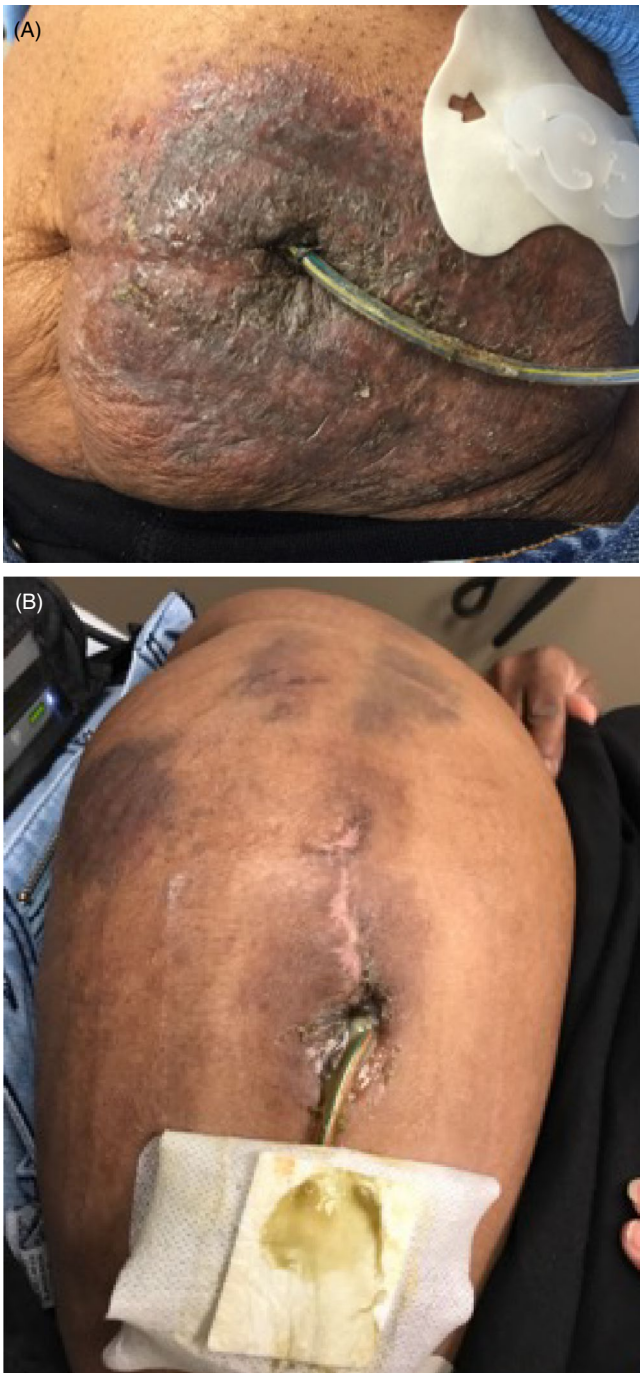

FIGURE 3 A, Severe contact dermatitis surrounding driveline exit site, attributed to topical chlorhexidine antisepsis. B, *Pseudomonas aeruginosa* driveline infection diagnosed on day +68 after HeartWare HVAD implantation

Blood cultures are imperative for diagnosis. At least two but preferably four or more cultures may be required prior to initiation of empiric antibiotics to properly identify infecting pathogenic bacteria. Echocardiography, particularly transesophageal echocardiography, is recommended to identify vegetations or turbulent flow through the device (particularly with HeartMate II), abscess, and/or cannula dehiscence. Other imaging modalities, specifically CT or SPECT/CT may define inflammatory changes around the cannula. Clinical identification of classic vascular and immunologic phenomena of endocarditis may enhance the diagnostic yield in certain settings.

3.3.1 | Recommendations

1. Clinicians must have a heightened suspicion for infection in patients with a VAD, as classic symptoms and signs of infection may be absent (strong, low).
2. Imaging, including ultrasound, CT, or echocardiography, may be helpful in identifying infected areas and determining extent of VAD-specific infection (strong, moderate).
3. It is important to obtain cultures of any potentially infected material evident on exam or imaging in order to establish a microbiologic diagnosis with susceptibility testing to target antimicrobial therapy and minimize excessively broad coverage (strong, moderate).

4 | MANAGEMENT OF INFECTION

Management strategies are directed in part by the site and severity of infection (Table 4); however, there is often substantial overlap in presentation.[20] Driveline infections may be associated with pump pocket infection, and bacteremic spread from these sites can result in cannula/pump infection. For patients who present with sepsis, broad-spectrum empiric therapy with activity against both gram-positive and gram-negative organisms, including methicillin-resistant *S aureus* and *Pseudomonas* species, is advised pending further investigation. Depending on patient-specific risk, an antifungal agent might also be considered.[28] As with other device-associated infections, all infected VAD components are ideally removed for cure of the infection, as would occur with transplantation (or with VAD explant in the setting of recovery of cardiac function). This is usually not immediately feasible due to timely availability of donor organs. And while surgical VAD exchange is an option, this carries a significant operative risk, and relapse of infection may still occur.[59,60]

Several reports have indicated that active VAD infection is not a contraindication to transplant,[13,14,39] but the status of the infection at the time of organ offer is an important consideration. Septic shock characterized by vasodilatory shock, tissue underperfusion, and need for vasopressor support[61] is, at a minimum, a relative contraindication to transplant. However, transplantation in the setting of reasonably controlled infection, even in the setting of active bacteremia without hemodynamic instability, is often lifesaving.[62] For further discussion of management strategies, these VAD-specific infections are listed separately. Additionally, the International Society for Heart and Lung Transplantation has published consensus document addressing prevention and management of mechanical circulatory support infections.[63]

4.1 | Driveline infection

For driveline infections, empiric antibiotic therapy is typically initiated after appropriate cultures are collected. A gram stain from the

exit site may help guide initial antibiotic choice, but the empiric regimen is also based on the local institution's pattern of infecting organisms and antimicrobial resistance, along with the patient's prior history of infections, microbial colonization, and antibiotic therapy. Treatment can be narrowed once the pathogen-specific antimicrobial susceptibilities are known.

Patients with superficial DLI but no signs of sepsis or deeper driveline infection can often be managed in the outpatient setting with empiric antibiotics and close follow-up of culture and susceptibility data to choose a more targeted therapy. Clinical course should be monitored carefully to ensure no evidence of rapid change. Assistance by an infectious disease consultant may be particularly helpful if the organism is unusual, resistant, or requires intravenous outpatient antibiotics.

If localized abscesses associated with driveline infection are found by exam or imaging, percutaneous or surgical drainage is recommended. Vacuum-assisted closure (VAC) treatment of sizable resultant wounds may promote healing and reduce time to complete closure.[23,64] Some surgeons routinely expose the driveline beyond the area of infection and, once treated, surgically relocate the driveline tract.[65]

For superficial DLES infections, a short course of antibiotics, typically of 14-day duration,[63] and until the area has healed is reasonable. Once infected, the driveline is rarely (if ever) infection-free, and recurrent treatment courses are often required. Due to the possibility of progression of superficial infection to deep, some advocate continuous antibiotics until transplantation.[23,66] Prolonged antimicrobial therapy, especially with parenteral agents, is much more problematic in patients with VAD as DT.[38] In any given patient, an approach that weighs the risk of prolonged antibiotics with the risk for infection progression is warranted.

Since deep driveline infections are usually accompanied by fever and systemic symptoms, hospital admission is recommended for full source control and empiric intravenous antibiotics. Once cultures are obtained from blood and any collections found along the driveline tract, directed antibiotics should be used. The recommended course of parenteral intravenous antibiotics is a minimum of 2 weeks, but the duration may be extended (4-8 weeks) particularly in setting of positive blood cultures or slow clinical response. At that time, assuming adequate source control and negative blood cultures, changing to an appropriate oral regimen (if available) is reasonable. Prolonged suppressive antibiotics are generally required to avoid further progression of the infection along the remaining driveline tract, local relapse and/or recurrent episodes of bacteremia.[39]

4.2 | Pump pocket infection

For suspected pump pocket infection or pericardial infection, intravenous antibiotics are warranted initially and drainage is often required. Occasionally this may necessitate surgical revision, with intraperitoneal relocation of the pump and use of an omental flap.[59,67,68] Even with surgical revision, chronic suppressive antibiotic therapy is typically used, initially with intravenous followed by oral administration, if an oral option is available.[59,67] Whether the antibiotics are stopped and restarted or simply continued depends on the organism involved, the available antibiotic options, the degree of tissue involvement, and the expected time to transplantation. Complete eradication of the infection is unlikely unless the VAD can be explanted in the setting of cardiac recovery or transplantation.

4.3 | VAD cannula/pump infection

Ventricular assist device cannula/pump infections, often accompanied by VAD endocarditis, are the least common but among the most serious of VAD-specific infections. Infection along the cannula or within the pump can lead to dehiscence of the pump anastomoses, pump failure due to obstruction of blood flow, and septic embolic phenomena, including mycotic aneurysms.[16,69,70] Control of infection, initially with intravenous antibiotics with possible transition to oral therapy for chronic suppression, until VAD exchange or transplantation is recommended.[16,72,73] Specific antibiotics should be tailored to the organism involved, as one might for a prosthetic heart valve or other infected endovascular device. Specific additions like synergistic aminoglycosides or rifampin have not specifically been studied in this context, but have been reported as beneficial (in relapse of *S aureus* bacteremia) and may be considered in the appropriate setting.[66] Attention to drug interactions between rifampin and other drugs metabolized through CYP-3A4 and CYP-2C9 (particularly warfarin) is required.[74]

4.4 | Benefits and risks of long-term antimicrobial therapy for VAD-specific and VAD-related infections

One report found that for a group with VAD-related infections (mixed local and bloodstream infections) use of continuous antibiotic therapy through the time of transplant was superior to limited courses of antibiotics, with fewer relapses and shorter time to transplant.[66] In this report, infections with *S aureus* were more likely to relapse with shorter courses of antibiotics. For more invasive infections, including pump pocket, VAD endocarditis, and VAD-related bacteremia, continuous antibiotics are often required through the time of VAD removal. However, despite continuous antibiotic suppressive therapy, both local and disseminated breakthrough infections may occur, most likely due to inadequate source control.

Despite prolonged antibiotic use, associated complications may be relatively few.[75] Potential antibiotic-associated side effects, evolving antimicrobial drug resistance, *C difficile* colitis and line-associated complications must be weighed against the need for antibiotics.

4.5 | Outcomes

In general, several studies have demonstrated that VAD infection does not significantly affect survival to transplantation or survival after transplant.[13,14,29,43,66,76,77] However, pretransplant VAD

implantation and VAD-specific infections may predispose to post-transplant infection, usually in the first 30 days following transplant.[51,78,79] In the Swiss Transplant Cohort Registry, the authors observed increased early post-transplant infectious mortality in this small cohort when preceded by VAD-specific or VAD-related infections.[79] In certain subgroups, such as those with early post-VAD implantation sepsis, VAD endocarditis, or bloodstream infection (which may or may not be VAD-related), mortality is higher and overall survival is impacted.[35,37,68]

Fungal VAD infections are less common and are typically due to *Candida* spp.[28,81] Reported mortality can be quite high in the post-transplant setting. However, this has not been found universally, and transplantation has been performed successfully in select patients with pretransplant *Candida* infection.[16,28,78,81] Non–*Candida* fungal infections, particularly with *Aspergillus* spp. have been reported and are often fatal.[15,29,82] Infection with such organisms would be a strong but relative contraindication to transplantation, as it would in the setting of mold infections for any patient being assessed for transplant.

Experience with mycobacterial infection in VAD is limited to five cases reported in the literature, including infections due to *Mycobacterim chimaera*, *Mycobacterium avium-intracellulaire* complex and *Mycobacterium abscessus* complex.[83,84] Such infections have resulted in superficial and deep driveline, mediastinal, and pump pocket involvement and may progress or disseminate. In general, these infections persist despite prolonged, often difficult to tolerate, combination antimicrobial therapy, and, ultimately, require removal of the VAD for future eradication. Explant of device either by VAD exchange or transplant are described but may still require prolonged combination antimicrobials to ensure resolved tissue involvement. The organism involved, the available antimicrobial treatment options, the extent of the infection, and the potential drug interactions will impact the decision for possible HT in this setting but may not be an absolute contraindication. Further experience is needed for data-driven recommendations.

4.6 | Pretransplant evaluation

For BTT VAD patients, routine and specific vaccinations should be updated (see Vaccine section of fourth edition of AST ID Guidelines). Pretransplant exposure risks should be ascertained and appropriate screening performed as in all organ transplant candidates (see Donor & Recipient Screening section of fourth edition of AST ID Guidelines). Routine VAD care remains essential during this time period. At the time of heart transplant, perioperative antibiotic therapy is often altered from the standard regimen to cover known pathogens of pre-existing VAD infections or colonization.[86,87]

4.7 | Post-transplant management

Intra-operative cultures should be obtained from any suspected infected site, including the mediastinum and the interior and exterior surfaces of the VAD.[20] Pus, along with tissue samples from suspicious tissue surrounding the VAD, driveline, or anastomoses, should be sent for gram stain and bacterial culture and fungal stain and culture, and tissue samples should be sent for histopathology.[20] Antibiotic therapy may be modified based on culture results. For patients who have been maintained on suppressive antibiotics for VAD infection, antibiotic therapy should be continued post-transplant, with length of therapy dependent on severity of infection. Mild infections may only require one week or less of ongoing antibiotics. For patients with more severe infections, such as VAD-related bacteremia or endocarditis, antibiotic therapy should be continued for at least two weeks post-transplant and are often extended longer.[39] During postoperative care, it is important to examine sites of prior infection, such as the former DLES, as purulent infections can recur. Rarely, but importantly, organisms related to pretransplant VAD infection can persist for many months after the device is removed at transplantation and should be considered during evaluation of unexplained post-transplant infection.[51]

4.7.1 | Recommendations

1. In general, VAD infection is not a contraindication to heart transplant, with certain exceptions such as septic shock or mold infection (strong, moderate). For superficial driveline infection, short, finite courses of antibiotics may suffice (weak, low). However, the specific infecting organism, degree of local inflammation and expected time to transplantation (if patient bridged to transplant) should affect the treatment duration (strong, very low).
2. For VAD-related bloodstream infections, especially VAD endocarditis, and pump pocket infection, antibiotic therapy should be continued through the time of transplantation or device removal (strong, moderate). After explant of the VAD at the time of heart transplant, antimicrobials should be continued in the immediate post-transplant period, with the length of therapy dependent on the severity of infection (strong, very low).

5 | INFECTION PREVENTION

5.1 | Perioperative prophylaxis

Antibiotic prophylaxis for VAD-related infections is typically confined to the perioperative setting. To date there have been no prospective trials comparing surgical prophylaxis regimens and VAD-related infection outcomes. A single-center retrospective comparison of single drug (mostly cefazolin) to multidrug (vancomycin, gram-negative agent, fluconazole, and rifampin) at the time of LVAD implantation (mostly HeartMate II) demonstrated no difference in infection-free survival.[88] Thus, surgical infection prophylaxis can be extrapolated in part from cardiothoracic surgery guidelines, which recommend perioperative cefazolin beginning within 1 hour of surgical incision and continuing no longer than 48 hours postoperatively.[86] Vancomycin substitution is recommended in selected environments where MRSA colonization is likely or documented. These would constitute minimum recommended guidelines for surgical infection prophylaxis for

VAD. Due to the distribution of pathogens involved in VAD-related infections, particularly a greater frequency and broader array of both gram positives and gram negatives including *P aeruginosa*, a wider spectrum of coverage has traditionally been used in most programs but is likely not required. Surveys indicate that antibiotic regimens differ between centers and range from vancomycin or cefazolin alone to four agents, typically vancomycin, an antipseudomonal beta-lactam or quinolone, rifampin, and fluconazole.[89,90] However, it is not clear that the gram-negative bacteria and yeast implicated in VAD-related infections are introduced at the time of VAD implantation, as they often emerge weeks to months after implantation[28,37,39] and, thus, may not be impacted by surgical infection prophylaxis. More recent VAD manuals recommend antimicrobial prophylaxis based on the hospital microbial sensitivity profile with sufficient coverage for gram-positive organisms including *S aureus*, coagulase negative staphylococcal spp. and *Enterococcus* spp.[91] This has evolved from earlier manufacturer recommendations for broader coverage of gram-negative and fungal pathogens and is consistent with recent ISHLT guidance on prevention and management of VAD infections.[63]

5.2 | Driveline care

Trauma to the DLES, such as dropping the battery pack or pulling on the driveline, has been associated with onset of driveline infection.[11,39,43] It is thought that loss of tissue ingrowth and exposure of nonepithelialized skin provides a medium for organism growth and biofilm formation. Methods to restrain the driveline are indispensable and various devices for this purpose are available, including binders and anchoring devices.[92,93]

Careful attention to topical care is also highly important for infection prevention, but the optimal method is not known. No dressing change strategy has demonstrated clear superiority. Wu et al[94] reported no difference in type or frequency of dressing changes during the index hospitalization after VAD implantation. Cagliostro et al[93] demonstrated a decrease in DLI incidence with a bundled approach containing dressing kits and an anchoring device compared to a preceding era without such an approach. In general, daily dressing changes are recommended until the exit site is sealed followed by three times a week or weekly changes. Chlorhexidine is the antiseptic of choice with limited data demonstrating decreased driveline infection prevalence compared with use of povidone iodine.[95] The standard dressing change protocol (now used as prepackaged kits in many centers) includes topical antisepsis with 2% chlorhexidine gluconate with a gauze covering or silver gauze topped with a bio-occlusive dressing. Showering may be permitted after effective tissue ingrowth, though specific recommendations vary by center. Driveline care following a traumatic break of tissue ingrowth may warrant intensification of cleansing and dressing changes to avoid bacterial contamination of at risk tissue.

5.2.1 | Recommendations

1. At the time of VAD implantation, perioperative antibiotic prophylaxis is mandatory with coverage provided at a minimum against staphylococcal species (strong, moderate) and limited data supporting single agent use compared to broad coverage used in early clinical trials.
2. Strict attention to driveline care, including avoiding trauma to the exit site, use of driveline fixation devices, and careful cleaning and dressing changes, is critical for infection prevention (strong, low).

6 | PEDIATRICS

Generally, the same principles for VAD infection prevention and management apply to the pediatric population. However, there are important differences in the types of devices utilized for mechanical circulatory support in pediatric patients. Biventricular devices, often paracorporeal, pulsatile, and pneumatically driven, are utilized in >40% in pediatric patients due to common involvement of the right ventricle in childhood cardiomyopathies and viral myocarditis.[96,97] From 2012 to 2015, continuous flow devices accounted for 51% of durable LVAD support in pediatric patients.[99] Increased utilization of continuous flow devices is feasible because HeartMate II and HeartWare HVAD are small enough to allow for implantation into adolescents and, in the case of HeartWare HVAD, larger (weight ≥ 15 kg) children.[100,101]

When reported according to time on device, the rates of VAD-specific infections and early sepsis events are higher with pulsatile flow devices and appear similar to that reported in adults.[98,99] However, localized non-VAD-related infections appear to be more frequent in children, regardless of device type.[99] Infections complicating pediatric VAD support are associated with inferior survival.[99,102] As with reporting of infection with adults, greater attention to definitions of infection and risk according to pre-VAD illness severity illuminating infection risk in this population.[99] Further study of infections complicating pediatric device implantation is warranted.

7 | FUTURE DIRECTIONS/RESEARCH

With the absence of controlled trials in this area, there are many opportunities to improve the evidence-based approach to VAD infection prophylaxis and management. Cooperative, multi-institutional studies are warranted to best define risk factors and prevention strategies for the less frequent, but more serious VAD-specific infections. Research on technological improvements is ongoing. While smaller continuous flow pumps have been introduced, infections remain a significant issue.[5,6,10,31,32,103] And as the driveline itself is the primary risk factor for the majority of VAD-associated infections, elimination of the percutaneous driveline with the use of transcutaneous energy transfer systems has been a longstanding goal.[2] Identifying risk for mortality on the waiting list and how to best include infection risk in a new heart allocation scoring system remain to be defined.

8 | CONCLUSIONS

Patients with VAD infection can, with rare exception, be managed with antibiotics and surgical interventions. HT is not contraindicated in patients with VAD infection and, in fact, is usually curative as the VAD is explanted at the time of transplant. As a general rule, infection does not impact post-transplant survival though those that go on to transplant are likely a selected population. VAD-related bacteremia or fungal infection may be associated with higher mortality and pretransplant VAD infection may lead to post-transplant infections with multidrug-resistant organisms. Careful attention to driveline care is critical for infection prevention.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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