Ventricular assist device-related infections

Rachel J Gordon, Bianca Quagliarello, Franklin D Lowy

Heart failure is a leading cause of death in developed nations despite medical management. Cardiac transplantation is a potentially lifesaving intervention for approximately 4000 advanced heart failure patients per year; however, the demand for donor hearts far exceeds the supply. Ventricular assist devices provide temporary support for patients with severe heart failure until myocardial recovery occurs or a donor heart becomes available. For those ineligible for transplantation, ventricular assist devices may be used permanently and have demonstrated reduced mortality and an improved quality of life compared with continued medical therapy. Nonetheless, these devices are under-used, in part due to the frequency of complications. Device-related infections are one of the most frequent sequela of ventricular assist device placement and occur in 18–59% of cases. Infections can involve any part of the device and confer substantial morbidity and mortality. Here, we provide an introduction to ventricular assist devices, explore the nature and pathogenesis of ventricular assist device-related infections, discuss problems with diagnosis, and present treatment and prevention strategies.

Heart failure

Heart failure occurs in 6–10% of individuals over the age of 65 years in developed nations; and over 2 million patients worldwide have end-stage disease. The prevalence of heart failure in Europe is 0.3–2%; and it affects approximately 10 million people living in nations represented by the European Society of Cardiology. According to the most recent American Heart Association statistics, 5 million Americans have congestive heart failure, with 550,000 new cases annually. In 2003, there were approximately 287,000 deaths where congestive heart failure was an underlying or contributing cause of death. The direct and indirect costs of congestive heart failure total $30 billion. Therapeutic options for those with severe disease are limited. Optimal medical management, including angiotensin converting enzyme inhibitors, beta blockers, and diuretics, may not sufficiently manage advanced heart failure in some patients. Heart transplantation offers definitive treatment for advanced heart failure, with a 1-year survival rate of 87%. Although 2800 transplantations are done annually in the USA, there is a limited supply of donor hearts available for those who could potentially benefit. At the end of 2004, there were over 3300 heart failure patients still on the transplant waiting list in the USA alone.

Ventricular assist devices

Ventricular assist devices were developed to improve circulation in patients with advanced congestive heart failure. These devices function as mechanical pumps for damaged ventricles to maintain adequate blood flow. They may also lead to an improvement in myocardial contractility and reverse remodelling, as evidenced by reduction of fibrosis and hypertrophy, and reversal of chamber enlargement while on ventricular support. There are three indications for mechanical assistance: bridge to recovery, bridge to transplantation, and destination therapy. The most short-term use of a ventricular assist device is as a bridge to recovery. Patients who cannot be weaned from cardiopulmonary bypass due to post-cardiotomy shock or who have dilated cardiomyopathy may require temporary support. If there is recovery from acute injury, ventricular assist device support may be discontinued. Another indication for ventricular assist device usage is as a bridge to transplantation. Patients with advanced congestive heart failure or other heart conditions in which adequate cardiac function is not expected to return (eg, acute myocardial infarction, refractory ventricular tachycardia, or pulmonary hypertension) may use ventricular assist devices for variable periods of time until a donor heart becomes available. Finally, ventricular assist devices may be used for destination therapy. They provide long-term support for patients with advanced heart disease otherwise ineligible for heart transplantation. In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial (REMATCH), patients with advanced heart failure who were ineligible for transplantation (due to factors such as advanced age, end-stage renal disease, or chronic obstructive pulmonary disease) and on ventricular assistance had a 0.52 relative risk of death compared with the medically managed group. This study demonstrates that left ventricular assist devices may serve as long-term myocardial replacement therapy. As such, destination therapy joins cardiac transplantation as a treatment option for advanced heart failure.

Generally, ventricular assist devices are implanted through a median sternotomy incision. They consist of inflow and outflow conduits, unidirectional valves, and a polyurethane chamber (for pulsatile ventricular assist devices) with a pump or rotor. The device is placed in a pocket (pre-peritoneal or intra-abdominal) and has a percutaneous driveline attached to a power/control source outside the body. Figure 1 depicts the most widely used ventricular assist device, the HeartMate left ventricular assist system. Table 1 summarises implantable ventricular devices that are approved for use or are currently being investigated in the USA, Europe, or both. Despite advances in design, substantial complications associated with ventricular assist device use commonly
arise. They include bleeding (30%), right ventricular failure (20–30%), thromboembolism (3–35%), primary device failure (6% at 6 months to 64% at 2 years), and, commonly, infection (18–59%). The frequency of complications varies considerably with device-type—eg, the rate of stroke is higher in the Novacor left ventricular assist device compared with the HeartMate device. Complications may affect the outcome of mechanical circulatory assistance to a significant degree, including both early and long-term mortality. In the REMATCH trial, infection and mechanical device failure in ventricular assist device patients were major contributors to the 2-year survival rate of only 23%.

Ventricular assist devices are costly and reimbursement is variable, which may prohibit their use in some centres. The HeartMate vented electric left ventricular assist device costs approximately US$60 000. In the REMATCH trial, “the mean cost for the initial implant-related hospitalisation was $210 187.” Other investigators commonly report first year costs exceeding US $180 000. Costs increase further when infectious complications occur. In the REMATCH trial, sepsis, pump housing infection, and perioperative bleeding were the three most important predictors of cost. Having sepsis increased predicted costs to $263 822. Prevention of ventricular assist device-related infections may help make ventricular assist device implantation more cost-effective.

Epidemiology

Ventricular assist device-related infections and their complications

Ventricular assist device-related infections occur in 18–59% of patients after ventricular assist device implantation. In a literature review by Baddour and colleagues, infections have been reported to occur in 13–80% of cases. The true incidence of ventricular assist device-related infections is difficult to ascertain for several reasons, including lack of a universal definition of device-related infection, use of historical data, different interpretations of culture results, and different measures of comparison (prevalence rather than incidence is often reported). Ventricular assist device-related infection can involve any aspect of the device: the surgical site, the driveline, the device pocket, or the pump itself. More than half of all ventricular assist device-related infections include multiple sites. In general, driveline infection is the most common type of device-related infection. It may remain local and uncomplicated with appropriate antimicrobial treatment and wound care. However, some patients with driveline infection may become systemically ill and the infection may spread to multiple sites, yielding serious complications. These manifestations include bloodstream infection, relapsing bacteraemia, sepsis, and ventricular assist device-associated endocarditis. Some studies have found locations other than the driveline site to represent most ventricular assist device-related infections. Weyand and colleagues described the predominance of pump chamber infections in infected ventricular assist device recipients (41%), 67% of whom died. In another study, more than half of ventricular assist device-infected patients were bacteraemic. Bloodstream infection is associated with a poor outcome in this population, including complications such as cerebral emboli and multiorgan failure, and several studies have found sepsis to be the number one cause of death during ventricular assist device support. Less common complications of ventricular assist device-related infection include mediastinitis, peritonitis, and pseudoaneurysm. Infections requiring long-term antibiotic use may also predispose patients to Clostridium


**Table 1: Approved and investigational implantable ventricular assist devices**

<table>
<thead>
<tr>
<th>Device Description</th>
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<tbody>
<tr>
<td>HeartMate left ventricular assist system (Thoratec Laboratories Corporation, Pleasonton, CA, USA)</td>
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<tr>
<td>Novacor left ventricular assist system (WorldHeart Inc, Ottawa, Canada)</td>
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<tr>
<td>ThoratecVAD and Implantable VAD (IVAD) system (Thoratec Laboratories Corporation, Pleasonton, CA, USA)</td>
</tr>
<tr>
<td>LionHeart-2000 ventricular assist system (Arrow International, Reading, PA, USA)</td>
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<tr>
<td>Novacor II left ventricular assist system (WorldHeart Corporation, Ottawa, Canada)</td>
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<tr>
<td>DeBakey ventricular assist device (MicroMed Technology Inc, Houston, TX, USA)</td>
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<tr>
<td>Flowmaker/Jarvik 2000 (Jarvik Heart Inc, New York, NY, USA)</td>
</tr>
<tr>
<td>HeartMate II left ventricular assist system (Thoratec Laboratories Corporation, Pleasonton, CA, USA)</td>
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<tr>
<td>HeartQuest (WorldHeart Inc, Ottawa, Canada)</td>
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</table>

**difficile enterocolitis.** Table 2 summarises studies that compare infected with non-infected ventricular assist device recipients.

**Timing of ventricular assist device-related infections**

Most ventricular assist device-related infections occur between 2 weeks and 2 months of implantation. In an investigation by Deng and colleagues, pump pocket infection, bacteraemia, and endocarditis occurred most frequently within the first month post-implantation and only 5–10% of patients developed infections beyond 3 months. The risk of driveline infection may peak earlier than pump pocket infection. In a case review, median time from device placement to diagnosis of ventricular assist device-related infection was 31 days, and in the REMATCH trial, the risk for sepsis peaked between 20 and 30 days post-surgery. The cumulative risk of infection increases with duration of ventricular assist device use.

**Microbiology of ventricular assist device-related infections**

Ventricular assist device-related infections are typically caused by Gram-positive organisms and are usually staphylococcal species. Simon and colleagues found 38% and 24% of bloodstream infections to be caused by *Staphylococcus epidermidis* and *Staphylococcus aureus*, respectively. Deng and colleagues demonstrated that staphylococci were cultured in 46% of driveline and device pocket infections and 36% of blood cultures. *S aureus* was responsible for 56% of ventricular assist device infection recurrences in one case review. Other Gram-positive organisms commonly implicated are enterococci. In one study, enterococci were
responsible for 18% of driveline and device pocket infections, and 20% of bloodstream infections. Enterococci have been associated with a negative outcome.19

Gram-negative bacilli—eg, *Pseudomonas aeruginosa*, *Enterobacter* species, and *Klebsiella* species—also have a prominent role in ventricular assist device-related infection15,24,34,38 and are associated with a poor outcome. In a review by Sivaratnam and colleagues,16 50% of deaths due to ventricular assist device-related infection before transplantation were caused by Gram-negative sepsis. Resistant organisms—eg, meticillin-resistant *S aureus* (MRSA), vancomycin-resistant enterococci, and pseudomonas—are common in the setting of device-related bloodstream infections.5,13,18

Fungi are also commonly implicated in ventricular assist device-related infections, and may pose serious risks. In one study, 35% of ventricular assist device recipients had positive fungal cultures.40 Although only 67% of those patients were clinically symptomatic, half of those who were symptomatic died. Gordon and colleagues46 found fungaemia in ventricular assist device patients to have the highest hazard ratio for death, followed by Gram-negative bacteraemia, and then Gram-positive bacteraemia. *Candida* spp are the most common fungi to infect ventricular assist devices,21,36,40 with little speciation recorded in studies to date. Aspergillus infrequently causes ventricular assist device-related infection.46 The use of broad-spectrum antibiotics may predispose ventricular assist device patients to fungal infection as well as complicate pre-existing infections. In one study, all fungal ventricular assist device-associated endocarditis patients had one or more concomitant bacterial infection(s) following the use of broad-spectrum antibiotics.46

Transplantation and ventricular assist device-related infection

Ventricular assist device-related infection may affect outcomes both before and after transplantation. Although several studies have not shown that ventricular assist device-related infection reduces overall survival to transplantation,19,40 the development of serious ventricular assist device-related infection, such as endocarditis, is associated with up to 50% mortality.21,22,33 Serious infections may also persist beyond transplantation. Poston and colleagues39 reported continued bacteraemia following transplantation in 80% of ventricular assist device patients with device-related bloodstream infections. This study also found device infection of any type during ventricular assist device support to be significantly associated with decreased survival after transplantation (p<0.01). Simon and colleagues40 reported increased early post-transplant mortality in patients with infection during ventricular assist device support, but there was no difference in long-term survival. In other studies, ventricular assist device-related infection did not appear to influence survival post-transplantation.23,48,52 The prevailing opinion is that although ventricular assist device-related infection may pose additional risks to the patient, infection does not preclude the procedure itself.5,46

Trends in ventricular assist device-related infections

Although infection remains a common complication of ventricular assist device placement, there is evidence that the infection rate is declining. A recent study comparing data from the REMATCH trial to the outcome of patients on destination therapy following market approval of the HeartMate left ventricular assist device demonstrated that the rate of sepsis had decreased from 0·60 to 0·46 events per patient-year and the rate of driveline/pocket/device infection had dropped from 0·54 to 0·38 events per person-year since 2001.52 These decreases may be due to improved patient selection and management, including better antimicrobial prophylaxis and improved devices (eg, smaller size, better durability). In addition, improved outcomes after the REMATCH trial may reflect physician experience, as evidenced by a lower incidence of sepsis at specific investigative centres during the trial.32 Despite these improvements, the rate of ventricular assist device-related infection still remains unacceptably high and limits the outcome of long-term therapy in the treatment of end-stage heart failure.

Pathogenesis

To date, there has been limited investigation of the pathogenesis of ventricular assist device-related infections. This complex process likely involves a combination of ventricular assist device-related, surgical, host, and bacterial factors.

Most ventricular assist devices are large devices and are susceptible to infections at numerous sites, including the internal components of the device (eg, pump membrane and inflow and outflow tracts), the pump pocket, and the driveline exit site. These infections are often associated with concomitant bloodstream infection.19 Ventricular assist device placement may also result in wound infection or other nosocomial infections.6,35 The pathogenesis of particular ventricular assist device-related infections, in part, is dependent upon the site infected. Given the high frequency of staphylococcal infections, many ventricular assist device-related infections are probably caused by the patients’ own commensal flora.40,35

Ventricular assist device-related endocarditis

When the inner components of the ventricular assist device are infected, a ventricular assist device-related “endocarditis” is established.29 The device may be inoculated during or after implantation.3,13,28 Ventricular assist device patients frequently have bacteraemias (and fungaemias) as a result of coincident nosocomial infections such as catheter-related infection, pneumonia,
<table>
<thead>
<tr>
<th>Reference, study design, number of patients, cohort dates</th>
<th>Device type (n)</th>
<th>Duration VAD implanted (days)</th>
<th>Definitions of infection used in study</th>
<th>Number (%) infected</th>
<th>Pathogens (by site when available)</th>
<th>Infection risk factors and outcomes</th>
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<tr>
<td>Argenziano et al.†,‡ prospective observational, 60 patients, 1990–95</td>
<td>HeartMate VE (44), IP (16)</td>
<td>Median: 93, range: 0–566</td>
<td>General definition (including BSI, driveline, PP infection): signs of infection (fever, leucocytosis, purulent drainage) associated with positive culture</td>
<td>Overall: 29 (48)</td>
<td>Driveline: Candida spp, Strep. spp, Staph. aureus, Pseudomonas spp</td>
<td>LVAD-IE showed trend towards high mortality (50%)</td>
</tr>
<tr>
<td>Gordon et al.**,† prospective observational, 214 patients, 1992–2000</td>
<td>HeartMate VE (88), IP (70), and Novacor (56)</td>
<td>Not reported</td>
<td>Nosocomial BSI defined by CDC criteria</td>
<td>Nosocomial BSI: 104 (49)</td>
<td>Nosocomial BSI: GPC (46·4%) including coagulase-negative staphylococci, Enterococcus spp (7·8%), GNR (29·5%) including P. aeruginosa 11·4% and Entrobacter spp (71·7%); Candida spp (15·7%); polymicrobial (8·6%)</td>
<td>BSI associated with increased mortality</td>
</tr>
<tr>
<td>Herrmann et al.,† prospective observational, 32 patients, 1993–96</td>
<td>Novacor (24)</td>
<td>Mean: 8.5, median: 55</td>
<td>LVAD infected: bacterial growth of pathogens from more than two non-adjacent sites proven identical in PFGE, with or without clinical signs of infection</td>
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<td>Proper explant cultures available for 25 patients Overall: 12 (48) infected, of whom seven had clinical signs infection</td>
<td>Older age Longer duration of ventilatory support Infected patients less likely to survive to transplant</td>
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<tr>
<td>Holman et al.‡ randomized clinical trial, 129 patients, enrollment 1998–2001</td>
<td>HeartMate VE (68); No VAD, optimised medical management (61)</td>
<td>40.8 (median survival) in device group vs 150 in medical management group</td>
<td>For both groups, localised infection defined as an infection localised to an organ system or region without systemic involvement and sepsis defined as a systemic response to a serious infection. For the VAD group only: driveline or PP infection defined as a positive culture and use of intravenous antibiotics. Pump housing or inflow/outflow tract infection defined by a positive culture</td>
<td>Among VAD patients, sepsis: 28 (41) Septic death: 20 (29), driveline/PP infection: 19 (28) Pump housing or inflow/outflow tract infection: 11 (16)</td>
<td>Pathogens from device surface (n): S. aureus (3), S. epidermidis (4), Corynebacterium spp (1), B. cereus (1), Candida albicans (1) Device pathogen identical to blood pathogen in four patients and to driveline exit site pathogen in three</td>
<td>Pre-operative history of renal disease and a subgroup of medical centres were risk factors for sepsis</td>
</tr>
<tr>
<td>Malani et al.,§ observational, 35 patients, 1996–99</td>
<td>HeartMate VE (36 in 35 patients)</td>
<td>Mean: 73 (SE 60), range: 2–262</td>
<td>Nosocomial and superficial and deep surgical site infections were defined by CDC/National Nosocomial Infections Surveillance System criteria Infections considered nosocomial if occurred 24 h after VAD implantation to 48 h after VAD explantation Overall: 36 nosocomial infections in 24 patients (68): Surgical site infection: 16 (46); superficial, six deep, involving device or pocket, and three deep soft-tissue</td>
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<td>For catheter site and BSI (not necessarily VAD-related): coagulase-negative staphylococci (4), Candida spp (3), Serratia marcescens (1) For SSI (VAD-related or sternal wound): coagulase-negative staphylococci (3), E. faecium (2), Candida spp (2)</td>
<td>Haemodialysis was associated with deep soft-tissue or organ space surgical site infections</td>
</tr>
<tr>
<td>Simon et al.‡,§ retrospective observational, 76 patients, 1994–2003</td>
<td>HeartMate VE (42), IP (34)</td>
<td>46 (mean) with VAD-related infection or 66 without VAD-related infection*</td>
<td>Infections categorised as local or BSI Local infection (driveline or PPI): purulence at the exit site or pump pocket, respectively, and isolation of one or more pathogen(s) BSI included LVAD-related BSI (same organism from more than one blood culture and from another device site), and presumed LVAD-related BSI (same organism from more than one blood culture, but no other source). LVAD-IE (same pathogen in more than one blood culture and histopathological evidence of infection inside the device) Overall: 38 (50) Incidence: 4.9 per 1000 LVAD-days Local infection: 17 (22)</td>
<td>Overall: 38 (50) Incidence: 4.9 per 1000 LVAD-days Local infection: 17 (22)</td>
<td>Isolated pathogens (n): S. aureus (6), Enterococcus spp (3), S. epidermidis (2), E. coli (2), Corynebacterium spp (1), P. aeruginosa (1), S. marcescens (1), Acinetobacter spp (1) 5·9 per 1000 LVAD-days</td>
<td>Patients with BSI were more likely to have diabetes mellitus (OR 7·7; 95% CI 2–30)</td>
</tr>
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Table 2: Selected clinical studies describing ventricular assist device-related infections

and urinary tract infection. Infections of other parts of the device, such as the pump pocket and driveline exit site, may also lead to bacteraemia or fungaemia. These bacteraemias or fungaemias provide an opportunity

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for pathogens to attach to portions of the ventricular assist device that are in contact with the bloodstream.

The probability of an organism in the bloodstream attaching to the ventricular assist device and causing ventricular assist device-related endocarditis depends on several factors, including characteristics of the device surface, the amount of turbulent blood flow in the device, and the adherence properties of the organism. Increased surface area of the device and areas of turbulent flow increase the chances a bloodborne pathogen will adhere. 

Device design may help determine susceptibility to ventricular assist device-related endocarditis—for example, rotary (axial) pumps with continuous rather than pulsatile flow may have lower infection rates. Certain pathogens—such as Staphylococcus aureus—may have the capacity to bind directly to the device surface, while others may not. However, the textured polyurethane membrane in some ventricular assist devices (eg, HeartMate) becomes coated with a “pseudoneointimal” surface shortly after insertion. First, platelets and fibrinogen attach and a fibrin matrix is established, followed by attachment of different cell types, including pluripotent haematopoetic cells. Connective tissue cells, including myofibroblasts, also associate with the fibrin matrix and produce a collagenous matrix consisting of extracellular matrix components such as proteoglycans and glycopeptides. Exposed extracellular matrix components and various cellular components in this pseudoneointimal layer also provide potential binding sites for pathogens. Arrecubieta and colleagues examined the interaction of S. aureus and polyurethane membranes from explanted HeartMate ventricular assist devices. Scanning electron microscopy demonstrated binding of S. aureus directly to extracellular matrix components as well as cellular components of the pseudoneointima (figure 2).

S. aureus, one of the most frequent pathogens in ventricular assist device-related infections, expresses microbial surface components recognising adhesive matrix molecules (MSCRAMMs) on the cell surface that mediate binding to host extracellular matrix components. MSCRAMMs are postulated to mediate adherence to the pseudoneointimal layer on the ventricular assist device. Arrecubieta and colleagues also studied the effect of several candidate MSCRAMMs on binding and demonstrated that clumping factor A (ClfA) and fibronectin binding proteins A and B (FnBPA and FnBPB) significantly increased binding to the ventricular assist device membrane in vitro as well as in an in-vivo murine model (p<0.05). When ventricular assist devices that had been implanted more than 6 months were used in experiments, bacterial binding was substantially decreased. This decrease likely reflects changes that occur in the pseudoneointima as it evolves and is consistent with a decreased infection rate as time from implantation increases.

Pump pocket infection

The pump pocket is also prone to infection. Generally the pump is placed in a preperitoneal space created below the lateral rectus sheath, but it may also be placed intraperitoneally. This space, which often contains a

![Figure 2: Scanning electron microscopy of the pseudoneointimal surface lining an explanted ventricular assist device polyurethane membrane (HeartMate)](http://infection.thelancet.com)
haematoma or fills with fluid, may be inoculated at the time of surgery or thereafter. It is postulated that organisms introduced via the driveline exit site may ascend to infect the pump pocket. Organisms may form biofilms on the device or persist in fluid in this poorly perfused space, which is surrounded by scar tissue, conferring protection from host defences and antibiotics. Larger devices, with greater surface area, may be more prone to infection. Pocket infections, akin to closed-space infections, are not uncommonly associated with systemic manifestations and bacteraemia.

**Driveline infection**

The driveline is the most common site of ventricular assist device-related infection. For ventricular assist devices that have drivelines, host tissues and the ventricular assist device are exposed to the external, contaminated environment. Current drivelines are large because they generally incorporate a power source and a vent. Drivelines are covered in velour to facilitate integration into patient skin and soft tissues. Healing of the exit site involves forming an adherent interface between the velour and the patient's tissues. This interface, when intact, protects against the entry of microorganisms and subsequent infection. Driveline trauma, especially as patients become mobile, is an impediment to healing. After shearing and torsion of the driveline disrupts the adherent interface, continued sliding of the driveline over the tissues can prevent readherence, resulting in a neoeinthelialised surface that forms a tract adjacent to the driveline. It is postulated that this tract predisposes to infection, since it allows organisms to enter, form biofilms, and grow along the driveline.

Driveline infections are often caused by staphylococcal species, probably because these species colonise the skin and nares and can easily inoculate the driveline and tissues surrounding the exit site. Particular MSCRAMMs may facilitate binding to the driveline. The commensal flora, which probably cause most of these infections, may be preselected by hospital environmental factors that include antibiotic selective pressure and virulence traits that facilitate colonisation. Organisms may also be introduced by the hands of caregivers.

Driveline infections are often associated with other infections of the ventricular assist device and bloodstream, indicating that the driveline may be the initial source of some of these infections. Herrmann and colleagues presented four of 12 cases where organisms cultured from the blood were identical by pulsed field gel electrophoresis to those cultured from the explanted ventricular assist device. In three cases, the same organism cultured from the ventricular assist device was also found at the driveline exit site. Vilchez and colleagues also presented three cases where organisms obtained from the driveline site were identical to or closely related to organisms obtained from blood cultures. Ventricular assist devices that are totally implantable, such as the Arrow LionHeart left ventricular assist system, may substantially decrease the risk of ventricular assist device-related infection.

**Host risk factors**

Advanced age, comorbid disease, immunosuppression, suboptimal nutrition, presence of indwelling catheters, and prolonged hospital stay are several factors that could contribute to an overall increased risk of infection in these patients. In a prospective study by Herrmann and colleagues, individuals with ventricular assist device-related infections were older (53 vs 38 years old) and required longer ventilatory support (90 vs 42 days) than those without infections. Poston and colleagues reported that length of intensive care unit stay and re-operation on ventricular assist device support were independent predictors of device-related bloodstream infection. Diabetes mellitus and/or hyperglycaemia may also increase the risk of bloodstream infection while on ventricular assistance. In a study by Malani and co-workers, patients requiring haemodialysis were at increased risk for deep surgical site infection compared with patients who were not in renal failure (77·8% vs 30·7%, p=0·02). Similarly, in the REMATCH study, a pre-operative history of renal disease was found to be a risk factor for sepsis. Hypoalbuminaemia at baseline (an indicator of poor nutritional status) may also be a predictor of device-related bloodstream infection.

Immune system dysfunction may predispose ventricular assist device recipients to infection. Independently, congestive heart failure contributes to relative immunodeficiency. However, ventricular assist device placement may further impair host immunity. Compared with congestive heart failure patients without ventricular assist devices, those with ventricular assist devices were less likely to respond to mump and candida antigens, demonstrating a diminished T-cell response. On average, ventricular assist device patients also had fewer CD4 T cells and showed signs of possible aberrant T-cell activation. T cells from ventricular assist device patients may have increased rates of apoptosis. Ventricular assist device placement also appears to induce B-cell hyper-reactivity and the production of auto-antibodies.

**Diagnosis and presentation**

Although infection is a common complication of ventricular assist device use, there are few documented, prospective, detailed comparisons of clinical signs and symptoms between infected and non-infected individuals. Ventricular assist device-related infections may be associated with few signs and symptoms or may be difficult or impossible to differentiate from infections at other sites. Positive cultures, representing contamination or colonisation, may be incorrectly interpreted as representing clinical infection. Currently, there are no
universally accepted criteria to diagnose the wide range of ventricular assist device-related infections in either the clinical or investigational setting. Different studies use different definitions. A set of validated criteria would help quantify ventricular assist device-related infections and promote proper comparisons of infection rates among different clinical centres, devices, and prevention strategies.

The clinical presentation of ventricular assist device-related infections is varied. In a review of 25 cases of ventricular assist device-related infection, Sivaratnam and colleagues reported several common signs and symptoms, including fever (n=14), leucocytosis (n=7), drainage from the exit site (n=7), and other abnormalities around the driveline exit site such as bleeding, pain, erythema, and necrosis. Infections at the driveline site and surgical site may be obvious, with signs such as purulent discharge, pain, and erythema. Concomitant bloodstream infections may occur. However, driveline infections may also present subtly, with new or persistent serous drainage, non-integration of the driveline, and/or wound dehiscence. Infections of the pump pocket may or may not show local signs of infection above the site. They may also present with systemic illness including bloodstream infection, fever, and leucocytosis.

Ventricular assist device-related endocarditis may present similarly to prosthetic valve endocarditis. Signs include persistent fever and positive blood cultures. There may be skin findings and/or evidence of embolisation to organs such as the brain and kidney. In several series, the presentation of ventricular assist device-related endocarditis has also included mechanical complications such as ventricular assist device inlet obstruction, ventricular assist device outflow rupture, and haemotoma or bleeding within the device. Ventricular assist device-related endocarditis sometimes exists without overt signs and symptoms. More subtle presentations may include signs such as progressive cachexia and slightly raised temperatures. In some reports, organisms have been cultured from the explanted device from patients who did not appear clinically infected before device removal. It is unclear whether these represent contaminated samples or undiagnosed infections.

The diagnosis of ventricular assist device-related infection depends on the criteria used. A patient could be regarded as infected in one study, but not in another. In some series, infection definitions were not specified or positive cultures alone were sufficient to define infection, while in others a positive culture had to be associated with clinical signs. Some studies attempted to distinguish device-related bloodstream infections from non-device-related bloodstream infections. Without using molecular typing techniques this is a difficult task, especially in the setting of indwelling catheters.

Given the difficulties with diagnosis of infection in the ventricular assist device patient, we recommend that these patients be fully evaluated, including a comprehensive physical examination, when infection is suspected. Non-ventricular assist device sources of infection—eg, pneumonia, urinary tract infection, and indwelling catheter infection—should be investigated with chest radiography and Gram stains and cultures, where applicable. Blood cultures (preferably two or more) should be obtained. When a wound or driveline infection is suspected, the site should be cleaned with antiseptic, allowed to dry, and swabbed (as deeply as possible) with a premoistened culturette, especially if fluid can be expressed from the site. The sample should be sent for culture and Gram stain.

The usefulness of imaging techniques in localising sources of ventricular assist device-related infections is unclear. The American Heart Association recommends ultrasound to evaluate pocket site infections. Transoesophageal echocardiography is recommended to evaluate endocarditis; vegetations may be seen on the inflow-tract, native, or prosthetic valves. Computed tomography imaging may be useful to identify collections around the device, but may be limited due to artifact and the inability to administer intravenous contrast in the setting of renal insufficiency. Imaging may reveal collections that can be cultured/evaluated, but collections, whether infected or not, are often associated with device placement. In some cases, immunoscintigraphy (labelled white blood cell scans) has been used to identify infected sites. Others have not found these imaging techniques to be helpful.

**Treatment**

Empiric treatment of ventricular assist device-related infections is dependent on the suspected site(s) of infection and the degree of illness. Often, empiric therapy is instituted early because of patients’ multiple medical problems. While blood cultures and a full diagnostic work-up are pending (when possible, cultures should be obtained before initiation of antibiotics), empiric treatment of sepsis includes broad-spectrum antibiotics, including Gram-positive (eg, vancomycin for possible MRSA), Gram-negative, and, often, fungal coverage. Antibiotic selection should include consideration of the institution’s microbial resistance patterns, resistance patterns of any organisms previously cultured from the patient, and the patient’s antibiotic history. Empiric antibiotic treatment for local infections, such as the driveline exit site, includes Gram-positive (especially staphylococcal) coverage. Consider adding systemic Gram-negative coverage for surgical wounds and pump pockets. It is important to obtain cultures of all relevant sites before the initiation of antibiotics.

Culture results should be used to guide and tailor antibiotic therapy. Wound care, drainage, and debridement should be done when indicated. Device infections are best treated by removal of the device. Unfortunately, donor hearts may not be available and
revisions and replacements of infected devices confer high risk of morbidity, perioperative mortality, and infection relapse.6 In the REMATCH trial,4 1 and 2 year actuarial survival rates following device replacement were 41% and 33%, respectively. Usually suppressive therapy is attempted and if necessary (ie, refractory sepsis, an embolic event), transplantation or a device change is done more urgently.35

Driveline infections can sometimes be managed solely with wound care and antibiotics, but relapse is common.18 One group reported successful treatment of a deep driveline infection with excision, drainage, and application of a vacuum-assisted closure system.46 Pump pocket infections require drainage. After drainage, some pump pocket infections have been successfully managed by placing antibiotic-impregnated polymethylmethacrylate beads in the pump pocket.49,52 Others have attempted to wrap the pump pocket in an omental or muscle flap to help control the infection.11,35 Simon and colleagues27 found continuous antibiotic use before, during, and after transplantation to be associated with fewer relapses than when a limited course of antibiotics was used; however, this comparison was made in an observational study and subject to selection bias.

The length of therapy necessary to treat ventricular assist device-related infections is unknown and in many cases is individualised. For local, superficial infections, antibiotic therapy generally should continue until drainage stops and the site has healed (eg, the driveline has re-integrated). When endovascular ventricular assist device-related infections are suspected, antibiotics should continue at least until the device is removed. If there was a recent Staphylococcus aureus bacteraemia or there are metastatic foci or native valve endocarditis, antibiotics are often continued after ventricular assist device explantation.

Prevention
Numerous strategies have been used to prevent ventricular assist device-related infections. Without any clinical trial data, the efficacy of these strategies is difficult to gauge based on clinical experience alone.39

Surgical prevention strategies
There are numerous techniques being used in the operating room to attempt to avert ventricular assist device-related infection; however, the effectiveness of ventricular assist device-specific strategies is based on clinical experience. Chinn and co-workers40 provide a comprehensive set of intraoperative infection prevention guidelines. In the operating room, traffic should be minimised, high efficiency particulate filters used, and operating room staff should dress in clean scrubs and cover all exposed hair.39,38 Some suggest wrapping the pump and driveline in antibiotic-soaked laparotomy pads (eg, vancomycin and gentamicin) before placement.35 Tunneling of the driveline contralateral to the pump pocket is recommended, since this increases the subcutaneous course, potentially delaying ascension of pathogens to the pump pocket.30,34 The driveline exit site should be well secured with an occlusive dressing.25,32 Poston and colleagues19 also suggest techniques that have been useful for general surgery patients, such as tight glucose control, skin warming, and 80% or more inspired oxygen during surgery.

Postoperative infection prevention
In the postoperative period, standard procedures such as extubating the patient, administering pulmonary toilet, and removing all unnecessary catheters and intravenous lines as soon as possible are recommended.13,35 Physical rehabilitation should commence and nutritional status should be addressed.19,68,84 The driveline exit site requires daily disinfection and dressing changes with aseptic technique. If necessary, dressing changes should be done more frequently to keep the wound dry and clean.24,38,39 Some recommend silver-impregnated dressings.18 Stabilisation of the driveline is also important. Abdominal binders are often used,34,39 while others recommend using additional gauze, tape, sutures, or stoma-adhesive devices.73 Education of the patient to avoid driveline trauma and to alert the care team if the driveline becomes unstable may also be helpful.70

Prophylactic antibiotics
Mupirocin ointment can be applied before surgery in attempt to eliminate nasal colonisation and prevent infections with staphylococcus. However, there is limited data to support its efficacy and mupirocin resistance may develop.39,56 Systemic antibiotics are routinely given before, during (re-dose if indicated), and up to 48 hours after ventricular assist device implatation. Different centres have reported using different regimens. New York-Columbia Presbyterian Hospital used vancomycin, a fluoroquinolone, rifampicin, and fluconazole during the REMATCH trial. Other groups have used similar regimens or fewer drugs.23,36,45,80 Selection of a prophylactic antibiotic regimen should depend on resistance profiles at the particular site and closely consider the prevalence of meticillin-resistant staphylococci and staphylococcal resistance profiles. In some instances, prophylactic antibiotic regimens should be amended for individuals with a history of colonisation or infection with resistant organisms. Care should be made to discontinue prophylactic antibiotics after 48 hours.18

New prevention strategies
New techniques to help prevent ventricular assist device-related infections are also being developed. Placement of the pump into the abdominal wall may be associated with more infections than intraperitoneal placement, although intraperitoneal placement confers other risks including injury to abdominal viscera. In nine patients, parts of the pump and inflow and outflow
tracts were wrapped in either Dacron or Hemashield (Boston Systems, Meadow Medicals Inc, Oakland, NJ, USA) material to help stabilise the device and promote integration into host tissues. In this study, pump pocket infection was decreased from 33% (in the previous 21 patients who were implanted) to 11% in those who received the graft material. Some surgeons place the pumps intraperitoneally within synthetic pouches, which helps protect the abdominal organs and may also reduce infection risk. Antibiotic-impregnated drivelines (eg, with chlorhexidine, triclosan, and sulfadiazine) are also being investigated. They may prove efficacious as they show potential in murine and rat models.

Advances in device development will likely decrease ventricular assist device-related infections. Smaller, axial devices or devices with improved flow dynamics may decrease the infection risk. In nine patients with 7-8 years of cumulative support with the DeBakey ventricular assist device, there was only one minor infection. Fully implantable devices, protected from pathogens in the external environment, will eliminate driveline infections and may potentially reduce all types of ventricular assist device-related infections.

Future studies
In the future, a set of criteria to diagnose ventricular assist device-related infections should be generated and validated. Universal criteria will help determine the incidence of ventricular assist device-related infections and allow comparisons of infection rates among different centres, device types, surgical techniques, and prevention strategies. New prevention and treatment strategies, such as those discussed above, should be rigorously investigated. Other prevention strategies—eg, an efficacious antistaphylococcal vaccine—should be developed as well.

Ventricular assist devices have great potential to ease the morbidity and mortality associated with heart failure. Since infection is one of the most common complications of ventricular assist device use, development of successful strategies to prevent and manage ventricular assist device-related infections is essential.


45 Herrmann M, Weyand M, Greshake B, et al. Left ventricular assist device infection is associated with increased mortality but is not a contraindication to transplantation. Circulation 1997; 95: 814–17.


52 Holman WL, Pamboukian SV, Blood M, Tallaj JA, McGiffin DC, Kirklin JK. Managing device infections: are we progressing or is infection an insurmountable obstacle? Asiao J 2005; 51: 452–55.


