Review

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Endocarditis in left ventricular assist device

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Summary **Heart failure is one of the leading causes of death in developed nations. End stage heart failure often requires cardiac transplantation for survival. The left ventricular assist device (LVAD) has been one of the biggest evolvements in heart failure management often serving as bridge to transplant or destination therapy in advanced heart failure. Like any other medical device, LVAD is associated with complications with infections being reported in many patients. Endocarditis developing secondary to the placement of LVAD is not a frequent, serious and difficult to treat condition with high morbidity and mortality. Currently, there are few retrospective studies and case reports reporting the same. In our review, we found the most common cause of endocarditis in LVAD was due to bacteria. Both bacterial and fungal endocarditis were associated with high morbidity and mortality. In this review we will be discussing the risk factors, organisms involved, diagnostic tests, management strategies, complications, and outcomes in patients who developed endocarditis secondary to LVAD placement.**

Keywords: Endocarditis, left ventricular assist device (LVAD)

1. Introduction

Heart failure is one of the leading causes of death in developed nations (*1*). As per Center for Disease Control, in 2013 around 5.1 million people were reportedly diagnosed with heart failure in the United States. Management of heart failure costs approximately 32 billion dollars each year. In 2009, 1 in 9 deaths were reported with congestive heart failure as the underlying cause of death. Cardiac transplantation is a widely known management for end-stage heart failure patients. But the patients who demand a transplant exceeds the donor pool and thus the time spent on the waiting list is too long. The introduction of a left ventricular assist device (LVAD) made a drastic evolvement in management of heart failure. It can be used as a bridging therapy while waiting for the recovery of the donor (*2*) and also can be used as destination therapy (*3*). Thus, it serves as an excellent solution to overcome the constraints of a limited donor pool and improves the overall survival of the patient. LVAD is reported to influence and improve myocardial contractility (*4*). It also reduces the ongoing hypertrophy and fibrosis, thus resulting in the reversal of remodeling (*5*).

As any other device-oriented medical therapy, LVAD has its own limitations and complications, with infections being reported in 60% of the patients (*6*). Patients who develop endocarditis secondary to LVAD placement have a very high mortality rate (*7*). Early diagnosis and management will help in reducing this mortality. The primary objective of this review is to outline and discuss the different types of endocarditis associated with LVAD, risk factors, diagnostic methods, management, complications, and outcomes.

2. Methodology

A systematic review of the MEDLINE database was conducted using the PubMed search engine. We included all articles published between January 1, 1990, and May

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1, 2016. In PubMed, the combination of medical text terms used included "endocarditis", "left ventricular assist device" and "LVAD". We included all prospective or retrospective studies, review articles, case series and case reports. We found in our search that there was a total of 9 studies reporting endocarditis in patients with LVAD. 3 of the studies were retrospective reviews and 6 of them were case reports. We also searched the reference lists of the manuscripts by this strategy and selected those found to be relevant. All pertinent reports and reference lists were searched to identify any additional studies that could be included. All data were accessed between February and May 2016.

3. Left ventricular assist device

The approach towards end stage heart failure has been revolutionized with the introduction of LVAD therapy, which acts as a mechanical pump to improve the patient's circulatory status. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial (REMATCH), randomized 129 end-stage heart failure patient's ineligible for cardiac transplant to medical therapy versus pulsatile LVAD therapy and demonstrated a significant improvement in one-year survival of patients with LVAD (53% in LVAD arm versus 25% in medical therapy arm) with a hazard ratio for LVAD being 0.5 compared to medical treatment. It was thus concluded that LVAD can serve as a long-term treatment therapy in patients with end-stage heart failure and an effective bridge or alternative therapy to cardiac transplantation (*8*). Over time, the device has now evolved into an efficient flow pump with smaller size and lighter weight specifications in comparison with the older heavy, large and fill to empty devices (*9*). The two types of devices available currently are continuous flow (Heartmate II LVAD and Heartware HVAD) and pulsatile flow (Heartmate XVE) LVAD. Continuous flow LVAD weighs 390 gm while pulsatile flow weighs 1250 gm. Both devices significantly enhance the functional capacity as well as the quality of life. Commonly, the pumps are implanted through a median sternotomy incision. The pump is textured to prevent thrombus formation (*10*). It consists of inflow duct, unidirectional valve and outflow duct. The implanted LVAD pumps draw blood from the left ventricle and delivers it to the ascending aorta. The pumps are connected to an external power source and controller which delivers electricity *via* percutaneous leads (*1,11*). By the year 2013, the number of mechanical circulatory support device implants in the United States was more than the number of heart transplants (*12*).

4. Infections in LVAD

Infection is a commonly associated complication of any implanted cardiac device. As mentioned previously, it has been reported that 60% of patients undergoing LVAD develop some sort of infection (*6*). These include bloodstream infection, sepsis, and endocarditis (*1*). The major cause of readmission in LVAD patients is an infection (*13*). In the REMATCH trial, infection and device failure in ventricular assist device patients were reported to be the dominant factors contributing to the drop in 2-year survival rates from 53% to 23%. The trial also listed sepsis, pump infection and peri-operative bleeding as the main predictors of cost-effectiveness (*8*). The pump pockets, drive line, and cannula/intravascular pump are susceptible to biofilm formation and acts as a nidus for chronic infection and bacteremia. Surgical site infection can also occur. Less common infections include peritonitis, mediastinitis, and pseudoaneurysms. Poor prognosis is associated with bloodstream infection, which can be complicated, by cerebral emboli and multiple organ failures (*1*). It has also been reported that few patients who underwent cardiac transplantation followed by removal of LVAD device developed late onset driveline infection leading to complications (*14*).

5. Endocarditis in LVAD

Endocarditis in patients with LVAD has a 50% mortality rate (*7*). LVAD-associated endocarditis is defined as clinical evidence of pump and/or cannula infection along with the presence of vegetation on echocardiography or a vascular phenomenon as defined by modified Duke's criteria (*15*).

5.1. *Risk factors*

LVAD devices usually get infected during or after implantation (*1*). Commonly the pathogens colonize the internal surface of LVAD *via* bloodstream infiltration and the external surface *via* local infiltration (*10*). The colonization of organisms on the device depends on multiple factors such as turbulence of flow, the device surface and the adherent nature of the pathogen. The surface of the device is commonly a textured polyurethane membrane, which is coated with a pseudo-neointimal layer. Platelets and fibrinogen adhere here and form a fibrin matrix, which acts as a trap for other types of cells. Connective tissue cells such as myofibroblasts attach here and form a collagenous matrix. This serves as a potential site for the adherence of pathogens, thus leading to infection (*16-19*).

5.2. *Bacterial Endocarditis*

In our review, bacterial endocarditis has been reported by 2 retrospective studies and 4 case reports (Table 1). The microbiological profile of LVAD endocarditis is very diverse. The common pathogen includes Staphylococcus, Pseudomonas and Streptococcus

Table 1. Studies reporting Bacterial Endocarditis in patients with LVAD

Reference	Study Date	Type of study	NP[a] (*n*)	NPE[b] (*n*)	Diagnostic method	Organism	Management	Outcome
Riaz *et al*. (*22*)	1/2005 to 12/2011	Retrospective review	247	3	Blood cultures, TEE	Pseudomonas aeruginosa, MRSA, Coagulase negative Staphylococci	Removal of LVAD, antibiotics	1 patient survived and 2 patients expired
Mendes *et al*. (*24*)	4/2011	Case report	1	1	Blood cultures, TEE	MR Staphylococcus epidermis, linezolid-resistant Streptococcus sanguinis , Pseudomonas Aeruginosa	Linezolid, Vancomycin, daptomycin.	Patient expired from other complications
De Jong *et al*. (*25*)	5/1998	Case report	1	1	Immunoscintigraphy with Tc-99m labeled anti-NCA 95 anti granulocyte antibodies	Staphylococcus aureus	Exchange of valves in the inflow and outflow tracts, oxacillin	Patient survived
Hill *et al*. (*2*)	9/2014	Case report	1	1	Positive blood cultures, Ultrasonography showing small fluid collections in the driveline	Pseudomonas aeruginosa	Ceftazidime and oral ciprofloxacin	Patient developed intraparenchymal hemorrhage due to a mycotic aneurysmof the brain and expired eventually
Motomura *et al*. (*26*)	6/2011	Case report	1	1	Positive blood cultures, negative TEE, positive CT scan for SMA and hemorrhagic lesions in the brain	Coagulase-negative gram-positive cocci	Vancomycin, micafungin, piperacillin and tazobactam	Patient expired due to multiple brain lesions and cerebral edema
Lahpor *et al*. (*23*)	3/1993 to 12/2001	Retrospective review	38	1 (suspected)	Positive blood cultures, negative TEE	NA	Long term antibiotics, explantation of device	Patient survived, explantation of device revealed no vegetations

[a]NP, Number of patients; [b]NPE, Number of patient with endocarditis.

species (*20*). Staphylococcus aureus is the most common pathogen in LVAD endocarditis, which has the propensity to adhere itself due to possession of Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMM) (*21*). In a retrospective review done at the Mayo Clinic by Riaz *et al*, which included 247 patients who underwent LVAD implantation, three patients developed endocarditis. All cases had either concurrent or prior LVAD infection apart from endocarditis. The microbiology revealed the agents to be pseudomonas aeruginosa in one case, methicillin-resistant staphylococcus aureus (MRSA) in another and coagulase negative staphylococcus in the third. The diagnosis was confirmed by means of positive blood cultures and positive transesophageal echocardiography (TEE). All patients underwent removal of the LVAD and were treated with a prolonged course of antibiotics. Only one patient survived (*22*). In another retrospective review done in the Netherlands, which included 38 patients who received LVAD between 1993 to 2001, 12 patients had complications due to infections. Endocarditis was suspected in one patient who required prolonged antibiotics. However, explantation of the device revealed no vegetation and the patient survived (*23*). Mendes *et al*. reported a case of a patient who had an LVAD placed for ischemic cardiomyopathy and eventually developed endocarditis. The culture revealed methicillin-resistant staphylococcus epidermis (MRSE) and the patient was treated with linezolid with no significant improvement. A repeated microbiological study with PCR and sequencing revealed linezolid-resistant streptococcus sanguinis with a 23S rRNA mutation leading to the development of cross-resistance to rRNA-targeting drug agents including linezolid made the treatment even more challenging. The patient was treated with different antibiotics and later blood cultures also revealed he developed pseudomonas aeruginosa bacteremia. Eventually, his blood cultures came back negative after a prolonged course of antibiotics but the patient died due to other complications (*24*).

Table 2. Studies reporting Fungal Endocarditis in patients with LVAD

Reference	Study Date	Type of study	NP[a] (*n*)	NPE[b] (*n*)	Diagnostic method	Organism	Management	Outcome
Nurozler *et al*. (*29*)	7/1991 to 12/1999	Retrospective review	165	5	1 patient had positive fungemia,	Candida parapsilosis, Candida albicans, Syncephalastrum racemosum	1 patient had LVAD changed and transplant, 3 patients had transplant and 1 patient had LVAD explanted	4 patient survived and 1 patient expired
Barbone *et al*. (*31*)	11/2004	Case report	1	1	Postmortem revealed friable material with fungal hyphae in the inflow and outflow valves, negative blood cultures	Aspergillus species	NA	Patient Expired in 21 days after implant of LVAD
Maly *et al*. (*20*)	3/2011	Case report	1	1	Explanted LVAD revealed thrombotic like obstruction of the outflow cannula, negative TEE and blood cultures	Aspergillus species, Candida albicans	LVAD was explanted due to worsening function and patient underwent urgent heart transplant	Patient survived after heart transplant

[a]NP, Number of patients; [b]NPE, Number of patient with endocarditis.

De Jonge *et al*. presented a case of a patient who developed high-grade temperatures after three years of LVAD implantation with blood cultures growing staphylococcus aureus. The routine investigation did not reveal any source of infection. T99m labeled anti-NCA 95 anti-granulocyte antibodies found a suspected focus of infection at the outflow tract. The patient underwent a successful exchange of the inflow and outflow tract and experienced accelerated recovery (*25*). Hill *et al*. reported a patient on LVAD who initially developed an abscess in the driveline with blood cultures growing pseudomonas aeruginosa requiring prolonged antibiotic therapy. This patient eventually developed a small mycotic aneurysm in the brain which was inoperable and eventually died (*2*). Motomura *et al*. reported a case of superior mesenteric artery mycotic aneurysm secondary to LVAD endocarditis. The patient was a 31-year-old male who underwent LVAD placement for non-ischemic cardiomyopathy and had a previous history of intravenous drug abuse. Seven months' post implant he was admitted to the hospital for sepsis and blood cultures grew coagulase-negative gram-positive cocci. During his hospital course, he developed a superior mesenteric artery mycotic aneurysm and eventually he developed multiple hemorrhagic lesions in his brain leading to death (*26*).

5.3. *Fungal Endocarditis*

Fungal endocarditis is a rare but fatal complication of LVAD placement (*27*). We came across 1 retrospective study and 2 case reports discussing LVAD fungal endocarditis (Table 2). Opportunistic fungal infections commonly occur in these patients due to diverse factors, which include poor nutritional status and reduced immunity. Long-term antibiotic use makes these patients susceptible to fungal infection flourishing (*28*). Candida is reported to be the most common fungal agent involved in LVAD endocarditis (*29*). 50-70% of fungal endocarditis present with a positive blood culture (*30*). In a retrospective review by Nurozler *et al*. involving 165 patients with LVAD, he reported that 22% of the patients developed some sort of fungal infection out of which 5 patients (3%) had fungal endocarditis. One of the five patients had a positive blood culture while the other patients had negative blood cultures. The organisms in the other four patients were identified as fungal growth during explantation of the LVAD due to persistent fever and leukocytosis. The organism's reports were *Candida parapsilosis*, *Candida albicans*, and *Syncephalastrum racemosum*. All the patients had their LVAD explanted and four of them had cardiac transplants. The microbiology of the material found in the LVAD revealed the above-mentioned organisms. 4 out of the 5 patients survived (*29*). Barbone *et al*. reported a patient who died on postoperative day 21 following the implant of a LVAD due to LVAD dysfunction and intractable high temperature. The patient had normal white blood cells and negative blood cultures. The patient was treated with empiric antibiotics with no response. The postmortem study revealed friable fungal (aspergillus) vegetation in inflow and outflow valves (*31*). Multiple authors recommend the use of empiric antifungal therapy in culture negative sepsis unresponsive to broad-spectrum antibiotics in patients with LVAD (*31*). Maly *et al*. reported a patient on LVAD who developed outflow tract obstruction secondary to fungal infection

thrombus formation. Months after the LVAD implant procedure, the patient presented with a dry cough and fatigue. He was afebrile. Lab abnormalities included hemoglobinuria and elevated inflammatory markers. Initial blood cultures were negative and TEE did not reveal any vegetation. During this readmission, a donor's heart became available and Cardiac transplantation was successfully done. The explanted LVAD revealed the fungal thrombus obstructing the outflow track with histopathology showing aspergillus. This emphasizes the fact that a normal TEE does not always rule out endocarditis (*20*).

6. Diagnosis

When LVAD driveline or pump pocket infection is suspected, blood cultures with gram stain should be obtained before the initiation of broad-spectrum antibiotic therapy (*32*). LVAD endocarditis is similar to prosthetic valve endocarditis, which can lead to a series of complications such as LVAD dysfunction, LVAD thrombosis and septic embolization (*1,6*). The patient can present with persistently elevated temperature, positive blood culture, skin signs of endocarditis such as Osler's nodes, Janeway lesions and mycotic emboli to systemic organs such as brain or kidneys. Certain patients also present with mild symptoms such as cachexia, low-grade temperature or anorexia (*33*). Also, there have been reports of asymptomatic patients who had an incidental diagnosis of LVAD endocarditis made through the histopathological study of the explanted device (*1*). Modified Duke criteria for diagnosis of Infective endocarditis is found to be more sensitive than Duke criteria or Von Reyn criteria (*34*). Implementing echocardiography to the modified Duke criteria has increased its sensitivity to 100% (*35*). Emphasis on signs, symptoms, and identification of causative pathogen using serological markers, additional cultures, recent molecular techniques and histological studies increased the therapeutic specificity and sensitivity of Modified Duke's criteria. Thus finding it to be more effective in diagnosing endocarditis even in patients with negative blood cultures (*36*). In the case of bloodstream infections, transesophageal echocardiography (TEE) is done to look for any vegetation on the LVAD surface. But TEE need not necessarily rule out the possibility of seeding at the reflective internal blood contacting metal surface of the device. TEE should be also considered in patients with negative blood cultures possibly due to recent antibiotic use (*15*) There have been reports of using Immunoscintigraphy with Tc-99m labeled anti-NCA 96 anti-granulocyte antibodies for the diagnosis of the infective focus (*25*) and also the use of ultrasonography to detect abscesses along the surfaces of the LVAD (*2*). Despite absent vegetation on TEE and the other tests, inability to clear bloodstream infection with appropriate antibiotics should raise concern for LVAD endocarditis (*15*).

7. Management

Initial management of LVAD driveline or pump pocket infection involves the use of broad-spectrum antibiotics after blood cultures have been obtained. In addition to systemic antibiotics, driveline infection also requires surgical drainage and incision of the driveline site with driveline revision, which allows for removal of dead tissue for faster recovery. Vacuum-assisted closure devices can also be used in driveline infection (*32,37*). In the case of pump pocket infection, if there is fluid collection around the device, exploration of the site with surgical incision and drainage is required. Antibiotic beads can also be used in these types of infections (*38*). Severe cases of pump pocket infection must be aggressively managed as LVAD endocarditis. The driveline or pump pocket infection in patients with LVAD can be managed with device removal and a limited course of antibiotic therapy but it's insufficient in case of LVAD endocarditis. The endovascular surface of LVAD must be presumed seeded in cases of implant device infection complicated by endocarditis. These cases should be managed with chronic suppressive antibiotic therapy until the infected LVAD is removed and replaced with a new device or until the patient undergoes cardiac transplantation (*22*). Conservative management of endocarditis without lead removal is reported as an ineffective treatment approach. Failure of treatment is strongly associated with failure to remove the infected LVAD (*1*). Currently, there is no data regarding specific approaches in the management of LVAD endocarditis, device exchange or explantation is generally based on the patient's overall clinical status. In our review, out of the 8 patients reported with bacterial endocarditis among all the studies, all of them received a prolonged course of antibiotics, 2 patients had explantation of the device and one patient had an exchange of the inflow and outflow valves (*2,22-26*). Aggressive management of infection, with prompt device removal and prolonged antibiotic therapy targeting the specific organism, is crucial to prevent catastrophic events (*1*).

The same approach applies to fungal endocarditis as well. Early detection of non-specific signs and symptoms as well as appropriate antifungal treatment in a timely manner is highly demanded to treat this deadly complication (*29*). The risk of opportunistic fungal infection is extremely high in patients who are immunosuppressed and it is recommended to administer prophylactic antifungal therapy to these patients (*27*). All high-risk patients on LVAD should be treated with fluconazole prophylaxis. Patients diagnosed with candida endocarditis should be treated with an echinocandin (*20*). Prophylaxis for aspergillosis is not routinely administered. Voriconazole is the first drug choice to treat the suspected invasive aspergillosis in

these patients (*31*). Out of the 7 patients reported with fungal endocarditis, 6 of them had anti-fungal treatment and LVAD explantation. Heart transplantation was done in 5 of the patient due to the availability of donor's heart (*20,29,31*). But it's strongly emphasized that eradication of fungemia with drugs alone without LVAD removal is an impossible task (*15*). In summary, the effective treatment methodologies for positive outcomes in patients with LVAD endocarditis were documented to be treating a patient with systemic antibiotic suppression therapy alone, LVAD replacement, LVAD transplantation and LVAD explantation without transplantation (*7*). More clinical data is required for a specific treatment approach for LVAD endocarditis regarding the use of just antibiotics versus device exchange and explantation.

8. Similarities and differences in prosthetic valve endocarditis and LVAD endocarditis

In both prosthetic valve endocarditis and LVAD endocarditis, there are signs of bloodstream infection causing symptoms such as fever, cachexia, low-grade temperature or anorexia, positive blood cultures, skin signs of endocarditis such as Osler's nodes, Janeway lesions and mycotic emboli to systemic organs such as brain or kidneys. However, in prosthetic valve endocarditis, TEE has a higher sensitivity in diagnosing the condition compared to that of LVAD endocarditis. Similar to LVAD endocarditis, immunoscintigraphy with indium-111 is useful in detecting myocardial abscesses or diffuse tissue infiltrations in prosthetic valve endocarditis (*39*). Treatment of both prosthetic valve endocarditis and LVAD endocarditis requires the use of a prolonged course of antibiotics. The primary difference in treatment of the two endocarditis situations is that in LVAD endocarditis, explantation of the device is always indicated along with antibiotic treatment. However, in prosthetic valve endocarditis, surgical intervention is required only if it meets one of the following criteria which includes large vegetation (> 10 mm), mobile vegetation, thromboembolic events with the presence of vegetation, persistent sepsis despite 48 hours of antibiotic treatment, congestion not relieved with medical treatment, and acute renal failure (*40*). Another important difference is the need for prophylaxis. Currently, there is no literature indicating the need for prophylaxis antibiotics in patients with LVAD to prevent endocarditis for procedures, however, antibiotic prophylaxis has been indicated for patients with a prosthetic valve for procedures involving the oropharynx, gastrointestinal tract, and urogenital tract (*39*).

9. Complications

Complications associated with the device implant include infection, bleeding, right ventricular failure, septic emboli, thromboembolism, and stroke (*1*). In bacterial endocarditis, the reported complications include mycotic embolism causing intraparenchymal bleeding and systemic mycotic emboli (*2,22-26*). In fungal endocarditis, the reported complications include vegetation obstructing the inflow and outflow valves and also obstruction of the outflow cannula (*20,29,31*).

10. Outcomes

The extensive review of the literature revealed only limited results on the outcomes of LVAD endocarditis. In our review, out of the 8 patients reported with bacterial endocarditis 3 patients survived (37.5%) and 5 patients died (62.5%). Two patients (25%) were reported to have peripheral emboli from the endocarditis. Among the 7 patients reported with fungal endocarditis 5 patients survived (71.4%) and 2 patients died (28.5%) (*2,22-26*). There is no significant difference in survival of transplanted patients with or without perioperative infection whereas patients with LVAD endocarditis are reported to have increased risk of morbidity and mortality (*41*). Overall mortality from sepsis in patients with LVAD is 4%. Other causes of death in patients with a continuous-flow left ventricular assist device are hemorrhagic stroke (9%), right heart failure (5%), external power interruption (4%), bleeding (3%), respiratory failure (3%), and cardiac arrest (3%). Among patients with a pulsatile flow LVAD, the leading causes of death are hemorrhagic stroke (10%), right heart failure (8%), multisystem organ failure (7%), and ischemic stroke (5%) (*11*). The overall estimated survival at the end of the 1st and 2nd year in the case of continuous flow LVAD is found to be 68% and 58% respectively while with pulsatile flow LVAD is found to be 55% and 24% (*11*).

11. Conclusion

In conclusion, endocarditis secondary to LVAD placement is a serious and difficult to treat condition with high morbidity and mortality. Both bacterial and fungal endocarditis have been reported in patients with LVAD. A negative TEE does not always rule out endocarditis associated with LVAD and persistent bacteremia should raise suspicion of endocarditis in these patients. Complications include systemic mycotic embolization and vegetation causing obstruction of the inflow or outflow tract leading to LVAD dysfunction. Explantation of the LVAD along with prompt antibiotic or antifungal therapy is needed for the treatment of endocarditis associated with LVAD.

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