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1 **Original article**

2 **Left ventricular assist device-related infections: a multicentric study**

3 **Running title: Left ventricular assist device-related infections**

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21 **ABSTRACT**

22 **Objectives.** Implantable left ventricular assist device (LVAD) is a major therapeutic progress
23 for end-stage heart failure in selected patients. As their use is expanding, infectious
24 complications are emerging, with limited data available to guide their management. We
25 aimed to better characterize LVAD-related infections.

26 **Methods.** We enrolled all consecutive patients diagnosed with LVAD-related infections in 3
27 referral centers in France, using standardized definition of infections in patients with LVAD.
28 Data were collected from medical charts using a standardized questionnaire.

29 **Results.** Between 2007 and 2012, 159 patients received LVAD for end-stage heart failure.
30 Among them, 36 (22.6%) –5 women, 31 men– presented at least one infectious complication,
31 after a median time of 2.9 months from LVAD implantation [interquartile range, 1.8-7.5],
32 with a median follow-up of 12 months [8-17]. Main comorbidities were alcoholism (33%),
33 diabetes (11%) and immunosuppression (11%). Mean age at implantation was 51 (\pm 11) years.
34 LVAD were implanted as bridge-to-transplant (n=22), bridge-to-recovery (n=8), destination
35 therapy (n=4), or unspecified (n=2). LVAD-related infections were restricted to the driveline
36 exit site (n=17), had loco-regional extension (n=13), or reached the internal pump (n=3). The
37 main bacteria isolated were *Staphylococcus aureus* (n=20), coagulase-negative staphylococci
38 (n=7), *Enterobacteriaceae* (n=14), *Pseudomonas aeruginosa* (n=10) and *Corynebacterium*
39 sp. (n=7), with polymicrobial infections in 19 cases. LVAD could be retained in all patients,
40 with the use of prolonged antibacterial treatment in 34 (94%), and debridement in 17 (47%).
41 One patient died due to LVAD-associated infection.

42 **Conclusions.** LVAD-related infections are common after LVAD implantation, and may be
43 controlled by prolonged antibiotic treatment.

44

45 **Introduction**

46 Heart failure is a major cause of morbidity and mortality worldwide [1,2]. The
47 prevalence and incidence of heart failure are increasing [3,4], and the constant shortage of
48 donor organs increases the need for alternatives to heart transplant in patients with end-stage
49 heart failure refractory to medical treatment [5]. Currently, around 2% of the adult population
50 in developed countries suffers from heart failure [6].

51 In this context, the advent of implantable left ventricular assist device (LVAD)
52 represents a major medical progress for end-stage heart failure in selected patients [7,8], and
53 is currently used as a bridge-to-heart transplantation, a bridge-to-recovery, or as destination
54 therapy (i.e., as the last resort in patients with neither perspectives of recovery, nor heart
55 transplant). Implantable LVAD intended for long-term use rely on a percutaneous driveline,
56 to carry electric signals and energy from the controller and batteries to the implanted pump.
57 As with any other implantable foreign device, LVAD is subject to LVAD-related infections,
58 a consequence of medical progress that is gradually emerging, proportionally to the number
59 of patients implanted with LVAD [9,10]. Indeed, the presence of a driveline piercing the skin
60 places the patient at a continuous risk for infections, that can affect the exit site, the
61 subcutaneous tunnel, the abdominal pocket (if present), the implanted pump, and disseminate
62 through bloodstream infections. The transition from pulsatile to continuous-flow LVAD
63 significantly improved clinical outcome [11], and decreased the risk of infectious
64 complications, but LVAD-related infections are still common [12,13]. Due to the scarcity of
65 data currently available in the medical literature, the management of these emerging
66 infections is poorly standardized, and mostly derives from the state-of-the-art for the
67 management of other cardiovascular devices-related infections (e.g. pacemaker, intra-cardiac
68 defibrillator, prosthetic valves, or vascular prosthesis), although their characteristics are

69 significantly different. We aimed to better characterize LVAD-related infections, their
70 treatment, and their outcome, through a multi-center study in three referral centers in France.

71

72

73 **Methods**

74 La Pitié-Salpêtrière is a 1663-bed university hospital located in Paris (France); Laennec is a
75 489-bed university hospital located in Nantes (Pays-de-Loire, France); and Pontchaillou is a
76 992-bed university hospital located in Rennes (Bretagne, France). They all serve as referral
77 centers for end-stage heart failure in their area. Although no national guidelines are currently
78 available for LVAD implantation in France, all three centers use antibacterial prophylaxis
79 with cefamandole for less than 24 hours from the time of LVAD implantation, under rigorous
80 aseptic conditions, with no continuous antibacterial prophylaxis following implantation.
81 Throughout the study period, skin preparation procedures included preoperative shower with
82 chlorhexidine gluconate solution the night before surgery, and two separate skin preparation
83 before incision with either povidone-iodine or chlorhexidine with ethanol in the three
84 participating sites.

85 Patients with LVAD receive repeated counselling and education by specialized nurse
86 before and after LVAD implantation, to reduce the risk of infection and trauma at the exit
87 site. When LVAD-related complication is suspected, cases are reviewed by the endocarditis
88 team in each site, including at least one cardiac surgeon, one infectious diseases specialist,
89 and one microbiologist. In the absence of any consensus on the management of LVAD-
90 related infections during the study period, patients were managed on a case-by-case basis,
91 taking into account clinical and microbiological data, including drug susceptibility profiles.
92 Follow-up was tailored to the characteristics of LVAD-related complications, and was mostly
93 performed by the cardiac surgery department, in association with infectious diseases

94 specialist for any suspicion of infectious complication. All patients enrolled in these
95 databases provided informed consent for observational studies.

96 Cases of LVAD-related infections were identified through a retrospective review of
97 medical charts for all patients with LVAD implanted from January 2007 to December 2012 in
98 the participating centers. LVAD-related infections were defined according to criteria
99 established by the Interagency Registry for Mechanically Assisted Circulatory Support
100 (INTERMACS) [14], the North American registry for mechanical circulatory support devices
101 (MCSD) that serves as a quality improvement system to assess the characteristics, treatments,
102 and outcomes of patients receiving MCSD. Briefly, percutaneous site infections were defined
103 as pain, erythema, or purulent drainage restricted to the LVAD entry site, with a positive
104 culture from the skin, and the decision to initiate systemic antimicrobial therapy. LVAD-
105 related infections were defined as loco-regional when the erythema or induration extended >1
106 cm along the subcutaneous part of the driveline, and/or in case of fever or leukocytosis not
107 explained by other conditions, with the decision to initiate systemic antimicrobial therapy.
108 Lastly, LVAD-related infections were classified as pump infections when an
109 indistinguishable organism (genus, species, and antimicrobial susceptibility pattern) was
110 recovered from 2 or more peripheral blood cultures taken at least 12 hours apart with no other
111 focus of infection, leading to the initiation of an antimicrobial treatment.

112 A standardized questionnaire was used to collect demographical, clinical, and
113 laboratory data from medical records, with a focus on the clinical features and microbiology
114 of LVAD-related infections, any surgical and antibacterial treatment, and outcome. Statistical
115 analyses were descriptive. Categorical variables were presented as number and percentages.
116 Continuous variables were presented as either means with standard deviations (SD), or
117 medians with first- and third-quartile [interquartile range, IQR], if the distribution of the data

118 were skewed. Statistical analyses were performed using STATA software, version 12
119 (STATA Corporation).

120

121

122 **Results**

123 Between January 2007 and December 2012, 159 patients underwent LVAD implantation at
124 La Pitié-Salpêtrière, Paris (n=103), Laennec, Nantes (n=32), and Pontchaillou, Rennes
125 (n=24). Of these, 36 patients (22.6%) presented at least one LVAD-related infection during
126 the study period, with a median follow-up of 12 months [IQR, 8-17]. Patients characteristics
127 and features of LVAD-related infections are presented in tables 1 and 2. The median delay
128 from LVAD implantation to the diagnosis of LVAD-related infection was 2.9 months [1.8-
129 7.5]. Microbiology documentation of LVAD-related infections was obtained using swabs
130 taken from the entry site (56%), surgical samples during debridement (20%) or during heart
131 transplant (7%), blood culture (10%), and transcutaneous puncture (3%). Infections were
132 polymicrobial in 54% of cases. Main pathogens were *Staphylococcus aureus* (n=20,
133 including 2 methicillin-resistant), *Enterobacteriaceae* (n=12, including 7 extended spectrum
134 beta-lactamase producers), *Pseudomonas aeruginosa* (n=10), coagulase-negative
135 staphylococci (n=6, including 2 methicillin-resistant), *Corynebacterium* sp. (n=6), and others
136 (*Acinetobacter baumannii*, *Haemophilus aphrophilus*, and *Stenotrophomonas maltophilia*, one
137 patient each).

138 LVAD-related infections required hospital admission in 28 cases (78%). All patients
139 received systemic antibacterial treatment, based on pathogen(s) identification and drug
140 susceptibility testing. Antibacterial treatment was temporarily administered by the
141 intravenous route in 27 patients (75%), while 9 patients only received oral antibiotics. The
142 median total duration of antibacterial treatment for LVAD-related infections was 90 days [40-

120] per patient. Surgical debridement and drainage were performed in 17 patients (47%). Indications for surgery were either loco-regional infection associated with collection documented by computed tomography scanning or ultrasound (n=12), or pump infection (n=5). Procedures were always implemented with concomitant antibacterial treatment. Three of the 17 patients treated with debridement required a second local surgery due to persistent drainage on appropriate antibacterial treatment. No patient required wound vacuum-assisted-closure (VAC), pump relocation, or antibiotic beads at the device pocket.

The outcome was satisfactory in most cases: LVAD was finally extracted because of heart transplant (n=17) - with a median time to transplantation of 11.3 months [8.9-15.0], or because of recovery from heart failure (n=4). No patient underwent LVAD extraction because of uncontrolled infection, and no LVAD-related infection was considered as a definitive contra-indication for heart transplant. During the study period, 3 patients died, of whom one was considered as attributable to LVAD-related infection. Of the 12 patients with the LVAD still in place by the time of last follow-up, three had stopped all antibacterial treatment - with a follow-up of 52, 98, and 138 days since last antibacterial treatment - and nine were on prolonged oral antibacterial treatment. Most patients (n=34, 94%) presented no sequel of their LVAD-related infection.

160

161

162 **Discussion**

The most salient features of this multi-center study of LVAD-related infections performed in three referral centers are as follows: Firstly, we confirmed that infectious complications are very common early after LVAD implantation, documented in almost one quarter of patients, with a median follow-up of one year. This is in agreement with previous

167 series, and not unexpected given the continuous percutaneous portal of entry, and the
168 comorbidities presented by these patients with end-stage heart failure. Secondly, we provided
169 a comprehensive documentation of the major pathogens involved in this emerging foreign
170 device-related infectious diseases, where the ‘big five’ are – as could be expected – *S. aureus*,
171 *Enterobacteriaceae*, *P. aeruginosa*, coagulase-negative staphylococci, and *Corynebacterium*
172 sp. Thirdly, we found that, despite the major challenges arising when infections occur on a
173 life-saving device, the overall outcome was favorable in most instances, at the price of
174 prolonged systemic antibacterial treatment for > 90% of patients, and surgical debridement
175 for almost half of them. This satisfactory outcome may be related to the destiny of these
176 devices, mostly implanted as bridge-to-transplantation, or bridge-to-recovery: Indeed, in this
177 situation, the main challenge for the management of LVAD-related infections is to keep the
178 device in place until it is no longer necessary, which is not the case for other foreign device-
179 related infections, such as prosthetic valve, vascular prosthesis, or prosthetic joints, usually
180 planned to remain in place lifelong.

181 To our knowledge, few studies have reported the incidence, the characteristics, and
182 the management of LVAD-related infections thus far. Previous reports found an incidence of
183 LVAD-related infections similar to our cohort, but with a median time from LVAD
184 implantation that was slightly longer, at 4.4 to 7.4 months [13,15], as compared to 2.9 months
185 in our study. These discrepancies may be related to the close monitoring routinely
186 implemented after LVAD implantation in our centers, to limited sample size, or to the fact
187 that 58% of our patients were classified as INTERMACS I by the time of implantation, which
188 has been associated with earlier first pump-related infection [16]. Microbiological
189 characteristics of previous series are remarkably similar to ours, although one previous series
190 also isolated fungi as potentially involved (17). Of note, 22 isolates were Gram negative
191 bacilli in our series, including 19 non-susceptible to the antibioprophyllactic regimen routinely

192 used during LVAD implantation in our sites (i.e. cefamandole): extended spectrum beta-
193 lactamase producing *Enterobacteriaceae* (n=7), and non-fermenting Gram negative bacilli
194 (n=12). However, given the median delay from LVAD implantation to infection diagnosis
195 (2.9 months), this is unlikely that an antibiopropylactic regimen with broader coverage would
196 have prevented these infections. We found that percutaneous driveline exit is the most
197 common site of LVAD-related infections, as in previous reports. Given that a number of
198 studies have demonstrated that trauma at the exit site favors the development of driveline
199 infections [10,18], prevention of driveline trauma may decrease the risk of LVAD-related
200 infections. Hence, patient education is an important component for the prevention of LVAD-
201 related infections, and goes behind hygiene and infection control education.

202 Up to now, the management of LVAD-related infections is poorly standardized, due
203 to the scarcity of therapeutic studies in the field, and the absence of consensus guidelines. To
204 assist therapeutic decisions in this challenging context, Koval et al proposed
205 recommendations based on observational studies and experts opinion [18]. The management
206 of LVAD-related infections in our center follows the main principles depicted in these
207 recommendations, including anti-infectious treatment adapted to microbiology in all cases,
208 with surgical revision in selected cases. Although LVAD exchange is an option, this high-risk
209 surgery is often contra-indicated, and the use of continuous or iterative course of antibiotics
210 until transplantation, or recovery, is the rule for most centers.

211 Our study has limitations. First, although data were prospectively collected, the
212 original database did not focus on infectious complications. Hence, collection of clinical data
213 and microbiological investigations were not standardized. To address this limitation, the three
214 participating sites have implemented a prospective database for all patients who receive
215 LVAD since January 2012, with systematic follow-up at the referral center at one month and
216 three months after implantation, and then at least every 6 months, as well as each time

217 requested by the patient and/or his general practitioner. Second, due to limited sample size,
218 and the participation of three centers with similar practices in a restricted geographic area,
219 our findings may not apply to other sites with different practices, different case mix, or
220 different bacterial epidemiology. Third, the management of LVAD-related infections was not
221 standardized during the study period. Indeed, patients were managed on a case-by-case basis,
222 by the local endocarditis team. This could have led to heterogeneity from one site to another,
223 although endocarditis teams follow the same basic principles, have access to similar
224 diagnostic tools and anti-infective treatment, and prioritize evidence-based medicine when
225 available.

226

227 **Conclusions**

228 LVAD is a significant progress that improves survival status, functional capacity, and
229 quality of life, but it carries a high risk of infectious complications, evaluated at 22.6% at one
230 year in this study. With systemic antibacterial treatment for all patients, and debridement in
231 selected cases, the final outcome is usually satisfactory, as most cases of LVAD-related
232 infections may be controlled, with no sequel, and no contraindication for heart transplant.

233

234

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239 workers who took care of them in the departments of cardiology, cardiac surgery, and
240 infectious diseases.

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1 **Table 1.** Characteristics of patients with left ventricular assist device-related infections
 2 (n=36) by time of implantation

Variables	
Demographic characteristics	
Age at implantation (years)	51 ± 11
Male	31 (86)
Comorbidity	
Immunocompromised	4 (11)
Diabetes mellitus	4 (11)
Chronic alcoholism	12 (33)
Left ventricular ejection fraction (%)	22 ± 7
Body mass index (kg/m ²)	25.4 ± 4.9
Aetiology of heart failure	
Ischemic cardiomyopathy	22 (61)
Dilated cardiomyopathy	14 (39)
Duration of heart failure	
< 12 months	17 (48)
1-5 years	9 (26)
> 5 years	9 (26)
Indication of LVAD implantation^a	
Bridge-to-transplantation	22 (65)
Bridge-to-recovery	8 (23)
Destination therapy	4 (12)
INTERMACS profile^b	
I	21 (58)
II	0 (0)
III	5 (14)
IV	3 (8)
V-VII	7 (20)
LVAD device	
Heartmate II (Thoratec)	33 (92)
Others ^c	3 (8)

3 Categorical data are summarized as Number (%) of patients and continuous data are
 4 summarized as mean ± standard deviation.

5 LVAD, left ventricular assist device; INTERMACS, Interagency Registry for Mechanically
 6 Assisted Circulatory Support

7 ^a Data available for 34 patients; ^b, INTERMACS profile I = critical cardiogenic shock, II =
 8 progressive decline on inotropic support, III = stable, but inotrope dependent, IV = resting
 9 symptoms, V = exertion intolerant, VI = exertion limited, VII = advanced New York heart
 10 association class 3; ^c Heartware, Thoratec (n=2); VentrAssist, Ventracor (n=1)

1 **Table 2**

2 Characteristics and management of left ventricular assist device-associated infections (n=36)

Variables	
Clinical manifestation	
Time from implantation to infection, months	2.9 [1.8-7.5]
Purulent drainage	31 (86%)
Pain	17 (47%)
Erythema	22 (61%)
Fever	28 (80%)
Infection site ^a	
Percutaneous driveline	17 (49%)
Locoregional	13 (37%)
Pump	5 (14%)
Laboratory variables	
White Blood Cell count, 10 ⁹ /L	11.8 [5.6-27.7]
Serum C Reactive Protein, mg/l	26 [3-362]
Positive blood culture(s)	4 (10%)
Microbiology	
<i>Staphylococcus aureus</i>	20 (56%) ^b
<i>Enterobacteriaceae</i>	12 (33%) ^c
<i>Pseudomonas aeruginosa</i>	10 (28%)
Coagulase-negative staphylococci	6 (18%)
<i>Corynebacterium</i> sp.	6 (18%)
Others	3 (8%) ^d
Management	
Systemic antibacterial treatment ^e	36 (100%)
Median duration (days)	40 [14-120]
Surgical debridement	17 (47%)

3 Categorical data are summarized as Number (%) of patients and continuous data are
4 summarized as median values [first quartile-third quartile].5 ^a data available for 35 patients6 ^b including 2 (10%) methicillin-resistant *Staphylococcus aureus*7 ^c including 7 (58%) extended spectrum beta-lactamase producers8 ^d *Acinetobacter baumannii*, *Haemophilus arophilus*, and *Stenotrophomonas malthophilia*,
9 one patient each10 ^e Antibacterial treatment included cloxacillin (n=21), pristinamycin (n=15), ciprofloxacin
11 (n=12), gentamicin (n=12), amikacin (n=9), vancomycin (n=7), imipenem (n=7), rifampin
12 (n=6), piperacillin-tazobactam (n=5), and ofloxacin, amoxicillin-clavulanate, amoxicillin,
13 trimethoprim-sulfamethoxazole, clindamycin, doxycycline, fusidic acid, ceftazidime,
14 ceftriaxone, cefamandole, and linezolid (n<5 for each).