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Ten-year retrospective cohort analysis of Ventricular Assist Device infections

Running title: Ventricular Assist Device infections

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Abstract

Background. The number of patients treated by ventricular assist devices (VAD) and the duration of VAD treatment is increasing. One of the main complications in terms of morbidity and mortality for VAD patients are microbial infections. With this study, we aimed to investigate the epidemiology and microbiological characteristics of infections occurring in a VAD population to identify modifiable factors.

Methods. We retrospectively analysed patient characteristics, treatments and outcomes of VAD-specific/related infections. All patients implanted in our institution with a continuous flow VAD, between January 2009 and January 2019 were included. Risk factors for VAD infection were assessed using simple and multiple linear regressions.

Results. Of the 104 patients screened, 99 were included in the analysis, the majority of which were men (78%). At implantation, the mean age was 56 years and the median time on VAD support was 541 days. The overall infection rate per year per patient was 1.4. Forty-seven patients (60%) suffered from VAD-specific/related infection. Half of all infection episodes occurred in the first 4 months but the proportion of VAD-specific/related infection was higher after the first 4 months (74% of all infection). Using regression models, no patient specific risk factors were associated with VAD-specific/related infections.

Conclusion. No predictive factors for infection during VAD support were identified in this study. By extension, diabetes, renal insufficiency, age or high BMI are not sufficient to deny a patient access to ventricular support.

Keywords: VAD**;** LVAD**;** device infection

INTRODUCTION

Ventricular assist device (VAD) therapy improves the quality of life for patients with advanced heart failure and has gained importance in recent years due to the imbalance between donors and candidates for heart transplantation[1,2]. The number of patients undergoing VAD implantation is increasing. The proportion of those implanted as destination therapy (DT, i.e., not listed for heart transplantation) has risen from less than thirty percent between 2008 and 2011 to nearly fifty percent between 2015 and 2016[3]. In addition, the proportion of patients undergoing transplantation with a previously implanted VAD increased from 34% in 2010 to 43% in 2018[4], and the mean waiting time for patients tripled between 2003 and 2014[4]. Consequently, time on support is longer, irrespective of the indication, and this increases the likelihood of device-related complications. Infection occurring during VAD support is the third most common cause of mortality for this patient population[3]. Further, infection represents the second most common cause of morbidity in the first three months after implantation and the most common cause after three months[5].

The most widely used classification of infections in VAD patients was proposed in 2011 by Hannan et al[6]. This classification distinguished VAD-specific infections (limited to the pump, cannula, surgical pocket or drive-line) from VAD-related infection (e.g. endocarditis, mediastinitis etc.[6]) and other infections (pneumonia, urinary tract and gastrointestinal tract infection).

Treatment strategies for VAD-specific/related infections range from conservative antimicrobial therapy through to surgical management[7]. Antimicrobials can be given as short-term treatments or as chronic suppressive therapy either throughout life for DT or until pump explantation[8]. Surgical therapy for VAD-specific infection depends on infection classification and ranges from local washout[9] with or without Vacuum Assisted Closure (VAC)[10] to, in more severe cases, pump exchange[7].

In order to establish effective prevention and empiric treatment strategies, knowledge of both the epidemiology of VAD infections and risk factors is necessary. As such, we have reviewed clinical and microbial data from a cohort of VAD patients over a 10-year period (2009 to 2019).

METHODS

We retrospectively reviewed all patients who underwent implantation of a permanent mechanical cardiac support device (LVAD or BiVAD) between January 2009 and January 2019 at Bern University Hospital. Patients that received a continuous flow VAD and agreed that their data could be used for research purposes (General Consent) were included. This study was approved by the Bern Cantonal Ethics Commission (BE, no. 2019-00769). Patient characteristics were collected using an electronic patient health record and bacterial culture results were extracted from our microbiological documentation system.

Our driveline care protocol has changed little over the study period; the driveline lining was changed once per week or as soon as it became wet, one or two anchoring devices were used, and disinfection was performed with chlorhexidine. An increase in the frequency of dressing changes is recommended if significant secretions are observed. In contrast to other institutions that empowered the patient or their relatives to perform the dressing, our institution uses systematically nurses visiting the patient's domicile. A mask and sterile gloves are used for the dressing process. The only notable change to the protocol during this period was the use of therapeutic honey for a period of 2 years between 2016 and 2018. Patients were allowed to take showers with the precaution of putting a waterproof plastic film on the dressing before the shower and to change the dressing after the shower.

The beginning of an infectious episode was defined by the time of first description in the medical record, and the end of the episode by the end of treatment. An episode was defined as recurrent upon description of a new infection after cessation of treatment, or upon escalation of therapy for patients treated with long-term suppressive antibiotic therapy. Hannan's classification was used to categorise each episode as either VAD-specific, VAD-related, or other[6]. Further details about definitions and classifications can be found in the supplemental material.

Independent predictors of VAD infections per year were assessed using a 2-step approach. First, a simple linear regression comparing all clinical variables (listed in table 1) with infections per year as the dependent variable was used to restrict the choice of candidate variables for the second step, which was multiple linear regression. Dichotomous variables were used as dummy variables in the regression. Assumption testing was performed following the multiple regression computation using the following statistical procedures: Multicollinearity between selected predicting variables in the multiple linear regression, assessed by the variation inflation factor with a threshold set as 5. Goldfeld Quandt test was used to detect the presence of heteroscedasticity requiring a $p>0.05$ for statistical significance. Statistical analyses were performed using R (version 4.0.3) with R-studio (Version 1.4.1103)[11].

RESULTS

During the study period, 108 LVAD implantations took place (4 BIVAD) in 104 patients. Five patients were excluded from analysis (2 pulsatile devices, 3 patients without general consent). Median time on VAD support for the 99 included patients was 541 days (IQR 204-797 days). During this period, patient survival at 1 year was 85% and at 4 years 67%. The intra-hospital mortality after LVAD implantation was 5.6%.

The epidemiological data is listed in table 1. At implantation, the mean age of the cohort was 56 years. Twenty-two of the patients were female (22%). Forty-six had suffered from a dilatative cardiomyopathy of a non-ischemic aetiology (46.5%). The median Body-Mass-Index (BMI) was 25kg/m^2 (IQR 22-28 kg/m^2). In 65 cases the INTERMACS score was 4 or above (66.3%). Sixty-four of the patients received a Heartware (HW) device (65%). Seventy of the patients were implanted with a Bridge-to-Transplant intention (73%). During the observation period, 43 patients were transplanted (43%) after a median time on VAD support of 481 days (IQR 214-656 days), 27 patients died on support (27%) after a median time of 276 days (IQR 87-760 days).

The key aim of the current study was to identify putative predictors of incidence of infection in patients with VAD support, to help to guide future interventional approaches. No statistically significant correlation with VAD-specific/related infection was observed using either simple nor multiple linear regressions (Table 2, Figure 3 and Table S3).

During the time on support (Table 4), 79 patients (80%) suffered at least one infection. Of those, VAD-specific or VAD-related infection occurred at least once in 47 patients (60%). The infect rate per patient (VAD-specific, VAD-related, and other infections) was 1.4 infection/patient/year (IQR- 0.4-2.9 infect/year). Only 4 out of the 27 (15%) deaths were associated with infection. A total of 229 clinical infectious episodes were identified (Figure 1A). Of those, 121 were VAD-specific/related (53%) and 108 episodes were non-VAD-related (46%) (Table S1, Table S2). Half of the infection episodes (115) occurred during the first 4 months of ventricular support. Of those, 39 episodes were VAD-specific/related (35%). Of the 114 episodes that occurred after 4 months, 82 were VAD-specific/related (72%) (Figure 1A, Table S1, Table S2)

A total of 416 cultures were performed, documenting 30 different pathogens. Two hundred and ninety-two unique infectious profile have been identified. Of those 61 cultures (21%) came back negative, not allowing any identification. Each microbial species (or grouping, i.e. coagulase-negative staphylococci) is presented in Table S4. The most frequent group of bacteria belonged to the taxonomic order Enterobacterales, which includes species such as *Escherichia coli*, *Enterobacter* spp. *Klebsiella pneumonia* and *Serratia marcescens* (76

positive cultures, 26% of the total, Table 3). The most common single species was the gram-positive opportunistic pathogen *Staphylococcus aureus*.

VAD-specific/related infections most often occurred at the driveline (62% of documented episodes before 4 months and 90% after 4 months; Figure 2). Driveline infection (DLI) was diagnosed in 37 patients (37%). The first episode of DLI occurred in median 152 days (76-214 days) after VAD-implantation for a total of 101 documented Episodes. Fortunately, in our series, deep DLI and sternal infections were rare (two episodes of each, respectively). None of the DLI episodes were diagnosed through blood culture. The most frequent pathogen in DLI was *S. aureus;* of the 122 DL-swabs taken, 40 were positive for S. aureus (33%, Figure 1B). Importantly, no instances of methicillin-resistant *S. aureus* (MRSA) was reported for this patient cohort. For the 20 patients who suffered from more than one episode of DLI, the following episodes were due to the same pathogen in 46 cases (74%) (Figure 1B). Duration of treatment between the VAD-specific/related and other infections varied significantly ($p < 0.002$, Wilcoxon rank-sum test), with a median of 22 days (IQR 14-42) for the VAD-specific/related and 12 days (IQR 8-30) for the non-VAD infection (Figure 2). For 22 DL-swabs (18%), no organism was identified.

DISCUSSION and CONCLUSIONS

Patients undergoing VAD therapy are prone to microbial infections. Our data show that more than half of the infections occur within four months of VAD implantation. However, during this period, these infections were mostly not related to the VAD and present mainly as respiratory tract and urinary tract infections. The average time between LVAD implantation and any infectious episode was 4 months. VAD-specific/related infections increased significantly in proportion after the first 4 months, mostly presenting as DLI (~90%) (Table S1, Table S2, Figure 1A, Figure 2). This distribution is also found in the literature[12]. Post-VAD implantation, clinicians should be aware of this repartition and treatment tailored accordingly.

The dominant pathogen in DLI was *S. aureus*. Additionally, fungal infections were very rare (across all infection). These results are comparable to previous published series[13–15]. Interestingly but not surprisingly, in cases of recurrent DLI, the same pathogen was most often culprit, occurring in about 75% of the cases. This highlights a probable colonization of the DL, most of the time asymptomatic, but with episodes of clinical recurrence. This has two implications; first, upon signs of infection recurrence, clinicians may consider rapid application of antimicrobial therapy covering the previous document pathogen, and secondly, systemic DL decolonization strategies could be assessed for VAD patients.

In ~20% of clinical infectious episodes, no microorganisms were cultivable despite signs consistent with local inflammation and infection. This highlights the importance of considering differential diagnosis that may cause local inflammation or swelling, such as driveline movement, allergic reactions to the dressing or secretion related to significant fluid retention in the context of cardiac decompensation.

Our infection prevention strategy uses a relatively standard protocol when compared to the protocol of other institutions and our infection rate is comparable to prospective studies on the subject (0-52%)[16]

This study did not identify any risk factors predicting the incidence of VAD-specific/related infection in VAD patients. In this topic evidence in the published literature is conflicting. Some studies show a relationship between certain patient characteristics, such as obesity[17,18], young age at implantation[19] or longer hospital stay[20] when others do not describe any risk factors associated with an increased risk of infection[21]. A 2019 systematic review of 34 articles shows 23 individual risk factors identified, the majority from a single study (18/34), or event factors associated with both increased and reduced risk of infection such as high BMI[22].

Our study is limited to the population followed and implanted in our center, and the size of our cohort was small. This implies a statistical limitation for the calculation of associations. The study also suffered from an over-representation of men in our cohort, unfortunately as in the

majority of cohorts treated by VAD[2,23]. Finally, the heterogeneity of the data concerning the driveline implantation technique did not allow us to carry out an analysis of its influence on the proportion of infection.

Derived from the findings of this study and in line with the published literature on the subject, we can presumed that if the parameters we studied here including BMI, renal insufficiency or even diabetes, influence the rate of infection, the effect sizes are likely small and are unlikely to be sufficient comorbidities to deny the implantation of a ventricular support to a patient based on an increased risk of infection related to VAD.

REFERENCES

1. Carrel T, Englberger L, Martinelli MV, et al.: Continuous flow left ventricular assist devices: a valid option for heart failure patients *Swiss Med Wkly* 142, 2012

2. Rogers JG, Aaronson KD, Boyle AJ, et al.: Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients *J Am Coll Cardiol* 55: 1826–1834, 2010

3. Kirklin JK, Pagani FD, Kormos RL, et al.: Eighth annual INTERMACS report: Special focus on framing the impact of adverse events *J Heart Lung Transplant* 36: 1080–1086, 2017

4. National Data - OPTN: *Transpl US VAD Status* Available at: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed April 24, 2019.

5. de By TMMH, Mohacsi P, Gahl B, et al.: The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS): second report *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 53: 309–316, 2018

6. Hannan MM, Husain S, Mattner F, et al.: Working formulation for the standardization of definitions of infections in patients using ventricular assist devices *J Heart Lung Transplant* 30: 375–384, 2011

7. Kusne S, Mooney M, Danziger-Isakov L, et al.: An ISHLT consensus document for prevention and management strategies for mechanical circulatory support infection *J Heart Lung Transplant* 36: 1137–1153, 2017

8. Leuck A-M: Left ventricular assist device driveline infections: recent advances and future goals *J Thorac Dis* 7: 2151-2157–2157, 2015

9. Olmsted RZ, Critsinelis A, Kurihara C, et al.: Severe LVAD-related infections requiring surgical treatment: Incidence, predictors, effect on survival, and impact of device selection *J Card Surg* 34: 82–91, 2019

10. Baradarian S, Stahovich M, Krause S, Adamson R, Dembitsky W: Case series: clinical management of persistent mechanical assist device driveline drainage using vacuum-assisted closure therapy *ASAIO J Am Soc Artif Intern Organs 1992* 52: 354–356, 2006

11. RStudio Team (2020): *RStudio: Integrated Development for R*, 2020.

12. Hannan MM, Xie R, Cowger J, et al.: Epidemiology of infection in mechanical circulatory support: A global analysis from the ISHLT Mechanically Assisted Circulatory Support Registry *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 38: 364–373, 2019

13. Siméon S, Flécher E, Revest M, et al.: Left ventricular assist device-related infections: a multicentric study *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 23: 748–751, 2017

14. Bejko J, Toto F, Gregori D, Gerosa G, Bottio T: Left ventricle assist devices and driveline's infection incidence: a single-centre experience *J Artif Organs Off J Jpn Soc Artif Organs* 21: 52–60, 2018

15. Tattevin P, Flécher E, Auffret V, et al.: Risk factors and prognostic impact of left ventricular assist device-associated infections *Am Heart J* 214: 69–76, 2019

16. Koken ZO, Yalcin YC, van Netten D, et al.: Driveline exit-site care protocols in patients with left ventricular assist devices: a systematic review *Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg* 60: 506–515, 2021

17. Akay MH, Nathan SS, Radovancevic R, et al.: Obesity Is Associated with Driveline Infection of Left Ventricular Assist Devices *ASAIO J Am Soc Artif Intern Organs 1992* 65: 678–682, 2019

18. Forest SJ, Xie R, Kirklin JK, et al.: Impact of body mass index on adverse events after implantation of left ventricular assist devices: An IMACS registry analysis *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 37: 1207–1217, 2018

19. Radcliffe C, Doilicho N, Niu YS, Grant M: Efficacy and safety of chronic antimicrobial suppression therapy for left ventricular assist device driveline infections: A single-center descriptive experience *Transpl Infect Dis* 22: e13379, 2020

20. Schlöglhofer T, Michalovics P, Riebandt J, et al.: Left ventricular assist device driveline infections in three contemporary devices *Artif Organs* 45: 464–472, 2021

21. Koval CE, Thuita L, Moazami N, Blackstone E: Evolution and impact of drive-line infection in a large cohort of continuous-flow ventricular assist device recipients *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* 33: 1164–1172, 2014

22. Pavlovic NV, Randell T, Madeira T, Hsu S, Zinoviev R, Abshire M: Risk of left ventricular assist device driveline infection: A systematic literature review *Heart Lung* 48: 90–104, 2019

23. Nienaber JJC, Kusne S, Riaz T, et al.: Clinical manifestations and management of left ventricular assist device-associated infections *Clin Infect Dis Off Publ Infect Dis Soc Am* 57: 1438–1448, 2013

FIGURE LEGENDS

Figure 1. Flow-chart of all clinical infections emerging in VAD patients (A) and those specific to the driveline (B). *VAD associated and VAD related. DL, driveline.

Figure 2: Distribution of VAD-related /-specific and total infectious episodes over time

Figure 3: Forrest plot of the estimates of the multiple linear regression with their confidence intervals.

TABLES

Table 1: Patient characteristics

	All patients (n=99)[a]
Female Sex - no. (%)*	22 (22.2 %)
Age - years[b]*	56
BMI – kg/m2	25.0 (IQR 22-28)
Hypertension at implant- no. (%)*	35 (36.5 %)
Diabetes at implant- no. (%)*	26 (26.3 %)
History of Smoking- no. (%)*	50 (50.5 %)
Chronic kidney failure at implant (eGFR<60ml/min/1.73m2) - no. (%)*	43 (43.4 %)
Cardiac failure aetiology- no. (%)	
Dilated Cardiomyopathy *	46 (46.5 %)
Ischemic Cardiomyopathy *	40 (40.4 %)
Other	13 (13.1%)
Previous valve operation- no. (%)*	16 (16.2 %)
Previous revascularisation procedure- no. (%)*	40 (40.8 %)
Previous sternotomy- no. (%)*	17 (17.2 %)
MCS before VAD implant- no. (%)*	15 (15.2 %)
INTERMACS- no. (%)*	
1-3	33 (33.7 %)
4-7	65 (66.3 %)
Type of device - no. (%)	
HW*	64 (64.6 %)
HM2*	10 (10.1 %)
HM3*	21 (21.2 %)
BIVAD (HW)	4 (4 %)
Intention of VAD implantation	
Bridge-to-Transplant	70 (73.0%)
Bridge-to-Candidacy	3 (3.1)
Destination	23 (24.0%)
Patient-years of support	1.57 (IQR 0.5-2.1)

[a]Hypertension at implant and intention of VAD implantation can be clearly determined in 96 patients, for Previous revascularisation procedure and INTERMACS in 98 patients.

[b]mean,

MCS: Mechanical Cardiac Support, INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support – score, HW: Heartware, HM2: Heartmate 2, HM3 Heartmate 3, BIVAD: bi-ventricular assistance.

Table 2: Simple linear and multiple regressions for VAD-specific or VAD-related infection

Multiple linear regression			
	Slope	Intercept	*p* value
Female Sex	-2.14 ± 1.93	7.4 ± 3.3	0.27
Dilated Cardiomyopathy	-1.75 ± 2.81	7.4 ± 3.3	0.54
Ischemic Cardiomyopathy	-0.38 ± 2.72	7.4 ± 3.3	0.89
History of hypertension	-2.62 ± 1.81	7.4 ± 3.3	0.15
Previous sternotomy	-3.94 ± 2.39	7.4 ± 3.3	0.1
MCS before VAD implant	-0.97 ± 3.04	7.4 ± 3.3	0.75
BIVAD	1.46 ± 4.95	7.4 ± 3.3	0.77
Cardiac Index	-0.95 ± 1.09	7.4 ± 3.3	0.38

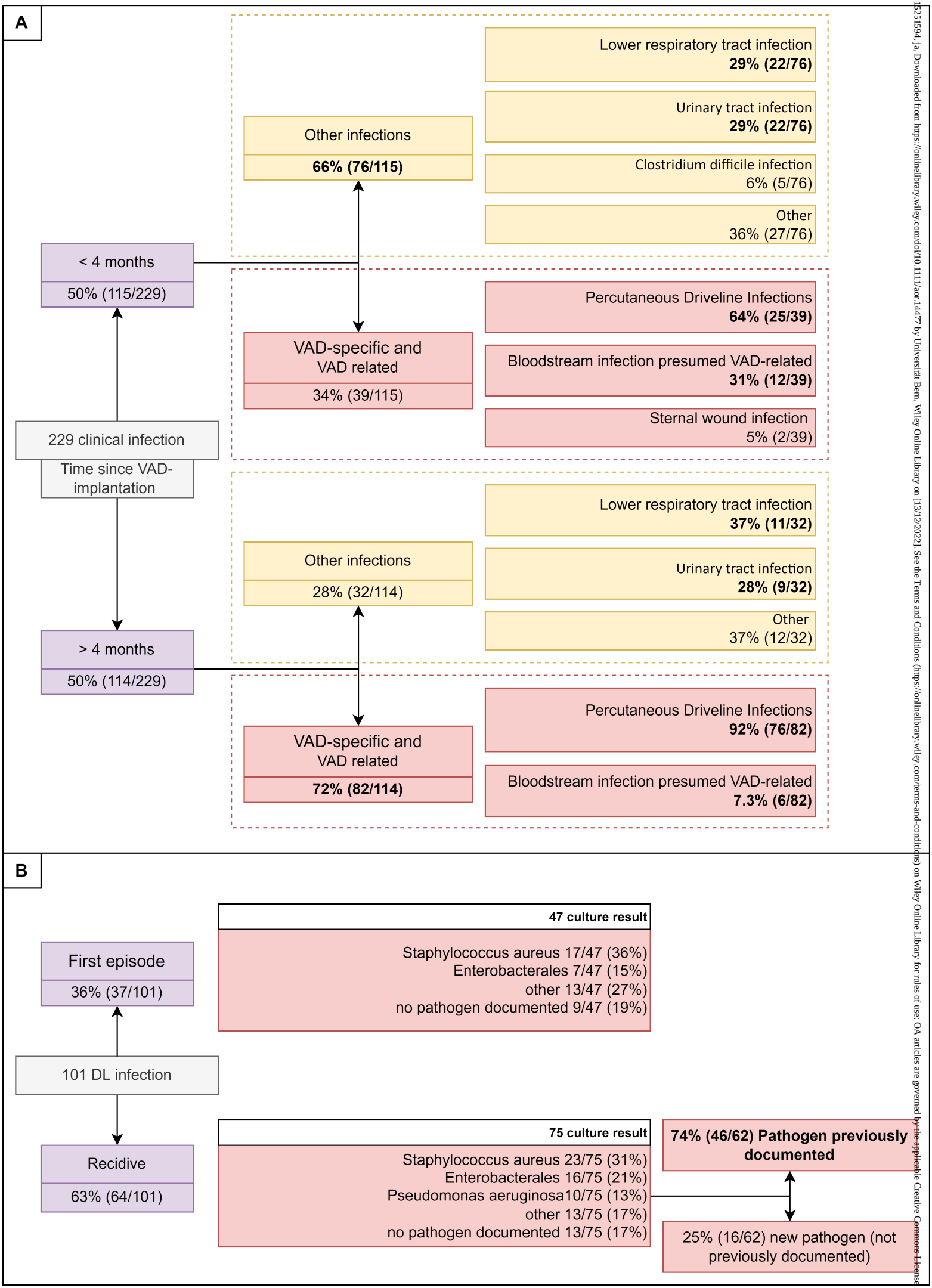
BIVAD, bi-ventricular assist device; HW, Heartware; HM2, Heartmate 2; HM3, Heartmate 3; MCS, mechanical cardiac support; VAD, ventricular-assist device.

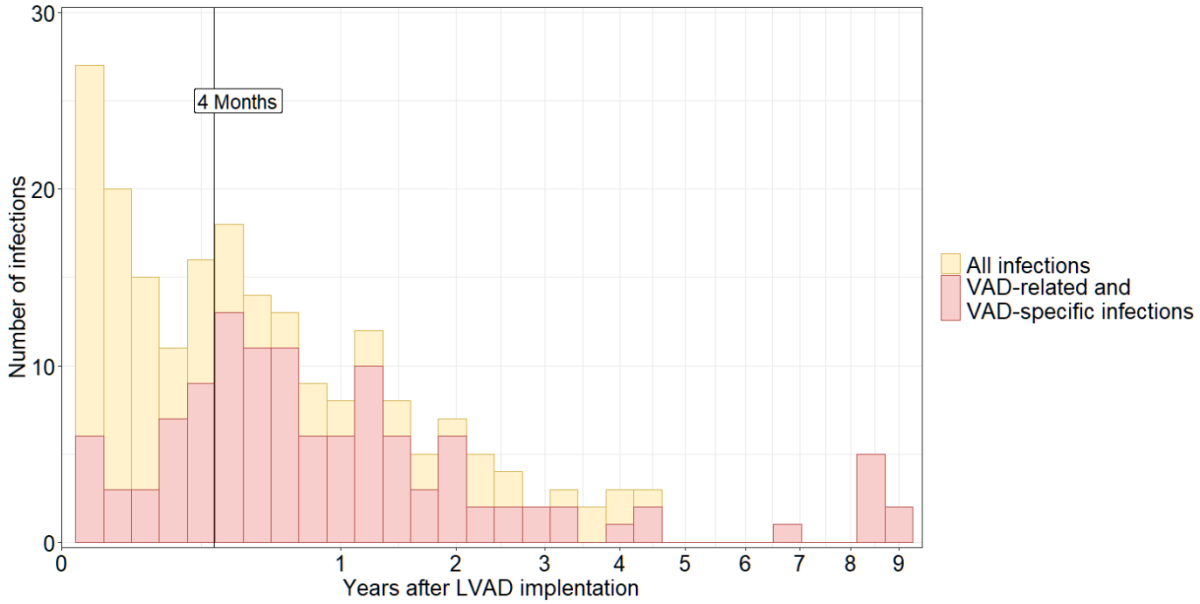
Table 3: All pathogens found in culture (VAD-specific infection, VAD-related infection, other). Further details are provided in Table S4.

Organism group	**N = 292**[1]
Enterobacterales	76 (26%)
Staphylococcus aureus	51 (17%)
Coagulase-negative staphylococci	20 (6.8%)
Pseudomonas aeruginosa	18 (6.2%)
Other gram negatives	12 (4.1%)
Candida spp.	11 (3.8%)
Other	43 (14%)
No organism identified	*61 (20.1)*
[1] **n (%)**	

Table 4: Total infection rate per 100 patient-year of support and total of infection events during follow-up (%) for VAD-specific/related infections as well as for all infections

	VAD-related and VAD-specific infection	**All infections**
Total infection per 100 patient-year of support	9 (IQR 0-14)	17 (IQR4-32)
Total of infection events during follow-up	47/99 patients; 60%	79/99 patients; 80%





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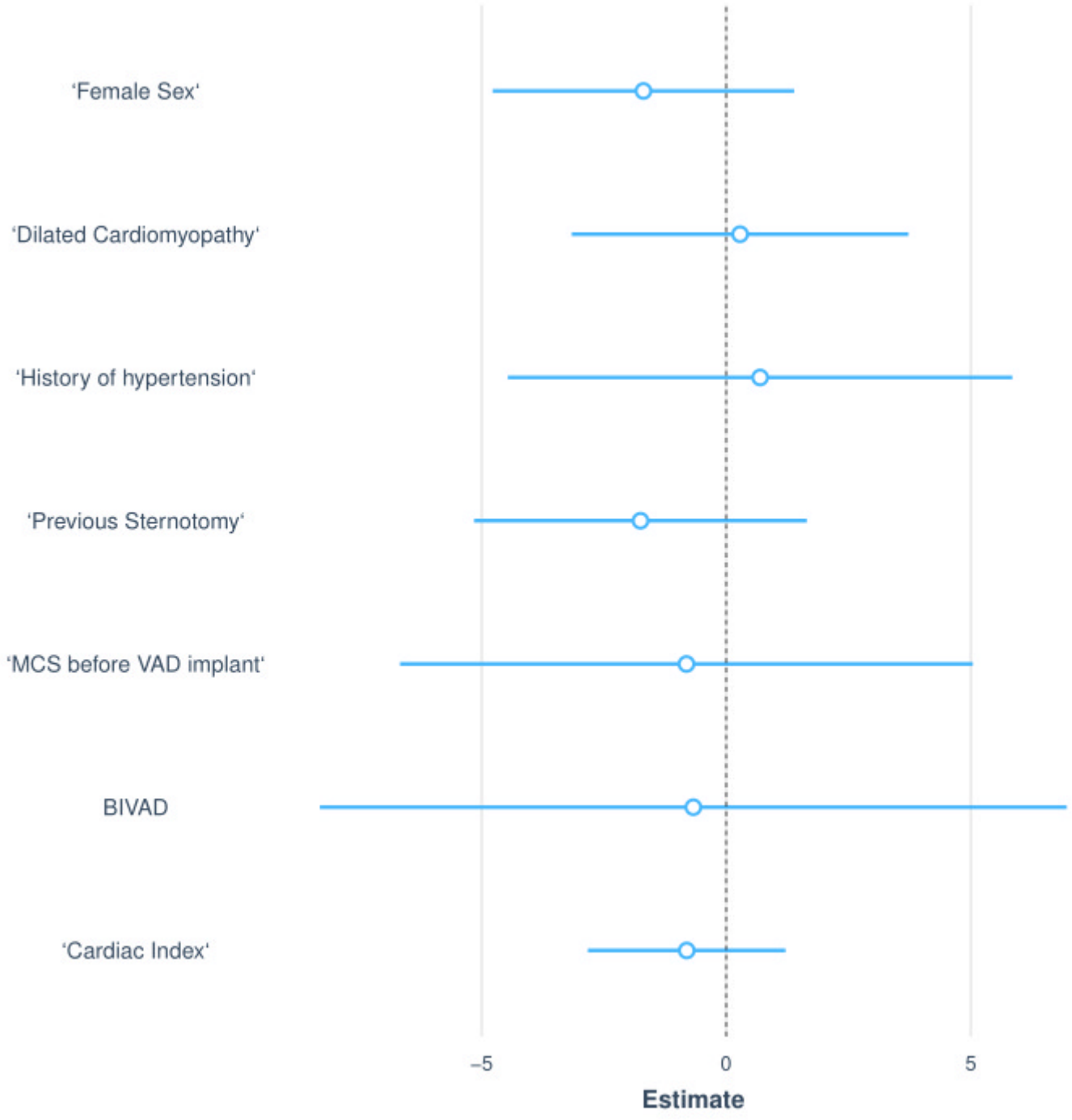

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