Rates and types of infections in left ventricular assist device recipients: A scoping review

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Use of left ventricular assist devices (LVADs) has increased over time as the number of patients with end-stage heart failure increases relative to the availability of heart transplant donor organs. Although outcomes in LVAD recipients have improved with advances in technology, infections remain a persistent problem and are the most common adverse event after LVAD implantation.1 Infections associated with LVAD implantation remain a persistent problem and are the most common adverse event during the first year after LVAD implantation, with only 59% of patients free from major infection at 1 year after implant.1 Although there are several subtypes of infections in LVAD recipients (eg, driveline infection, bacteremia, pneumonia, and urinary tract infection), all of them have been linked to an increased risk of postimplant complications (eg, rehospitalization, need for device exchange, stroke, or death) as well as associated increased expenditures.2-4

Despite the burden of infections in LVAD recipients, existing literature investigating this complication are mostly limited to small, single-center observational series. In addition, existing systematic reviews have focused on a limited number of infection subtypes rather than comprehensively studying all infection subtypes among patients receiving contemporary LVADs.5 This gap in this literature limits generalizability and application of the findings.

The objectives of this scoping review were to synthesize published evidence related to rates of different types of infections in LVAD recipients to report clinical trial and real-world infection rates, identify research gaps, and highlight methodological concerns to improve future studies.

METHODS
Study Design and Search Strategy

This scoping review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews guidelines (Appendix 1).6 Using existing literature among patients receiving LVAD, this study evaluated rates and types of infections and risk factors, including patient characteristics, processes of care, and device characteristics.

A scoping review methodology was selected rather than a systematic review due to lack of high-quality studies addressing the research questions and risk factors, including patient characteristics, processes of care, and device characteristics.

Central Message

This scoping review found that most studies of infections in LVAD recipients did not utilize standardized infection definitions and did not complete information on infection locations and types.

Perspective

In this scoping review of 132 studies reporting infections in LVAD recipients, most studies did not use standardized infection definitions and most studies did not report complete demographic information. To advance the scientific rigor of investigations into infections in LVAD recipients, future studies should use standardized definitions and meet minimum reporting guidelines.

See Commentaries on Pages 412, 414, and 416.
and large variability in study designs, definition of infections, and study methods. Accordingly, this study included randomized trials, cohort, case control studies, case reports, and case series.

Search Strategy
The following electronic databases were searched between January 2006 to February 2019 to include contemporary LVADs: PubMed.gov, Scopus, Embase (including Embase Classic), Cumulative Index to Nursing and Allied Health Literature Complete (EbscoHost), and Web of Science Core Collection (Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (A&HCI), Conference Proceedings Citation index - Science (CPCI-S), Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH), Book Citation Index - Science (BKCI-S), Book Citation Index - Social Science & Humanities (BKCI-SSH), Emerging Sources Citation Index (ESCI), Current Chemical Reactions (CCR-EXPANDED)]. References of all included articles as well as narrative and systematic reviews were reviewed to ensure inclusion of all pertinent articles. There were no other restrictions. Search key words were compiled by 3 authors (S.S., T.W., and W.T.) using the population (adult patients with a durable LVAD), concept (LVAD infections), and context (risk factors for infection) approach to designing scoping review search strategy. (Appendix 2). Deduplication was performed using Covidence systematic review software (Veritas Health Information, Melbourne, Australia).

Screening Sources of Evidence
Three authors (S.S., T.W., and D.L.) independently assessed the title and abstract of each item identified in the initial search to determine suitability for full-text review. At this stage, all studies were included if the study population was aged 18 years and older and received a durable continuous-flow LVAD. Any article deemed appropriate by either author was advanced to the next stage. Next, 4 independent authors (S.S., T.W., G.Y., and D.L.) reviewed the full text of selected articles to only include studies meeting the inclusion criteria listed below. Each full-text article was reviewed by 2 authors and disagreements were resolved by a third author.

The criteria for inclusion for analysis were:

- Adults aged 18 years or older;
- Contemporary LVADs used in the United States (HeartMate II [Abbott, Abbott Park, Ill], HeartMate 3 [Abbott], and HeartWare HVAD [Medtronic, Minneapolis, Minn]). If the study included other LVADs but infections were specified for LVADs of interest, it was included;
- Published full-text article in English language available for review;
- Studies with at least 10 patients; and
- Described rate of any infection and/or looked at predictors of infection in LVAD recipients.

The criteria for exclusion were:

- All narrative and systematic reviews, editorials, or study protocols; and
- If details on LVAD type studied were not provided.

Data Charting and Synthesis
Four independent authors (S.S., M.P., G.Y., and D.L.) extracted data from selected full-text articles for review. A review form was developed and utilized to collect prespecified elements from each study (Appendix 3). Extracted information included author names, study design, country of origin, study population, patient demographic characteristics, follow-up duration, infections subtypes and rates, use of standardized infection definitions as per the International Society for Heart and Lung Transplantation (ISHLT) Consensus Statement. Each article was reviewed independently by 2 authors and disagreements were resolved through discussion with involvement of a third author to arrive at consensus.

Statistical Analysis
Analyses were descriptive and displayed in tabular or graphical formats. Summary statistics were generated where appropriate using Stata IC (StataCorp, College Station, Tex). Frequency and percentage were reported for categorical variables and median with interquartile range (IQR) were reported for continuous variables. Results were displayed with tables, a bar chart, and a box plot. A variety of study designs and end points were included so outcomes and results were not pooled.

RESULTS
After screening 9680 titles and abstracts for eligibility, and reviewing 480 full texts, 132 full texts were included for data extraction (Figure 1). The study characteristics are described in Table 1. References for all studies meeting inclusion criteria included are summarized in Appendix 4.

Scope of the Literature
The majority of studies were conducted in the United States (n = 88 [66.7%]), followed by Germany (n = 11 [8.3%]). Studies were identified from 11 different countries with 11 studies reporting data from multiple countries. Most studies were observational (n = 118 [89.4%]) and were conducted at a single institution (n = 93 [70.4%]). A total of 72 identified unique patient cohorts were represented in this report (Appendix 5). The number of patients per study ranged from 16 to 1064 with a median of 137 (IQR, 60-282). The gender distribution was provided in 119 (90.1%) studies, with men representing the majority (median proportion, 79.3%; IQR, 75.0%-83.3%) in most studies. The racial distribution was reported in 33 studies with White patients representing the majority (median proportion, 68.1%; IQR, 55.4%-74.5%) of the population.

Follow-up duration was included in 93 studies (67.9%). The most commonly studied device was HeartMate II (96 studies; median number of devices, 134.5; IQR, 70-268.5) followed by HeartWare (70 studies; median number of devices, 44; IQR, 19-123) and HeartMate 3 (12 studies; median number of devices, 50; IQR, 12.5-101). The number of articles related to LVAD infection published per year increased over time from 1 in 2007 to 39 in 2018 (Figure 2). Most studies did not utilize standardized infection definitions, with only 48 (36%) using ISHLT definitions. The number of articles using ISHLT definitions steadily increased over time after 2011 with 58% studies in 2017 using standardized definitions (Figure 2).
LVAD-Specific Infections
The most commonly studied LVAD-specific infections were driveline infections (98 studies) followed by pocket infections (20 studies) and pump or cannula infections (3 studies). Driveline infection incidence for the entire cohort was reported in 92 studies with the number of patients ranging from 16 to 1064 (median, 123; IQR, 55.5-248). For studies reporting infection rates within the first 30 days of LVAD implant, the incidence ranged from 0% to 2.6%. Reported driveline infection rates ranged from 5.0% to 56% within the first 6 months postimplant, 7% to 71% at 1 year, and 7% to 65% at 2 years. In studies using standardized definition for infections in LVAD recipients provided by ISHLT, variation in rates of driveline infection persisted (Figure 3).

The incidence of pocket infections was reported in 20 studies, although the number of patients per study ranged from 28 to 414 (median, 139; IQR, 96-273.5). The reported incidence of pocket infections within the first month postimplant was 0%,9 0% to 2% within the first 6 months postimplant, 7% to 71% at 1 year, and 7% to 65% at 2 years. In studies using standardized definition for infections in LVAD recipients provided by ISHLT, variation in rates of driveline infection persisted (Figure 3).

LVAD-Related Infections
Bloodstream infections were the most commonly studied LVAD-related infections (n = 54 studies with number of patients ranging from 23 to 896; median, 139.5; IQR, 67-332). Rates for bloodstream infections within the first 1 month ranged from 2.6% to 10%,16,17 13% to 20% within the first 6 months of implant,10,18 and 3% and 27% within 1 year of implant.19,20

Rates for mediastinitis were reported in 6 studies, with the number of included patients ranging from 23 to 734 (median, 173.5; IQR, 111.75-326). The incidence of mediastinitis ranged from 0.5% to 22%. Infective endocarditis was reported in 2 studies, with the number of patients of 212 to 364 and reported rates of 0.5% to 2%.

Non-LVAD-Related or Any Infections
Non-LVAD-related infections were reported in 41 studies, with pneumonia (11 studies; rate, 1.8%-22.2%), urinary tract infections (6 studies; rate, 1.9%-18.8%), and sepsis

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**FIGURE 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses scoping review flow chart. LVAD, Left ventricular assist device.
The increased annual publications documenting LVAD infections parallels the increased use of continuous-flow LVAD implantations (<500 in 2008 to more than 3100 in 2019). Despite advancements in technology with newer Food and Drug Administration-approved devices, this literature documents the persistent influence of postimplant infections. An analysis from the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) trial demonstrated that freedom from infection is similar between the HeartMate II and HeartMate 3. Nonetheless, a lack of adherence to minimum reporting criteria limited the ability to compare the findings across studies, with age, gender, and race reported in <1 of 3 studies. Likewise, although 67.9% of studies reported follow-up duration, the type of follow-up information reported varied, with different studies reporting mean number of days, median number of days, or patient-years. Studies also varied in reporting follow-up duration for the whole study cohort or individually for subgroups. Similarly, although the number of publications evaluating infections in LVAD recipients has increased over time, this review identified significant overlap in the patient populations from which these data were derived. Of the 132 studies included, there were only 72 unique patient cohorts. This overlap in the published literature may further limit generalizability of the findings of these studies.

Furthermore, there was wide variability in how postimplant infections were defined. To standardize the reporting of infections within the setting of LVAD, ISHLT published a consensus statement in 2011. Although the goal of this consensus statement was in part to facilitate comparisons of outcomes across studies, only 51 of the 132 studies (38.2%) in this report adhered to ISHLT criteria. More recently, the Mechanical Circulatory Support Academic Research Consortium has published a consensus statement with updated adverse event definitions. The lack of standardization in reporting limits the ability to compare infection rates across centers as well as identify determinants of their occurrence. This limitation is especially pertinent with respect to identifying best practices for LVAD, a rare therapy for which randomized controlled trials of management strategies are usually not practical and lessons are frequently learned from observational studies after the initial clinical trials.

Results of this review also document that most research studies focus on reporting LVAD-specific infections, and most notably driveline infections. Non-LVAD and LVAD-related infections are the most commonly occurring infections in this setting, and are also

### Table 1. Study characteristics

| Characteristic | Result |
|---------------|--------|
| **Country of origin** | |
| United States | 88/132 (66.7) |
| Germany | 11/132 (8.3) |
| Multiple | 10/132 (7.6) |
| Japan | 5/132 (3.8) |
| Turkey | 5/132 (3.8) |
| United Kingdom | 3/132 (2.3) |
| Italy | 2/132 (1.5) |
| Netherlands | 2/132 (1.5) |
| Canada | 2/132 (1.5) |
| Denmark | 2/132 (1.5) |
| Kazakhstan | 1/132 (0.7) |
| Singapore | 1/132 (0.7) |
| **Study design** | |
| Observational | 118/132 (89.4) |
| Randomized | 4/132 (3.0) |
| Interventional, non-randomized | 10/132 (7.6) |
| **Use of ISHLT infection classification** | |
| Pathogen reported | 48/132 (36.4) |
| Follow-up duration reported | 93/132 (69.7) |
| Patient age reported | 97/132 (73.5) |
| Patient sex reported | 119/132 (90.2) |
| Patient race reported | 33/132 (25) |
| **Device type** | |
| HVAD | 134.5 (70-268.5) (n = 96 studies) |
| HMII | 44 (19-123) (n = 44 studies) |
| HM3 | 50 (12.5-101) (n = 12 studies) |

Values are presented as n/n (%) or median (interquartile range). ISHLT: International Society for Heart and Lung Transplantation; HVAD, HeartWare HVAD (Medtronic, Minneapolis, Minn); HMII, HeartMate II (Abbott, Abbott Park, Ill); HM3, HeartMate 3 (Abbott).

(5 studies; 2-study report rate for entire cohort at 3.35% and 31.6%) the most frequently evaluated. A composite rate for overall infections was reported in 40 studies. Only 23 studies reported the specific infectious pathogen, with the most common involving *Staphylococcus aureus* (17 studies) followed by *Pseudomonas aeruginosa* (11 studies).

### Discussion

The objective of this scoping review was to provide an overview of the literature evaluating infections among patients with contemporary LVADs. This study identified a total of 132 reports between 2007 and 2019, with an increased annual frequency of published studies over time. Nonetheless, a substantial proportion of studies did not report according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines, including demographic information or follow-up time. Although the majority of studies were conducted in the United States, the diversity of study locations highlights the global influence of infections related to LVAD therapy. Furthermore, studies varied in their infection definitions as well as reporting by type and location of infections (Figure 4).
associated with an increased risk of stroke and mortality.\textsuperscript{3} LVAD-specific infections are more likely to occur during the later postimplant follow-up period, whereas non-

LVAD–related and LVAD–related infections are more likely to occur shortly after implant.\textsuperscript{4} There are several factors specific to LVAD recipients that makes them more prone to infections, including a large burden of comorbidities as well as frequent hospitalizations and procedures or instrumentation.\textsuperscript{8} Accordingly, studies looking at LVAD–related and non-LVAD–related infections are urgently needed.

Limitations

The findings of this scoping review should be interpreted in the light of several considerations. Studies with fewer than 10 patients were excluded from consideration for this review. Although this criterion may have excluded potentially relevant studies, these smaller studies may not have provided stable estimates of observed infection rates. Although this search was limited to full-text, English-only studies, there were no geographic restrictions and the exclusion of non-English language studies is recognized as a potentially necessary tradeoff within scoping review methodology to balance feasibility, breadth, and comprehensiveness.\textsuperscript{24} In accordance with prior scoping reviews, the reported findings did not include data from published abstracts (eg, from presentations at scientific conferences) because many abstracts focused solely on preliminary data.\textsuperscript{25}
The goal of this scoping review was to synthesize all available evidence related to rates of infections (including location and types) in left ventricular assist device (LVAD) recipients. A total of 132 studies met inclusion criteria. The majority of studies did not use standardized reporting criteria for infections.

CONCLUSIONS
This scoping review examined studies evaluating the rates of infections in LVAD recipients, and provides a consistent message that the published literature largely comprises studies that do not adhere to minimum reporting criteria and do not use standardized definitions of infections. The results of this review have several implications for future investigations. Journals should consider requiring authors to report infections in accordance with established standardized definitions (eg, ISHLT) to enhance scientific rigor and facilitate comparison of outcomes across studies. Additionally, studies have predominantly focused on LVAD-specific infections, mainly driveline infection, resulting in a lack of scientific investigation among the more commonly occurring LVAD-related and non-LVAD-related infections. Accordingly, higher quality research studies adhering to standardized definitions are required to advance the scientific rigor of this literature.

Conflict of Interest Statement
Dr Likosky received extramural support from the Agency for Healthcare Research and Quality (AHRQ, R01HS026003). Dr Pagani is a member of the scientific advisory board of FineHeart, Inc; a member of the Data Safety Monitoring Board for Carmat, Inc; a member of the Data Safety Monitoring Board for the National Heart, Blood, and Lung Institute PumpKIN clinical trial; and chair of The Society of Thoracic Surgeons Intermacs Task Force. All other authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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