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Working formulation for the standardization of definitions of infections in patients using ventricular assist devices

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In 2009, the International Society for Heart and Lung Transplantation (ISHLT) recognized the importance of infection-related morbidity and mortality in patients using ventricular assist devices (VADs) and the growing need for a consensus-based expert opinion to provide standard definitions of infections in these patients. The aim of these standard definitions is to improve clinical-investigator communication, allowing meaningful comparison in practice and outcomes between different centers and different VAD devices. In 2010, a core group of experts, including infectious diseases specialists, cardiologists, pathologists, radiologists, and cardiothoracic surgeons, formed an ISHLT Infectious Diseases Working Group to develop agreed criteria for definitions of infections in VAD patients. These definitions have been created by adapting and expanding on existing standardized definitions, which are based on the pathophysiology of equivalent infectious processes in prosthetic devices, such as cardiac prosthetic valve infections, intravascular catheter-related infections, and prosthetic joint infections. These definitions have been divided into 3 sections: VAD-specific infections, VAD-related infections, and non-VAD infections.

Owing to the constant shortage of donor organs, new allocation systems, and improved medical therapies for congestive cardiac failure, the overwhelming trend in cardiac transplantation has been toward listing principally the most critically ill patients, that is, those requiring inpatient inotropic therapy for mechanical circulatory support (MCS). The ventricular assist device (VAD) has an expanding role in the management of these patients, both as a bridge to transplantation and as a destination therapy (ie, alternative to transplantation). According to United Network of Organ Sharing (UNOS) registry data, 9,000 transplant candidates have undergone MCS since 1999, comprising 33% of all listed patients and 75% of all listed inpatients.[1]

Furthermore, in line with improving technology and outcomes, the VAD is increasingly being deployed as an alternative to transplantation (destination therapy). The latest figures from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry indicate that from 2006 to 2010, approximately 45% of devices were implanted as a bridge to transplant, 45% as a bridge to candidacy, and 10% as destination therapy.[2]

One of the major challenges and limits to the successful use of VADs is infection. VAD-specific and VAD-related infections are difficult to treat and remain a major cause of death in these patients.[2] The effect of VAD-specific and VAD-related infections depends on the site and the severity of the infection, and infection mortality rates as high as 70% in those developing VAD-related infective endocarditis (IE) and mediastinitis have been reported.[4] Recently published INTERMACS adverse event data on major infection in pulsatile left VADs identified the first 3 months after VAD implant as the period of highest incidence of major infection.[3]

Currently, there are no standard international definitions for VAD infections. Various infection rates have been published from different centers during the last decade, but

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practice variation in device, implant technique, and infection diagnosis have limited meaningful comparisons to improve care.[3–14] The high prevalence of infection-related adverse events in recent studies was similar to previous reports confirming the continued major role of infection to the survival and quality of life for device recipients.[3,8]

The purpose of this document is to provide consensus-derived, standard international definitions that include not only major infection but also comprehensive details of all aspects of VAD-specific and VAD-related infection in these patients. Clinical, microbiologic, histopathological, and radiologic criteria are included in these definitions. We believe this will improve communication between clinicians and investigators to help validate clinical practice and research to improve patient care and outcome. To this end, the following definitions have been reviewed and approved by a multidisciplinary working group of the International Society for Heart and Lung Transplantation (ISHLT).

Scope

Providing a standard definition of infection in VAD recipients will permit analysis of the source, natural history, pathophysiology, and management of such infections. Thus, through internationally uniform data sets, we hope to gain insights that will lead to meaningful changes in practice to limit such infections.[15] The proposed definitions are suitable for epidemiologic purposes but are also intended to assist clinicians in the clinical decision making process.

Source

The Infectious Diseases Council of the ISHLT created the novel parts of these definitions by adapting from existing internationally recognized definitions of pathophysiologically equivalent infectious processes in other patient cohorts, including the modified Duke's criteria for diagnosing IE,[16,17] the Infectious Diseases Society of America (IDSA) guidelines for diagnosing intravascular catheter-related blood stream infection (CRBSI),[18] the Surgical Infection Society and IDSA intra-abdominal infection guidelines,[19] cardiovascular prosthetic device infections,[20,21] prosthetic joint infections (PJI),[22] and soft tissue infections.[23] These infections involve implanted or transcutaneous devices with the potential for alterations in pathogen recovery due to a biofilm-related pathologic process.

The definitions have been divided into 3 sections: (1) VAD-specific infections, (2) VAD-related infections, and (3) non-VAD infections (Table 1). When investigating any case of suspected VAD infection, prompt investigation is required, and testing as outlined subsequently should be pursued (Table 2):

- VAD-specific infections include infections that are specific to patients with VADs, are related to the device hardware, and do not occur in non-VAD patients; for example, pump and cannula infections, pocket infections, and percutaneous driveline infections.[4,8,20,24]
- VAD-related infections refer to those that can also occur in patients who do not have VADs; however, there may be unique considerations in patients with VADs with respect to making the correct diagnosis or determining the cause-and-effect relationship (eg, mediastinitis and IE).
- Non-VAD infections are essentially not affected by the presence of the VAD, and are unlikely related to the VAD presence but are included to encourage comprehensive and comparable data recording of all infections in this patient population to facilitate multi-center review.

Table 1 Classification of Infections in Patients Using Ventricular Assist Devices

VAD-specific Infections
- Pump and/or cannula Infections
- Pocket Infections
- Percutaneous Driveline Infections
  - Superficial infection
  - Deep infection

VAD-related Infections
- Infective endocarditis
- Bloodstream infections (including CVC-associated BSIs)
  CVC present
  - Bloodstream infection presumed VAD-related
  - Bloodstream infection presumed CVC-related
    No CVC present
  - Bloodstream infection VAD-related
  - Bloodstream infection non VAD-related
- Mediastinitis
  - VAD-related
    - Sternal wound infection SSI-organ space
    - Pocket infection (continuous with mediastinum or already situated in the mediastinum depending on the device used)
  - Non-VAD related
    - Other causes of mediastinitis, perforation of the esophagus

Non-VAD Infections
- Lower respiratory tract infection
- Cholecystitis
- *Clostridium difficile* infection
- Urinary tract infection

BSI, blood stream infection; CVC, central venous catheter; VAD, ventricular assist device.

VAD-specific infections

VAD-specific infections may be of the hardware itself or the body surfaces that contain them and include infections of the pump, cannula, anastomoses, the pocket infections, and the percutaneous driveline or tunnel. Accurate VAD-specific infections required new definitions to be constructed to reflect the specifics of such infection to enable study of the potential sources or risk factors for these infections. Guidelines on the diagnosis of PJI,[22] IE,[16] cardiovascular device infections,[20,21] intra-abdominal infections,[19] CRBSI,[18] and skin and soft tissue infections[23] have provided the basis on which the definitions were constructed. These infections share many features of VAD-specific infections because they are often difficult to diagnose conclusively and are difficult to treat due to the

Table 2 Investigations for Suspected Infection in a Patient Using a Ventricular Assist Device[a]

All patients:
- White blood cell count, serial C-reactive protein, or erythrocyte sedimentation rate
- Sterile aspirate for Gram stain, KOH, routine bacterial and fungal culture of driveline at exit site if pus present
- Echocardiogram (a TEE, if a TTE is negative)
- Blood cultures: At least 3 sets of cultures taken at different times over 24 hours; 2 sets from peripheral sites preferably. At least 1 central and 1 peripheral set of blood cultures should be taken at the same time if there is a CVC in situ. Each set including aerobic and anaerobic bottles with at least 10 ml of blood per bottle in adult cases or 1 ml/kg of blood per bottle for pediatric patients (up to a max of 10kg)[b]
- Chest X-ray

If VAD removed: samples to be obtained at the time of explantation
- Aspirate from external aspect of VAD (anterior) for culture
- Aspirate from external aspect of VAD (posterior) for culture
- Aspirate from outflow cannula part of VAD (internal aspect) for culture
- Aspirate from inflow cannula part of VAD (internal aspect) for culture
- Culture of saline instilled into VAD (internal aspect)
- Sample of pus from for Gram stain, KOH, bacterial and fungal culture
- $\geq$ 2 tissue samples from suspicious tissue surrounding VAD, driveline or anastomoses sent for histology, Gram stain, KOH, bacterial and fungal culture

When clinically indicated:
- Nasal, throat and groin aspirate for *Staphylococcus aureus* carriage
- If suspicious of a pocket infection obtain an abdominal US, CT abdomen/thorax, $\pm$ nuclear imaging study
- Image guided aspiration or brush of pocket/driveline
- Rule out all other possible causes of the septic episode (e.g. sputum culture and urine for microscopy and culture etc.)

CT, computed tomography; US, ultrasound; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

[a]See Figure 1 for labelling of samples to be sent to the laboratory for analysis.

[b]Special consideration in pediatrics: occasionally only results from blood samples obtained via the catheter (and not peripherally) are available in children to guide management.[18]

presence of biofilms on prosthetic surfaces that markedly reduces the likelihood of successful treatment with anti-infectives alone.[25–29]

The first group of VAD-specific infections are hardware-related (eg, pump and/or cannula infections; Figure 1, Tables 3 and 4). The "pump" or "VAD" refers to that part of the device that is involved in the propulsion of blood and includes continuous-flow and/or pulsatile-flow (intracorporeal and paracorporeal) devices. "Inflow cannula" refers to that part of the device connecting the ventricle to the pump device. "Outflow cannula" refers to that part of the device connecting the pump device to the patient's cardiovascular system. "Suture lines" refer to the surgical anastomoses between the pump and the patient's cardiovascular system. These generic terms have been chosen to allow as many VAD devices (including left VADs and right VADs) as possible to be incorporated into this definition framework.

The definition of pump and/or cannula infections has been partly based on the modified Duke's criteria, which have a high degree of sensitivity and specificity in the diagnosis of IE.[16] Prospective validation of these VAD definitions will, however, have to be done, and future modification of these definitions may be required.

A patient must have at least one of the microbiologic, histopathologic, radiologic, or clinical criteria to achieve a firm diagnosis, as outlined in Tables 3 and 4. The retrieval of a pathogen or an indistinguishable organism from more then one site is critical for validating the microbiologic criterion. Laboratories may wish to store isolates for further molecular typing in some difficult cases, during institutional outbreaks, or in all cases where possible for future studies. *Staphylococcus lugdunensis* has been included here, along with *S aureus* in the definitions, and not with coagulase-negative staphylococci, to reflect this organism's propensity to form a biofilm resulting in persistent infections, as has been discussed in recent IDSA guidelines on central venous catheter (CVC) infections.[18]

The term "pocket" in these definitions is used to describe infections that occur in the body space or pocket that holds the pump inside the patient's body (Figure 1, Tables 5 and 6). Classically, the pocket may be newly created within the abdominal wall or close to the pericardium and the diaphragm. The most recent devices use natural body cavities and are placed entirely within the left ventricle or within the pericardial sack. Pocket infections in those devices that still require a surgical pocket may be diagnosed without removing the VAD at the time of surgery if samples from the inner surface of the pocket and the exterior surface of the VAD are taken (Table 2, Figure 1). Cardiothoracic surgeons, cardiologists, and in certain specialized centers, interventional radiologists working closely with microbiology teams may be able to aspirate diagnostic fluid surrounding devices by imaging guidance.

Percutaneous driveline infections are important but challenging to define. Objectively, they lie between existing standards for tunnelled central lines and implantable intraports.[18,20,21] It is difficult to strike a balance between fully comprehensive definitions and definitions that are practical and useful for clinicians. Consequently, percutaneous driveline infection definitions have been adapted from Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance definitions of health-care–associated infection and classified as superficial or deep according to the depth of the infection.[30]

In this report, definitions have been sub-classified into proven, probable, and possible superficial and deep infections. Each sub-classification is described under the following 4 categories: surgical and histology, microbiology, clinical, or general appearance (Table 7) and should allow for detailed analysis of the etiology and risk factors for both superficial and deep percutaneous driveline infections. This is considered the most useful way to define driveline infections, because man-

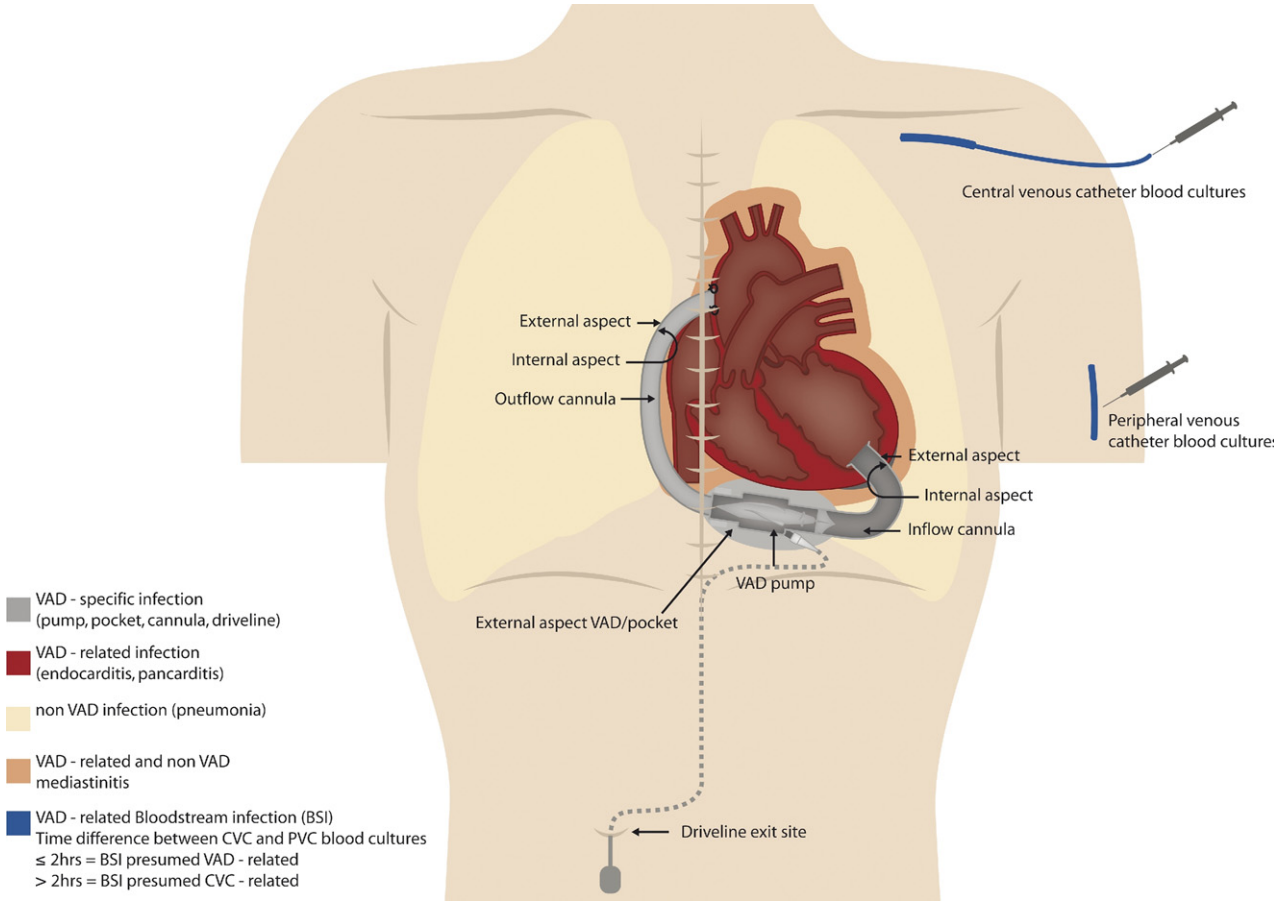

Figure 1 Illustration of ventricular assist device VAD-specific, VAD-related, and non-VAD infection. CVC, central venous catheter; PVC, peripheral vascular catheter.

agement of driveline infections typically depends on the depth of the infection, which likely correlates with the source of the infection (Table 7).[23] All percutaneous drivelines should be surgically and histopathologically examined at the time of removal or replacement, and an infection that involves both superficial and deep incisions will be classified as a deep infection.

Percutaneous driveline infections are the most commonly occurring infections in VAD patients and may reflect the presence of a deeper infection of the pocket space or pump and/or cannula. These infections may be the result of local trauma at the exit site during device implantation, which may act as a cutaneous source of infection at a later date.[31] Ultrasound (US) imaging and computed tomography (CT) angiography can on occasion reveal cuffs of fluid around the drivelines, cannula, and pump. Indium-labelled white blood cell scanning may also be helpful, but as yet, has not been validated for diagnosing these infections. The intra-operative exploration of the percutaneous driveline exit site at explantation or revision is required to satisfy these definitions, making them more useful for epidemiologic study than for clinical diagnosis.

VAD-related infections

VAD-related infections include IE, BSI, mediastinitis, and sternal wound infection (Table 8). Standard terms to refer to each type of VAD-related infection have been outlined in Table 8 to ensure that there is a consistency when centers are describing an infection. The full definition for each infection has not been replicated in this document because the definitions are already widely used. Imaging has a particular role in revealing new inflammatory change in the mediastinum, and newer cardiac CT techniques can show large valve vegetations and cannula insertion infections. CT may have a role in sternal wound infection characterization, although we would mainly use it today to define the extent of deep-seated infection or collection and occasionally to guide tissue sampling by core biopsy for culture if aspirates have not yielded a specific diagnosis.[32]

Diagnosing VAD-related BSI in the presence of a CVC may be particularly difficult. The technique of the "differential time to positivity" as a method of determining which infections are due to the VAD and which are due to the CVC is recommended, consistent with recent IDSA guidelines.[18] This method uses a 2-hour time to positivity differential to determine the source of infection when a CVC is present. This method, although not 100% accurate, may implicate the CVC as the source of the bacteriemia. Efforts can be made to avoid secondary seeding of the infection from the VAD by prompt removal of the CVC and repeating blood cultures after appropriate anti-microbial treatment of the CVC-related BSI has been accomplished and anti-infectives are no longer present. Once CVC-related BSI has been ruled out, then other causes

Table 3 Definition of Terms Used for the Diagnosis of Ventricular Assist Device-Specific Pump And/Or Cannula Infection[a]

Major Clinical Criteria
- If the VAD is not removed, then an indistinguishable organism (genus, species, and antimicrobial susceptibility pattern) recovered from 2 or more peripheral blood cultures taken >12 hours apart with no other focus of infection or
  All of 3 or a majority of ≥4 separate positive blood cultures (with the first and last sample drawn at least 1 hour apart) with no other focus of infection
- When 2 or more positive blood cultures are taken from the CVC and peripherally at the same time, and defined by criteria in Table 5 as either BSI-VAD-related or presumed VAD-related
- Echocardiogram positive for VAD-related IE (TEE recommended for patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess] and in any patient in whom VAD-related infection is suspected and TTE is non-diagnostic; TTE as first test in other patients) defined as follows: intracardiac mass suspected to be vegetation adjacent to or in the outflow cannula, or in an area of turbulent flow such as regurgitant jets, or consistent with a vegetation on implanted material, or abscess, or new partial dehiscence of outflow cannula.

Minor Clinical Criteria
- Fever ≥ 38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracerebral or visceral, conjunctival hemorrhage, and Janeway's lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spot
- Microbiologic evidence: positive blood culture that does not meet criteria as noted above (excluding single positive culture for coagulase-negative staphylococci excluding *Stapylococcus lugdunensis*)

CVC, central venous cannula; BSI, blood stream infection; IE, infective endocarditis; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram; VAD, ventricular assist device.
[a]Adapted from the Modified Duke's Criteria.[16]

(non-VAD infection) of BSI in VAD patients should also be assessed, because the VAD may not always be the source of the BSI.[11] Mycotic aneurysms have also been reported in patients using VADs and associated with persistent or relapsing BSI (S. Gordon, personal communication). Mycotic aneurysms may be visceral or intracerebral (usually presenting as an intracranial hemorrhage).

Non-VAD infections

Non-VAD infections are essentially "independent" or not directly related to the presence of the VAD but are infections occurring in a sick population of immunocompromised hosts with underlying comorbidities such as diabetes, prolonged hospitalization, multiple drug regimens, and renal impairment. The purpose of including non-VAD infection is to provide a comprehensive overview of all infections in this population and, in particular, to determine which international definition standards should be used for registry data gathering (the most common non-VAD infections are listed Table 9).

Investigating suspected infection in a patient using a VAD

Patients with VAD infections may present in a variety of ways, making definitive diagnosis difficult. Patients often present with non-specific symptoms such as lethargy, fatigue, fever, or anorexia, as well as a wide spectrum of ailments ranging from minor erythema at the percutaneous driveline exit site to severe sepsis and clinical shock. All clinicians must be alert to the possibility of infection in VAD patients and should be educated regarding the clinical symptoms and signs, which ensure early detection and guide the most efficient diagnostic algorithm.

The initial evaluation should include a careful history and review of symptoms. Physical examination, review of the VAD function, surgical wounds, and percutaneous driveline exit site are essential because early detection and treatment of a localized process may prevent progression to more serious VAD infections. It can also help to direct the clinician to

Table 4 Definitions of Ventricular Assist Device-Specific Pump Infections And/Or Cannula Infection

Proven
- Microbiology. Isolation of indistinguishable organism (genus, species, antimicrobial susceptibility pattern) at explantation or intra-operatively from
  - ≥ 2 positive internal aspect culture samples from pump and/or cannula or
  - 1 positive peripheral blood culture and 1 positive culture from VAD internal aspect aspirate or endovascular brushings, (internal aspect refers to the inner lumen of the cannula) or
  - In the case of coagulase–negative staphylococci excluding *Staphylococcus lugdunensis*; 2 or more positive sets of peripheral blood cultures and a positive internal aspect culture of pump and/or cannula
- Histologic features of infection from heart tissue samples from around the VAD pump and/or cannula at explantation or intra-operatively.
- Clinical criteria (see Table 3)
  - 2 major criteria

Probable
  - 1 major criterion and 3 minor criteria or
  - 4 minor criteria

Possible
  - 1 major and 1 minor or
  - 3 minor

Rejected
- Firm alternative diagnosis explaining the clinical findings
- Resolution of evidence of pump and /or/cannula infection with antibiotic therapy for ≤ 4 days or
- No pathologic evidence of pump and/or cannula infection at surgery or autopsy with antibiotic therapy for ≤ 4 days or
- Does not meet criteria for possible pump and/or cannula infection

Table 5 Definition of Terms Used for the Diagnosis of Ventricular Assist Device-Specific Pocket Infection

Major clinical criteria
- Microbiologic: aspirated fluid culture positive or fluid/pus diagnostic of infection.[a]
- Radiologic: New fluid collection by radiologic criteria-CT/US/Indium (enhancement or gas or sinus tract or leukocyte migration)

Minor clinical criteria
- Fever ≥ 38°C with no other recognized cause
- New local erythema over the pocket site
- Local pain and tenderness
- Induration or swelling
- Radiologic evidence: lymphangitis seen radiologically or
- New fluid collection without major criteria (above) and without diagnostic culture but not explained by other clinical conditions such as failure/anasarca/seroma

CT, computed tomography; US, ultrasound.
[a]Image-guided aspiration.

non-VAD infections that may be present, such as a urinary tract infection (UTI) or *Clostridium difficile* infection. Laboratory studies, including a full blood count,[33–35] serial erythrocyte sedimentation rate,[33] or C-reactive protein are recommended in all patients.[33–37] If pus is visible at the percutaneous driveline exit site, then an aspirate of this pus should be sent for bacterial and fungal cultures. Routine surveillance cultures of exit sites may be considered, because colonization often precedes infection and can serve as valuable information for a subsequent infection. Initial imaging should include a standard chest X-ray; an echocardiogram will be needed if there is suspicion of native valve IE or concomitant cardiac implantable electrical device IE.

At least 3 sets[38] of blood cultures should be obtained, at different times over 24 hours, with preferably two sets from separate peripheral sites consistent with Modified Duke's criteria[16,17] before commencing anti-infectives (Table 3), and in the presence of a CVC a set of blood cultures from the CVC should be obtained at the same time as one peripheral set of blood culture to distinguish CVC related bloodstream infection from VAD-related bloodstream infection (Table 8).[18] Difficulty in obtaining blood samples from children and concerns about drawing large volumes may result in lower volumes of blood being submitted for culture and may reduce the negative predictive value of the culture.[18] When clinical, laboratory and microbiology culture data point to a particular VAD or non-VAD infection, imaging can play a role in supporting such suspicions or directing tissue samples. Further, when infection source eludes standard evaluation, imaging can have a role in primary diagnosis.

US imaging is a useful tool to visualize fluid around percutaneous and tunnelled drivelines and in pump pockets and can be used to direct tissue samples or lavage. Owing to ease of access, widespread practice, and rapid diagnosis, US imaging has become the first-line study for infections.[19] Various CT protocols beyond the scope of this report can be used to evaluate lungs, pleural space, mediastinum, and other organs structures. They are clearly of value in investigating suspected infection in a patient using a VAD.[39] Because MRI is largely precluded, CT and digital subtraction angiography are the tests of choice for mycotic pseudoaneurysm assessment and treatment. The ability of modern scanners to provide whole body assessment is very helpful. We have also found it of value to assess cannulae, thrombi, and vegetations. Sternal wound infections have been assessed by CT or bone/indium-labeled leukocytes[40] scan with specific protocols may have a role in characterization of infection, but may have limited value in the surgically damaged sternum.[32] There is debate on the future role of single photon emission tomography-CT.[41]

In selected patients, the VAD may need to be removed due to uncontrolled infection or for technical reasons. When this happens, the VAD should always be sent to the pathology laboratory for processing. Sterile aspirates or sterile syringe aspirates (from surgery) should be taken for Gram stain, KOH, bacterial, and fungal cultures at the time of explantation from the internal and external aspect of the inflow cannula and from the internal and external aspect of the outflow cannula when a

Table 6 Definition of Ventricular Assist Device-Specific Pocket Infection

Proven

Pathologic/microbiologic criteria
- Patient has organisms cultured from the pocket space obtained during a surgical operation or needle sampling, taken intra-operatively or with radiologic guidance.
- Isolation of indistinguishable organism (genus, species, antimicrobial susceptibility pattern) from aspirate taken intra-operatively
  - 2 exterior aspect culture positive samples from VAD
  - 1 exterior aspect culture positive sample from the VAD and 1 culture from pocket space surrounding VAD obtained intra-operatively.
- Abscess or other evidence of infection seen in the pocket area during a surgical operation/imaging or histopathology examination

Clinical criteria (Table 5)
- 2 major criteria

Probable
- 1 major criteria and 3 minor criteria or
- 4 minor criteria

Possible
- 1 major and 1 minor or
- 3 minor

Rejected
- Firm alternative diagnosis explaining clinical findings
- Resolution of evidence of VAD pocket infection with antibiotic therapy for ≤ 4 days or
- No pathologic evidence of VAD pocket infection at surgery or autopsy with antibiotic therapy for ≤ 4 days or
- Does not meet criteria for possible VAD pocket infection
- Rejected microbiology evidence; negative culture or scanty growth of coagulase-negative staphylococcus excluding *Staphylococcus lugdunensis* and non-purulence aspirated fluid or tissue obtained during surgical operation or needle aspiration from the pocket area.

VAD, ventricular assist device.

Table 7 Definitions of Ventricular Assist Device-Specific Percutaneous Driveline Infection

	Surgical/histology	Microbiology	Clinical	General wound appearance
A. Superficial VAD-specific Percutaneous Driveline Infection				
Proven = Surgical/histology criteria ± other criteria	• Involvement of tissues superficial to the fascia and muscle layers of the incision documented	• Aseptic skin culture positive or not cultured	• Local increase in temperature around the exit site	• Purulent discharge from the incision but not involving fascia or muscle layers or • Erythema spreading around the exit site[a]
Probable = No surgical/histology criteria with purulent discharge ± other criteria	• Surgical debridement not performed • No histology	• Aseptic skin culture positive or negative but patient already on antibiotic or had antiseptic used to clean wound	• Local increase in temperature around the exit site and • Treated as superficial infection with clinical response	• Purulent discharge from the incision but not involving fascia or muscle layers or • Erythema spreading around the exit site[a]
Possible = No surgical/histology or purulent discharge ± other criteria	• Surgical debridement not performed • No histology	• Aseptic skin culture positive or negative and patient not on antibiotics or had antiseptic used to clean the wound	• Local increase in temperature around the exit site and • Treated as superficial infection with clinical response	• No discharge • Erythema spreading around the exit site[a]
B. Deep VAD-specific Percutaneous Driveline Infection				
Proven = Surgical/histology criteria ± other criteria	• Involves deep soft tissue (eg, fascial and muscle layers) on direct examination or on direct examination during re-operation • An abscess is found on direct examination during re-operation	• Culture positive or histology puncture positive for infection	• Temperature >38°C • Localized pain or tenderness	• A deep incision spontaneous dehiscence • Abscess deep to the incision around the driveline
Probable = No surgical/histology criteria with spontaneous dehiscence ± other criteria	• No surgical debridement • No histology	• Culture negative but patients already on antibiotics or had antiseptic used on exit site	• Temperature >38°C or • Localized pain or tenderness and • Treated as a deep infection	• An incision spontaneous dehiscence
Possible = No surgical/histology criteria with positive ultrasound ± other clinical criteria	• No surgical debridement • No histology	• Cultures not reserved	• Localized pain or tenderness and • Treated as a deep infection with clinical response	• Positive ultrasound

VAD, ventricular assist device.
[a]Erythema excluding stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).

VAD is removed. A small volume of sterile water (< 5 ml) should be instilled into the explanted VAD and then aspirated and sent for bacterial and fungal culture.

Defining the optimal method of culture of VADs is beyond the scope of these guidelines; however, in the future it would be beneficial to devise a standardized culture process for VADs so that the microbiology laboratory practice can be standardized across all centers (eg, VAD sonication or even scraping of the biofilm).[40] In particular, the use of broth cultures for the retrieval of organisms (currently used for explanted heart valves) should be considered where possible. Cardiothoracic surgeons, cardiologists, and in certain specialized centers, interventional radiologists working closely with microbi-

Table 8 Definition of Ventricular Assist Device-Related Infections

Clinical condition	Classification of disease
Endocarditis	
All cases (default)	VAD-related endocarditis
Vegetation seen on native valves and not on VAD	Valvular VAD-related endocarditis
(Define native valve IE using modified Duke's Criteria[16])	
Bloodstream Infection	
CVC present:	
• Central culture positive ≤2 hours before peripheral	BSI *presumed* VAD-related
• Central culture positive >2 hours before peripheral culture	
(Definitions made using the IDSA guidelines when CVC present[16])	BSI *presumed* CVC-related
No CVC present:	
• BSI due to VAD infection or cause unclear	Bloodstream infection VAD-related
• BSI due to cause other then VAD infection (e.g. UTI, pneumonia)	Bloodstream infection non-VAD-related
(Definitions made using CDC/NHSN definitions when no CVC present[30])	
Mediastinitis	
VAD-related: This is when mediastinitis is due to the VAD device (1) Sternal wound infection related, SSI-organ space (2) Pocket infection (continuous with mediastinum or already situated in the mediastinum depending on the device used) Classify as (1) and (2) A per "Surgical site infection-organ space" in CDC/NHSN surveillance definitions for healthcare-associated infection.[30]	Mediastinitis VAD-related
Non-VAD mediastinitis: This is when mediastinitis is definitely due to another cause (eg, esophageal perforation during endoscopy). Classify as "CVS infections-mediastinitis"in CDC/NHSN surveillance definitions for healthcare-associated infection.[30]	Mediastinitis non VAD-related

CDC/NHSN.

ology teams may be able to aspirate diagnostic fluid surrounding devices by imaging guidance.[19] The risk of introducing infection into a sterile fluid collection using this technique should be considered, and the performance of such procedures must have direct oversight for specimen handling by those involved in the infection management.

Any purulence present in the pocket area should also be sent for Gram stain, KOH, bacterial and fungal culture, and a further 2 aspirates processed in the same way taken from the external anterior and posterior surfaces of the VAD. Finally, at least 2 samples of tissue from the pocket area and insertion site of the cannulae into the heart should be sent for histology and tissue stains for bacteria, and for microbiology, Gram stain, KOH, bacterial, and fungal cultures.

It may also be necessary to send additional samples to the microbiology laboratory if non-VAD infections are suspected (eg, urine, stool for *C difficile* toxin A and B, sputum, and wound aspirates). The investigation of suspected VAD infections should be done in consultation with an infectious disease physician or clinical microbiologist, a cardiologist, and a cardiothoracic surgeon to optimize the diagnosis and management of the potential infection. The anti-infective regimen must be carefully chosen, because prolonged, even life-long therapy may be required.

Table 9 Recommended International Definitions for Non-VAD Infections for Registry Data Gathering

- Lower respiratory tract infections[a]
- Cholecystitis[a]
- *Clostridium difficile* infection[b]
- Urinary tract infection[a]

[a]Defined as per Centers for Disease Control and Prevention/National Healthcare Safety Network[30] definition.

[b]Defined as per Health Protection Agency, UK definitions and Infectious Disease Society of America definition.[47,48]

Discussion

Prevention and control of infection in patients using VADs will be most effectively accomplished if the risk factors for these infections are clearly known. Publications to date have used variable and heterogeneous definitions of VAD infection using various VAD devices, thereby limiting the comparison between the types and incidence of infection and the generalizability of this data across transplant centers.

These single-center studies have been small retrospective, record reviews using different definitions of infection, various VAD devices, and varying surgical techniques.[4,5,12,42] Larger recent studies using a standard definition for "major" infection have been used by the INTERMACS registry group, which began data collection in June 2006.[2,3] Major infection listed as an adverse event in the INTERMACS registry were broadly defined into 4 categories: (1) localized non-device related, (2) percutaneous site and/or pocket infection, (3) internal pump component, inflow tract infection, and (4) sepsis, without using internationally recognized clinical and microbiologic criteria to

define the time course, incidence, outcome, and risk factors for infection in VAD recipients.[43,44] Therefore, these broad definitions may vary across centers and countries unless standardized. On behalf of the ISHLT, the Infectious Diseases Working Group has proposed standard definition criteria for clinical, microbiologic, and radiologic diagnosis of infection in patients using VADs in 3 categories: VAD-specific, VAD-related, and non-VAD infections. These new definitions will allow for sophisticated statistical analysis of time course, incidence, outcome, and risk factors for infection in all VAD recipients.

The epidemiology of infecting organisms in patients using VAD will be analyzed as part of these validation studies and routine screening for multi-resistant bacteria (eg, MRSA, VRE, ESBL-producing Gram-negative bacteria, etc) should be considered in most countries but particularly in counties where high colonization rates are suspected. If multi-resistant bacteria are isolated, peri-operative prophylaxis will be altered to cover these organisms, which may influence outcome and so will be included in data collected. Likewise, in centers where MSSA or MRSA screening and decolonization is standard practice in patients before VAD implantation, decolonization may influence outcome and will be included in the data collection.[45,46]

The goal of this current working formulation of standardized definitions of infection is to provide a baseline for developing and validating internationally recognized definitions of infection in patients using VADs and ultimately identify the risk factors for these infections and provide effective diagnostic and treatment strategies for clinicians managing these challenging infections. As always, this working formulation should be regarded as a living document that will no doubt require further modification in the future with changing device technology, improved diagnostics, more accurate epidemiology, and advanced research. Rigorous prospective evaluation of data collected in multiple centers should be carried out to validate and then revise these proposed definitions. Validation is needed particularly in the clinical criterion for diagnosing VAD-specific driveline exit site, pump, and/or cannula and pocket infections to enhance the diagnostic sensitivity and specificity of the clinical criteria for defining these infections. We encourage others to assist in evaluating future modifications to these important definitions of infection.

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