

1 **A 2010 Working Formulation For The Standardization Of Definitions Of Infections In**
2 **Patients Using Ventricular Assist Devices (Vads).**

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6 The goal of this document is to provide consensus derived, expert opinion of standardization
7 of definitions of infections in patients with ventricular assist devices (VADs), to improve
8 communication between clinicians and investigators, to enable comparison in outcomes
9 between different centres and different devices, to facilitate multicenter clinical trials, and to
10 promote future studies to validate clinical criteria to assist in clinical decision-making.
11 Infections have been shown to occur in 16% of patients with VADs¹. Publications to date
12 have varied in their definitions of infections related to VADs² and thus it has been difficult to
13 compare infection rates between different types of VADs and between different institutions.
14 Currently there are no standard international definitions for infections related to VADs.
15 Providing a standard definition of infections related to VADs will allow for a more uniform
16 analysis of patient outcome and allow for multicenter analysis to identify risk factors that
17 may be reduced or avoided³. The definitions should also assist clinicians when assessing
18 patients for the possibility of VAD infections.

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20 The following definitions have been reviewed and approved by a core multidisciplinary
21 working group of the International Society of Heart and Lung Transplantation (ISHLT). The
22 Infectious Diseases (ID) Council of ISHLT created the novel parts of these definitions by
23 adapting from other internationally recognized standardized definitions of
24 pathophysiologically equivalent infectious disease processes, including cardiovascular device
25 and prosthetic valve infections, intravascular-catheter related infections and prosthetic joint
26 infections (PJI).

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28 The definitions have been divided into three sections: VAD-specific infections, VAD-related
29 infections and non-VAD related infections (Table 1). When investigating any case of
30 suspected VAD infection, prompt investigation is required and testing as outlined below
31 should be pursued (Table 2). VAD-specific infections include infections that are specific to
32 patients with VADs; pump and cannula infections, pocket infections and percutaneous
33 driveline infections^{2, 4, 5, 6}. VAD-related infections refer to those that can occur in patients
34 who do not have VADs, however in patients with VADs there may be unique considerations
35 with respect to making the correct diagnosis or determining the cause of a particular cause of
36 sepsis. Non-VAD related infections are essentially not affected by the presence of the VAD,
37 but are included with references to internationally accepted definitions to encourage centres
38 to maintain uniformity in all definitions of infections in this patient population to allow for
39 inter-center comparisons and meta-analysis.

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41 **How to Investigate a Patient for suspected VAD infection**

42 Patients with VAD infections may present in a variety of ways and often it can be difficult to
43 achieve a conclusive diagnosis. A patient may complain of non-specific symptoms such as
44 lethargy, fatigue, fever or anorexia. Patients can present with minor problems such as local
45 erythema around the exit site of the driveline or with severe sepsis and signs of clinical
46 shock. All clinicians must be alert to the possibility of infection in VAD patients and should
47 be educated regarding clinical symptoms and signs of which to be aware.

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49 At first investigation should start with basic history and review of symptoms. A full physical
50 examination and review of the VAD function and exit-sites is also essential at this stage. This
51 may alert the clinician to the potential aetiology of the symptoms and to early VAD
52 infections which may prevent deeper, more serious VAD infections from occurring. It can
53 also help to direct the clinician to non-VAD related infections that may be present such as a
54 urinary tract infection (UTI) or *C. difficile* infection (CDI). A full blood count, erythrocyte

55 sedimentation rate and C-reactive protein should be sent in all patients⁷. If there is pus visible
56 at the exit site then a swab of this pus should be sent for routine culture, including fungal
57 culture. Routine surveillance cultures of exit sites are not recommended as any isolates that
58 would be grown will likely reflect colonisation only in the host. An echocardiogram will be
59 needed if there is suspicion of an infective endocarditis (IE) being present. At least two sets
60 of blood cultures should be taken aseptically, with at least one set of blood cultures being
61 taken from a peripheral site and not from a central venous catheter. Both aerobic and
62 anaerobic cultures should be sent with sufficient volume to achieve a diagnosis, taking into
63 account the size of the patient.

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65 In certain cases the VAD may need to be removed due to infection or for technical reasons.
66 The VAD should be sent to the laboratory for processing. Swabs should be taken at the time
67 of explantation from the anterior aspect, posterior aspect, internal aspect of the inlet and also
68 the internal aspect of the outlet of the device. A small volume of sterile water (<5mls) should
69 be instilled into the explanted VAD and then aspirated. This water should also be sent for
70 culture. Any pus that is present in the pocket area should also be sent for Gram stain and
71 culture. Finally at least two samples of tissue from the pocket area and insertion site of the
72 cannulae into the heart should be sent for histology, tissue stains for bacteria, fungi and
73 *Mycobacterium spp.*, and for culture for bacteria, fungi and *Mycobacterium spp.*. Defining
74 the optimal method of culture of VADs is beyond the scope of these guidelines, however in
75 the future it would be beneficial to devise a standardized culture process for VADs so that the
76 microbiology laboratory practice can be standardized across all centers. In particular, the use
77 of broth cultures for the retrieval of organisms (currently used for explanted heart valves)
78 should be considered where possible.

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80 It may also be necessary to send other samples to the microbiology laboratory if non-VAD
81 related infections are suspected such as urine, stool for *C. difficile* toxin, sputum and wound

82 swabs. In cases of suspected CDI samples should be tested by kits that can detect the
83 presence of both toxin A and B⁸. The investigation of suspected VAD infections should be
84 done in consultation with Infectious Disease Physicians or Clinical Microbiologists and
85 Surgeons so as to optimise both the diagnosis and management of the infection and also to
86 maximise the anti-infective regimen.

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88 **VAD-Specific Infections**

89 VAD specific infections required new definitions to be constructed so as to allow for
90 infections to be defined uniformly in these cases, as there are currently no international
91 standard definitions of VAD infections in use at present. Guidelines on the diagnosis of
92 prosthetic joint infections⁹ and also cardiovascular infections^{4, 10} have provided the basis on
93 which the definitions were constructed. These infections are very similar to VAD infections
94 as they are often difficult to diagnose conclusively and difficult to treat.

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96 The first group of VAD-specific infections are pump and/or cannula infections. The “pump”
97 refers to the part of the device that is involved in the propulsion of blood, and includes both
98 continuous and/or pulsatile (intracorporeal and paracorporeal) flow devices. The term
99 “cannula” refers to the part of the VAD connecting the pump device to the patient’s
100 cardiovascular system. These terms have been chosen to allow as many devices as possible to
101 be incorporated into this definition framework. The definition of pump and/or cannula
102 infections has been based in part on the modified Duke’s criteria which have been shown to
103 have a high degree of sensitivity and specificity in the diagnosis of infective endocarditis¹¹.
104 Prospective validation of these VAD definitions will however have to be carried out and
105 future modification of these definitions may be required thereafter.

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107 A patient must have at least one of the microbiological, histopathologic or clinical criteria to
108 achieve a firm diagnosis (Table 3). The retrieval of a pathogen or an indistinguishable

109 organism from more than one site is critical for the microbiological criterion. Laboratories
110 may wish to store isolates for further molecular typing in some difficult cases, during
111 institutional outbreaks, or in all cases where possible for future studies. *Staphylococcus*
112 *lugdenensis* has been included here along with *Staphylococcus aureus* in the definitions and
113 not with Coagulase-negative *Staphylococci* to reflect this organism's propensity to cause
114 biofilm formation and persistent infections as has been discussed in recent Infectious Disease
115 Society of America (IDSA) guidelines on Central Venous Catheter infections
116 (Recommendation 77)¹². The clinical criteria have been based largely on the modified Duke's
117 criteria, and modified where necessary to reflect the presence of the VAD. These clinical
118 criteria will require prospective validation in the future as a matter of urgency.

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120 The term "pocket" in these definitions is used to describe infections that occur in the space
121 that holds the pump device in VADs where the device is kept inside the body cavity of the
122 patient. The pocket may be either intra-abdominal or intra-thoracic. Pocket infections may be
123 diagnosed without removing the VAD at the time of surgery if samples from the inner surface
124 of the pocket and the exterior surface of the VAD are taken (Table 3). In certain specialised
125 centers interventional radiologists may be able to aspirate pus that is seen on imaging as fluid
126 surrounding the VAD for diagnostic purposes similar to investigation of an intra-abdominal
127 abscess¹³. Risk of introducing infection into a sterile fluid collection using this technique will
128 need to be considered and monitored. Data in this regard are currently lacking.

129
130 Percutaneous driveline infections are an important but challenging area to define. It has been
131 difficult to strike a balance between having fully comprehensive definitions and having
132 definitions that are practical and useful for clinicians. These infections have been broken into
133 three groups depending on the depth of the infection. This is felt to be the most useful way to
134 define the infections as management of driveline infections typically depends upon the depth
135 of the infection ¹⁴(Table 4). These infections are the most commonly occurring infections in

136 VAD patients and may reflect the presence of a deeper infection of the pocket space or pump
137 and/or cannula or subsequently act as a cutaneous source of infection at a later date¹⁵.

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139 **VAD-Related Infections**

140 VAD-related infections include infective endocarditis (IE), bloodstream infections (BSIs) and
141 mediastinitis (Table 5). In this section we have aimed where possible to use internationally
142 approved definitions, such as the CDC/NHSN definitions¹⁶ as their basis and then adapt
143 where necessary to reflect particular pathophysiologically related issues pertaining to the
144 VAD-related infection. Although there may be many internationally acceptable definitions
145 available for each of these infections we have chosen a single definition set so that
146 international comparisons may be made between different centers, allowing for more useful
147 epidemiological data to be obtained. Standard terms to refer to each type of VAD-related
148 infection have been outlined in table 5 to ensure that there is a consistency when centers are
149 describing an infection. The full definition for each infection has not been written out here as
150 the definitions, which are referred to, are widely used already.

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152 Diagnosing VAD infections in the presence of a Central Venous Catheter (CVC) is
153 particularly difficult. It has been decided to rely on the technique of the “differential time to
154 positivity” as a method of determining which infections are due to the VAD and which are
155 due to the CVC. This method has been advocated in recent IDSA guidelines and a cut-off of
156 two hours difference has been taken. This method, though not 100% accurate, will implicate
157 the CVC as the source of the bacteraemia. Efforts can be made to avoid secondary seeding of
158 the VAD by removal of the CVC and repeating blood cultures after appropriate antimicrobial
159 treatment of the CVC related BSI has been accomplished and anti-infectives are no longer
160 present. If CVC related BSI has been ruled out then other causes of BSI in VAD patients
161 should be looked for as the VAD may not always be the source of the infection¹⁷.

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163 **Non VAD-related infections**

164 Non-VAD related infections are essentially not affected by the presence of the VAD. The
165 purpose of including them here is to decide on which international definition standards
166 should be used by centers reporting on all infection rates in VAD patients. This section is
167 primarily present to ensure that non-VAD related infections are standardized and can be
168 compared between centers when studies of adverse events are being carried out and for
169 registry data gathering. The most common non VAD-related infections included lower
170 respiratory tract infections, cholecystitis, and *Clostridium difficile* infection (CDI). This list is
171 not exhaustive, and other infections may be added during data collection for registries or
172 during clinical studies. CDI has specifically been included as VAD patients are at a high risk
173 of CDI as they have a high antimicrobial exposure, protracted hospital admissions and high
174 use of proton pump inhibitors. CDI can cause significant morbidity and mortality in this
175 patient group as they have limited cardiac reserve to tolerate dehydration or aggressive fluid
176 resuscitation that may be needed. At an institutional level, *C. difficile* also can create large
177 outbreaks of diarrhoeal illness putting strain on isolation facilities and also impacting on
178 elective surgery admissions.

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180 **Discussion**

181 Defining infections in VADs is a particularly difficult area as it is not possible to easily
182 sample the intracorporeal parts of the VAD and also there may be other potential causes for
183 sepsis in this particular patient population, including other nosocomial infections such as
184 CVCs or urinary catheters. The ultimate goal of this working formulation of standardized
185 definitions of infection is to provide a baseline for developing and validating standardized
186 international definition of infection in VADs. As always this working formulation should be
187 regarded as a live document that will no doubt require further modification in the future. The
188 Committee hopes that these definitions will be adopted without delay by key VAD centres
189 where prospective data will be collected, analysed and based on these results

190 recommendation made by the ISHLT VAD Definitions working group to allow timely
191 validation and revision of these definitions. Validation is needed particularly in the area of
192 the clinical criterion for diagnosing exit site infections and, pump and/or cannula infections
193 and also for the optimal way to process samples from VADs in the microbiology laboratory.

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Classification of Infections in VAD patients

A. VAD-Specific Infections

- I. Pump and/or Cannula Infections
- II. Pocket Infections
- III. Percutaneous Driveline Infections
 - a. Minor exit site erythema
 - b. Superficial infection
 - c. Deep infection

B. VAD-Related Infections

- I. Infective Endocarditis
- II. 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
- III. Mediastinitis
 - VAD-related
 - VAD non-related

C. Non VAD- Related Infections

- I. Lower Respiratory tract infection
- II. Cholecystitis
- III. *Clostridium difficile* infection (CDI)

212 Table 1: Overview of the classification of infections in VAD patients. *VAD= Ventricular*
213 *Assist Device, CVC=Central Venous Catheter, BSI=Bloodstream infection,*
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Investigation of a Suspected VAD Infection

All patients:

- WBC count, CRP, ESR
- Swab 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 one central and one 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 10ml of blood per bottle in adult cases or 1ml/kg of blood per bottle for paediatric patients (up to a max of 10kg).

If VAD removed:

- Swab from external aspect* of VAD (anterior) for culture
- Swab from external aspect* of VAD (posterior) for culture
- Swab from outlet part* of VAD (internal aspect) for culture
- Swab from inlet part* of VAD (internal aspect) for culture
- Culture of saline instilled into VAD (internal aspect)
- Sample of pus from peritoneal pocket for Gram stain and culture
- ≥ 2 tissue samples from heart sent for histology, Gram stain and culture, auramine/ZN stain and culture for *Mycobacterium spp.*

* See diagram 1 for labelling of samples

When clinically indicated:

- Nasal, throat and groin swabs for *Staphylococcus aureus* carriage
- If suspicious of a pocket infection obtain an abdominal US, CT abdomen/thorax, +/- nuclear imaging study
- Rule out all other possible causes of the septic episode (e.g. CXR, urine for microscopy and culture etc.)

221 Table 2: Investigations for a Patient Suspected of VAD Infection
222 VAD=Ventricular Assist Device, WBC=white blood count, CRP= C-reactive protein, ESR=
223 Erythrocyte sedimentation rate, CVC= Central Venous Catheter, TEE=transesophageal
224 echocardiogram, TTE= transthoracic echocardiogram, US= Ultrasound scan, CT=
225 Computerised topography scan, CXR= chest X-ray)

Pump and/or Cannula infections

To be considered a VAD specific infection a patient must meet one of these 3 criteria (adapted from the Modified Duke's Criteria¹¹)

1. MICROBIOLOGY

- Isolation of indistinguishable organism (genus, species, antimicrobial susceptibility pattern) from
 - ≥ 2 internal aspect culture samples from VAD
 - 1 peripheral blood culture and 1 culture from VAD internal aspect swab or endovascular brushings, (internal aspect refers to the inner lumen of the outlet or inlet cannula).
 - In the case of Coagulase –negative *Staphylococci* excluding *Staphylococcus lugdenensis*; 2 or more positive sets of peripheral blood cultures and an internal aspect culture of VAD

2. HISTOLOGY

- Histological features of infection from heart tissue samples from around inlet or outlet of VAD.

3. CLINICAL (In cases where VAD is not removed)

This requires either 2 major criteria, 1 major and 3 minor criteria or 4 minor criteria

- Major Criteria
 - If the VAD is not removed, then an indistinguishable organism (genus, species, and antimicrobial susceptibility pattern) recovered from 2 or more sets of peripheral blood cultures obtained over a 4-week period, with no other focus of infection.
 - When positive blood cultures are taken from the CVC and peripherally at the same time, the positive blood culture taken from CVC becomes positive ≤ 2 hours after peripheral blood culture positive
 - Positive echocardiogram showing oscillating mass that is adherent to the VAD
- Minor Criteria
 - Fever $\geq 38^{\circ}\text{C}$
 - Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway's lesions
 - Immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots
 - Microbiological evidence: positive blood culture that does not meet criteria as noted above (excluding single positive culture for CNS and organisms that do not infect devices)

Pocket infections

Pocket infections must meet at least 1 of the following criteria:

- Patient has organisms cultured from the pocket space obtained during a surgical operation or needle sampling, taken intra-operatively or with radiological guidance.
- Isolation of indistinguishable organism (genus, species, antimicrobial susceptibility pattern) from
 - 2 exterior aspect culture samples from VAD
 - 1 exterior aspect culture sample 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 or histopathologic examination.
- At least 2 of the following signs or symptoms with no other recognized cause: fever ($>38^{\circ}\text{C}$), nausea, vomiting, pain in the area where the pocket is, or jaundice
 - and at least 1 of the following:
 - Organisms seen on Gram stain of aspirated fluid or tissue obtained during surgical operation or needle aspiration from the pocket area.
 - Organisms cultured from pocket area

- Organisms cultured from blood and radiographic evidence of infection (abnormal findings on ultrasound, CT scan, MRI, or radiolabel scans [gallium, technetium, Indium, etc.] or on plain film x-ray) in the pocket area.

226 Table 3: VAD specific infections; Pocket and Cannula infections and Pocket infections.
227 VAD= Ventricular Assist Device, CT= Computerised Topography scan. MRI= Magnetic
228 Resonance Imaging Scan, CVC= Central Venous Catheter
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Percutaneous Driveline infections

A. Minor erythema

- Involves superficial layer of skin only *and* Patient has **all** of the following:
 - No purulent discharge coming from the exit site
 - An area of erythema <2cm radius from the margin of the incision
 - Systemically well with no local increase in temperature around the exit site.

B. Superficial Infection

- Involves tissues superficial to the fascia and muscle layers of the incision *and* Patient has at least 1 of the following:
 - Purulent discharge from the incision but not involving fascia or muscle layers
 - Cellulitis spreading around the exit site (≥ 1 cm radius from the margin of the incision) with erythema and increased local temperature

C. Deep Infection

- Involves deep soft tissues (e.g. fascial and muscle layers) of the incision *and* Patient has at least 1 of the following:
 - Purulent discharge from the incision with involvement of fascia and muscle layers
 - A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive or not cultured when the patient has at least 1 of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), or localized pain or tenderness.
 - An abscess or other evidence of infection involving the deep incision is found on direct examination during re-operation.

265 Table 4: VAD specific infection definitions; Percutaneous Driveline Infections.

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VAD RELATED infections	
Clinical Condition	Classification of disease
<p>Endocarditis All cases (default)</p> <p>Vegetation seen on valve and not on VAD (Definitions made using modified Duke's Criteria¹¹)</p>	<p>VAD-related endocarditis</p> <p>Valvular VAD-related endocarditis</p>
<p>Bloodstream infection CVC present:</p> <ul style="list-style-type: none"> Central culture positive ≤ 2 hours before peripheral Central culture positive > 2 hours before peripheral culture <p>(Definitions made using the IDSA guidelines if CVC present¹²)</p> <p>No CVC present:</p> <ul style="list-style-type: none"> BSI due to VAD infection or cause unclear BSI due to cause other than VAD infection (e.g. UTI, pneumonia) <p>(Definitions made using the CDC/NHSN definitions¹⁶ if no CVC is present)</p>	<p>BSI <i>presumed</i> VAD-related</p> <p>BSI <i>presumed</i> CVC-related</p> <p>Bloodstream infection VAD-related</p> <p>Bloodstream infection non VAD-related</p>
<p>Mediastinitis Related: This is when mediastinitis is due to the VAD device. Classify as per "Surgical site infection-organ space" in CDC/NHSN definitions¹⁶.</p> <p>Non-Related: This is when mediastinitis is definitely due to another cause e.g. esophageal perforation during endoscopy. Classify as per "CVS infections-mediastinitis" in the CDC/NHSN¹⁶ definitions.</p>	<p>Mediastinitis VAD-related</p> <p>Mediastinitis non-related to VAD</p>

Deleted: Blood stream infection *presumed* VAD-related¶

Deleted: Central culture positive ≤ 2 hours before peripheral¶

Deleted: Bloodstream infection VAD-related¶

Deleted: BSI due to VAD infection or cause unclear¶

Comment: Suggest we discuss adding skin and soft tissue infection as a category

269 Table 5: VAD related infections. VAD=*Mechanical Circulatory Support*, CVC= *Central*
270 *Venous Catheter*, IDSA= *Infectious Disease Society of America*, CDC= *Center for Disease*
271 *Control and Prevention*, NHSN= *National Healthcare Safety Network*, CVS=
272 *Cardiovascular*, CDAD=*Clostridium difficile associated diarrhoea*, HPA= *Health Protection*
273 *Society, UK*

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Non VAD-Related infections
<ul style="list-style-type: none">• Lower Respiratory Tract Infections (defined as per CDC/NHSN¹⁶ definition)• Cholecystitis (defined as per CDC/NHSN¹⁶ definition)• CDI (defined as per HPA⁸ definitions)

282 Table 6: Non-VAD related infections. *CDC=Center for Disease Control and Prevention,*
283 *NHSN= National Healthcare Safety Network, CDI=Clostridium difficile infection, HPA=*
284 *Health Protection Agency, UK*
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