

MECHANICAL CIRCULATORY SUPPORT INFECTIONS

An ISHLT consensus document for prevention and management strategies for mechanical circulatory support infection



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Introduction and background

Heart failure (HF) remains a major cause of morbidity and mortality. Heart transplantation (HT) is a life-saving procedure for patients with advanced heart failure, but availability is limited by donor organ shortage.¹ Durable mechanical circulatory support (MCS) is a major advance in HF management and can provide hemodynamic support until myocardial recovery or HT, or as permanent therapy (destination therapy, DT) for those ineligible for HT.² MCS has continued to enhance patient survival and quality of life through continued improvements in device design and durability.² However, MCS infection remains as a major complication and a significant cause of morbidity and mortality in MCS recipients.² Furthermore, there is considerable practice variation regarding patient selection for MCS, implant technique, infection prevention strategies anti-microbial prophylaxis, drive-line care and management of infection.

In 2015, the International Society for Heart and Lung Transplantation (ISHLT) recognized the importance of a consensus document on strategies for both prevention and management of MCS infections. The multidisciplinary consensus document is the result of a collaboration between the ISHLT and the International Consortium of Circulatory Assist Clinicians (ICCAAC). The effort involved a number of ISHLT Councils, including: Infectious Disease; MCS; Nursing; Health Sciences and Allied Health (NNSAH); Heart Failure and Transplantation; Pharmacy; and Pediatric Thoracic Transplantation and Heart Failure. The panel members addressed the epidemiology and microbiology of MCS infections, pre-operative evaluation of the MCS candidate, peri-operative surgical and anti-microbial prophylaxis management, post-operative drive-line management and treatment of MCS infections.

The purpose of this document is to provide expert consensus-derived recommendations and, whenever possible, evidence-based recommendations for the prevention and management of infection in MCS recipients. Extensive literature review and the results of the ISHLT-supported international survey for infection control, prevention and management practices for MCS³ were utilized to develop the consensus-derived recommendations presented here.

The survey of infection control practices in ventricular assist devices (VADs) included detailed questions regarding infection control practices in VAD programs and was completed by 137 centers worldwide.³ Two additional surveys of VAD infection control practices were also conducted (Kaan A et al, unpublished data, 2017).⁴ Proposed recommendations at the end of each section are ungraded due to the predominance of expert opinion.

The creation of the consensus document required multiple steps, but, briefly, the following was accomplished. The ISHLT Councils were contacted and names of experts interested in the project were suggested. After selecting a chair and co-chairs, the structure of the consensus document was established, and the writing teams were then chosen in collaboration with ISHLT councils. Face-to-face meetings and periodic conference calls were arranged and the writing process was then initiated. During this process, unclear areas and disagreements were identified. Because of lack of comparative trials, some of the statements in the consensus document required a decision based on majority vote. Several edits were required and, once the consensus document was created and reviewed by the authors, it was sent to external reviewers and revisions were incorporated.

In this document, MCS includes durable left ventricular assist devices (LVADs), right ventricular assist devices (RVADs), biventricular assist devices (BiVADs) and total artificial hearts (TAHs).² These terms are used interchangeably throughout the document unless otherwise specified. Although the published literature pertains mostly to LVADs as the most widely used device type, the principles for infection prevention, diagnosis and management apply to all implantable and paracorporeal durable MCS devices with percutaneous drive-lines or cannulas, including pulsating and continuous-flow devices. It should be noted that there may be differences in infection rates and outcome between these devices, but the current literature does not provide any distinctions in infection prevention.

ISHLT definitions of infection

Standardized international definitions of MCS infections were developed in 2011 by an ISHLT multidisciplinary

working group. Three categories of infection were defined for VAD patients: VAD-specific infections; VAD-related infections; and non-VAD infections.⁵ These definitions were developed to allow for consistent data collection for each specific infection diagnosis and facilitate research in the field. A VAD-specific infection may involve any aspect of the device (pump, cannula, pocket or drive-line) and may cause sepsis. Infection may be introduced intra-operatively in the pump, cannula or pocket; may enter via the drive-line exit site; or may occur as a result of a bloodstream infection (BSI) from another focus of infection.⁵⁻⁷

The VAD-specific infection definitions are each subdivided into “proven, probable or possible” infection and include microbiologic, radiographic and clinical criteria for a “proven” diagnosis. The pump, cannula or pocket “proven” diagnosis is defined by intra-operative samples or needle aspiration of fluid from the MCS pocket. “Probable” or “possible” diagnoses are defined only by appropriate clinical assessment. The VAD-specific infections can be further divided into superficial drive-line or deep infections. A superficial drive-line infection involves soft tissue outside the fascia and muscle layers, whereas deep infection requires infection beyond these structures.⁵

VAD-related infections are those that occur in patients without MCS but may be more common with presence of the device, such as endocarditis and mediastinitis.⁵ Non-VAD infections are unrelated to the presence of the device (e.g., urinary tract infection) but are included as a category to provide a comprehensive description of infection in this population.⁵ Standard surveillance definitions for these infections have been applied.⁸

Epidemiology of infection in MCS

There are currently 3 large, multicenter MCS registries: (1) the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a North American registry⁹; (2) the European Registry for Patients with Mechanical Circulatory Support (EUROMACS)¹⁰; and (3) the ISHLT Registry for Mechanically Assisted Circulatory Support (IMACS).¹¹ These registries collect and report data on major infections, and are partly linked to each other (e.g., IMACS includes INTERMACS and EUROMACS data). Infection occurs in up to 60% of MCS recipients with the increased rate related to duration of device placement.^{6,7,12} In many reports it is difficult to determine the true incidence of MCS-associated infections because standardized definitions were only recently employed, and earlier databases lack detailed infectious disease-related variables.

Since the mid-2000s there have been 2 major changes in LVAD practice. First, smaller continuous-flow devices have replaced larger pulsatile flow pumps and currently represent >95% of LVAD implants. The smaller pocket and drive-line dimensions of continuous-flow devices have been associated with decreased LVAD infection rates.^{2,13,14} Second, LVAD use for DT has increased over time.^{2,13,15} In the most recent INTERMACS data, DT accounted for

45.7% of MCS implants and 100% of these were continuous-flow devices.²

The fifth INTERMACS report included data on 6,561 patients and demonstrated that infection was considerably less common with continuous-flow devices. It also showed that pump interior infections and pocket infections were uncommon events, but the risk of drive-line infection persisted as long as patients were monitored.¹³ The seventh INTERMACS report included data on >15,000 patients who received a primary implant from June 2006 to December 2014.² Infection was the fourth most common cause of death within 1 year after implant (228 of 9,781, or 8.8%), following neurologic complications (15.6%), multi-system organ failure (MSOF) (15.6%) and withdrawal of support (10.4%). The infection incidence may be higher than reported as it is not clear whether infection was an important factor in patients with MSOF or those with withdrawn support. Although risk of death from neurologic complications remained stable in the second year post-implantation, the risk of infection-associated death gradually increased over the monitored time period and became a major cause of late mortality (together with neurologic and MSOF).²

The first EUROMACS report included data on 741 patients. Continuous-flow devices predominated, as with INTERMACS, and infection was the most common major adverse event in this cohort. Of the 433 major adverse events, 153 (35.3%) were due to major infections, which represented the second most common cause of death. Of the 293 deaths, 69 (23.5%) were caused by infection or sepsis.¹²

There is a subset of advanced HF patients who require BiVAD or TAH as bridge to transplant (BTT). In addition to BTT, the United States Food and Drug Administration has approved 1 biventricular device (Syncardia TAH) for investigational use in DT.¹⁶ However, there are other BiVADs under investigation and used elsewhere. One report described 101 TAH patients with a median support of 53 days (range 1 to 441 days).¹⁷ In that study there was a 63% infection rate, with 50% of cases occurring in the first 30 days post-implant. Late complications were evaluated in 47 TAH patients beyond 1 year from 10 centers, with 53% and 27% of these patients having systemic and drive-line infection, respectively.¹⁸ Infection and hemorrhagic events (intracranial and gastrointestinal) were the major causes of death. Mediastinitis developed in up to 4% of LVAD and TAH recipients due to direct spread from drive-line infection.¹⁷⁻²¹

Microbiology

Despite the emergence of continuous-flow devices and increased DT use, which has changed patient profiles and increased the duration of MCS support, pathogens associated with MCS infection have not changed over time.²²⁻²⁶ Bacteria are the dominant etiology of early and late infections, and fungi are less prevalent (<10%).²³⁻³⁵ The most common pathogens are Gram-positive bacteria that colonize skin and adhere to implanted material and create

biofilm,³⁰ particularly *Staphylococcus aureus* and *Staphylococcus epidermidis*, causing >50% of MCS infections. *Enterococcus* species are the third most common Gram-positive organism (2%). The most common Gram-negative bacteria is *Pseudomonas aeruginosa* (22% to 28%), followed by Enterobacteriaceae such as *Klebsiella* (2% to 4%) and *Enterobacter* (2%).^{22–28}

It is important for clinicians to be familiar with local geographic and institutional microbiology and antimicrobial resistance patterns. The National Healthcare Safety Network's (associated with the Centers for Disease Control and Prevention) surveillance of antibiotic-resistant pathogens in surgical site infections (SSIs) showed a decrease of 9.0% in methicillin-resistant *S aureus* (MRSA)-caused SSIs between 2007 to 2008 and 2009 to 2010. However, there was a substantial increase in other resistant organisms, including vancomycin-resistant *Enterococcus* (VRE, by 34.7%), and multidrug-resistant Gram-negatives, including *Escherichia coli* (by 41.8%), *Pseudomonas* (by 8.4%) and *Enterobacter* (by 10.6%).³⁶

Although uncommon, fungal infections may also occur and are extremely difficult to eradicate.^{31–34} Candidemia has been reported in 1.3% to 9.7% of MCS recipients, with an overall mortality of 15% to 25%.^{33,34} *Candida albicans* is the most common fungal pathogen (70%) in MCS infection, followed by *Candida glabrata* (10%). *Aspergillus* species have also been identified as a rare cause of life-threatening MCS infections, but there are limited data regarding incidence. In most reported cases, *Aspergillus* device infection was detected post-mortem.³⁴

Risk factors for infection

Clinicians evaluating patients for MCS should be aware of the risk factors for infection in this population. The majority of studies evaluating risk factors were retrospective cohort studies with a predominance of pulsatile MCS devices. Risk factors for MCS-related infections include older age,²⁶ diabetes,^{37–39} renal failure,²⁵ greater severity of heart failure,²⁶ malnutrition,^{40,41} T-cell dysfunction associated with the device,⁴² hypogammaglobulinemia,⁴³ intravascular lines and organisms capable of biofilm formation,^{44–46} obesity,^{39,42} delayed sternal closure,⁴⁷ longer intensive care unit (ICU) stay⁴⁸ and prolonged duration of MCS support.^{28,48}

Infection risk factor analysis specifically for continuous-flow devices recipients is limited. In an analysis of 332 BTT HeartWare recipients, risk factors for drive-line infection and sepsis included larger body mass index (BMI) and diabetes.³⁹ A prospective study that included continuous-flow VAD devices identified elevated serum creatinine and history of depression as independent risk factors for infection.²⁵ There was no difference in risk factors for infection between pulsatile- and continuous-flow devices, or between BTT and DT. Neither length of time spent in ICU nor total hospital length of stay was associated with increased infection in that study.²⁵ Trauma to the drive-line has been identified as a major risk factor for

development of drive-line infection in both pulsatile- and continuous-flow devices. Accidental pulling of the drive-line and disruption of the seal between drive-line and surrounding skin are commonly reported causes of infection.²⁸ In contrast, 1 single-center, retrospective study of 194 HeartMate II recipients, showed no association between drive-line infection and the following factors: BMI; age; education level; insurance provider; and velour position at exit site.⁴⁹ Another study,⁵⁰ which followed BTT patients between 2009 and 2014, demonstrated that the number of re-admissions for infection was higher in HeartMate II compared with HeartWare HVAD recipients (both continuous-flow devices).⁵⁰ It is expected that a larger device requiring pocket creation in HeartMate II would be prone to higher infection rate compared with the smaller device without a pocket creation in HeartWare HVAD. However, the ENDURANCE trial showed no difference in infection rate between the HeartMate II and the HVAD.⁵¹

Clinical outcomes

In the current era of continuous-flow devices, the short- and long-term survival outcomes after HT in patients bridged with MCS are similar to those without pre-HT MCS.^{52–54} A “best evidence topic in cardiac surgery” report reviewed 428 articles studying the impact of BTT on survival after HT.⁵³ In that study it was concluded that patients' survival of BTT followed by HT was comparable to that seen in those with HT who did not have MCS beforehand.⁵³ In patients who did not have HT, those who developed infection had poorer prognosis.⁵⁵ MCS infection is associated with an increased rate of re-hospitalization, morbidity and mortality if MCS is not followed by HT.^{28,46,48,49,56} Superficial drive-line infection (DLI) may progress over time to become a deep tissue infection.^{49,57} Patients with deep tissue infection were found to be more likely to develop bacteremia.⁴⁹ Sepsis is the most common cause of death associated with DLI. The organisms causing sepsis may be different from those causing DLI, and patients on suppressive therapy after DLI may develop secondary infection.^{39,49,55} In the INTERMACS registry, 22% of deaths among those who developed DLI occurred within 1 month of DLI diagnosis, suggesting a potential association.^{2,55} Infection is the fourth most common cause of death within 1 year, and the risk of infection was shown to rise steadily over a 4-year follow-up.²

Numerous studies have shown that patients with MCS infection can be transplanted successfully, with outcomes similar to those without MCS infection.^{28,39,46,48,49,55,58,59} A recent report has contradicted this assumption. A review of United Network for Organ Sharing (UNOS) data from 2006 to 2012 noted increased mortality in HT recipients after MCS-related infection compared with MCS without infection, showing survival rates of 85.6% vs 89.9% and 78.0% vs 82.7% at 1 and 3 years ($p = 0.01$), respectively.⁵⁹

The INTERMACS registry followed 301 TAH recipients and noted no change over time in 1-year survival (59%) in the periods 2008 to 2011 and 2012 to 2014.² In 1 single-

center report, 7 infected TAH recipients underwent HT, 5 of whom were alive at a median time of 181 days and 2 deaths secondary to intra-operative bleed and cardiac arrest. The successful HT outcome in infected TAH patients was assumed to result from meticulous pre- and post-HT medical and surgical management.¹⁹ Patient selection for HT⁶⁰ and post-HT management is considered essential to successful HT in patients with MCS infection.^{19,60}

Infectious disease evaluation of MCS candidates

General considerations

Formal infectious disease (ID) consultation may be considered based on individual circumstances, but it is not routinely required. However, all MCS candidates should be evaluated for active infection that would need to be addressed before surgery and for identification of modifiable risk factors for infection post-MCS. In BTT candidates, the heart transplant ID evaluation may be initiated at this time. Patient-specific factors should guide the extent and frequency of ID evaluation.

Infection should be excluded or appropriately treated before MCS implantation when clinically feasible. Evaluation of suspected infection in potential MCS recipients is not different from that in other patients and should be guided by clinical signs and symptoms. In patients with unexplained fever and/or leukocytosis, evaluation should include blood cultures, urinalysis, urine culture and chest X-ray, with additional imaging as needed until a diagnosis is established and the source has been treated and cleared.

ID consultation should be performed in all MCS candidates with suspected or proven infection. MCS candidates with bloodstream infections should be treated with targeted anti-microbial therapy. A consideration for delaying MCS implantation is recommended until the following goals are met: source control (e.g., incision and drainage of abscess, removal of infected catheter or tooth extraction for dental abscess); negative blood cultures; and resolution of illness and sepsis. MCS candidates with other infections (e.g., pneumonia, urinary tract infection) should be treated with appropriate anti-microbial therapy until resolution. There is insufficient evidence to define a minimum duration of anti-microbial therapy for an active infection before proceeding to MCS implantation.

Nosocomial infection and indwelling catheters

Nosocomial BSI is a major cause of morbidity and mortality after MCS placement.⁶¹ Indwelling lines are a major source of nosocomial infection. By definition, long-term catheters are those indwelling for ≥ 14 days.⁶²

The infection risk associated with catheters varies based on host factors (age, immune status) and catheter type, location and duration.⁶³ Although all intravascular catheters are a potential source of BSI, temporary non-cuffed/non-tunneled central venous catheters (CVCs) are associated

with a higher risk of BSI compared with peripherally inserted central catheters (PICCs) and cuffed/tunneled central catheters.^{62–67} CVCs placed in femoral locations carry a higher infection risk than jugular and subclavian locations.^{67,68} Most importantly, catheter duration has consistently been shown to be a risk factor for BSI. Although not studied specifically in the MCS population, taking a proactive approach to eliminate unnecessary catheters has been shown to reduce BSI in the ICU and post-surgical settings.^{65–67,69,70}

Catheter-associated urinary tract infection (CAUTI) is the most common nosocomial infection and is one that is preventable⁷¹ by limiting the number of days of catheterization. One study showed a 3-fold increased mortality risk in hospitalized patients who had required an indwelling urinary catheter.⁷² In 2 other studies, CAUTI was found to be the second most common cause of nosocomial bacteremia⁷³ and the most common cause of Gram-negative bacteremia.⁷⁴ This is important because seeding of the device may occur in MCS recipients.

Strategies to reduce the risk of CAUTI include: placement of indwelling catheter only if indicated, not for routine incontinence; development of a list of legitimate indications together with staff education; requirement of a physician's signature for each indwelling catheter placement; and consideration of a bladder scanner use to check if catheterization is necessary post-operatively.⁷¹

Colonization

Based on the ISHLT-supported survey, 94% of VAD centers perform nasal colonization surveillance culture for MRSA and 28% perform rectal VRE colonization surveillance in MCS candidates.³ Ninety-two percent of centers use antiseptics to reduce colonizing bacteria before MCS implant surgery.³ Mupirocin nasal decontamination has been shown to decrease *S aureus* infections in surgery patients.^{75,76} Although there have been no specific studies in MCS recipients, many centers have adapted this practice. Daily bathing with chlorhexidine using disposable washcloths has been shown to reduce the rates of hospital-acquired infection with multidrug-resistant organisms.⁷⁷ Pre-operative chlorhexidine bathing has been shown to reduce skin bacterial counts but not post-operative wound infection rates after cardiac surgery.⁷⁸ According to The Society for Healthcare Epidemiology of America/Infectious Diseases Society of America practice recommendations, there are not enough data to support routine pre-operative chlorhexidine bathing.⁷⁹ The recent 2017 CDC guidelines for prevention of SSIs recommend showering or bathing with soap or an antiseptic agent at least the night before surgery.⁸⁰

Assessment for infection risk factors

At pre-operative evaluation, risk factors for infection should be identified (see Section I), and interventions to reduce risk should be implemented when possible. Poor nutritional status is associated with increased risk of MCS-related

infection. Nutritional assessment through history and laboratory data (e.g., BMI, serum pre-albumin) is indicated. Consultation with a nutrition expert may be needed.

Other conditions, such as psoriasis, hidradenitis suppurativa, previous sternal radiation therapy, long-term use of immunosuppression or steroids, renal failure and presence of percutaneous endoscopic gastrostomy tube or colostomy, may impact wound healing and should be considered in the care plan. Last, evidence of poor dentition with septic dental foci, such as periodontitis and abscesses, should be addressed before MCS implantation, similar to candidates for organ transplantation, but these procedures are not without morbidity.^{81,82} Therefore, dental evaluation should be included and, if necessary, a dental consultation should be obtained.⁸³

Allergy

We recommend clarifying the accuracy and significance of all reported anti-microbial allergies. Consultation with an allergy specialist may be useful to confirm or exclude reported antibiotic allergies.

Recommendations:

1. Femoral line placement should be avoided if possible.
2. Tunneled catheters are preferred for prolonged use (e.g., dialysis catheters).
3. All vascular access sites (including intra-aortic balloon pump sheaths, arterial lines, Swan–Ganz catheters and PICCs) should be carefully evaluated on a daily basis.
4. Lines should be examined for signs of infection and exchanged if necessary as part of a pre-VAD decontamination strategy.
5. Catheters with evidence of infection should be removed and replaced using a strict sterile technique.
6. Exchange over a wire is strongly discouraged due to risks for bacterial seeding unless done in special circumstances (e.g., no other access).
7. Indwelling urinary catheter placement should be done only if indicated and removed as soon as possible.
8. MRSA screening should be considered, and mupirocin and chlorhexidine used in those patients colonized.
9. Screening for other resistant bacteria should be based on local epidemiologic patterns.
10. Before surgery, the patient should shower or bathe with soap or antiseptic agent at least the night before operation.
11. Dental evaluation before MCS implantation is recommended. If poor dentition with septic foci, such as periodontitis and abscesses, are found, then these should be dealt with before MCS implant.
12. Review antibiotic allergies and obtain specialist assessment as necessary.

Surgical management

The surgical management during MCS implantation may have a major impact on peri- and post-operative infectious

complications. Although the surgical implantation procedure of MCS devices is not standardized, and the surgical approach varies based on center, surgeon and device-specific preferences, the basic principles of surgical sterility and infection prevention are universally followed. Nevertheless, there are many common features of the MCS implant procedure and only few that are unique to the specific type of device.

Most MCS devices implanted today are continuous-flow LVAD pumps, which are preferred over the older generation of bulky, pulsatile pumps. Anti-microbial prophylaxis is the standard of care for patients undergoing any cardiac surgical procedure. General recommendations for prevention of SSIs in MCS are presented in the following section, “Anti-microbial prophylaxis”. In general, no difference in surgical sterility is maintained during implantation of the device in comparison to any other cardio-surgical procedure. Although meticulous attention to sterility measures must always be undertaken, extreme measures like laminar flow and helmet usage, as seen in orthopedic surgery, are not routinely practiced in cardiac surgery.

The surgical implant procedure starts with clipping of the chest hair, immediately preceding the operation, followed by appropriate prepping and draping of the patient. Alcohol-based agents should be used for skin preparation in the operating room unless contraindicated.⁸⁰ Patients’ potential allergies must be taken into consideration when local disinfectants are used. At many centers, an additional sterile anti-microbial incision drape containing bound iodine is used for coverage of the incision sites. Topical anti-microbial irrigation of the subcutaneous tissue is done after placement of the sternal wires before closure of the sternal wound. This approach is based on data showing that topical use of anti-microbials, mainly gentamicin and vancomycin, in combination with systemic antibiotics may significantly reduce SSIs.⁸⁴ However, 2 more recent randomized studies could not confirm the usefulness of topical antibiotics in cardiac surgery,^{85,86} and the 2013 Guidelines for Anti-microbial Prophylaxis in Surgery does not recommend their routine use for cardiac procedures.⁸⁷ The recent CDC guidelines for SSI prevention do not recommend application of anti-microbials in the form of ointment, solution or powder to surgical incisions.⁸⁰

During surgery, glycemic control, with blood glucose level target <200 mg/dl, and normothermia are recommended to prevent SSI.⁸⁰ An increased fraction of inspired oxygen should be given during surgery and after extubation in the immediate post-operative period, and transfusion of blood products should not be withheld in attempts to prevent SSI.⁸⁰

Essential to the surgical approach is to minimize surgical stress and trauma to reduce inflammatory responses related to the procedure. The size of the incision, as well as the duration of surgery, may have a major impact on development of infectious complications after implantation. Many of the devices are directly attached to the heart and/or the aorta, and an open access to these internal structures must be made. Approximately 95% of all VAD implants are performed via median sternotomy, which provides good

access to the heart and the ascending aorta. Unfortunately, this approach has been associated with a greater risk of SSI. Due to the shape and size of certain pumps in use today (e.g., HeartMate II), an additional pre-peritoneal pump pocket must be achieved. Other smaller pumps can be placed inside the pericardium, which prevents potential bleeding into the pump pocket and may decrease infection risk related to blood retention and clot formation.⁸⁸

In recent years, a less invasive surgical approach for implantation of new-generation pumps (HeartWare HVAD and Jarvik 2000) has been developed. This approach includes a small left-sided mini-thoracotomy in combination with an upper mini-sternotomy or right-sided mini-thoracotomy in place of a full median sternotomy.^{89–91} However, due to small patient numbers, evidence is still lacking that this limited incision is associated with fewer SSIs compared with the full sternotomy procedure.

Before implantation, the pump is tested in a bath of sterile saline or dextrose, which is performed on a sterile back table. This pump testing is typically performed by a VAD coordinator or perfusionist, simultaneously to the opening of the chest and preparation of the surgical implant site. After testing, the VAD is kept wrapped in a sterile towel until implantation. There is no consensus as to whether the towel should be soaked with an antibiotic solution to prevent contamination during the resting period on the back table before implantation. Also, there is no consensus as to whether the outflow graft and the Dacron-velour coating of the drive-line should also be soaked with antibiotic solution before implantation. This technique of soaking vascular grafts before implantation with antibiotic solutions (mainly rifampin) is practiced by vascular surgeons in some centers throughout the world.⁹² The approach has some potential risks, including allergy, toxicity and drug–drug interactions from absorption of these antibiotics into the systemic circulation, and may need careful evaluation. There are no randomized, controlled trials to evaluate the practice of soaking prosthetic devices with antibiotics, and therefore this practice is not currently recommended according to the recent CDC guidelines.⁸⁰

To stabilize the subcutaneous course of the drive-line and facilitate tissue ingrowth, all pump drive-lines are partially coated with Dacron-velour. Using a modified surgical tunneling technique, the entire drive-line velour portion is kept in the subcutaneous tunnel, resulting in a silicone–skin interface at the exit site.^{93,94} This modified surgical approach has shown better long-term post-operative hygiene and easier care of the exit site and the drive-line. It proved to be associated with fewer SSIs than the conventional technique, which leaves a portion of the velour outside the skin, and thus has been adopted by the majority of centers.^{3,93,94} An important step during VAD implantation is determination of the location of the VAD drive-line exit site. Historically, the drive-line exit site was positioned in the right upper abdominal quadrant with a long subcutaneous tunneled course, and many pump manufacturers adapted their length of the drive-line based on this approach. To prevent subcutaneous extension of infection from the drive-line exit site toward the pump or pump pocket, several centers started to increase the subcutaneous tunneled course by creating a “C-shaped” course of the

drive-line, exiting on the left lower abdominal quadrant.⁹⁵ A recent series described the different surgical approaches in continuous-flow VAD implantation including the classical approach with median sternotomy, minimally-invasive without sternotomy, and the lateral implantation to the descending aorta.⁹⁶

To reduce the mechanical irritation of the drive-line exit site and promote the healing process in the early peri- and post-operative periods, some centers have adapted the technique of fixation of the drive-line to the skin with 1 or 2 sutures for a period of 2 or 3 weeks. This facilitates healing of the exit site with less mechanical irritation and may prevent early and late infections.⁹⁷

Recommendations:

1. General principles of infection control and SSI prevention should be followed.
2. Allergy should be taken into consideration when local skin antiseptics are used.
3. Clipping of chest hair is done immediately before surgery.
4. Before implantation, the device is to be tested on the back table under sterile conditions.
5. Skin preparation in operating room should be performed with an alcohol-based agent unless contraindicated.
6. During surgery, glycemic control, with blood glucose target <200 mg/dl, and normothermia should be maintained.
7. Increased fraction of inspired oxygen is important to maintain during surgery and after extubation in the immediate post-operative period.
8. Transfusion of blood products should not be withheld but given if necessary.
9. The velour coverage of the drive-line is kept under the skin at the exit site for better care of the drive-line exit site.
10. To lessen shearing and foster granulation along the drive-line exit site, the drive-line should be secured in the immediate post-operative period.

Anti-microbial prophylaxis

To date, no randomized trials have evaluated optimal peri-operative anti-microbial prophylaxis (AP) for MCS implant surgical procedures. However, consensus guidelines recommend AP in surgical patients, including cardiothoracic surgery, to prevent SSIs, which are associated with significant morbidity and mortality.⁸⁷ The selection of the optimal AP regimen is based on general principles from the clinical practice guidelines for anti-microbial prophylaxis in surgery⁸⁷ and have been adapted here to the MCS recipient and implant procedure by the ISHLT MCS Consensus Expert Panel. Guidance is presented on the selection of the AP regimen and peri-operative dosing strategies to maintain therapeutic levels. Relevant results from an ISHLT-supported MCS infection prevention survey of 137 international MCS centers are included.³

Peri-operative anti-microbial prophylaxis: Evidence summary

In general, cardiothoracic surgery is considered “clean surgery.” Selection of the AP regimen should be targeted against skin flora as the most likely contaminants of the surgical site. Up to 20% of skin-colonizing bacteria may be found beneath the skin, in sebaceous glands and hair follicles, and are therefore not affected by topical antiseptics at time of surgery.⁹⁸ Despite the fact that in the past decade the frequency of multidrug-resistant Gram-negative bacteria and yeast has increased,³⁶ the risk of Gram-negative bacterial and yeast infections in proximity to MCS placement is significantly lower compared with Gram-positive bacteria.

In the REMATCH study, peri-operative antibiotics were very broad and included vancomycin, rifampin, levofloxacin and fluconazole.⁹⁹ Although some centers still use this original combination for prophylaxis, currently most centers do not include Gram-negative or fungal coverage.³ According to cardiac surgery prophylaxis guidelines, a cephalosporin is usually recommended (cefazolin or cefuroxime), which can provide some Gram-negative coverage for 24 to 48 hours.^{78,87,100} Rifampin is not routinely used because its benefit in short-term prophylaxis has not been proven and also because of its interaction with many other drugs, such as warfarin.¹⁰¹ Ninety-eight percent of surveyed centers use intravenous peri-operative AP.³ Vancomycin was found to be a consistent component of both published studies and the ISHLT-supported survey.^{3,14,26,28,102–106}

In 2016, the ISHLT published guidelines for the management of fungal infections in MCS and cardiothoracic organ transplant recipients.¹⁰⁷ Fungal infections (FIs), mostly secondary to *Candida* sp, are not common, but are associated with significant mortality.³³ Given the relatively high rates of FI seen in earlier reports, there has been great interest in utilizing anti-fungal prophylaxis for MCS procedures. However, an analysis of retrospective observational studies demonstrated a similar rate of FI with and without anti-fungal prophylaxis (11.8% vs 10.4%, $p = 0.9$).^{104,108} Fluconazole prophylaxis was included in the pre-operative prophylaxis in the REMATCH trial.⁹⁹ In the ISHLT-supported survey, 50% of centers were found to use anti-fungal prophylaxis, with 92% of these centers using fluconazole. A duration of up to 48 hours was employed by 63% of these centers.³ Fluconazole use was favored to avoid nephrotoxicity from amphotericin B and high cost of the echinocandins. However, it is not clear whether *Candida* sp was introduced at the time of MCS implantation. Many of these types of infection manifest weeks to months afterward.^{33,108} Prospective multicenter studies are needed to evaluate the impact of fluconazole or other anti-fungal prophylaxis on SSI in MCS recipients. In summary, low rates of FI have been noted in recent studies and there has been no evidence that the routine use of anti-fungal prophylaxis decreases risk of FIs in MCS recipients. Routine anti-fungal prophylaxis was not recommended in the 2015 ISHLT guidelines for the management of fungal infection in MCS and cardiothoracic transplantation.¹⁰⁷

The majority of published studies have not addressed timing of antibiotic initiation with respect to MCS surgery. Significant variation seems to exist with timing reported to range from 30 minutes to 3 days before first incision.^{26,28,105} Most ISHLT-supported survey respondents reported initiation of antibiotics within 1 hour of skin incision.³ This is consistent with the Surgical Care Improvement Project (SCIP) guidelines for AP (vancomycin specifically is addressed in what follows).^{109,110}

The recommended AP duration of 48 hours is unlikely to produce antibiotic resistance,¹¹¹ but AP >48 hours introduces increased concern for developing anti-microbial resistance with no impact on SSI rates.^{112–115} According to the The Society of Thoracic Surgeons and American Society of Healthsystem Pharmacists/Infectious Diseases Society of America, the presence of an indwelling catheter, a drain or a chest tube is not an indication to extend AP beyond 48 hours after cardiac surgery.^{87,111} Further studies are needed to determine whether shorter AP duration is appropriate.¹¹¹

Peri-operative anti-microbial prophylaxis recommendations

There are no studies to guide the specific choice of anti-microbial agents for prophylaxis in MCS. The AP regimen should always target *Staphylococcus* sp and, in colonized patients or in centers with high MRSA prevalence, coverage for MRSA is recommended. Centers should use their local institutional epidemiology data to guide the AP protocol for MCS implant procedures. Routine use of broad-spectrum Gram-negative^{87,111} or fungal¹⁰⁷ prophylaxis is not recommended.

Most prophylactic antibiotics should be infused within 1 hour of skin incision, based on lower rates of SSI observed in other surgical models following this time course.^{87,116} In contrast, vancomycin infusion should be started within 2 hours before skin incision. The duration of AP should not exceed 48 hours.¹¹¹ The goal is to achieve therapeutic levels (above the minimum inhibitory concentration of the pathogens of concern) at the time of first incision, and until final chest closure.^{87,111} For cases in which the surgery is longer than 2 half-lives of the antibiotic used, an additional intra-operative dose may be needed to ensure adequate tissue levels.⁸⁷ In cases of significant blood loss during the procedure (>1,500 ml or >2 units of packed red blood cells given), antibiotics may need to be re-dosed to obtain adequate tissue levels.^{87,117–119}

Secondary prophylaxis

According to the 2007 American Heart Association guidelines,¹²⁰ the only conditions that would qualify for secondary prophylaxis to prevent infective endocarditis, before a dental procedure, are those with the highest risk for adverse outcome once endocarditis occurs. These conditions would include: history of infective endocarditis; prosthetic cardiac valves; certain congenital heart diseases; and valvulopathy in heart transplant recipients.¹²⁰ VADs and TAHs are not considered valvular cardiovascular devices and their presence is not an

indication for routine secondary prophylaxis before dental, respiratory, gastrointestinal or genitourinary procedures.¹²¹ However, both would qualify for secondary prophylaxis in the following conditions: (1) incision and drainage of infection like an abscess; and (2) residual leak after closure of patent ductus arteriosus, atrial septal defect or ventricular septal defect.¹²¹ Nevertheless, the 2013 ISHLT guidelines for MCS consider secondary prophylaxis a reasonable strategy.⁸³ We agree with this and endorse the ISHLT's recommendation. MCS recipients are at high risk of developing bacteremia, which may lead to seeding of the device and be associated with adverse outcome.⁸³

Other considerations

Chest tube insertion and maintenance until drainage resolves is standard practice after MCS implantation. Although 25% of centers in the ISHLT-supported survey continue AP until chest tube removal, there is evidence that this practice is not justified due to concerns about cost, drug toxicity and emergence of anti-microbial resistance.^{111,112} Therefore, AP duration should not be based on the presence of a chest tube.^{87,111} Similarly, there are no data to support continuation of AP when the sternum remains open. Most ID physicians discourage this practice; however, as there are also no data to refute this practice, AP is often continued until chest closure.⁴⁷

After the initial antibiotic prophylaxis period of 48 hours, further use of antibiotics should be judiciously guided by clinical status and microbiology data. In the absence of signs of infection, antibiotics should be discontinued after the AP period to prevent emergence of antibiotic resistance. Guidance from the ID consultant is helpful when considering extension of anti-microbial therapy beyond 48 hours.

Recommendations:

1. The AP regimen should target *Staphylococcus* sp.
2. The AP regimen should cover MRSA in colonized patients.
3. Local institutional epidemiology should guide adjustments to AP protocol in MCS implant procedures.
4. Routine broad-spectrum Gram-negative prophylaxis is not recommended unless guided by local institutional epidemiology data.
5. Rifampin prophylaxis is not routinely recommended due to drug–drug interactions
6. Routine anti-fungal prophylaxis is not recommended.
7. Most AP agents should be infused within 1 hour before skin incision.
8. Vancomycin should be started within 2 hours before skin incision.
9. Duration of AP should not exceed 48 hours.
10. In procedures lasting longer than 2 half-lives of the AP agent(s), an additional intra-operative dose(s) is recommended to ensure adequate tissue level.
11. If there is significant blood loss during the procedure (>2 units or red blood cells given, or > 1,500 ml), the antibiotic should be re-dosed to obtain adequate tissue levels.

12. Duration of AP should not be based on the presence of chest tubes, drains or an open sternum.
13. An ID consultation should be considered before extending AP beyond 48 hours.

Post-operative nursing management

There is little published research examining the optimal management of the VAD drive-line exit site (DLES) in continuous-flow (CF) VADs. Published studies consist of single-center and multicenter observational studies. For purposes of this document, a “qualified health professional” (QHP) is defined as a registered nurse, advanced practical nurse or other health care provider who has had thorough training in VAD management and care.

Patient and caregiver education

As DLIs are frequently associated with trauma (e.g., dropping the battery) or sub-optimal drive-line exit site care, patients and caregivers should receive ongoing education about LVAD component care and drive-line immobilization. Patient education has been demonstrated to improve infection prevention; adherence to instructions; and the quality, frequency and efficacy of dressing changes. Consideration should be given to optimize the technique for drive-line dressing changes and drive-line immobilization, personal hygiene, nutrition and any other lifestyle factors that may affect the risk of infection.^{122,123}

Drive-line immobilization

The drive-line should be stabilized using a binder or anchoring device immediately after surgery and, thereafter, with the aim to minimize line movement to allow for rapid healing and prevention of subsequent trauma to the DLES, a risk factor for infection.^{27,28,55,83,124}

Dressing procedure

Dressings should be changed using aseptic technique in accordance with institutional policies in the immediate post-operative period. There is some variation, but some consider sterile gloves and a mask the minimum required.^{125,126} A mild antiseptic solution should be used when performing DLES dressings. Most commonly, chlorhexidine-based solutions are used. However, other solutions may be utilized depending on the presence of localized skin reactions and institutional policy.¹²⁷ The DLES should be covered with a protective dressing based on availability as well as the patient's allergy and hypersensitivity profile (Kaan A et al, unpublished data, 2017).³ The use of alternative solutions, bacteriostatic gauzes and dressings can be considered and have been described in small single-center studies to be non-inferior to standard gauze-based dressings with respect to infection.^{128,129} The use of silver-impregnated gauze may reduce DLIs in the first 6 months post-implant¹²⁹ and could be used if readily available to patients. The safety of novel

dressings solutions and dressings should be discussed with the VAD manufacturer before implementation to rule out a possible harmful reaction with the drive-line.

Frequency of dressing changes

Dressing changes should be performed daily with close inspection of the DLES until fully healed. More frequent dressing changes may be needed depending on the volume of drainage.¹²⁵ One small retrospective study compared daily, weekly and 3-times-weekly dressings after discharge from the critical care ward during the index admission and found no difference in infection rates between the 3 groups. This suggests that less frequent dressings may be feasible and safe in selected patients.¹³⁰

Once healed and with no drainage present, the frequency of dressing change can be decreased to 1 to 3 times weekly. Reduction in dressing change frequency should be determined by the QHP.^{125,130} Dressing changes should be timed to occur immediately after the patient showers (Kaan A et al, unpublished data, 2017).¹²⁵

Patients and/or caregivers should be trained by a QHP to change the dressings before discharge according to learning style and ability. Competency of the patient/caregiver performing the DLES care should be reviewed regularly.⁸³ The VAD center should take into account social factors that may influence the type of dressing used, including lifestyle, availability of supplies in the community, financial limitations and individual ability.

It is known that the incidence of DLES infection increases with longer duration of MCS.^{27,28} However, long-term compliance with rigorous, expensive dressing change regimens may be challenging for DT patients. Involving patients and caregivers in seeking suitable alternatives may lead to improved adherence and movement toward the goal of attaining concordance.¹³¹ Further research in this area is needed. If the patient uses a technique not recommended by the team, it is advised that the DLES be checked regularly by a QHP.

Hygiene

Most centers allow the patient to shower once adequate healing has occurred at the DLES, usually between 1 and 8 weeks.^{3,125} If the patient is able to shower, the peripherals must be covered with appropriate protective equipment provided by the VAD manufacturer. Most centers currently cover the DLES with a waterproof dressing during a shower. A small number of centers allow the fully healed DLES to be either exposed or the old dressing to get wet during the shower.¹²⁵ Although there is limited literature available, there is no evidence to indicate that exposure of surgical wounds to water during a shower increases infection rates.¹³² Therefore, for situations in which the DLES is fully healed, some teams may consider allowing the DLES to be completely exposed to water during a shower. If so, it should be cleaned and fully dried, with a new dressing applied immediately after exposure.

If the DLES becomes infected, VAD team members should review hygiene practices with the patient and an individualized plan be created (see Section VI).

Assessment of drive-line site and infection surveillance

Patients are instructed to contact the MCS center immediately if there has been trauma to the drive-line site or there is pain or a change in the character or appearance of the DLES, that is, erythema or drainage. The DLES should be checked at each clinic visit by a QHP for signs of infection, local trauma, line damage or torsion.^{24,83} More frequent checks are warranted during periods of infection or irritation (e.g., trauma to the DLES).

Photographs may be used in circumstances that prevent direct visualization provided the local privacy policies are not violated. Alternatively, a pictorial guide can be useful in situations where a photograph is not possible but a verbal description from the patient is required.¹²⁸ The standardized ISHLT “definitions of ventricular assist device-specific percutaneous drive-line infection” should be used to categorize the infection of the DLES.⁵

Recommendations:

1. Patients and/or caregivers should be deemed competent by a QHP to care for the DLES and VAD peripherals.
2. Patients and/or caregivers training should take into account patient/caregiver circumstances, learning style and ability.
3. The drive-line should be stabilized using a binder and/or anchoring device.
4. Dressing changes should be performed daily initially and, once healed, consideration could be given to reducing the frequency (1 to 3 times weekly).
5. Dressing changes should be timed to occur immediately after the patient showers.
6. The patient may shower once the DLES is adequately healed.
7. If the DLES is exposed to water during a shower, it should be cleaned and fully dried, and a new dressing applied immediately after exposure.
8. The DLES should be checked at each clinic visit by a QHP for signs of infection, local trauma, line damage or torsion.
9. More frequent checks may be warranted during periods of infection or irritation (e.g., trauma to the DLES).

Management of infection

There are no randomized, controlled studies regarding the management of MCS infections. The principles in the management of MCS infections are thus guided by observational data and expert opinion,^{24,56,126,133} and are based on the following factors: (1) identification of the responsible pathogens; (2) MCS-specific infection location (pump/cannula, pocket, drive-line); (3) MCS-related infection type (infective endocarditis, bloodstream infection, mediastinitis); and (4) transplant candidacy status (BTT vs DT). The table

Table 1 Therapeutic Options for Management of MCS-specific and MCS-related Bacterial Infections

	Medical intervention	Surgical intervention
MCS-specific		
Pocket/drive-line Superficial DLI	Treat with intravenous or oral antibiotics for a minimum of 2 weeks or until infection has resolved (drainage, redness, tenderness, etc.). Reinforce patient and caretaker education about DL immobilization technique(s).	
Deep DLI/pocket	Antibiotics: intravenous until clinical stabilization and improvement of infection (usually 6 to 8 weeks), followed by long-term oral suppression therapy. Specific duration as per ID consultant.	Surgical debridement with or without wound VAC. New drive-line exit site away from previous infection may be required.
DLI, uncertain depth	Depends on clinical circumstances, may need to treat like deep DLE	
MCS pump and/or cannula Initial treatment	Empiric antibacterial treatment (most common bacteria are <i>Staphylococcus</i> sp and <i>Pseudomonas aeruginosa</i>) followed by targeted therapy based on susceptibility testing. Initial empiric antibiotic selection should be directed at pathogens reflecting the local institution's susceptibility patterns until directed therapy is initiated. Duration of antibiotics: In BTT antibiotics should continue until after HT. Specific duration as per ID consultant. There is no available literature regarding this topic. Longer antibiotic course (4 to 6 weeks) may be offered to patients with positive intra-operative cultures at time of explant. In DT, intravenous antibiotic treatment is followed by long-term oral antibiotic suppression. Intravenous therapy is usually 6 to 8 weeks, but may vary based on pathogen and clinical course. Specific duration of intravenous or oral antibiotics as per ID consultant.	Surgical drainage and surgical debridement may be required to control infection. Source control: in BTT, explant of the device for HT; in DT, explant of the device for control of infection (see below)
Persistent bacteremia, relapsing infection, septic emboli, sepsis despite adequate antimicrobial and surgical therapy	In BTT, intravenous antibiotics should continue until after HT. In DT, intravenous antibiotic treatment is followed by long-term oral antibiotic suppression. Intravenous therapy is usually 6 to 8 weeks, but may vary based on pathogen and clinical course. Duration of antibiotics treatment after device exchange or HT depends on clinical course and pathogen. Longer course (4 to 6 weeks) may be offered in positive intra-operative cultures or recent pre-operative bacteremia, and a shorter course (14 days) in the absence of such conditions. Specific duration of intravenous or oral antibiotics as per ID consultant.	In BTT, timing of device replacement should be before other end-organ failure occurs, as this may preclude candidacy for HT. In DT, device replacement may be required to control infection.
MCS-related		
Bacteremia	Duration of antibiotics depends on source, organism and clearing of bacteremia. CRBSI secondary to <i>Staphylococcus aureus</i> is treated for 4 to 6 weeks and the catheter is removed. If not <i>S aureus</i> , blood cultures become negative within 24 to 48 hours and no signs of metastatic infection, 2 weeks from first negative blood culture may be adequate (e.g., urinary tract source). If no source is identified, treatment may be considered as with MCS pump and cannula infection.	

Continued on page 1148

Table 1 (Continued)

	Medical intervention	Surgical intervention
Bacterial mediastinitis	Duration of anti-bacterial therapy is at least 6 to 8 weeks after last surgical debridement. ID consultation is recommended.	Surgical debridement is often indicated. Open chest and VAC wound closure may also be required.
Infective endocarditis	Duration of anti-bacterial therapy is the same as for MCS pump and cannula infection. ID consultation is recommended.	Surgical intervention may be required.

BSI, bloodstream infection; CRBSI, catheter-related bloodstream infection; CT, computed tomography; CVC, central venous catheter; DC, discontinue; DL, drive-line; DLES, drive-line exit site; DLI, drive-line infection; DT, destination therapy; HT, heart transplantation; ID, infectious disease; MDR, multidrug-resistant; MCS, mechanical circulatory support; NM, nuclear medicine; VAC, vacuum-assisted closure.

lists proposed general therapeutic options for management of MCS-specific and MCS-related bacterial infection. We acknowledge that treatment and duration may vary and depend on many factors (e.g., the pathogen, specific clinical circumstances, response to treatment), and therefore should not be generalized. Nevertheless, the majority of the authors of this document believe that a general treatment concepts reference would be helpful to clinicians [Table 1](#).

Initial management

The observation of a local change in the DLES (pain, erythema, drainage) or fever should prompt the patient to contact the treating MCS center for further evaluation.^{83,134}

The initial step in the management of a patient with suspected device-related infection is assessment of clinical status and type of device infection to determine whether management should be performed in the ambulatory or hospital setting. In patients with infection limited to the superficial DLES and no signs of sepsis or systemic illness, cultures of drive-line site are collected, and ambulatory management for 2 weeks may be considered. Patients with suspected deep DLI, pocket infection, pump, cannula infection, systemic illness or sepsis should be hospitalized. Cultures and Gram stain of drained or aspirated fluid, 2 sets of peripheral blood cultures and 1 through central venous line (if present), should be obtained to guide anti-microbial therapy.⁵ Skin cultures from normal-appearing exit sites should be avoided and interpreted with caution if performed. Gram stain can identify inflammatory cells consistent with infection rather than bacterial colonization.

No imaging modality is presently available that can definitely exclude deep tissue space infections. Computed tomography (CT) or ultrasound are recommended imaging modalities to help identify deep drive-line, pocket, pump and cannula abnormalities in a specific anatomic space. It should also be acknowledged, however, that CT and ultrasound imaging may lack specificity.¹³⁵ Leukocyte radiolabeled scintigraphy has been used successfully to identify deep infections, but, like CT scanning, it lacks specificity. Combining single positron emission tomography scan (SPECT/CT), with radiolabeled leukocytes has increased the sensitivity for infection detection and retained the specificity for anatomic location of the MCS infection; it can also identify distal foci if infected emboli are present.^{136–139} Transesopha-

geal echocardiography (TEE) is recommended in bloodstream infection (BSIs) in looking for vegetations and turbulent flow across the device, but a negative finding does not rule out infective endocarditis in the right clinical setting.^{5,24,140}

Empiric and targeted anti-microbial therapy

In patients with superficial DLIs but without BSI or systemic illness, empiric anti-microbial therapy can be initiated and adjusted to targeted antibiotic treatment once the pathogen has been identified and susceptibilities are known; in a stable patient, some clinicians prefer to wait and start antibiotic therapy once culture result is known.^{83,133,134}

Oral therapy targeting the cultured pathogens should be initiated when feasible. If cultures are negative but DLI is still not ruled out, empiric anti-bacterial therapy should be initiated and evaluated based on clinical response. In the presence of systemic illness and/or sepsis, empiric intravenous anti-bacterial therapy targeting *Staphylococcus* sp and *Pseudomonas* should be initiated. The choice of empiric therapy should also be influenced by local institutional epidemiology and susceptibility patterns.

Therapeutic drug monitoring should be considered for specific anti-microbial therapies (e.g., vancomycin, aminoglycosides, voriconazole, posaconazole). As anti-microbial therapy may affect the international normalized ratio (INR), close monitoring of INR to maintain the appropriate anti-coagulation therapy window is warranted. Rifampin should usually be avoided and used with great caution when clinically indicated due to its significant impact on INR.¹⁰¹

Surgical management

When feasible, it is essential to achieve source control including drainage and debridement of any infected collections. Recurrent infection in the original site occurs more frequently if treated with antibiotics alone and without surgical debridement. In one center, recurrent infection occurred in 100% when driveline infection was treated with antibiotics only, 40% after pump exchange, 66% after drive-line debridement, and 66% after surgery followed by suppressive antibiotics.¹⁴¹

Local debridement of the DLES may be needed in the setting of fluctuant, indurated or necrotic tissue and sometimes the DLES is moved to a new location, away

from the previous site of infection. In patients with deep infection, surgical drainage and possible use of wound vacuum-assisted closure (VAC) system should be considered.^{142,143} In patients with pump and cannula infections, complete device explant followed by exchange/heart transplant are necessary for definitive cure.

Indications for device exchange include persistent BSI and/or relapsing or persistent infection, septic emboli or sepsis, despite adequate anti-microbial and surgical therapy, and remains the only option for DT.^{141,144,145} However, an advanced-age DT patient with multiple comorbidities may not be a candidate for device exchange. In hemodynamically stable transplant candidates without multiple-organ failure, the best option is transplantation, which may be considered in the setting of BSI, provided a safe and effective targeted anti-microbial therapy is available.¹⁴⁶ In transplant candidates with persistent sepsis due to device infection, exchange may be the only choice to stabilize the patient and maintain transplant candidacy.^{28,39,46,48,49,55,56,58}

Nursing care for active infection

Optimal nursing care and ongoing patient education regarding management of the infected DLES should continue, as described in “Post-operative nursing management”. Surgical debridement of an exit site abscess may require removal of infected drive-line material (velour) or drive-line repositioning. This may result in larger and deeper wounds for which there appears to be an increasing role for negative pressure therapy with a wound VAC device.^{142,145} The benefits of negative pressure therapy include removal of fluid and local debris, decreased local edema, increased peripheral wound perfusion, promotion of granulation tissue formation, and a more rapid decrease in wound size. The appropriate wound dressing depends on the phase of wound healing and institutional policy. Care should be taken to check with the MCS manufacturer for compatibility issues before applying a dressing that may affect the integrity of the drive-line.

End-point of therapy

The duration of anti-bacterial therapy is based on clinical response, type of device infection, pathogen and transplant status (BTT vs DT). In patients with superficial DLI, but without BSI, anti-microbial therapy may be discontinued when all signs of infection have resolved and the exit site has healed (minimum 2 weeks). Deep DLI may frequently persist despite appropriate medical and surgical therapy due to biofilm formation. Although continuous suppressive anti-bacterial therapy may be considered in this setting, there are conflicting data regarding its impact on relapse and superinfection with resistant organisms. The literature has suggested in some series that antibiotic suppression is associated with fewer relapses or superinfections, whereas other series demonstrated a 30% to 100% risk of relapse.^{24,144,147} However, the data are limited by small sample sizes; no distinction between superficial and deep DLIs; and no recognition of possible progression from the initial DLIs to pocket, pump and cannula infections.

In patients with BSI and/or sepsis, intravenous treatment should be provided until clinical stabilization and improvement is achieved, usually 6 to 8 weeks, although it may vary based on source, pathogen and clinical course, followed by oral suppression therapy. A short course (2 weeks) is given for MCS-related BSIs with a known source, such as the urinary tract. In cases of BSI secondary to CVC, it should be removed and a short course of antibiotic given if blood culture is negative within 24 to 48 hours after removal and there is no evidence of metastatic infection. Extended intravenous treatment (≥ 6 weeks) is recommended for patients with *S aureus* BSI, even after resolution of bacteremia, and may be needed for other pathogens when reliable oral therapy is not available. Input from an ID consultant is recommended in these complex patients. In the presence of mediastinitis or deep surgical site infection, at least 6 to 8 weeks of anti-microbial therapy after last surgical debridement or draining is typically recommended.

Device seeding or endovascular infection should be considered in the setting of persistent BSI, and intravenous antibacterial therapy should be given pending evaluation for endocarditis and refractory pump and cannula infection. In patients with pump-pocket infections, intravenous therapy is necessary, at least until source control has been achieved. In pump and cannula infections, source control cannot be achieved until device removal at the time of HT or device exchange.

In patients with persistent infection despite appropriately treated pocket or pump and cannula infection, or infection limited to the DLES, long-term suppressive anti-microbial therapy (orally, when feasible) is recommended to prevent progression of infection.

Most patients on anti-microbial therapy for MCS infections at the time of device exchange or HT will need to continue the therapy after surgery to minimize the risk of relapse. There are no studies to guide the duration of treatment after device exchange or HT. Therefore, duration of treatment should be individualized according to pathogen and clinical course. Longer antibiotic course (4 to 6 weeks) may be offered to patients with positive intra-operative cultures or recent pre-operative bacteremia and shorter courses (14 days) to those patients with negative intra-operative cultures and no evidence of recent pre-operative bacteremia.

Recurrent or relapsed infection

Published literature is limited with regard to incidence, prevalence, consensus definitions and epidemiology of relapsed or recurrent MCS infections. Niehaber et al²⁴ defined relapse as recurrent infection at the same site with the same organism within 1 year of initial resolution, and reported a 17% (13 of 78) relapse rate in their cohort. Relapse is hypothesized to be related to persistence of a biofilm-associated pathogen or known risk factors for initial DLI, such as drive-line mobility, hobbies associated with repetitive movement, repeat trauma to the drive-line or patient-related factors like diabetes. Poor adherence to previous anti-microbial therapy should also be assessed as a potential contributing factor.

Long-term suppressive antibiotic therapy, device exchange and HT with associated device removal should be considered in recurrent or relapsed LVAD infection. However, there have been few studies guiding the management of these options. Device exchange or HT has been performed in the setting of multidrug-resistant DLI.^{144,145} Exchange of a HeartMate II for a HeartWare HVAD has also been reported to eliminate the need for a pump pocket and provide more flexibility with drive-line placement.¹⁴⁵ There have been no studies addressing whether relapsed infection is associated with worse HT outcomes. Therefore, relapsed infection should not be considered a contraindication for HT.

Recommendations:

1. Change in the DLES (pain, erythema, drainage) or fever should prompt evaluation for infection.
2. In patients with superficial DLIs and without BSI or systemic illness, empiric anti-microbial therapy can be initiated and adjusted in the ambulatory setting once DLES culture results are obtained.
3. Patients with suspected deep DLI, pocket infection, pump, cannula infection, systemic illness or sepsis should be hospitalized.
4. Drained fluid culture, 2 sets of peripheral blood cultures and 1 blood culture obtained through CVC (if present) should be obtained to guide anti-microbial therapy.
5. Skin cultures from normal-appearing exit sites should be avoided.
6. In patients with systemic illness and/or sepsis, empiric intravenous anti-bacterial therapy targeting *S aureus*, and *P aeruginosa* should be initiated in the hospital setting.
7. Local debridement of the exit site should be performed in the setting of fluctuant, indurated or necrotic tissue.
8. In patients with deep infection, surgical drainage and installment of a wound VAC system should be considered whenever feasible.
9. Surgical debridement and device exchange should be considered in the setting of persistent or relapsing BSI despite adequate anti-microbial and surgical therapy in DT. An advanced-age DT patient with multiple comorbidities may not be a candidate for pump exchange; palliative/hospice therapy for end-of-life comfort care may be considered.
10. In hemodynamically stable transplant candidates with BSI, HT should be considered provided there is safe, effective, targeted anti-microbial therapy.
11. In patients with persistent sepsis and instability due to device infection, exchange should be performed if feasible to stabilize the patient (HT candidates or DT patients). Some patients may not be candidates for device exchange, as noted in Recommendation 9 (above).
12. In patients with superficial DLI, anti-microbial therapy should be discontinued when all signs of infection have resolved and the exit site has healed. DLES should be monitored by a QHP for early recurrence of superficial infection.
13. In patients with pocket, pump and cannula infection, anti-microbial therapy should be continued until

clinically stable after device exchange or HT. A longer antibiotic course (4 to 6 weeks) may be offered to patients with evidence of positive intra-operative cultures or recent pre-operative bacteremia, and shorter courses (14 days) to those without such evidence.

Summary

A recent ISHLT-supported survey confirmed that centers are using protocols for infection prevention guided by expert opinion. This document summarizes the consensus recommendations of a multidisciplinary panel of experts from the ISHLT in collaboration with the ICCAC to guide the prevention and management of infection in MCS recipients. Future directions should focus on collaborative, international, multicenter research initiatives to address key knowledge gaps in the prevention and management of MCS infection.

Disclosure statement

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