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CONSENSUS STATEMENT

ISHLT consensus statement for the selection and management of pediatric and congenital heart disease patients on ventricular assist devices



Endorsed by the American Heart Association

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Background

Heart failure (HF) is a significant cause of mortality in children and therefore there is interest in understanding the optimal way to support these children with Ventricular Assist Devices (VAD) to improve outcomes. VAD therapy is now regarded as an important treatment option in pediatric HF. The 2019 International Society for Heart and Lung Transplantation (ISHLT) registry report shows that there is an increasing trend towards using VADs as a bridge to transplant (BTT) with currently over one-third of patients transplanted being bridged with a VAD.¹

The **immediate** aim of VAD therapy is to provide hemodynamic stability for a failing circulation unresponsive to medical therapy. The VAD should be implanted before the development of severe end-organ dysfunction in order to optimize clinical outcomes. The goal is to improve tissue and organ perfusion, improve quality of life (QoL) and improve waitlist survival. Importantly, VAD therapy may not only lead to patient stability but may also afford the opportunity for patient rehabilitation prior to heart transplantation (HT).

Despite the increase in VAD use within pediatrics over the last decade, the majority of centers implant less than 10 VADs in children per year.² Thus, local data is limited for analysis of outcomes and therefore multi-center collaboration and consensus is essential in understanding this complex and dynamic field.

ISHLT has recognized the importance of a consensus statement on the selection and management of pediatric and congenital heart disease (CHD) patients undergoing VAD implantation. The purpose of this document is to provide expert-consensus derived recommendations and whenever possible, these recommendations shall be guided by evidence. The creation of this consensus document required multiples steps including the engagement of the ISHLT councils, identification and selection of experts in the field, and the development of 13 Task Forces. Extensive

literature searches were performed but due to the lack of comparative trials in pediatrics, this document was written as a literature review with expert opinion rather than based on level of evidence.

Patient selection

Timing of VAD

Optimal timing for the implantation of a VAD in pediatric patients should be determined by an assessment of the potential risks and benefits of the intervention. The complexity of this decision-making is amplified by the numerous variables impacting VAD risk profile, including patient age/size,³⁻⁵ anatomy,⁶⁻⁸ developmental hemostasis,⁹ and device type,¹⁰⁻¹² as well as factors related to illness severity and comorbidities prior to implantation.^{7,11,12} Many of these factors are interdependent. Paracorporeal devices are most often placed in younger, smaller patients who are more likely to be sicker, have CHD, and end-organ dysfunction at the time of VAD implantation, making it difficult to assess which of these factors drives inferior outcomes.¹¹⁻¹³ While this complex reality precludes the formulation of any generalizable guidelines for the optimal timing of VAD placement for all pediatric patients, one consistent theme to emerge from the literature is the inferior outcomes of VAD support for pediatric patients in cardiogenic shock (INTERMACS Profile 1) or with end-organ dysfunction prior to implant.^{11,12,14} (Figure 1) Despite these data, the most recent Pedimacs report reveals that 33% of patients are still INTERMACS Profile 1 at the time of implant, including 40% of patients receiving paracorporeal pulsatile devices, 49% of patients receiving paracorporeal continuous flow devices, and 19 % of patients receiving intracorporeal continuous flow devices.¹² Similarly, the last Paedi-Euromacs report showed that 21% of patients were implanted as INTERMACS Profile 1.¹⁵

Although, patients have better outcomes if implanted before they become too ill, there are times when pediatric patient present in cardiogenic shock and/or with end-organ injury. In these cases, attempting to reverse the shock process before implantation of a durable VAD may possibly result in better outcomes. The role of paracorporeal

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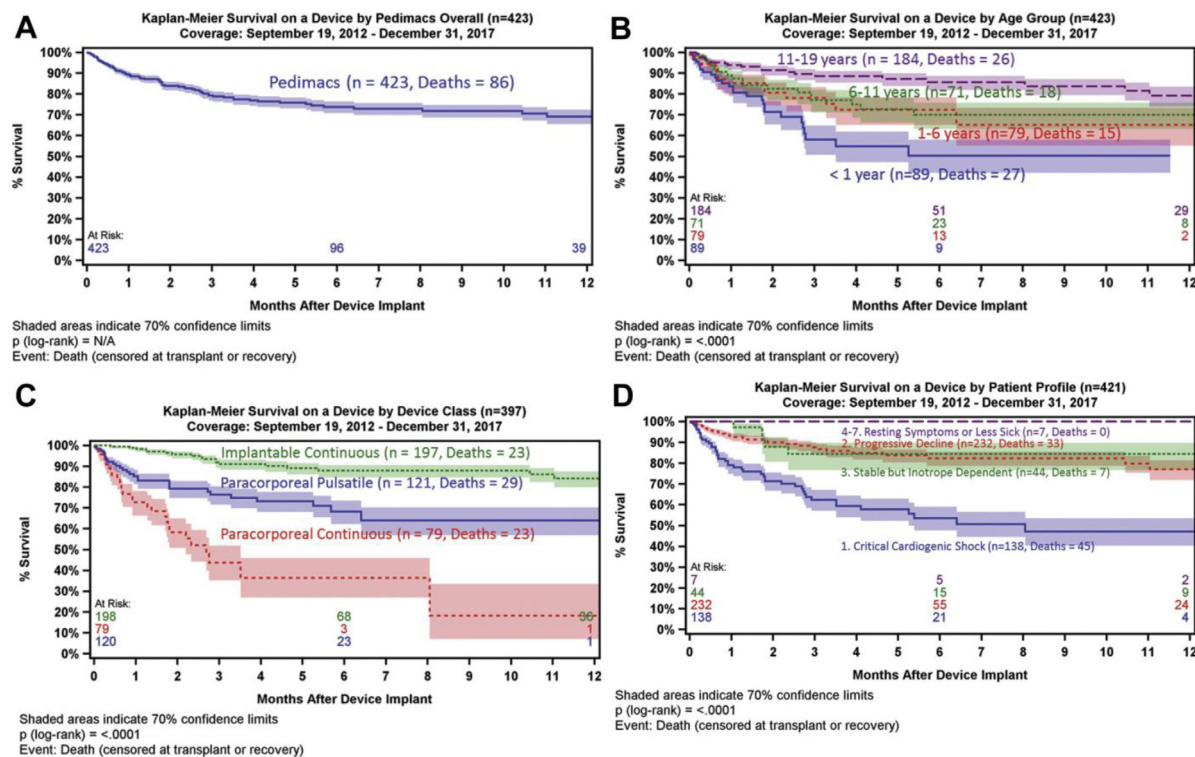


Figure 1 Survival curves from 3rd Annual Pedimacs report.¹²

continuous flow (CF) and percutaneous VADs, or venoarterial extracorporeal membrane oxygenation (ECMO) in stabilizing/salvaging critically ill pediatric patients with advanced HF to make them better candidates for long term support is not well understood to date. There is evidence that end-organ dysfunction in children can improve significantly with a paracorporeal CF device and this may have a beneficial effect on outcomes.^{16,17,18} ECMO support prior to VAD implantation has not been associated with better survival post VAD,^{8,12} although it is difficult to separate the impact of ECMO from the level of illness requiring ECMO in interpreting this data.

Indications for VAD

Failure of medical management: In many cases, medical management does allow stabilization of patients with HF. In some cases, HF progresses and VAD therapy is the only option for stabilization. Progressive respiratory (requiring non-invasive and invasive support) decompensation, liver dysfunction, kidney injury and feeding intolerance are commonly reported measures of congestion and/or inadequate cardiac output (CO) that may develop despite optimal medical management. End-organ dysfunction is common in pediatric VAD patients prior to implantation, with 45% of patients intubated (paracorporeal devices 75-85% of patients compared to intracorporeal devices 21%), 94% on inotropes, 64% requiring feeding tubes/TPN, 40% with hyperbilirubinemia and 30% having a glomerular filtration rate (GFR) < 60 mL • min⁻¹ • 1.73 m.^{2,12} These findings

are notable given end-organ dysfunction is associated with poor outcomes among VAD patients and following transplantation^{3,7,14,18} and timely implantation can result in reversal of end-organ dysfunction and better outcomes.^{16, 19}

Post-cardiotomy failure to wean from cardiopulmonary bypass (CPB): The presence of a previous sternotomy or additional cardiac surgery in pediatric VAD patients ranges from 23% to 39%.^{12,20} Post-cardiotomy patients (in most circumstances those with CHD), who fail to wean from cardiopulmonary bypass (CPB) are more likely to be converted to ECMO or implanted with paracorporeal CF devices. With respect to the use of more durable VADs, failure to wean from CPB or decompensation during the index hospitalization after cardiac surgery is a significant risk factor for mortality among patients supported with a EXCOR.⁷

Uncontrollable Arrhythmias: Cardiogenic shock from uncontrolled tachyarrhythmia is rare and most of the literature pertaining to mechanical circulatory support (MCS) involves case reports and the use of ECMO. VAD support was deemed necessary in 10% (n=39) of patients in the only multicenter retrospective review²¹ of pediatric patients with arrhythmias.

Intent of VAD

The primary indication for pediatric VAD use in North America remains BTT, with 55% of patients listed at time of implantation and 34% being assessed for candidacy.¹² Additional, implantation strategies include bridge to recovery (BTR) (6%), and destination/chronic therapy (DT) (2%)

and other (3%).¹² Similar frequency of intent has also been recently reported in the second Paedi-EUROMACS report with 85% of patients implanted with an intention to transplant with 56% BTT and possible BTT 29%.¹⁵ Although most patients are implanted with the intent to transplant, pediatric DT is becoming more common especially in patients with muscular dystrophy (MD) and congenital heart disease (CHD) patients.²²⁻²⁵

Pre-implant planning

End-Organ Assessment: Although pre-operative renal, hepatic, respiratory and nutritional failure have been associated with worse post-VAD outcomes, many patients have pre-operative end-organ dysfunction.²⁶ This likely is due to late presentation, late diagnosis or delayed timing for implantation. Irreversible renal dysfunction has been considered a relative contraindication to VAD implantation in the past but identifying irreversible dysfunction remains a significant challenge. Current data is complicated by various definitions of renal dysfunction including: serum creatinine > 1.6 mg/dl for patients aged > 10 years, or creatinine > 1.0 mg/dl for patients aged ≤ 10 years, or by the estimated glomerular filtration rate (eGFR) using the Schwartz formula^{3,11,12} being < 90 mL/min/1.73 m².² In the 3rd Pedimacs report, the threshold was defined as <60 mL/min/1.73 m² and found that 30% of patients had renal insufficiency with 5% found to have an eGFR <30 mL/min/1.73 m² or requiring dialysis.¹² Post-VAD outcomes have been shown to be worse if the patient has renal dysfunction prior to VAD implantation.^{16,27}

Congestive hepatopathy resultant from HF has also been associated with both morbidity and mortality post-VAD. Elevated ALT/AST values are reported in up to 22% to 25% of patients, and abnormal bilirubin in 40% to 45% of patients at the time of VAD.^{3,11,12,14} Mortality has been shown to be higher in patients with elevated bilirubin levels, and is particularly high for patients with additional risk factors, such as patients, weighing less than 10kg (mortality 70%).^{3,14}

The use of mechanical ventilatory support is reported in up to 45% to 49% of patients with 23% to 27% requiring ongoing medical paralysis at the time of VAD implantation.^{11,12} However, significant differences are seen between the device type implanted, with only 21% of intracorporeal CF-VAD patients intubated at the time at implantation.¹²

Poor pre-operative nutrition secondary to poor appetite, abdominal discomfort and nausea may represent symptoms of inadequate gut perfusion from low CO states or venous congestion. The presence of tube feeding, TPN or a combination of both has been reported in up to 64% of patients undergoing VAD implantation.¹²

Right Heart Assessment: “Right heart failure” (RHF) in children after LVAD implant is difficult to quantify, but has been shown to have an incidence as high as 42%.²⁸ Although right ventricular dysfunction is common, this can typically be managed medically as BiVAD is relatively uncommon in the pediatric VAD population (15% of

patients in the most recent Pedimacs cohort).²⁶ Many clinical and imaging parameters have been used to assess the right ventricular (RV) function prior to VAD, however none of the individual parameters have been a sole predictor of the need for RV support. Echocardiography may be used to qualitatively assess RV systolic function, and semi quantitative measures such as tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change can be used for RV functional assessment; however, the value of any individual echocardiographic parameter in predicting RV failure and/or the need for BiVAD support is limited.²⁹ Estimation of RV pressure through measurement of tricuspid regurgitation jet velocity and position of the inter ventricular septum can also be used to screen for elevated pulmonary arterial pressures as an indicator of elevated pulmonary vascular resistance (PVR). Cardiac catheterization to measure CO, central venous pressure (CVP), and pulmonary capillary wedge pressure often occurs prior to VAD placement, but this is neither practical nor safe in all patients. Finally, assessment of cardiac rhythm is imperative. Sustained ventricular arrhythmias not controlled by pharmacologic measures may contribute to RHF and need for BiVAD support in the perioperative period.^{30,31} Numerous clinical, imaging, and hemodynamic parameters have been identified in the adult VAD literature as tools for predicting the need for BiVAD support; these include pre-operative mechanical ventilation, preoperative renal replacement therapy, elevated CVP, and severe RV systolic dysfunction.³² In the pediatric population, data regarding these variables are more limited, but include preoperative ECMO and elevated blood urea nitrogen.²⁸ Despite these parameters, the decision to proceed with BiVAD support is typically made intraoperatively. If RVAD support is needed, temporary RV support may be considered to allow RV recovery following CPB and decompression of the RV and improvement of fluid overload.³³

Support Type Assessment: After establishing that a patient requires a VAD, an important subsequent step is determining the kind of support needed. This refers to the support of the systemic or LV alone (SVAD or LVAD) versus biventricular support (BiVAD). While support of the RV alone (RVAD) may also be considered, it is uncommon. Consideration of LVAD versus BiVAD support is relevant only to patients with biventricular circulations. For patients with single ventricle circulation, however, it is critical to recognize that adequate support of the circulation with a systemic VAD (SVAD) may result in suboptimal outcomes if the patient’s circulatory derangement results wholly or in part from perturbations in the Fontan pathway.³⁴

Psychosocial Assessment: A thorough patient and family psychosocial assessment is critically important pre-VAD implant. The goal of the psychosocial assessment is to identify patient and family strengths, weaknesses and intervention needs, particularly as they relate to VAD care demands. Similar to pediatric pre-heart transplant listing, primary domains of the pre-VAD psychosocial evaluation should minimally include: patient and family treatment adherence, barriers to medical management, disease and VAD-related knowledge, cognitive and/or

neurodevelopmental functioning, current and historic mental health, substance use, social support, family functioning, and abuse and legal history.^{35,36}

Device “fit”: Innovative imaging techniques using virtual device implantation have become available and evolved as an accepted pre-operative planning tool.³⁷⁻⁴⁰ This is especially relevant to children that are being considered for a device that has been U.S. Food and Drug Administration (FDA)-labeled for a larger-sized patient. Accurately scaled 3-dimensional (3D) surface rendering of the device are placed within a 3D reconstruction of the chest to assess for individual fit. Thus device compression of pertinent intrathoracic structures may be ruled out as well as assessing the ability of the inflow cannula to fit within the ventricular cavity.⁴¹ It must be emphasized that these virtual assessments are typically performed on the preoperative geometry of the heart. Cardiac geometry, however, can be significantly different once decompressed with VAD, which has become more predictable as experience has increased.

Key Points

- In general, VAD implantation should be considered, prior to significant end-organ dysfunction or clinical deterioration.

- Patients in cardiogenic shock, or INTERMACS Profile 1, have increased mortality rates post VAD therefore stabilization prior to durable support should be considered.
- Pre-implant planning is a key step in determining eligibility for VAD therapy and should include assessment of end-organs, surgical planning and psychosocial assessment.

Device selection

Devices available for children with end-stage HF can be classified in a number of ways (Table 1). They can be dichotomized by anticipated duration of therapy (temporary or durable) or by design and function (PF or CF). Devices can further be separated by site of implantation (paracorporeal, extracorporeal, intracorporeal, or intravascular) as well as by what form of circulatory support they provide: LV, RV, SV, BiV or total heart replacement (TAH).

Pulsatile Flow Devices: The Berlin Heart EXCOR (Berlin, Germany) is a pneumatically driven paracorporeal VAD, which has been the mainstay of support throughout the world for children for over two decades. In the U.S., the EXCOR is the only device FDA-approved VAD for children. The EXCOR pump comes in a number of sizes (named after their stroke volume) allowing support of children and adults across a broad weight range (3 kg and

Table 1 Devices Used in Children and Adolescents

Device	Manufacturer	Pediatric FDA indication	Type	Output	Patient Size Industry Recommendation	Approval	
						Support Time	Configuration
Short term VAD							
RotaFlow™	Getinge		PC/CF	Up to 10 LPM	All	6 hrs (US)/ Up to 30 d (Europe) ⁶	LVAD, RVAD, BIVAD
PediMag™	Abbott	x	PC/CF	Up to 1.5 LPM	<20 kg	LVAD: 6 hrs (US), 30 d (Europe)/RVAD: 30 d	LVAD, RVAD, BIVAD
CentriMag™	Abbott		PC/CF	Up to 10 LPM	Not studied in patients <18 yrs	LVAD: 30 days (US), 30 d (Europe)/RVAD: 30 d	LVAD, RVAD, BIVAD
TandemHeart™	LivaNova		PC/CF	Up to 5 LPM	>1.3m²	6 hrs	LVAD, RVAD, BIVAD
Tandem Life Protek Duo™	LivaNova		PC/CF	Up to 4.5 LPM	Requires 29F Sheath	6 hrs	RVAD
Impella 2.5™, CP™, 5.0™, 5.5™	Abiomed		IC/CF/IV	2.5: up to 2.5 LPM/CP: up to 4.3 LPM/5.0: up to 5.0 LPM/5.5: >5.5LPM	2.5, CP: advisory board >1.0m² 5.0, 5.5: advisory board >1.5m²	4 days Impella 2.5, CP) to 14 d (Impella 5.0 and 5.5)	LVAD
Impella RP™	Abiomed		IC/CF/IV	Up to 4.0 LPM	>1.5 m²	14 d	RVAD
Long term VAD/TAH							
Berlin Heart EXCOR®	Berlin Heart	x	PC/PF	0.6 – 8 lpm	>2.2 kg (smallest patient)	BTT (US), BTT, DT (Europe)	LVAD, RVAD, BIVAD
HeartWare HVAD System™	Medtronic		IC/CF	2 - 10 lpm	≥1.2 m²	BTT, DT	LVAD
HeartMate 3 System™	Abbott		IC/CF	Up to 10 lpm	≥1.2 m² (Momentum trial inclusion criteria)	BTT, DT or short and ling term	LVAD
Jarvik 2015™	Jarvik		IC/CF	0.5 – 3 lpm	Study Cohort 8-30kg	No approval, trial ongoing	
SynCardia TAH 50cc™	SynCardia	x	C/PF	Up to 7.5 lpm	>1.2 - 1.85 m² Needs room in the chest	BTT	BiVAD
SynCardia TAH 70cc™	SynCardia		IC/PF	Up to 9.5 lpm	≥1.7 m² Needs room in the chest ⁵	BTT/DT	BiVAD

PC, Paracorporeal; CF, Continuous Flow; IC, Intracorporeal; IV, Intravascular; C, Corporeal

greater). However, the device is being used most frequently in children <20 Kg.¹² Various implantation options are available and the pump can be used to as a LVAD, RVAD, SVAD or BiVAD configuration. The EXCOR can only be used for inpatients in the U.S., but other countries allow patient discharge on a mobile driver. The Syncardia (t-TAH, Tucson, Arizona, USA) is a pulsatile, durable device that is intracorporeal and pneumatically driven. The device provides biventricular support following cardiectomy. In the pediatric and CHD population, it has played a role in many scenarios including support of the patient with graft failure post-transplant (as immunosuppression can be withdrawn after TAH implantation) and support of complex CHD including the Fontan circulation.⁴²⁻⁴⁴ Only two sizes of device are available, both FDA approved, one with 70 mL chambers and one with 50 mL chambers. The smaller device used in patients with a Body Surface Area (BSA) <1.5m.² The device was developed with intent to discharge patients post-implantation, and hence mobile drivers exist for use out of the hospital.

Continuous Flow Devices: Various paracorporeal, temporary pump heads are available that can be used to provide support of either or both ventricles in children. The most commonly used pumps are the RotaFlow (Maquet) centrifugal pump and the Centrimag/Pedimag (Abbott Laboratories) magnetically levitated devices. In either case, various cannulas can be used to surgically connect the pump head to the circulation allowing flexibility in application and the potential to initiate support without going on cardiopulmonary bypass. This flexibility makes these devices useful for both recovery and in challenging settings such as CHD. While these devices are by their nature temporary forms of support that require in hospital admission, they may be utilized as a long-term BTT or BTR.^{45,46} Other products exist as short-term circulatory support devices primarily targeted at circulatory rescue in adults. The TandemHeart is an intravascular device connected to a centrifugal pump that can be placed intravenously to support the RV with ejection to the pulmonary artery (or the LV through a trans-septal approach) and has been used in pediatrics as an extracorporeal device for Left Ventricular (LV) support and Single Ventricular (SV) support.^{47,48} The Impella (Abiomed) device, available in multiple sizes, is also an intravascular device with an axial pump designed to be placed across the aortic valve and into the LV to allow short term emergent ventricular support.⁴⁹ The Impella can also be used for RV support, although there is limited experience in pediatrics.

Various intracorporeal durable devices are available for adults and are also used (off-label in the U.S.) for larger children and adolescents in many countries. The current implantable continuous flow (CF) devices includes the axial flow, HeartMate II, (Abbott Laboratories, IL, US), centrifugal hydrodynamic flow HVAD System, (Medtronic, Minneapolis, MN, US) and centrifugal full-mag Lev HeartMate 3 (Abbott Laboratories). These devices are designed for long-term support and are implanted with the intention to discharge. The size of these devices limit their use in children and implantation is generally considered at >15 -20 kg (although smaller implantations have been described).^{50,51-53}

The HVAD device has been utilized more frequently in smaller children due to the size of the pump, although the new HM3 has gained attention in children due to its shorter inflow and favorable adverse event profile.^{53,54} Similar to the adult intracorporeal devices, a miniature CF axial pump, the Jarvik (Jarvik Heart Inc, New York City, New York, USA), is currently under study through an industry collaboration with the NIH (PumpKIN trial).⁵⁵

Key Points

- After the decision to place a VAD has been made, the next crucial step is to determine the level of support needed (LVAD vs SVAD or BiVAD in biventricular circulation).
- Important considerations for device selection include patient-device size matching; implant configuration (LVAD, SVAD or BiVAD); duration of support and support intent.
- VADs can be broadly characterized by duration of support (temporary vs durable), design (pulsatile vs continuous flow), or site of implantation (paracorporeal, intracorporeal, or intravascular).
- Currently intracorporeal CF devices are generally considered in children >15-20kg and use has been increasing over the last decade. The Berlin EXCOR is used mostly in children <20kg. The paracorporeal continuous flow devices are used in patients that may recover, those that need BiVAD support and as a BTT in some high-risk populations such as small children with CHD.
- TAH can be used in children but has mainly been used in unique situations such as complex CHD and transplant graft failure.

Operative management

Optimal surgical technique depends on the device and the patient's unique characteristics. In children, challenges due to anatomic and pathophysiologic variations remain.⁵⁶

Surgical Considerations: Achieving an ideal inflow configuration is vital and dependent on the patient's anatomy. When positioning an apical cannula, regardless of whether it is an intracorporeal or paracorporeal VAD, the cardinal rule is to position the inflow cannula parallel to the interventricular septum, facing the systemic AV valve. With dilated ventricles, apical cannulation is less challenging; however, in non-dilated hearts such as restrictive, hypertrophic cardiomyopathy or CHD this can be more difficult. In these cases, strategies to accommodate the LV apical cannula including extended LV myectomy, mitral valve leaflet/apparatus excision and even prosthetic valve removal have been successfully reported.⁵⁷ However, for the restrictive and hypertrophic diagnoses apical cannulation may not ideal due to contraction around the inflow cannula compromising flow. Alternatively, an atrial cannulation may be considered. This strategy also has the benefits of avoiding a ventriculotomy, and the use of CPB.⁵⁸ The next challenge

can be the outflow graft anastomosis to the ascending aorta due to the length and diameter of the vessels. Several modifications have been reported including the interposition of a vascular graft between the outflow cannula tip and the aortic wall or the innominate artery.⁵⁹ In general, the outflow graft cannula should be positioned as proximal as possible to aid with future transplantation; but making sure it does not impinge on the right ventricle especially with the EXCOR cannulae. Therefore, it should be placed about 45 degrees off the anterior surface of the aorta to the patient's right.

Pediatric alternatives to inflow implantation sites have include utilization of the diaphragmatic surface of the LV.⁶⁰ Such a technique may not be suitable in small pediatric hearts because of the risk of posterior descending coronary artery injury with the sewing ring and/or sutures.⁶¹ Some authors describe creation of a small pocket above the left hemi-diaphragm while coring the LV apex.⁶¹ Placing the pump in the pocket requires relocation of the LV apex medially and caudally, which orients the inflow cannula in a more vertical plane, parallel to the interventricular septum.⁶¹

For RVAD placement, there are three sites for potential implantation: (1) the right atrium (standard site for EXCOR), (2) the diaphragmatic wall or (3) the free wall of the RV. The location depends on the device and cannulas selected. The EXCOR cannulas are tunneled through the skin and secured on the RA free wall directly opposite the tricuspid valve. For all implant sites, correct orientation of the inflow cannula is crucial to ensure unobstructed flow into the pump. The outflow graft is tunneled through the skin and is anastomosed (with or without a graft extension) to the pulmonary artery.

Driveline and cannula exit sites are important to plan before incision. For the EXCOR, the LV apical cannula must exit at a few cm below the left costal margin at or lateral to the mid-clavicular line. The LVAD arterial outflow cannula exits a few cm below and to the right of the xiphoid process. An RVAD outflow cannula to the pulmonary artery would be to the left of the midline and the inflow cannula would exist to the right of the LVAD aortic cannula. For proper connection the cannula have to cross either outside the body or within the chest. The latter is rarely done and is in not practical in those less than 10kg. The crossing of the outflow cannulae externally on the upper abdominal wall results in the LVAD EXCOR pump laying upside down (blood side up) compared to the right pump. At least several cm of skin should be preserved between adjacent cannulae exit points to prevent erosion and breakdown. Furthermore, the Dacron cuff on each cannula should extend at least 1 cm beyond the skin exit site to allow for tissue in growth.

There are times when concomitant surgery must occur. The most common is aortic and atrioventricular (AV) valve repair. Presence of significant aortic incompetence should be addressed with replacement, repair or over-sewing at the time of VAD implantation regardless of chosen device. AV valve stenosis has to be avoided when implanting the inflow cannula into the ventricle but there are mixed reports of treatment of AV valve regurgitation including AV valve repair, replacement or removal.

In all pediatric VAD patients, determination of the presence of intra and extracardiac shunts is required.^{38,62-65} While some surgeons leave a small Patent Foramen Ovale (PFO) or atrial fenestration intentionally, especially in the Fontan patients, larger intracardiac communications should be closed either percutaneously or at time of VAD placement to avoid cyanosis.³⁸

Perioperative antimicrobial prophylaxis should be targeted to skin flora as the most likely contaminants of the surgical site. Limited data are available in pediatric VAD⁶⁶ and no randomized data exists looking at surgical prophylaxis for pediatric VAD. Recommendations are based on available guidelines, including ISHLT, for adult VAD therapy.⁶⁷

Key Points

- When evaluating for a durable VAD it is important to review cardiac morphology and physiology data, including the presence of shunts, collateral vessels, and the location and course of great vessels.
- In pediatric patients with residual shunting, shunt closure (exceptions may exist in the Fontan patients) should occur at the time of VAD implant.

Post-operative hemodynamic goals

Device settings should be optimized in the operating room with both TEE and hemodynamic monitoring before and after chest closure. After returning to the ICU, the primary postoperative goals are to obtain sufficient systemic perfusion and maintain normal systemic and venous pressure while avoiding VAD-related complications. Establishing appropriate device settings requires identification of physiologically appropriate CO goals as well as careful assessment of imaging and hemodynamic parameters. In biventricular physiology, the goal CI is commonly 2-3 L/min/m². In the case of single ventricle physiology, a much higher CO goal to achieve pulmonary venous unloading and optimal end-organ perfusion may be needed.⁶⁸

For the EXCOR, pump parameters should be manipulated to maintain a full device fill and ejection with each cycle. The maximal output of the device is calculated by the product of the device size (stroke volume) and set rate. The actual output is generally less, but difficult to accurately estimate given the volume of a half sphere is related to the radius to the third power. Several strategies targeting both the patient and the device can be employed to increase fill and thus increase output when desired. Decreasing the percent systole, the rate and diastolic pressure will increase the time spent in diastole and thus device filling, but this must be balanced by a commensurate increase in systolic pressure to ensure full device emptying. The broad availability of digital photography/video, particularly slow-motion, has emerged as a useful tool for assessment/troubleshooting.

For all of the CF devices, optimizing CO must be accomplished by optimizing preload and afterload while simultaneously preventing excessive leftward interventricular septal shift. Each pump is developed to function within a given range of power consumption for a given impeller/rotor set speed. When the relationship of these indices falls outside of that which is expected, an underlying etiology should be sought (excessive/ineffective pump speed, device thrombosis, device malfunction, etc.). Patient management should take into account the interaction between native cardiovascular system, physiology and device function. Though each device intrinsically has a unique pressure-flow response (H: Q) curve, all are innately sensitive to afterload. During diastole there is a large difference in pressure across the pump and therefore lower flow, while during systole the differences is smaller producing a higher flow state.

For BiVAD support, an imbalance can occur in flow of the pulmonary versus systemic circulation resulting in venous congestion upstream from the relatively under-supported circuit. As such, when RVAD output overwhelms that of LV support, pulmonary edema ensues. Alternatively, when LVAD support is in excess of RVAD support, hepatic, renal and digestive dysfunction may become apparent. Once biventricular support is balanced and unobstructed, the hemodynamic management is focused on avoidance of hypo- or hypervolemia and afterload reduction to achieve a normal CO.

Key Points

- EXCOR settings should be targeted to allow a full fill and ejection with each cycle, use of digital image capture with slow-motion can aid in the assessment of membrane movement.
- CF device support parameters should be individualized to physiologic support needs and optimized not only through changes in parameters but also manipulation of afterload and preload.

Anticoagulation management

Post-operative Hemostasis: Bleeding is a significant issue following VAD implantation. The risk for bleeding stems from disturbances in the coagulation profile in pediatric patients and are related to developmental hemostasis, heart failure cachexia, liver dysfunction, and coagulation factor/platelet consumption. Coagulation deficits including thrombin generation factors, adhesive proteins concentrations [fibrinogen and Von Willebrand factor (VWF)], and platelet function should be regularly assessed and normalized to stop bleeding. Thromboelastography (TEG) and ROTEM can diagnose specific deficits in the early post-operative phase. Factor deficiencies resulting from blood and volume administration must be avoided through concurrent use of blood products, coagulation concentrates, and other hemostatic agents guided by functional hemostatic evaluations. Anticoagulation may be considered only after achieving hemostasis.

Developmental hemostasis: There are qualitative and quantitative changes in hemostasis from fetal to adult life making following adult anticoagulation protocols difficult in pediatric VAD. For example, infants and adults may share similarities in size and numbers of platelets but their pharmacological responses vary. The response to agonists may be decreased in neonatal platelets compared to adults and more so in pre-term infants. However, despite blunted reactivity, infants compensate by having higher levels of VWF and multimers in addition to the higher hematocrit.⁶⁹ As well, in the neonate, the plasma levels of pro-coagulant factors (which are produced by the liver), including the vitamin-K dependent ones, are at approximately 50% of what an adult may have. This reflects the differences in neonatal and adult partial thromboplastin time (PTT).⁷⁰ Furthermore, the concentration of antithrombin (AT3), protein C and S are lower in infants compared with adults, and infants have a reduced ability to break down fibrin due to decreased levels of plasminogen. The changes in AT3 concentrations in neonates have led to difficulty with titration of heparin.

Anticoagulation and Antiplatelet Therapy: Historically, unfractionated heparin (UFH), low molecular weight heparin (LMWH) and vitamin K antagonists (VKA) have been the standard of care for paracorporeal and intracorporeal VADs in children.⁷¹⁻⁷³ However, there has been a shift towards increased use of direct thrombin inhibitors (DTI), namely bivalirudin, for anticoagulation, especially in the setting of paracorporeal VAD support.⁷⁴⁻⁷⁶ Centers have also reported modification of the traditional antiplatelet therapy, with weight-based dosing of anti-platelet drugs in paracorporeal PF devices being associated with lower stroke rate.⁷⁷

Monitoring of anticoagulation and antiplatelet therapy remains a challenge, with limitations surrounding the consistency and interpretability of all laboratory tests. UFH can be titrated using activated prothrombin time (aPTT) or anti-Xa level. LMWH is titrated to anti-Xa levels, while VKA is monitored via International Normalized Ratio (INR) with device specific ranges.^{73,78, 79} DTI can be monitored using aPTT and dilute thrombin time (dTT). The DTI appear to have more linear and predictable dose response curves.⁷⁸ In pediatrics, antiplatelet titration used to be heavily dependent upon Thromboelastography (TEG) with platelet mapping (TEG PM), however recent studies have demonstrated less dose response correlation with platelet mapping.^{80,81} VerifyNow and Platelet Function Analyzer-100 (PFA-100) have been used to assess antiplatelet agent resistance; however these have yet to be validated in a pediatric population.⁸¹ Many medications (i.e. Milrinone, nitroprusside and inhaled Nitric Oxide) used to support VAD patients have been shown to inhibit platelet function.⁸²⁻⁸⁴

Effect of inflammation and infection on anticoagulation: Due to the shared nature between inflammation and anticoagulation, derangement of the normal coagulation function can occur during infection/inflammation. There are several markers of inflammation that can be used clinically including white blood cell counts, platelet counts, C-reactive protein, fibrinogen, and the presence of fevers,

though it is not clear which marker is associated with the greatest likelihood of a bleeding or clotting complication. From a practical standpoint, the presence of fevers (in the absence of infection), elevated C-reactive protein levels, and elevated fibrinogen levels may lead to a change in anticoagulation or the addition of corticosteroids.^{77,85} While the data are limited regarding the efficacy of this therapy, there are small single-center studies that suggest steroids do decrease markers of inflammation and may decrease the incidence of stroke in patients on EXCOR support.^{85,86}

Key Points

- In North America, there is a shift towards the use of DTI therapy for paracorporeal VAD support in children.
- In EXCOR patients, post-VAD inflammation may increase the risk of thrombosis, bleeding and stroke and steroids have been used in small single center cohorts to treat the inflammatory state in an attempt to decrease the incidence of stroke.

Adverse events

See Table 2 from Pedimacs report for common adverse event rates.²⁶

Infection: Infection remains a significant complication following implant of VADs. These infections are grouped according to ISHLT infection guideline nomenclature⁶⁷ as non-VAD (i.e. pneumonia), VAD-related (i.e. infective endocarditis or mediastinitis) or VAD-specific infections (driveline infections (DLI), pocket infections and pump

infections).⁸⁷ Infections account for about 17% of all the adverse events (AE) with these events more commonly occurring >3 months post implant and accounting for nearly 1 out of 3 of readmissions following discharge.^{66,88,89} Identified risk factors of infections have included: time on device, prior infection and prior non-infectious adverse events.^{66,88} Single-center studies report that approximately 15% - 50% of patients will develop a DLI.⁹⁰⁻¹⁰⁰ The EXCOR trials suggest that while infections overall are common (occurring in 41% - 63% of patients), cannula infections are less common (0% -17%).^{71,101} While early reports suggested that infection was not associated with decreased survival, recent data from Pedimacs suggests an increased mortality with infection in patients on CF devices.^{66,102} In the Pedimacs data, 77% of infectious AEs were treated with intravenous antibiotics, 11% with oral therapy and 8% required both surgical and antimicrobial therapy.⁶⁶ Adult-focused recommendations suggest management be based on the site and extent of the infection with consideration for secondary prophylaxis in some patient awaiting transplantation.⁶⁷ Prevention of VAD-specific infections relies primarily on infection control principles.⁶⁷

Right Ventricular Failure (RVF): RVF is manifested by elevated CVP, liver dysfunction, ascites, and renal injury. It usually occurs within 2 weeks of LVAD implant and is associated with both morbidity and mortality.^{103,104} In adults, early RVF is defined as use of inotropes > 14 days, inhaled nitric oxide > 48 hours or unplanned RVAD. Incidence of early RVF in adults with CF-VADs is 15% to 40% but may be lower in children.^{32,105-108} Etiology of RVF is multi-factorial with contributing factors including shift of

Table 2 Adverse Event Rates from Pedimacs 3rd Annual Report²⁶

Event	Period ^a	Overall		Paracorporeal Pulsatile			Paracorporeal Continuous			Implantable Continuous		
		Patient Percent (%)	Rate ^b	Patient Percent (%)	Rate ^b	Device Incidence ^c (%)	Patient Percent (%)	Rate ^b	Device Incidence ^c (%)	Patient Percent (%)	Rate ^b	Device Incidence ^c (%)
Bleeding	Early	27	2.7	25	1.9	27	38	6.5	30	23	1.9	28
	Late	5	0.3	3	0.4		1	0.4		8	0.2	
Infection	Early	24	2.2	23	2.3	26	28	4.4	24	22	1.6	30
	Late	9	0.7	8	1.2		3	1.3		13	0.6	
Device malfunction	Early	20	2.4	27	3.8	33	32	7.3	30	11	0.6	19
	Late	7	0.6	11	1.7		1	0.4		9	0.4	
Neurologic dysfunction	Early	23	1.8	27	2.3	33	37	4.6	29	15	0.9	18
	Late	5	0.3	6	0.6		3	0.9		6	0.2	
CVA	Early	11	0.8	18	1.3	19	13	1.4	10	8	0.5	10
	Late	2	0.1	3	0.2					4	0.1	
Ischemic stroke	Early	8	0.5	13	0.9	13	9	0.9	8	5	0.3	6
	Late	1	0.08	1	0.07					2	0.08	
Hemorrhagic stroke	Early	4	0.2	5	0.4	6	3	0.4	3	3	0.2	5
	Late	1	0.07	2	0.1					2	0.05	

^a Early: within 3 months after implant; late: beyond 3 months after implant. ^b Rates are reported per patient-year. ^c Device incidence indicates overall percentage of patients within the device group experiencing the specified event.

CVA = cerebrovascular accident.

the interventricular leftward, increased RV preload, and arrhythmias.^{104,109}

A major pre-operatively goal is to implant LVAD before RVF develops, and, if already present, to optimize RV hemodynamics before LVAD implantation.^{104,110} Aggressive pre-operative management of patients with RV dysfunction should focus on diuresis (goal CVP < 15 mmHg), institution of milrinone ± epinephrine for contractility, and pulmonary vasodilators to reduce RV afterload.

Intra-operatively, TEE monitoring of RV function should occur during LVAD implant.¹⁰⁴ Strategies to preserve RV function include: maintenance of adequate blood pressure, avoidance of pulmonary vasoconstriction and use of pulmonary vasodilators, use of continuous ultrafiltration during bypass, minimization or avoidance of cross clamp time, judicious use of blood products, arrhythmia control, consideration of delayed sternal closure, and maintaining the septum in a midline position.¹¹¹⁻¹¹⁴ If RVF occurs, elective early rather than delayed emergent mechanical RVAD support has been associated with improved outcomes.¹¹⁵⁻¹¹⁷ Such short-term RV mechanical support options include paracorporeal CF VADs, percutaneous VAD, and ECMO; long-term RV support includes biventricular durable intracorporeal CF, TAH, or PF VAD devices.^{118,119} Post-operatively, signs of RVF include decreased LVAD flow, suction events and decreased CO, acute kidney injury, and hepatic dysfunction. Management should incorporate aggressive use of pulmonary vasodilators as well as inotropes for RV CO support and avoidance of bradycardia until RA pressures are near normal. RV preload should be optimized with diuresis or hemodialysis to maintain CVP < 15 mmHg. Maintenance of sinus rhythm should be aggressively pursued.

Pump thrombosis (PT): PT is a less common but a significant complication of VAD therapy. It results from a variety of patient and pump factors and can develop slowly over time or have a rapid onset. The definitions and recognition of PT vary by device type with the current EXCOR pumps allowing visual inspection and intracorporeal pumps requiring a combination of abnormal VAD parameters, lab values consistent with hemolysis or symptoms of HF; with conformation only occurring if the pump is removed. Symptoms of hemolysis can include scleral icterus, dark urine (hemoglobinuria), and fatigue with signs including one or more of the following: elevated serum Lactate Dehydrogenase (LDH) (most sensitive marker), elevated plasma free hemoglobin, and low haptoglobin.¹²⁰ Recent studies have shown the rate of PT in adults to be 4-8% in HeartMate II and HeartWare^{121,122} and 1% in the HM3 device.¹²³ PT in the pediatric patients with a CF-VAD occurs in 11% - 44% of patients, with the largest series reporting a rate of 15%.^{10,51,52,124}

Management of PT in adults has largely been based on expert opinion with published algorithms focused on both the device type and presentation.^{125,126} These algorithms focus on both medical and surgical interventions, with medical management including augmentation of anticoagulation (ex: Heparin or Bivalirubin) or antiplatelet agents (oral or intravenous), use of thrombolytic therapy and surgical management including pump exchange, heart transplant

(HT), or explantation.¹²⁵⁻¹³⁰ The choice between medical and surgical management depends on device type, stage of pump thrombosis, clinical presentation and potential complications of treatment. As there are few reports in children, it is unclear whether these strategies are applicable to pediatrics. One potential approach in pediatrics is to initiate heparin or Bivalirudin with rising LDH with or without changes in pump parameters. If no response and ongoing increases in LDH with changes in the pump parameters, in some institutions, low dose systemic tPA could be considered if no contraindications exist.¹²⁸ Lastly, if there are contraindications to tPA, evidence of rapid progression or no response to any of the above treatments, pump exchange should be considered.¹²⁸ In some institutions pump exchange occurs without a trial of tPA.

Neurological Events and Stroke: Device-related neurological events (NE) as defined by INTERMACS include: cerebrovascular accidents (CVA), seizures, encephalopathy, asymptomatic neuroradiological findings, confusion and extra-axial bleeding. Using this definition, NE comprise 12% of all adverse events and tend to occur early (23% within 3 months vs 5% thereafter).¹²⁴ NE are more common in PF VADs (early 19.6 and late 5.6 events per 100 patient-months) vs. CF VADs (early 4.1 and late 0.7 events per 100 patient-months). However, patient characteristics differ between those receiving PF vs CF devices and in turn event rates are likely not solely related to device type. Ten percent of patients with intracorporeal CF devices had strokes, compared to 24% among paracorporeal CF and 21% among PF devices with most being ischemic.^{26,45,51} The ACTION Network has recently undertaken a multi-center quality initiative (QI) to decrease stroke rates through use of standardized blood pressure goals, meticulous anticoagulation including DTI and improved communication between teams.^{77,131}

Additionally, VAD-related stroke management has challenges in pediatrics due to lack of standardized protocols. The ACTION Network has recently developed a stroke management bundle aimed at developing algorithm for pediatric stroke management. This emphasizes early recognition of stroke symptoms as critical, urgent neurological evaluation including a non-contrast head CT (within 30 minutes). If non-contrast head CT is negative but neurological symptoms persist, consideration should be for a CT angiogram. Institution of neuroprotective measures, intracranial pressure monitoring and potential interventions including thrombectomy or cranial decompression may be considered. In setting of ischemic stroke with evidence of vessel occlusion and large territory involvement, thrombectomy or intravenous tPA may be potential options for intervention.¹³²⁻¹³⁴ For patients with paracorporeal VAD, pump exchange should be considered if there is evidence of a clot. Anticoagulation management after VAD-related CVA is challenging. If invasive interventions are being considered, or for large territory ischemic strokes with high risk for hemorrhagic conversion, holding and potentially reversing anti-thrombotic therapy should be discussed. In setting of hemorrhagic stroke, if bleeds are small without neurological deficits, antithrombotic therapy should be held and

resumed if stable neuroimaging and neurological exam. However, if there is interval expansion or large hemorrhagic involvement, antithrombotic therapy should be held and potentially reversal. Timing of re-initiation of antithrombotic therapy should be discussed among care team with consideration of repeat CT after initiation.

Bleeding : Bleeding is a major complication of VAD implantation and affects approximately 30% of pediatric patients.^{2,124} The highest hazard for bleeding is in the immediate perioperative period when patients are extremely susceptible from suture lines and dissection planes.^{2,124} Bleeding is diagnosed when chest tube output is excessive and drops in hemoglobin necessitate transfusion. Bleeding can lead to pericardial tamponade when blood is not adequately evacuated via chest tubes. In LVAD patients, the initial clinical presentation of pericardial tamponade is typically an increase of CVP, followed by a decrease in LVAD flow (depending on the amount of RA/RV compression). As a consequence, blood pressure is usually decreased and frequently vasoactive substances have to be initiated or increased. Other clinical signs for the impaired hemodynamic state are decrease in urine output and rise of serum lactate. The clinical presentation of tamponade in BiVAD patients can be very vague. Often, only an increase of CVP is initially observed which can early on be accompanied by a decrease of urine output (due to elevated CVP). Adequate hemodynamics can be obtained for a long time, depending on adequate volume replacement and VAD flow only decreases when venous return is severely compromised by compression. The threshold for surgical revision usually is persisting chest tube output despite normalization of coagulation parameters. Hemodynamic instability or tamponade should prompt immediate surgical exploration.

The hazard for bleeding decreases with increasing support times.^{2,99,124} While perioperative bleeding usually originates from areas affected by the VAD implantation, late bleeding events typically affect other regions and are a consequence of medication levels and vWF degradation that is a result of VAD induced blood trauma. The most frequent source of late bleeding is the gastrointestinal tract, although less frequent than the adult population.¹³⁵

Support strategies for unique pediatric populations

CF VAD in small patients: The encouraging outcomes in adult VAD technology have had a profound impact on its use in children. In children, with a weight >15-20 kg requiring VAD, the use of an implantable LVAD may be feasible with results that are non-inferior to the extracorporeal devices,^{65,136,137} and discharge from the hospital is possible, resulting in a better QoL,^{10,65,136,138-140} decreased costs,¹⁴¹ and the potential for chronic therapy. It remains unclear what the size cut off is for the use of these devices in smaller children.¹⁴²⁻¹⁴⁵ The limited thoracic space might not be large enough to ensure proper position of an intra-corporeal device. Distortion of the rotor housing can position the inflow cannula in a plane that significantly increases the risk of inadequate

drainage, suction events and/or pump thrombus formation. If necessary the pump housing may be placed in a pre-peritoneal pocket fashioned by dividing the left diaphragm anteriorly⁶¹ or to allow the device to sit within the left pleural cavity, caudal to the left lower lobe and posterior to the diaphragm at the costo-diaphragmatic angle. In smaller patients, not only the angle of the inflow cannula, but its depth in the ventricular cavity should be considered. If placed in a small heart, the tip of the inflow cannula may approach the mitral valve, which could either impede mitral valve function or, importantly obstruct the inflow cannula. Therefore LV apex to mitral valve distance must be precisely measured on preoperative imaging.^{146,147} Of note, the newer HM3 has a shorter inflow when compared to the HVAD (22 mm vs 32.2 mm).⁵⁵ Alternatively, if the mitral valve is obstructing inflow, excision of the valve may be considered with a CF device.

Muscular Dystrophies (MD): HF is a significant cause of mortality in patients with MD.¹⁴⁸ Patients with MD are often not candidates for HT because of the progressive nature of their multi-system disease, affecting pulmonary, neurological functioning and mobility. Some centers have reported the use of DT VADs for medically-resistant HF in these patient groups.^{25,149} The use of DT in these patients require ethical and local institutional considerations.¹⁵⁰

Chemotherapy-Induced Cardiomyopathies (CCMP): Improvements in oncologic therapies has increased life expectancy and cure rates for many types of cancer. The cardiotoxicity risk of many chemotherapeutic regimens are well documented.^{151,152} VADs have been used for DT in patients with CCMP, or for BTT in patients with sustained remission. Pediatric data is limited and consistent with this being an uncommon indication for VAD therapy or HT.^{153,154} In adult populations, it is estimated that 2% to 3% of patients undergoing VAD have CCMP.¹⁵⁵ Considerations including the increased risks related to RV dysfunction, bleeding and sternotomy after radiation therapy should be noted prior to VAD implantation.¹⁵⁵

Support Strategies for Adult Congenital Heart Disease (ACHD): The prevalence of HF in ACHD is diagnosis-specific, increases with age¹⁰ and exceeds that in the general population.¹¹ HT has been the optimal therapy for end-stage HF in ACHD.²²⁻²⁵ Experience is limited using VAD and/or TAH in ACHD patients as a bridge to transplant. Overall, <1% of all VADs in adults are implanted in ACHD patients. Nevertheless, ACHD patients spend more time awaiting HT^{21,26,27} and the sickest are more likely to deteriorate while awaiting HT than the non-ACHD population.^{28,29} In this setting, VAD support has the potential for benefit in the ACHD population^{26,30} without impacting post-transplant outcomes.³¹ Earlier use of VAD therapy may help to decrease the early hazard associated with HT among ACHD patients by decreasing end-organ dysfunction and relieving pulmonary hypertension secondary to CHD.¹⁵⁶ Although ACHD patients that receive VAD have an earlier rate of mortality post VAD they have similar rates of adverse events and improved functional capacity if they survive the first 30 days.¹⁵⁷

There are times when an underlying anatomical issue leads to HF in a patient with ACHD and in these cases

correction of the underlying lesion if possible and utilization of temporary MCS strategies to support the patient perioperatively should be considered. This approach has been shown in select cases to lead to excellent outcomes avoiding long-term VAD support and HT.³² Durable VADs may still be required despite best efforts to address the etiology of ventricular failure. Underlying lesions should be corrected at the time of VAD implant including uncorrected shunts, stenotic lesions of the left AV valve and regurgitation of the aortic valve to allow optimal VAD function. If multiple residual lesions requiring surgical intervention are present or BiV support may be necessary, consideration should be given to the use of a TAH.

Use of VADs in patients with a morphologic systemic LV is generally more conventional and fits the paradigm of non-CHD patients. Still, additional obstacles must be appreciated such as dextrocardia/heterotaxy syndrome and the risk of multiple sternotomies should not be underestimated. Furthermore, the possible need for BiV support should be assessed during surgical planning and be available in the operating room. Adults with a morphologic systemic RV and a sub-pulmonary morphologic LV typically have a diagnosis of either D-TGA following atrial switch or unrepaired ccTGA, or ccTGA following physiologic repair. The systemic RV is predisposed to systemic atrioventricular valve regurgitation (AVVR), ventricular dysfunction, and pump failure. Outcomes of VAD support for systemic RVF are limited to case series, but survival appears to be acceptable.³⁵⁻³⁷ Implantation may be complicated by changes in RV anatomy; the free wall and septum are much thicker and more trabeculated than in a normal RV. For intracorporeal CF-devices three different implantation sites for the RV that have been reported: diaphragmatic,^{158,159} free wall¹⁵⁸ and right atrium (RA).¹⁶⁰ In patients after Mustard/Senning operations, the free wall of the systemic ventricle is easily accessible. Diaphragmatic implantation can be technically more challenging, thus carrying a higher risk of bleeding. With a ventricular inflow position, excision of muscular trabeculae including the moderator band from the inflow cannula site may be necessary.^{161,162-164} If the RA is chosen, correct orientation of the inflow cannula is necessary with the inflow cannula being positioned toward the tricuspid valve orifice so that unobstructed flow is possible. Resection of valve leaflets might be necessary to ensure unobstructed flow towards the inflow cannula.

Key Points

- Patients with ACHD, refractory to medical management should be evaluated for MCS early before progression of end-organ dysfunction.
- Although ACHD patients have a higher earlier mortality rate they have similar adverse event rates and improvement in quality of life when compared to non-ACHD patients.

Support strategies for single ventricle patients

There is a wide range of CHD that result in single ventricle physiology.¹⁶⁵ In the single ventricle, myocardial injury, hypertrophy, fibrosis and dysfunction often result from multiple, cumulative insults which may include volume loading, pressure loading, chronic cyanosis, coronary ischemia, chronic upregulation of the renin-angiotensin-aldosterone system, chronic underfilling and overlapping genetic factors that cause CHD and cardiomyopathy.¹⁶⁶⁻¹⁷² By the age of 6, 14% of HLHS patients who have undergone the Norwood operation will develop severe HF and HF is the most common cause of death for Fontan patients.^{169,173} In single ventricle patients with severe, progressive ventricular dysfunction, significant AVVR and HF refractory to maximal medical therapy, SVAD support can be considered.

Pre- or post- stage 1 palliation support strategies: HF secondary to dysfunction or AVVR, intractable arrhythmias, RV or LV-dependent coronary circulation with evidence of ischemia or large coronary fistulae may be used as criteria for SVAD. Successful use of paracorporeal CF (Pedimag/Centrimag, Rotaflow) or PF VADs (Berlin Heart EXCOR) have been described though overall outcomes remain poor.¹⁷⁴⁻¹⁷⁶ There is increasing use of the paracorporeal CF devices with more durable cannulation in this population.¹⁷⁵⁻¹⁷⁸ Inflow cannula is typically placed in the common atrium post atrial septectomy and the outflow cannula is placed into the ascending neo-aorta post Norwood operation^{174,175} or pulmonary artery after hybrid palliation (which may require graft extension) in HLHS.^{174,177} The outflow cannula is placed in the aorta in PA/IVS both prior to or after shunt placement.¹⁷⁵ VAD support after the Norwood operation requires pulmonary blood flow from either an aortopulmonary or Blalock-Tausig (BT) shunt.^{175,179} Therefore if a RV to PA conduit exists, it needs to be taken down. Following implant, a higher-than-expected cardiac index is often required to maintain the parallel systemic and pulmonary circulations with some centers reporting goals of approximately 4-6 L/min/m.^{174,175} The balance of pulmonary and systemic circulations (Qp/Qs) and shunt size need to be carefully considered, as a grossly imbalanced Qp/Qs will not be remedied with a higher CI alone.

Post-stage 2 palliation (superior cavopulmonary anastomosis or Glenn operation) support strategies:

Indications for SVAD after stage 2 include poor ventricular systolic or diastolic function or AVVR with signs of HF. Complete understanding of the etiology of symptoms, hemodynamics and presence of aortopulmonary and venovenous collateral vessels is critical. Successful use of PF (EXCOR)^{180,181} and CF VADs (both implantable and paracorporeal)^{182,183} have been described and device selection depends on patient size and center experience. The inflow cannula can be placed in the systemic ventricle or common atrium¹⁸² and the outflow cannula is placed in the ascending aorta. Cyanosis can persist and worsen post-VAD due to right to left shunting from the IVC when there is atrial cannulation or from venovenous collaterals. To improve pulmonary blood flow, centers have described

reverting back to Stage 1 circulation at the time of VAD implant by taking down the superior cavopulmonary anastomosis and placement of an aortopulmonary or BT shunt.¹⁸³ Alternatively, others have described for those larger bidirectional Glen patients (usually greater than 2 years-old) successful concomitant Fontan completion and VAD implantation.¹⁸⁴ In either situation higher than expected VAD flows are often required if there is systemic-to-pulmonary blood flow. CF devices are thought perhaps to work better in unrepaired SV, Post stage 1 or 2 patients because of the minute to minute changes in inflow volume flow from systemic to pulmonary shunting (e.g. BT shunt, AP collaterals) to which these devices can respond to unlike the fixed volumes of the EXCOR.

Fontan patient: Fontan physiology can result in chronic low CO and systemic venous congestion.¹⁷¹ There are different clinical phenotypes of Fontan circulatory failure including decreased systemic ventricular systolic and/or diastolic function and elevated CVP. Patients can present with Fontan circulatory failure with or without ventricular dysfunction. Those without ventricular dysfunction may manifest by intractable protein-losing enteropathy (PLE), plastic bronchitis (PB), and/or signs of significant end-organ congestion which are associated with morbidity and mortality.^{185,186} Long-term, sinus node dysfunction/arrhythmias can also contribute to Fontan patient's morbidity.¹⁸⁷⁻¹⁹¹

Treatment options for the Fontan patient with circulatory failure include: optimization of medical therapies and consideration for surgical options, including Fontan conversion for atrio-pulmonary connections, Fontan fenestration, and heart or heart-liver transplantation.¹⁷¹ While outcomes for transplantation in Fontan patients have improved,¹⁹² a shortage of available donor hearts results in long wait times and waitlist mortality, as well as worse HT candidates that adversely impacts post-transplant outcomes. Given donor shortage, there are many reports in recent years (2014-2019) of SVAD support for Fontan patients as BTT.^{42,180,184,193-203} There are also case reports of DT SVAD support for Fontan patients,²⁰⁴ as well as VAD support of the pulmonary circulation.²⁰⁵ Additionally, SVAD support in Fontan patients as bridge to combined multi-organ (heart-liver, heart-kidney) transplant have not yet been reported.

VAD referral and pre-VAD evaluation should include the standard VAD assessment and additionally focus on potential anatomic and physiologic barriers to SVAD support. Timing of referral is important to VAD outcomes. Consensus from the ACTION network about referral timing can be found on www.actionlearningnetwork.com. Increasingly recognized is the multi-organ disease associated with long-term Fontan physiology, which should be evaluated alongside traditional cardiac assessment in preparation for either SVAD support or HT.¹⁷¹

Indications for SVAD include poor systemic ventricular systolic or diastolic function and/or AVVR with signs of HF. VAD support is unlikely to be useful for Fontan patients with PB or PLE with preserved ventricular function, competent AV valve and normal filling pressures.

Durable CF^{184,193-198, 204} and PF devices,^{180,198-201} as well as temporary support devices,²⁰² have been used in Fontan patients as BTT. Recently, there has been increasing use of durable CF devices including the HeartMate 3¹⁹⁷ and HVAD.^{184,193-196,198,204} PF devices (EXCOR) should be considered for patients who cannot receive a durable CF device (typically due to size).^{180,198-201} Right and left sided ("biventricular") support has been reported using the TAH⁴² or BiVAD support (with EXCOR¹⁹⁹ or HVAD¹⁹⁴).

Inflow cannula is placed either in the systemic ventricle^{184,193,194,196-198,200,201} or common atrium^{195,196,198}; resection of trabeculations may be necessary, especially for systemic RVs.^{184, 193,197} Resection of the AV valve has been reported in some cases.^{193,195} Mechanical AV valves can be left intact, or resected.¹⁹⁵ Outflow graft is typically anastomosed to the aorta/neo-aorta in the standard manner; bioprosthetic aortic valve replacement¹⁹⁶ or partial/complete closure of the aortic valve²⁰³ may be considered if aortic regurgitation is a concern. Fontan fenestrations are closed (to decrease thromboembolic risk) by some centers, but others have found that if left open^{193,197} or created²⁰⁰ they will allow for greater unloading of systemic venous system, particularly if there are concerns for pulmonary vascular disease. Fenestration has anecdotally not caused excessive cyanosis and the saturation post VAD placement may increase significantly even if the fenestration is present because of the overall increase in cardiac output and decrease in central venous pressure which leads to decreased flow through the venous collaterals.

MCS in Fontan patients has become more prevalent recently. The multicenter data that is available includes a recent report of adult VAD support from the INTERMACS registry. In that report there were 17 VAD-supported adult Fontan patients among whom there was no difference in survival between VAD supported single ventricle subjects and those with biventricular congenital heart disease.⁶⁵

Key Points

- To support stage 1 patients with parallel circulations, SVAD flows to achieve a higher cardiac index are often required and a balanced Qp/Qs is crucial.
- In stage 2 patients, converting to shunted or Fontan physiology at the time of SVAD implant may be considered for improved pulmonary blood flow.
- There is increasing experience and success using durable VADs to support Fontan patients with HF due to systemic ventricular dysfunction.

Discharge of the pediatric patient on a VAD

Advancements in VAD technology have allowed for improved survival, QoL, and the potential to achieve hospital discharge. Despite these advancements, fewer than 60% of children with intracorporeal CF devices are discharged in the US or Europe.⁸⁸ Suitability for safe discharge depends on (1) medical stability, (2) a suitable social

context including the presence of caregivers who can be trained to recognize and manage acute device and medical concerns and (3) the ability to access appropriate medical care in the community in a timely fashion.²⁰⁶ The latter, in turn, requires consideration of proximity to medical care, appropriate training of emergency response and hospital emergency staff, and well-defined pathways for access to the VAD team.²⁰⁷

As with most medically complex patients, discharge planning for a pediatric VAD patient should begin early, ideally at initial evaluation. This allows the multidisciplinary team to evaluate the patient, the family structure, and available resources to develop an understanding of the potential to achieve discharge. This evaluation allows for early recognition and resolution of potential barriers and setting expectations. Figure 2 is a discharge roadmap from ACTION, which can be posted in the patient's room and allows the team and family to visualize progress.

In general, providing a clear training schedule for both the child and the family consisting of short and frequent training sessions facilitates effective training. Training may employ a combination of didactic teaching, reading materials, and hands on training to practice skills such as battery changes, controller changes and self-testing. If local resources permit, modalities such as online training, and case-based simulation training have been effective vehicles for training in some centers though published literature is limited.²⁰⁸

It is expected that a caregiver who can troubleshoot acute VAD alarms or complications and initiate an appropriate response always accompanies a pediatric patient. Considerations should be made for the teenage VAD population who can gradually be trained to be more independent in certain settings such as school. Simulation scenarios have been developed to ensure the child and family are comfortable prior to discharge and ongoing education should be offered at designated times post discharge.

Outpatient Team: The VAD coordinator often serves as a key point of contact. Unlike adult VAD programs, the low center volumes lead to a decrease in local experts making it even more important to have a team member on call to troubleshoot any acute issues. Outpatient surveillance should routinely include monitoring anticoagulation and markers of hemolysis; assessment of blood pressure; inspection of driveline and equipment; and periodic echocardiograms for optimization of VAD settings.

Readmission: Pedimacs data as well as several small series have shown that a majority of discharged VAD patients are readmitted for reasons such as driveline or other infections, anticoagulation management, suspected pump thrombosis, and device malfunction or alarm.^{10,140,206}

Preparing for transplantation

Sensitization while on a VAD: The development of anti-HLA antibody after VAD has been reported in adult and pediatric patients.^{209-222,223-225} While it is clear that patients on VAD support have a transient increase in anti-HLA antibodies it remains unclear how VAD-related sensitization impacts waiting list and transplant outcomes.^{223,224,226,224,227}

However, despite higher sensitization in VAD patients, the post-transplant outcomes for pediatric VAD patients are equivalent to non-VAD patients.

Rehabilitation after VAD: A prolonged time for VAD recovery and cardiac rehabilitation (CR) before listing for HT has led to improved outcomes in some studies.^{228,229} CR is safe and effective after heart surgery, including LVAD placement, in both children and adults.^{89,230-234} A structured, multidisciplinary approach improves functional capacity as measured by peak $\dot{V}O_2$ and 6-minute walk distance,^{231,234} peak heart rate with exercise,²³¹ and patient-reported QoL.^{230,231,234}

Physical and occupational therapy should start early in the ICU with achievement of hemodynamic and respiratory stabilization.²³² Range of motion exercises can be performed safely in the first few post-operative days with progression to sitting in a chair, standing, and walking.²³² Patients should be encouraged to leave the acute care floor and travel to the rehabilitation gym with VAD-trained staff at the discretion of the VAD team. Early understanding of specific debilities and attainable goals is necessary for creating an effective personalized rehabilitation prescription.

While frequency and duration vary, a common program structure consists of 2-3 therapy sessions per week for 8-12 weeks.^{231,235} Goals of therapy include improvement of functional capacity, return to age-appropriate activities of daily living, and increased patient and parent-reported QoL. Attention is also given to nutritional education, regular at-home exercise, and psychosocial recovery. Despite the clear benefits, CR attendance rates are low due to session frequency and distance from home.²³¹ This reality has led to the discussion of home-based therapy, where patients demonstrate competency with therapies at a rehab center before finishing the remainder of CR at home. Home-based rehabilitation is an attractive option for VAD patients due to a paucity of pediatric rehabilitation sites outside of the implanting center.

Listing for transplant after VAD: An evolving area of practice is the timing of listing for HT after VAD placement. The classical approach is to activate a patient on the transplant list simultaneously with VAD placement to reduce exposure to potential VAD complications that could alter transplant candidacy. Lower adverse event rates seen with CF-VADs have led some centers to optimize post-VAD recovery prior to activation on the HT waiting list and may be associated with better HT outcomes.²²⁸ Consideration may be given to delaying listing for transplant to allow for rehabilitation, this is especially true after implantation of a durable CF LVAD. Should such a paradigm be utilized, it is imperative to maximize physical, nutritional, and psychological healing and CR during the recovery interval. This recovery period also provides time for reverse cardiac remodeling in which myocardial function may improve, allowing VAD explantation in selective cases.²³⁶ At present, there is insufficient data for which wait list strategy optimizes patient outcomes. However, it is clear that pediatric patients with intracorporeal CF VADs are being supported for longer periods of time with 20% being supported greater than a year.

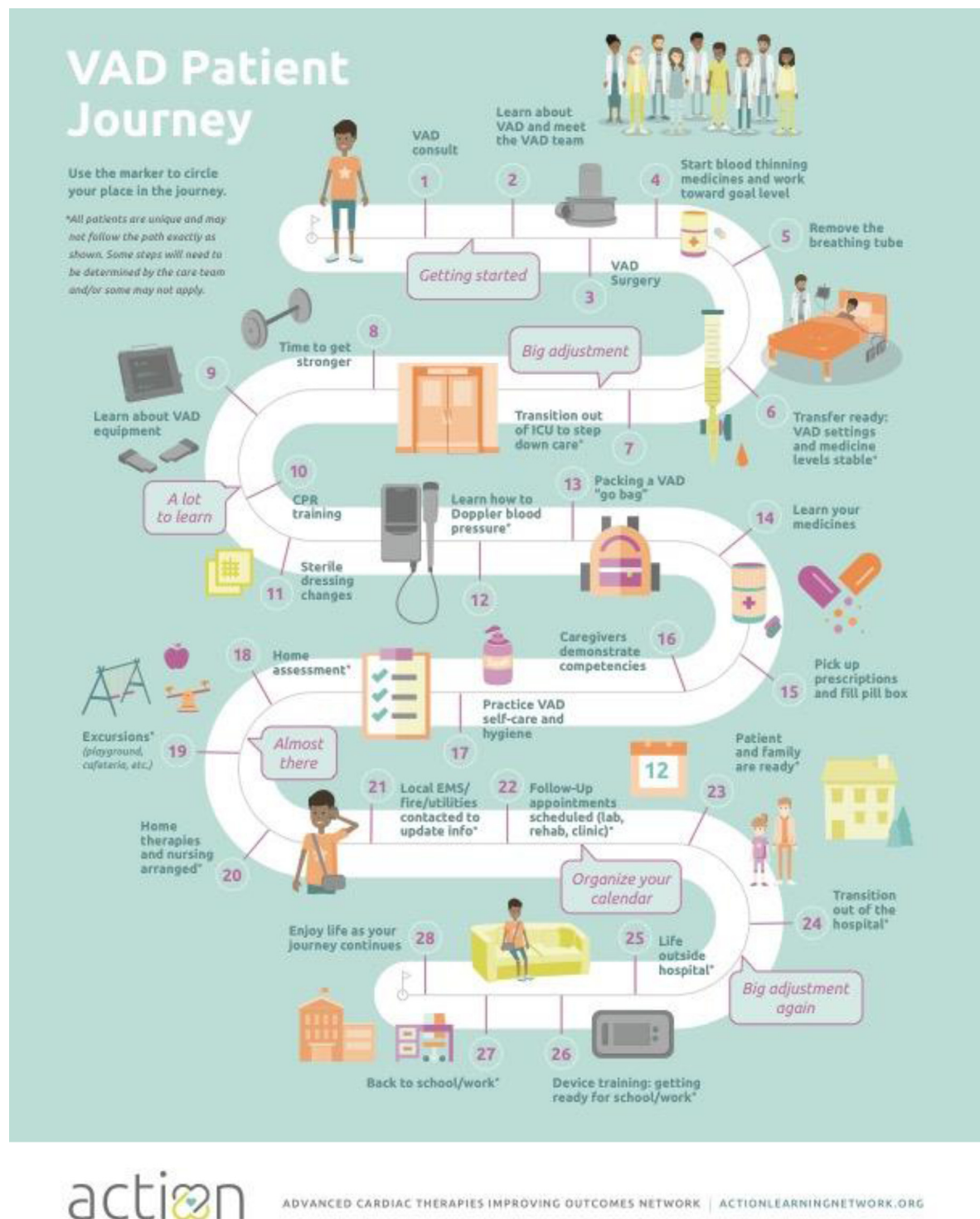


Figure 2 Discharge journey map from ACTION network (www.actionlearningnetwork.org) for patients on CF VADs.

Optimizing nutrition to improve post-transplant outcomes: Children with HF are often underweight as a result of poor appetite, increased metabolic demands of the failing heart, neurohormonal activation from heart failure, and poor gastrointestinal perfusion. VAD support provides a window for optimization of nutritional status prior to HT. BMI less than the 5th percentile at the time of HT is an independent predictor of decreased graft survival,²³⁷ though that finding is not universal.²³⁸ A recent OPTN registry study demonstrated that BMI > 95% or <1% were

independent risk factors for waitlist mortality in children with cardiomyopathy, but BMI did not influence post-transplant survival.²³⁹ Nutritional status stratified by the percentage of ideal body weight at listing or at HT in children aged < 2 years was associated with the increase in waitlist mortality, but not associated with post-transplant outcomes (mortality rate, the incidences of infection, stroke or rejection before hospital discharge).²⁴⁰ Children less than 1 year of age with hypoalbuminemia (< 2.0 g/dL) have worse post-transplant survival.²⁴¹ VAD utilization in children

with advanced HF allows for improvement of hemodynamics, symptoms, and nutrition prior to transplant.²⁴² Children on VAD (EXCOR or HVAD) have been shown to have greater improvement in nutritional status while awaiting transplant than non-VAD supported candidates.²⁴³

VAD explant for transplantation: Each VAD patient should have a peri-operative plan established at the time of transplant listing. LVAD patients are at increased risk of post-transplant vasoplegia and consideration should be given to holding vasodilator medications such as ACE inhibitors or ARNIs.^{244,245} Anticoagulation management should aim to reverse anticoagulation prior to skin incision when possible.

Post-transplant survival after VAD

Children supported with the EXCOR had equivalent 1- and 5-year post-transplant survival, infection rates and rejection rates when compared to children who did not receive VAD support in CHD and non-CHD patients.^{246,247} A linkage analysis of patients enrolled in Pedimacs and Pediatric Heart Transplant Society (PHTS) demonstrated similar post-transplant survival, freedom from infection, and freedom from rejection between VAD and non-VAD HT recipients.²⁴⁸ Morbidity related to end-organ function may also be mitigated by VAD support. Lower eGFR at VAD implantation and failure to normalize eGFR during the VAD support period are risk factors for post-transplant chronic kidney disease.²⁷ Transplant center procedural volume does not appear to influence 1-year post-transplant survival among children BTT with VAD.²⁴⁹

Key Points

- Testing for anti-HLA sensitization should occur in patients on VAD support listed for HT with the understanding that some antibodies may only be present transiently and has not seem to effect post-transplant outcomes.
- Cardiac rehabilitation should begin early post-operatively and advance to a multidisciplinary approach with the goal of whole-body rehabilitation for HT or explantation when possible.
- Nutritional status should be optimized for all patients both before and after VAD implantation.

End of life care of the pediatric patient on VAD

As VAD outcomes have improved in pediatrics, the focus is no longer upon survival. Children are expected to survive their VAD support course and there has been a recent focus on their QoL. This has been the case in adult VAD literature as well, with an increasing number of centers assessing QoL before, during, and after VAD support, using patient reported outcome (PRO) tools.

Communication with patients/families about VAD care, risks/benefits, and prognosis is critical. Although these conversations can be challenging, pediatric cardiologists

believe they should have primary responsibility for such discussions and generally feel comfortable discussing goals of care and code status with parents.²⁵⁰ Conversations of this nature with children and adolescents are understandably more difficult, as such, these topics are broached much less with organ failure patients themselves.²⁵¹ Emerging literature suggests that many young people prefer to be involved in decision making about their end of life (EOL) care if seriously ill.²⁵² Among a pilot sample of adolescents with HF, 83%, indicated a preference to be involved in their EOL decision making.²⁵³ In addition to cultural considerations, care teams regularly assess preferences regarding communication and decision making about EOL care. Care teams should establish time points for assessing and revisiting these preferences, such as pre-implant, emergence of VAD complication, and upon discharge. Honest conversations that occur throughout the pediatric VAD course will decrease the likelihood for unexpected decision-making during highly stressful times for families and care teams.²⁵²

Advance care planning allows one to specify healthcare decisions if unable to speak for themselves. Across pediatric illness and ACHD populations, a number of studies have shown that many young people believe completing an advance directive would be helpful.²⁵⁴⁻²⁵⁶ Adolescents with HF report a preference for these conversations to be initiated by a member of the healthcare team.²⁵³ Following assessment of patient and family preferences, participation of all patients in advance care planning should be considered.

The potential need for compassionate deactivation should be discussed before a VAD is implanted. In the event that EOL decision-making leads to a need for compassionate deactivation, there exist few resources for support. The scope of this challenge in pediatrics was initially described by Hollander et al.,²⁵⁷ then a provider survey illustrated a need for better education of clinicians in this regard.²⁵⁸ Fortunately there now exist both adult²⁵⁹ and pediatric²⁶⁰ checklists for compassionate deactivation, which can improve on this process, as can the early involvement of pediatric palliative care services.

Bereavement support following the death of a child has been recommended by both the American Academy of Pediatrics (2013) and Institute of Medicine (2014). Acknowledgement of the child's death (e.g., condolence letter, phone call) should be provided, along with psycho-educational materials about grief responses and available support services through the hospital or community. Support groups, referral to individual counseling and annual memorial services are helpful services to consider.²⁶¹

Key Points

- Communication with parents and patients concerning symptom management, decision-making, and advanced care planning for known potential adverse events should occur early and regularly.
- Program guidelines for when and how to proceed to compassionate deactivation are critical to support patients, families and clinicians.

Quality improvement and registry development

Pedimacs/INTERMACS/EUROMACS/IMACS/JMACS:

Relatively early in the evolution of mechanical circulatory support, the Institute of Medicine recognized that the nature and outcomes of MCS would be best understood through a longitudinal registry.¹ Aligned with that observation, in 2005 the NHLBI awarded a contract to the University of Alabama to develop the INTERMACS registry for patients in North America. Shortly after, INTERMACS began to develop a pediatric component, Pedimacs, and was launched in 2012.³ In 2018, INTERMACS and Pedimacs became part of the STS National Database, joining the Adult Cardiac Surgery Database, the General Thoracic Surgery Database and the Congenital Heart Surgery Database.

EUROMACS is the European registry for MCS that is designed to improve the outcomes of patients on MCS. The EUROMACS Committee of the European Association for Cardio-Thoracic Surgery (EACTS) governs the registry, which was launched in 2009 and became operational in 2012. EUROMACS is the only European-based durable MCS registry for all devices with the CE Marking implanted in children and adults.²⁶² International Mechanically Assisted Circulatory Support (IMACS) collects data from non-European countries but does not collect data on pediatrics.²⁶³ JMACS collects data from hospitals in Japan but does not collect data on children at this time.²⁶⁴

ACTION Network: ACTION is a multi-center learning network whose initial aim was to minimize stroke rates among pediatric patients requiring MCS. While clinical data are being collected for more traditional hypothesis-driven research, quality improvement (QI) science will be the primary modality through which ACTION is achieving its goals. ACTION has employed the Institute for Healthcare Improvement (IHI) approach to QI.^{6,265}

ACTION QI work to reduce stroke rates began with projects to improve anticoagulation, hemodynamics (i.e. blood pressure control) and clinical team communication. Early results have shown that interventions to standardize processes for achieving anticoagulation to target goals, controlling hypertension and checklists to improve team communication have been successful across the consortium. Subsequent QI initiatives are now in process and involve topics such as cardiac rehabilitation and hospital discharge, as well as another focus on pre-VAD patient care to include optimizing pharmacologic management of decompensated HF to reduce in-hospital end-organ complications and death.

Harmonization by Doing (HBD): HBD is an innovative concept that targets the limitations associated with low center volumes. The pilot HBD initiative was launched in 2003. The HBD program for global cardiovascular device innovation is a collaboration of Japanese and US regulators, industry, and academic clinicians, working to improve device investigation by “sharing lessons learned from these experiences”. One of the HBD working groups is a “study on post-market registry”, encompassing real-world evidence.¹²

Clinical Trials: Thus far, the only pediatric VAD device completing a clinical trial has been the Berlin EXCOR although the 50 cc TAH trial did include pediatrics and the

device has been approved for children that are the appropriate size.^{8,9} However, there is an ongoing trial (PumpKIN Trial) that is sponsored by NIH on a small CF axial flow pump (Jarvik Heart) for children.⁵⁵

There are many limitations to device trials in pediatrics, including patient volume and heterogeneity of population. An additional limitation is understanding the relevance to real-world practice. Although clinical trials are the gold standard to develop scientific evidence regarding safety and efficacy of a treatment, the limitations of clinical trials, in pediatrics, have encouraged regulatory bodies and clinical researchers to explore more diverse, real-world research settings. The advancements in electronic health records, clinical registries and technology integrated health systems have enabled access to data that were not previously accessible and have offered possible sources for “real-world evidence”.¹¹ For the field of pediatric VAD, there is an important role for real-world evidence, particularly in modifying or expanding device labeling. In addition to its QI limb, the ACTION network also provides a prospectively collected, adjudicated clinical registry as a source for real-world evidence for pediatric MCS devices.²⁶⁵

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