

What's New in Pediatric MCS



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Introduction

Approximately 450 pediatric heart transplants are performed in the US yearly with a total of about 600 yearly performed worldwide, compared to over 2,000 adult transplants per year. Incidence of heart failure in the pediatric population is largely unknown due to lack of a comprehensive database, but estimates are that 12,000-35,000 pediatric patients are diagnosed with heart failure yearly with a majority diagnosed with congenital heart disease (>50%). Because of the nature of pediatric heart failure and the limited availability of transplant donors, the waitlist mortality can be as high as 30-40% in some populations. The use of MCS as a bridge to transplant or recovery has reduced waitlist mortality and has primarily been limited to the use of ECMO and temporary extracorporeal centrifugal devices. Approximately 35% of pediatric patients listed for heart transplantation are bridged with MCS (28% VAD, 5% ECMO, 2% other modes). The post-transplant survival curves of children bridged with VADs parallel that of children not bridged and are significantly improved over those bridged with ECMO.

VAD use in children is in its infancy when compared to use in adults, mostly due to lack of adequate sized devices. Early durable VADs, such as the Heartmate II, could be used in older children and adolescents with BSA $\geq 1.3 \text{ m}^2$, but available devices for smaller children and infants were essentially nonexistent. Thankfully, the Berlin Heart EXCOR Pediatric VAD (PVAD) was developed for use in children. First introduced in Europe in 1991 and approved for use in 1996, this pulsatile pneumatic paracorporeal device made its way into the US in 2000 as a compassionate use device. Variable sizes (10 cc to 60 cc) allow the EXCOR PVAD to be used in children typically $\geq 3 \text{ kg}$ to BSA 1.5 m^2 . It is also relatively easy to use in a BiVAD configuration. Following the IDE trial demonstrating superior survival to transplant over ECMO EXCOR PVAD received US FDA approval in 2011 as a bridge to transplant for pediatric patients in both LVAD and BiVAD configurations. Smaller implantable devices have since made an appearance, such as the HeartWare HVAD, which can be used as bridge to transplant in patients down to a BSA of 0.7 m^2 . The EXCOR PVAD is the only pediatric approved device widely used in the US. Other adult approved devices do not have exclusions for use in pediatric patients, but may have limitations related indications and patient size. For those devices off label use, compassionate use, or emergency use is permitted by the US FDA depending on the approval status of the device.

As a response to the need for smaller implantable devices the NHLBI has sponsored the Pumps for Kids, Infants and Neonates (PumpKIN) trial to assess a continuous flow device for children. And, as a response to the need for more complete and unified data regarding VAD use in children the PediMACS registry was developed in 2012 and recently reported on 222 primary durable VAD implants performed over a nearly 3-year period. While pediatric VAD numbers are small in comparison to our adult counterparts we have witnessed a rapid increase in VAD use in children as evidenced by the manuscripts reviewed.

Article Reviews

Annals of Thoracic Surgery

- Adachi I, Khan MS, Guzmán-Pruneda FA, et al.: Evolution and impact of ventricular assist device program on children awaiting heart transplantation. *The Annals of thoracic surgery* 2015;99:635-40.

There has been a dramatic shift in the frequency and type of VADs used to bridge children to transplant. The group from Texas Children's is in the unique position to describe the changes happening within the broader community given their patient volume and program maturity.

This report documents the changes in device strategy and mortality between 1995 and 2013. Patients were stratified based on the era of implantation (before or after 2005 when the EXCOR was first used). There was a dramatic shift from temporary device support toward long term VAD in the current era (% long term VAD use 89% vs 57%, $p=0.0001$). There was also an increase in the proportion of patients bridged to transplant with a VAD in the current era (37% vs 13%, $p=0.0002$) with a concurrent decrease in waitlist mortality (11% vs 25%, $p=0.006$).

The report by Adachi et al. catalogues the shift in device strategy prompted by the introduction of durable VADs and the positive impact on waitlist mortality. The development of smaller, durable VADs has greatly benefitted children with end-stage heart failure. These improvements underscore the importance of ongoing attempts to develop size friendly, current generation devices for children.

- Zafar F, Jefferies JL, Tjossem CJ, et al.: Biventricular Berlin Heart EXCOR pediatric use across the united states. *Ann Thorac Surg* 2015;99:1328-34.

Biventricular VAD (BiVAD) use is significantly higher in children compared to adults, despite consistent data showing BiVAD use associated with higher morbidity and mortality. Zafar et al assessed the impact of BiVAD use on clinical outcomes in the 204 patients included in the Berlin EXCOR IDE and compassionate use cohorts.

Patients supported with BiVADs had similar adverse event rates and time on device, however BiVAD patients had significantly lower survival compared to patients who received an LVAD (100 day survival 60% vs 80%; log-rank $p=0.03$). Multivariate predictors of mortality on BiVAD included severe renal dysfunction, lower site experience and pump size. BiVAD use was not associated with improved survival in patients who were INTERMACS 1 or had an elevated bilirubin at implantation, but was associated with increased mortality among patients supported with ECMO prior to implantation.

This reports confirms the results of single center studies which have shown that BiVAD use is associated with worse outcomes. Multiple adult and pediatric series have shown BiVAD use decreases as programs mature. There are clearly patients who require BiVAD support, however the current data suggest pediatric VAD treatment algorithms may require further refinement to obtain optimal outcomes.

- Byrnes JW, Bhutta AT, Rettiganti MR, et al.: Steroid therapy attenuates acute phase reactant response among children on ventricular assist device support. *Ann Thorac Surg* 2015;99:1392-8.

The systemic inflammatory response syndrome (SIRS) is a common occurrence in children following VAD implantation, and increased risk of thrombus formation is known to occur during increased inflammatory states, such as infection. Byrnes et al. report on their institutional use of corticosteroids to attenuate the SIRS response in children supported with VAD therapy.

This study consisted of 44 children implanted with the Berlin Heart EXCOR pediatric VAD between the years 2005 and 2013. Thirty-two patients (73%) received corticosteroid therapy for SIRS ($n=12$), peri-extubation

(n=11), adrenal insufficiency (n=6), or combination of the three (n=3). Corticosteroid therapy protocol for SIRS was started when CRP measured >30 mg/dL, fibrinogen >500 mg/dL, and blood cultures were negative. Therapy consisted of methylprednisolone 2 mg/kg at initial dose, and then, 1 mg/kg every 12 hours, which was increased to 4 mg/kg/day if CRP and fibrinogen elevation persisted. Steroids were then weaned after acceptable response (CRP <30 mg/dL, fibrinogen <300 mg/dL).

Significant reduction in mean CRP and fibrinogen levels were noted at day 2 following initiation of corticosteroids. Five patients required more than one course of corticosteroid therapy due to recurrence of SIRS. Steroid use did not significantly alter the need for insulin, rate of infection, or duration of VAD therapy.

This report did not evaluate clinical outcomes; however, institutional changes were made based on the results in order to address the acute postoperative inflammatory response noted after VAD implantation. Treatment of the inflammatory response may reduce the overall risk of thrombus formation noted following VAD placement.

- Reinhartz O, Maeda K, Reitz BA, et al.: Changes in Risk Profile Over Time in the Population of a Pediatric Heart Transplant Program. *Ann Thorac Surg* 2015;100:989-94

Reinhartz et al. report on Stanford University's changing risk profile and outcomes for pediatric heart transplant over a 40-year period (1974-2014) divided into three eras (1974-1994, 1995-2004, and 2005-2014). A dramatic increase occurred in the use of pre-transplant durable VADs from 1% in era 1 to 15% in era 2 and 30% in era 3 (nearly 50% in the latter part of era 3). Kaplan-Meier survival analysis demonstrated no post-transplant survival differences in those supported by pre-transplant durable VAD versus those without support (p=0.3), a change from earlier studies.

IACC: Heart Failure

- Conway J, St Louis J, Morales DL, Law S, Tjossem C, Humpl T: Delineating survival outcomes in children <10 kg bridged to transplant or recovery with the Berlin Heart EXCOR Ventricular Assist Device. *JACC Heart Fail* 2015;3:70-7.

Small patient size has been shown to be a risk factor for mortality in multiple studies examining outcomes for children with mechanical circulatory support. This study provided an in depth examination of outcomes for children < 10 kg among the 204 patients from the EXCOR IDE and compassionate use cohorts.

When compared to patients > 10 kg, the smaller patients were more likely to be ventilated (86% vs 69%, p= 0.005) and have required ECMO (49% vs 34%, p= 0.03). The smaller patients were less likely to achieve a successful outcome as well (p<0.001). The worse outcomes were driven in part by the poor outcomes for the 33 patients < 5 kg. Seventy two percent of patients 5-10 kg experienced a successful outcome while only 9 (27%) of patients < 5 kg experienced a successful outcome. Sixty-five percent of patients < 5 kg were supported on ECMO prior to VAD implant and 11 of the ECMO patients < 5 kg had congenital heart disease. None of the patients < 5 kg with CHD who were on ECMO prior to VAD survived.

This study provided the most in-depth assessment of VAD outcomes among very small children to date. The most significant findings from this study include the poor outcomes among children < 5 kg, especially among those with CHD who were bridged with ECMO. The poor expected outcome among so-called "salvage VADs" in this population should be understood when discussing circulatory support options in small patients.

American Journal of Transplantation

- Schweiger M, Vanderpluym C, Jeewa A, et al.: Outpatient management of intra-corporeal left ventricular assist device system in children: a multi-center experience. American journal of transplantation 2015;15:453-60.

The development of the HVAD has significantly altered the landscape of pediatric VAD support. The device has not only expanded the age/size range of children who may be supported with a durable, continuous flow VADs, but also provides the opportunity for hospital discharge in an era when waitlist times are increasing. This study described the first significant outpatient experience with the HVAD in children.

This study included 12 children ranging from 8-15 years of age. This included a child as small as 0.8 m². All of the patients were discharged to home and the mean home support time was 290 days. Five (42%) of the 12 patients were bridged to transplantation, 5 patients (42%) were awaiting transplant at the time the study ended and 1 patient (8%) was explanted after normalization of function. A single (8%) family decided to pursue chronic VAD therapy with the device. This study also catalogued the range of community education/training protocols, device operating parameters (in the setting of a BSA less than manufacturer guidelines) and readmission rates (0.02 readmission/patient/month).

This study is notable for a few reasons. First and foremost, this study has shown that pediatric VAD discharge can be successful. This report also encompasses the experiences of multiple centers and this is reflected in the range of patient management strategies/protocols. Multi-center studies will be needed to establish best practices for topics such as discharge given the limited number of implantations at most centers.

Journal of Heart Lung Transplantation

- Zafar F, Castleberry C, Khan MS, et al.: Pediatric heart transplant waiting list mortality in the era of ventricular assist devices. The Journal of Heart and Lung Transplantation 2015;34:82-8.

The study by Zafar et al expanded nicely on the impact of VAD use on waitlist mortality noted in the single center study by Adachi et al discussed above. This study examined waitlist outcomes among children listed in the UNOS database between 1999 and 2012. Patients were stratified by era (before and after 2005 given the introduction of pediatric specific VADs in 2005). The proportion of patients supported with a VAD at listing increased from 6% in the early era to 16% (p< 0.001) in the current era. There was a 50% decrease in waitlist mortality in the current era (28 deaths/100 waitlist years vs 55 deaths/100 waitlist years). Waitlist mortality was lower in VAD patients overall (3% mortality at 3 months vs 10% in non-VAD patients) and for each era compared to non-VAD patients. Patients with less favorable VAD options (< 10 kg or with CHD) had higher risk of dying in each era.

This study demonstrates how introduction of pediatric specific VADs filled a clear need for support in children with end stage heart failure. Furthermore, it demonstrated the significant positive impact these devices have had on waitlist outcomes. This underscores the need for improved support options in specific sub-groups such as small children and patients with CHD, in whom outcomes trail the broader pediatric population.

- May LJ, Montez-Rath ME, Yeh J, et al.: Impact of ventricular assist device placement on longitudinal renal function in children with end-stage heart failure. J Heart Lung Transplant 2015.

Renal dysfunction is common in the setting of end-stage heart disease (ESHD) and has been associated with poorer outcomes influencing candidacy for heart transplantation or VAD placement. Adult studies have reported improved renal function both in the short-term and long-term following VAD placement. May et al. report retrospectively on renal function after VAD placement in patients aged < 21 years with ESHD from their institution.

Sixty-three patients underwent VAD placement in this study. The estimated glomerular filtration rate (eGFR) by Schwartz formula and development of acute kidney injury (AKI) were determined before and at serial points after VAD placement. Thirty-four patients (54%) had pre-VAD renal dysfunction (eGFR < 90 ml/min/1.73m²) with median eGFR of 63.8 ml/min/1.73m² (84.0 ml/min/m² for the entire cohort). eGFR reached a nadir on POD 1 of 62.9 ml/min/1.73m² (p<0.001) and rapidly returned to baseline and above over the first post-operative week (99.0 ml/min/1.73m² at POD 5, p<0.003 vs pre-op values). There was no significant difference in time to nadir or return to baseline between those with pre-VAD renal dysfunction (POD 2) and those without (POD 4). eGFR of the entire cohort remained at or above baseline over the entire 180-day study period. Although eGFR trended upward for 180 days, significance over baseline was reached at POD 30 (103 ml/min/m², p=0.01) for the entire cohort. Of those with pre-VAD renal dysfunction there was no significant decline in eGFR post-VAD (change -6 ml/min/1.73m², p=0.228) with a significant increase over baseline maintained through POD 90 and a continued upward trend to 180 days without significance likely due to declining cohort size. Those without pre-VAD renal dysfunction experienced a significant decline in eGFR (change -57 ml/min/1.73m², p<0.001) and no significant increase over baseline from PODs 7 and 180.

The rate of rise to baseline or above was greater in those with pre-VAD renal dysfunction. Sixty percent of all patients met criteria for AKI in the first post-operative week with no significant difference in patients with or without pre-VAD renal dysfunction.

May et al. demonstrate that VAD support maintains or improves renal function in the vast majority of their patients. Those with pre-VAD renal dysfunction had a significant improvement in renal function following VAD placement maintained for the 6 months of the study. Those without pre-VAD renal dysfunction maintained to slightly improved over baseline throughout the study period.

ASAIO Journal

- Adachi I, Guzman-Pruneda FA, Khan MS, McKenzie ED, Fraser CD, Jr.: Ventricular Assist Device in Children with Cardiac Graft Failure. ASAIO J 2015;61:729-30.

In this brief communication Adachi et al. report on their experience using VAD support in children with cardiac graft dysfunction following heart transplantation. They demonstrated that short-term VAD use was successful as a bridge to recovery of function resulting in 89% survival (8 of 9 patients). However, longer term use was less successful with 71% mortality (5 of 7 patients). Three of the five mortalities were related to sepsis. They conclude that infection risk in the setting of immunosuppressive therapy limits the role of long-term VAD support for cardiac graft dysfunction.

Pediatric Critical Care Medicine

- Mansfield RT, Lin KY, Zaoutis T, et al.: The Use of Pediatric Ventricular Assist Devices in Children's Hospitals From 2000 to 2010: Morbidity, Mortality, and Hospital Charges. Pediatr Crit Care Med 2015;16:522-8.

Mansfield et al. queried the Pediatric Health Information System (PHIS) database for patients up to 20 yo undergoing VAD placement for the years 2000-2010 (era 1 2000-2003, era 2 2004-2006, era 3 2007-2010) in an attempt to define VAD use in pediatric hospitals as well as the resulting mortality and hospital costs.

There were 475 pediatric patients who received VADs during the study period (69 patients in era 1, 135 in era 2, and 271 in era 3). The median age of all patients at VAD implantation was 6 years. There was an

increased proportion through the eras of patients 1-12 years old (29% era 1 to 47% era 3) and patients with the diagnosis of cardiomyopathy (52% era 1 to 72% era 3, $p=0.003$). Median hospital length of stay (LOS) increased from 37 days in era 1 to 69 days in era 2 ($p<0.0001$). Median ICU LOS increased from 4 days in era 1 to 28 days in era 3 ($p<0.0001$). Median adjusted hospital charges increased from \$630,630 in era 1 to \$1,577,983 in era 3 ($p<0.001$). Hospital mortality decreased from 42% in era 1 to 25% in era 3 ($p=0.004$) with 52% of all patients undergoing heart transplantation. Increased risk of hospital mortality was seen in infants, presence of acute renal failure or cerebrovascular event, use of ECMO, and use of dialysis ($p<0.05$ for all). The diagnosis of cardiomyopathy was associated with lower mortality as was VAD placement in era 3. Larger volume hospitals (20-64 VAD patients) had lower mortality and higher median charges than smaller volume hospitals.

Use of VADs in children has increased with an improvement in hospital survival and an increase in hospital charges. Hospital and ICU LOS have also significantly increased.

European Journal of Cardiothoracic Surgery

- van der Meulen MH, Dalinghaus M, Maat AP, et al.: Mechanical circulatory support in the Dutch National Paediatric Heart Transplantation Programme. *Eur J Cardiothorac Surg* 2015; 48(6):910-6.

End-stage heart failure (ESHF) is an important cause of morbidity and mortality in children with an estimated 50% of patients diagnosed with dilated cardiomyopathy experiencing death or heart transplantation within 5 years of diagnosis. van der Meulen et al. describe their outcomes with VAD (Berlin Heart EXCOR Pediatric and Levitronix Centrimag) support in children with heart failure and effects on waitlist mortality.

Fifteen patients listed for heart transplantation were placed into the historical pre-VAD control group (Cohort I, years 1998-2006) and 43 patients into Cohort II (Sept 2006-July 2014, start of VAD use). Eighteen patients (42%) in Cohort II underwent VAD placement. Mortality in Cohort I was 47% (7 of 15 patients) with the remaining 53% undergoing heart transplantation. In Cohort II mortality was 21% (8% of non-VAD patients, 39% of VAD patients) and 72% underwent transplantation (88% of non-VAD patients, 50% of VAD patients). Median time to transplantation of non-VAD survivors was 137 days. Median time to death in the VAD group was 18 days with median time to transplantation of survivors at 66 days. Of patients on VAD support 61% (11 patients) required pump replacement for thrombus, 39% (7 patients) experienced neurologic dysfunction from thrombus or hemorrhage, 28% (5 patients) required reoperation for bleeding/effusion, and 11% (2 patients) suffered significant renal dysfunction. Five VAD patients were > 15 kg of which 60% (3 patients) experienced a thromboembolic event (versus 31% of VAD patients > 15 kg). Four of the seven patients with neurologic dysfunction due to stroke died with the remaining having some residual neurologic deficits not precluding transplantation. Causes of death on VAD support predominantly included thromboembolic stroke (43%) and systemic embolic events (29%).

van der Meulen et al. conclude that despite a considerable morbidity and mortality in VAD patients, overall mortality of ESHF has improved with the use of VAD support as a bridge to transplantation.

- De Rita F, Hasan A, Haynes S, et al.: Outcome of mechanical cardiac support in children using more than one modality as a bridge to heart transplantation. *Eur J Cardiothorac Surg* 2015;48:917-22.

Mechanical circulatory support (MCS) has been used to bridge children to heart transplantation, through the use of ECMO or VAD. Often times multiple modalities are used along the way to transplantation. De Rita et al. report the experience at Freeman Hospital with single and multiple modality MCS as a bridge to transplantation.

A total of 92 children from the years 1998-2014 were bridged to transplantation with MCS. Twenty-one patients (23%) used more than one mode of MCS. Of the 71 patients receiving single mode therapy 43 were supported with the Berlin Heart EXCOR Pediatric, 17 with VA-ECMO, 6 with Medos HIA, and 5 with Levitronix PediVas. The most common multiple modality support was VA-ECMO to VAD (7 patients) followed by VAD to VA-ECMO (4 patients), LVAD to BiVAD (4 patients), pulsatile to continuous flow VAD (1 patient), and 5 patients with 1-2 discontinuations and reinitiations of MCS. Children receiving multimodal MCS were younger with at initiation with a larger proportion of infants and those < 10 kg receiving multiple modalities (p=0.008 and 0.02, respectively). The mean overall days of support was twice as long in the multiple modality group at 84 days versus 40 days for single mode group (p=0.0003). There was no statistical significance between the two groups related to underlying diagnosis or pre-MCS arrests. There also was no statistically significant differences in single versus multiple modality for CVA (25% vs 33%), bleeding (21% vs 38%), sepsis (24% vs 28%), mortality on MCS (23% vs 19%), transplanted (69% vs 71%), explanted (8% vs 10%), post-transplant ECMO support (14% vs 13%), survival to discharge (72% vs 76%), infant mortality (25% vs 23%), and mortality for weight < 10 kg (27% vs 27%). All four patients who went from VAD to VA-ECMO died with ECMO initiation one month or more following VAD initiation.

This experience suggests that a bridge to transplantation using more than one modality of MCS has comparable outcomes to single mode MCS with equal survivability to recovery or transplantation despite need for longer duration of use. Although smaller children and infants were more likely to receive multiple modality support, overall morbidity and mortality were not different than single modality MCS.

Journal of the American Heart Association

- Jordan LC, Ichord RN, Reinhartz O, et al.: Neurological Complications and Outcomes in the Berlin Heart EXCOR® Pediatric Investigational Device Exemption Trial. *Journal of the American Heart Association* 2015;4:e001429.

Multiple studies have catalogued the favorable outcomes for children supported with a VAD; however, adverse event rates remain high. Perhaps the most significant adverse event is neurologic injury. Jordan et al, examined the neurologic complication and outcomes for EXCOR patients from the 204 patients included in the EXCOR IDE and compassionate use cohorts.

Fifty-nine patients (29%) experienced a total of 73 neurologic events. The cumulative neurologic event rate was 0.51 events/100 patient days. Fifty-two of the events were described as strokes and 47 (89%) of strokes were ischemic. The greatest risk for neurologic event occurs early after support and decreases to a baseline rate by day 50. There was no significant difference in neurologic event rate if the center was an IDE or non-IDE site (27% vs 32%). The study attempted to construct a risk-stratification tool based on variables that were felt to be clinically relevant. Surprisingly, female gender and pump exchange were the only risk factors that predicted risk.

This study provided an important characterization of the neurologic events associated with the EXCOR device. Ultimately, the most significant finding of the study may be that many of the pre-implant characteristics thought to contribute to risk for a neurologic event were not statistically significant. Only female gender and pump change were predictive of an event. This study also made it clear that pediatric specific neurologic event definitions and evaluations are needed for future VAD trials.