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Cardiology/CT Surgery (K Gist, Section Editor)

Current Challenges and Strategies of Ventricular Assist Device Support in Infants and Small Children

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Abstract

Purpose of Review Ventricular assist devices (VADs) have become a mainstay of advanced heart failure therapy in pediatrics, with outcomes in adolescents that parallel the excellent outcomes in adults. Unfortunately, outcomes for younger children and infants remain suboptimal. This review discusses the patient and device specifics that contribute to this discrepant outcome, highlight current treatment strategies, and suggest areas for future improvement.
Recent Findings The field of pediatric mechanical circulatory support (MCS) continues to be driven by advancements in patient selection, timing of VAD implantation, and patient management strategies particularly with regard to anticoagulation. The use of direct thrombin inhibitors, such as bivalirudin, and weight-based antiplatelet therapy has shown promise in reducing the incidence of bleeding and stroke. While the number of devices remains limited, providers continue to leverage current technology and novel cannulation strategies to support smaller and more complex patients.
Summary Despite the challenges of supporting infants and small children, it remains a hopeful time for the field of pediatric MCS. While individual centers may only care for small number of VAD patients, the ACTION learning network has

sparked collaboration across the field broadly with rapid dissemination of best practices to all centers. This collaboration has led to many advances and holds promise for driving future advancements.

Introduction

The population of children with end-stage heart failure has steadily increased over the past decade. This dramatic growth has been driven by improved education and advanced imaging techniques for the recognition of myocardial disease in children. In addition, advances in surgical palliation of congenital heart disease (CHD) have improved survival, but at the cost of increased heart failure morbidity later in life. Unfortunately, the number of heart transplants has remained fairly constant since the early 2000s, averaging around 500 transplants annually [1]. With these shifts in supply and demand, mechanical circulatory support (MCS) offers a means for patient stabilization and optimization prior to transplantation or for chronic therapy for patients who may not be eligible for transplantation.

While initially seen as salvage therapy only offered at a limited number of institutions, the field of mechanical circulatory support (MCS) has seen dramatic growth and maturation. In 2011, the Berlin EXCOR became the first pediatric-specific ventricular assist device (VAD) to be FDA approved for children between 3 and 60 kg. Since that time, VAD therapy has become a critical component of advanced heart failure in children. The Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) is a National Heart, Lung, and Blood Institute supported registry of MCS in the pediatric population. Per the last Pedimacs annual report, more than 400 pediatric patients from more than 30 hospitals have been implanted with a VAD between 2012 and 2017 [2••]. Furthermore, outcomes in children and older adolescents now parallel the excellent outcomes that have been previously described in adults. While actuarial survival of all pediatric VAD patients at 6 months was 74% (censored at the time of explant for recovery, death, or explantation), older children and adolescents, age 11 to 19 years, faired the best with a 6-month actuarial survival of 86%. Conversely, infants (< 1 year of age) had the highest mortality with 6-month survival of approximately 50% [2••]. Conway et al. also previously showed that children supported by the Berlin Heart EXCOR weighing < 10 kg were much less likely to achieve a successful outcome (survival to transplant or explant) compared with children weighing ≥ 10 kg (57% vs. 83%, $P < 0.001$) [3]. Children < 5 kg fared the worst with only 27.3% experiencing a positive outcome. The most common reasons for death were neurological events, followed by respiratory, bleeding, and multisystem organ failure. For smaller children, CHD and elevated bilirubin ≥ 1.2 mg/dL were both identified as important risk factors portending a poor outcome. The discrepant outcomes of infants and small children is likely multifactorial with both patient and device specific factors at play. We hope to highlight what current treatment strategies are available for this challenging patient population, as well as offer some insights into future areas for improvement within the field.

Current challenges

Many initial treatment paradigms were directly extrapolated from the care of adults. While some of these approaches may hold true for adolescents, infants and young children have many unique physiologic differences. First, the concept of "developmental hemostasis" describes the fundamental and dynamic differences in the hemostatic profiles between infants, young children, and adults with both quantitative and qualitative changes in plasma proteins which impact coagulation, fibrinolysis, and antithrombotic therapy effect [4]. Thus, while standardized anticoagulation protocols exist, such as the Edmonton

Protocol used in the Berlin EXCOR IDE trial, developmental hemostasis is a major reason that a "one-size-fits-all" anticoagulation strategy for infants and small children has been suboptimal. Additionally, while adolescents and adults can be transitioned to oral chronic anticoagulation agents such as coumadin, infants with ongoing VAD therapy may have issues with oral absorption due to poor gastrointestinal function secondary to feeding intolerance or bleeding complications. Low molecular weight heparin has been used as an alternative, but there is not a clear consensus on optimal dosing targets for this patient population. Thus, many children on VAD support require hospitalization with indwelling central catheters for chronic intravenous anticoagulation. Monitoring of anticoagulation may also be challenging in small children due to poor vascular access and limits on the amount of blood available to be drawn for testing. Furthermore, proper blood pressure control has been identified as a key patient management principle to reduce the risk of stroke in adults [5, 6]. For children, obtaining accurate blood pressure measurements may be challenging when they are active, noncooperative, or upset. In addition, for children on VADs, there are no evidence-based or widely accepted blood pressure targets which has led to wide practice variation between centers.

The etiology of advanced heart failure in pediatrics is diverse and can include myocarditis, cardiomyopathy, and various forms of CHD. Due to the anatomic and physiologic complexity, previous surgeries, and related end-organ effects, CHD patients on VAD support have higher mortality rates (36.4% vs. 12.1%) and decreased transplant rates compared with non-CHD patients [7]. Infants and younger children are much more likely to have CHD and single-ventricle physiology as the etiology of their heart failure, and these patients experience the highest mortality compared with any other subgroup [7]. VAD support for the shunted (stage one) single-ventricle patient has proven especially difficult due to the vexing problem of trying to support and balance parallel systemic and pulmonary circulations. While outside of the scope of this review, there have been many published case series describing different approaches including options for cannulation and different device selection [8–11, 12•]. The field of CHD VAD support continues to mature and likely holds much promise for this complex, ever-increasing population.

There are also many device limitations that create unique challenges for infants and small children. To date, the Berlin Heart EXCOR is the only ventricular assist device FDA approved for use in children. Other VADs designed for much larger adults have been used off-label in pediatric patients but are subject to the many hurdles of trying to fit large hardware into small thoracic cavities. Multiple centers have published their limited case series of use of intracorporeal continuous flow devices in small children. While these devices have been used as a bridge to transplant in patients as small as those with a body surface area (BSA) of 0.6 m^2, there can be difficulties related to device fit and as a consequence changes in pulmonary mechanics, difficulty with feeds, and chest wall pain [13]. Since use has been off-label, industry support training and recommendations to specifically guide pediatric VAD providers has been lacking. Only 55% of pediatric patients implanted with an intracorporeal VAD were able to be discharged home which limits other potential benefits of VADs including improved rehabilitation, quality of life, and independence that adult patients often achieve [2••]. Furthermore, the equipment and accessories are designed for use by adult sized patients. The weight and size of carrying

controllers and batteries can become substantial in small children. Similarly, accessory bags are designed to fit and be carried by adults not children. Many pediatric programs have had to modify, adapt, and design bags to give children the mobility to participate in rehabilitation and return to home and school.

Device options

Different device strategies have been used in infants and small children, including paracorporeal pulsatile, paracorporeal continuous, and intracorporeal continuous flow devices. Patient-specific factors such as patient size, underlying diagnosis, and anticipated support duration must be considered when selecting a support strategy.

Pulsatile flow devices

Early, predominantly single center studies provided the earliest evidence that pulsatile VADs could be used as a bridge to transplant in pediatric patients [14–18]. These results also suggested that pulsatile VADs may have reduced morbidity and mortality compared to ECMO and served as the impetus behind the Berlin EXCOR IDE study. The Berlin EXCOR was eventually approved by the FDA in 2011 and remains the only ventricular assist device approved as a bridge to transplantation in pediatric patients. While the investigational device trial demonstrated superior outcomes (88–92% bridged to transplant or recovery) versus historical ECMO controls (67–75%), there remained significant morbidity, predominately from neurologic events [18]. Neurologic injury was the leading cause of death, and thromboembolic strokes were more than twice as common than hemorrhagic strokes [19, 20]. While low body weight has been a well-established risk factor in children supported on the EXCOR, there have been some encouraging data to suggest that as the field of pediatric MCS advances, we are making strides in improving the outcomes of small children. Case series have reported use of the Berlin Heart EXCOR in patients as small as 2.2 and 2.9 kg with BSA of 0.2m^2 [21, 22]. Nevertheless, the smallest children continue to have the highest mortality on device. Miera et al. recently compared worldwide outcomes of children < 10 kg between a historic cohort implanted between 2000 and 2012 and a more modern cohort implanted between 2013 and 2017. The authors found that these infants and small children had substantially improved survival in the modern era with the smallest and most complex infants showing the largest improvement across eras (Fig. 1) [23••]. In the recent era, there was no longer any difference in mortality between children weighing between 5–10 kg and > 10 kg. Need for biventricular support remains a significant risk factor in the most recent era [23••].

Continuous flow (CF) devices

Second- and third-generation intracorporeal continuous flow devices, such as the HeartWare HVAD and Heartmate 3, have now become the mainstay of adult MCS support, accounting for 100% of destination VADs since 2010 [24]. CF-VADs are designed for patients with a BSA ≥ 1.2 m^2 and have improved survival free from stroke and device failure in adults when compared to pulsatile devices [13]. Given these potential benefits, pediatric VAD utilization has

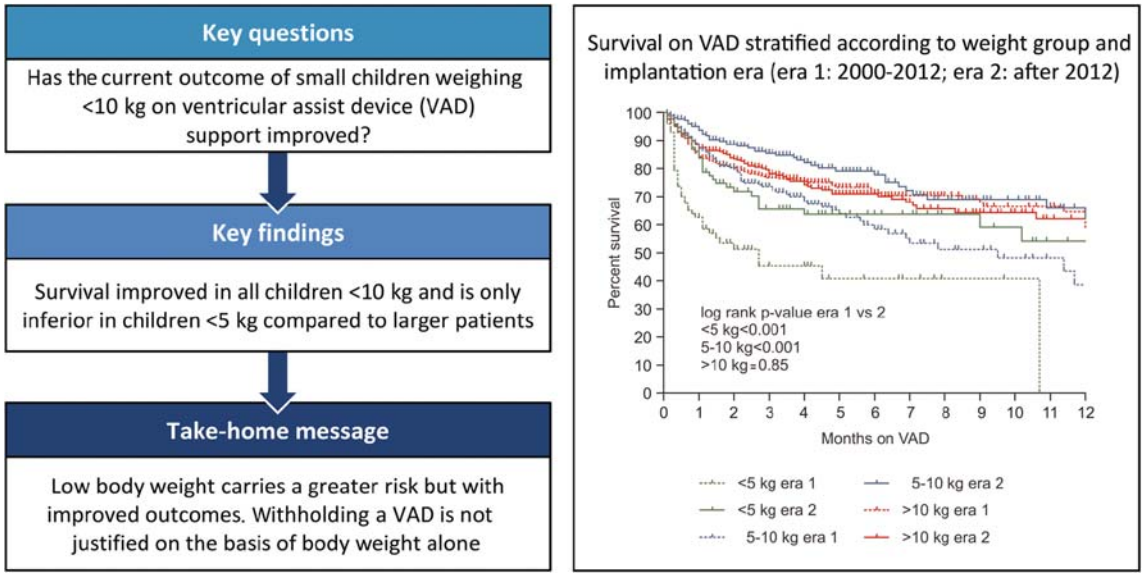

Fig. 1. Survival on VAD stratified by weight and era. Reproduced with permission from Miera 2019.

paralleled the adult trends with increasing use of CF-VADs, especially in older children and adolescents. A recent analysis of the Pedimacs experience examined 109 patients implanted at 35 centers and demonstrated a favorable competing outcome at 6 months post implant with a positive outcome in 92% [25]. Encouraged by these results, many centers have attempted to utilize CF-VADs in smaller and smaller children. While children with as low as a BSA of 0.6 m^2 have successfully been supported, small children may face added challenges. An analysis of children with a BSA ≤ 1 m^2 demonstrated that while excellent survival rates were achieved, patients experienced significant complications including device thrombosis [26]. It was hypothesized that this was likely a consequence of having flows at the lower acceptable limits as well as adapting adult-based anticoagulation protocols to these smaller children. The Heartmate 3 is a fully magnetically levitated device with potential advantages of a reduced thrombotic and hemolytic profile that was approved for use in adults in 2017. The Heartmate 3 has also been demonstrated to have decreased stroke (10.1% vs. 19.2%) and pump malfunction (1.6% vs. 17%) in comparison to the Heartmate 2 [27]. Use of the Heartmate 3 is expanding within pediatrics. To date, the ACTION (Advanced Cardiac Therapies Improving Outcomes Network) has described 14 Heartmate 3 implantations at 6 centers. While the device was used predominantly in older, larger children (median weight 70 kg, median BSA 1.8 m^2), there have been reports of a patient as small as 27 kg and 1.3m^2 being successfully supported [28].

Additional concerns that have been raised about using CF-VADs in smaller children have been potential for inflow cannula obstruction. Surgical modifications such as avoiding closure of the pericardium, infra-diaphragmatic pump placement, and mitral valve excision have been described to avoid potential

surgical complications [26, 29]. Advanced imaging techniques such as virtual fit studies using CT or MRI, as well as virtual reality simulations, may offer additional information when considering placement of a durable device within a small child.

Many centers have also begun to utilize paracorporeal continuous flow VADs. Without the restraints of having to fit within the chest wall cavity, paracorporeal continuous flow devices such as the CentriMag/PediMag (Abbott) and RotaFlow (Maquet) are able to provide continuous flow technology to a wide range of patient sizes. While initially utilized as a short term means to provide patient stabilization and end-organ resuscitation, paracorporeal CF-VADs have had an increasing role when combined with tunneled, durable cannula in providing long-term VAD support in pediatrics. A recent analysis of Pedimacs found that paracorporeal CF-VADs now account for 19% of pediatric VADs entered into the database [30]. Overall, 71% of children supported with paracorporeal CF-VADs had a positive outcome of transplantation, recovery or alive on device. While this is less than described for intracorporeal CF-VADs, it is important to note that many of these patients were younger, smaller, and had a higher proportion of children with CHD or were critically ill with cardiogenic shock. Children with CHD accounted for 41% of children implanted and overall had relatively good outcomes. Sixty percent of children with single-ventricle physiology had a favorable outcome, including 63% of stage I patients. Several aspects of CF-VADs may explain some of this survival advantage. Especially in the setting of aorta-pulmonary collaterals and systemic to pulmonary shunts, the ability to easily titrate flow to an optimal cardiac output may enable better preservation of systemic cardiac output. In addition, paracorporeal CF-VADs enable alternative cannulation strategies in cases of complex anatomy and, if necessary, the ability to add an oxygenator.

Lastly, there have been many attempts at the development of a miniaturized intracorporeal CF-VAD that could be used in pediatric patients. The National Heart, Lung, and Blood Institute (NHLBI) launched the Pediatric Circulatory Support Program in 2004 with the aim to develop MCS device specifically tailored to small children. With extensive collaboration between clinicians, scientists, industry, and federal agencies, the Jarvik 2015 has become the first implantable continuous flow VAD designed specifically for children between 8 and 30 kg [31]. The initial study design of the PumpKIN (Pump for kids, infants, and neonates) had hoped to provide direct comparison to the Berlin EXCOR, since this is the only FDA approved VAD in pediatrics; however, both clinical and logistical challenges have since shifted the focus to demonstrating feasibility. The device has been implanted in a limited number of institutions, but its role within pediatric MCS remains to be seen [32].

Medical management

A critical component to successful mechanical circulatory support is optimizing patient selection and timing of VAD implantation. It has been demonstrated in both adult and pediatric populations that the

presence of end-organ dysfunction is associated with increased mortality. Within the Berlin EXCOR study, children with renal dysfunction or elevated bilirubin had a four- to sevenfold increase in mortality than those that did not [18]. Specifically for children < 10 kg, Conway et al. also found that hyperbilirubinemia was an important independent risk factor for mortality [26]. Even more, VAD implantation for patients in cardiogenic shock and requiring ECMO has consistently been associated with increased mortality [2••, 23]. Still, one third of children, the majority of which are smaller and require paracorporeal VADs, are implanted in a state of cardiogenic shock [2••]. Careful patient selection and earlier VAD consideration before significant end-organ dysfunction and significant decompensation may be one way to improve outcomes. This proactive approach has led to some success with the highest risk single-ventricle infants at one center [33]. Thus, one should consider any infant or child for durable VAD implantation if they (1) have severe, symptomatic heart failure with intolerance of inotropes, (2) have evidence of end-organ dysfunction (i.e., need for positive pressure ventilation, renal dysfunction, hepatic dysfunction, or inability to participate in age specific physical therapy) despite inotropic support, and/or (3) are unable to separate from temporary MCS or ECMO in a short amount of time. While there may be less consensus regarding VAD indications in children with CHD, these principles should at least trigger further patient evaluation to weigh the patient-specific risks and benefits.

Following VAD implantation, improved medical management, particularly with regard to anticoagulation, has resulted in improved outcomes. Unfractionated heparin is fraught with problems related to its heterogeneous biochemical composition, dependence on highly variable antithrombin levels, and unpredictable pharmacokinetics. Given that many infants and young children are at higher risk of bleeding, thrombosis, and stroke, direct thrombin inhibitors have been used as an alternative [34–36]. A cohort of 43 pediatric patients (< 19 years of age) treated with a paracorporeal VADs (Berlin EXCOR, paracorporeal continuous flow, or combination) was recently described [37•]. Overall, these patients had lower major bleeding (2.6 events per 1000 patient days) and stroke event rates (1.7 events per 1000 patient days) than previously described in pediatric VAD patients treated with other anticoagulation strategies. With these results and reported improved stability within a therapeutic range, many centers have switched to direct thrombin inhibitors, such as bivalirudin, for anticoagulation of all paracorporeal VADs.

The use of antiplatelet agents similar to use of systemic anticoagulation agents has also largely been extrapolated from adult anticoagulation protocols. With acknowledgment of developmental hemostasis and the fact that young children are implanted with different devices than adults, we have also seen a clinical shift in the management of antiplatelet agents. Initially, aspirin, clopidogrel, and dipyridamole were included in the Edmonton Antithrombotic Guideline and were dose adjusted according to data from Platelet Mapping, a platelet function companion assay to the thromboelastogram. With increased clinical use, there has been little clinical correlation between the antiplatelet dosing and various platelet assays including Platelet Mapping, Verify Now, and thromboelastogram [38]. As a result, many

centers have abandoned dose titration to platelet assay treatment ranges and have instead favored using a weight-based methodology with some continuing to use platelet studies only if clinical concerns arise or as an adjunct used with other clinical data (appearance of the device, patient's bleeding status, etc.) [39].

Conclusions

Despite the challenges presented here, it remains an exciting and innovative time for pediatric mechanical circulatory support. As a field, we continue to expand our knowledge and experience in caring for more patients, including smaller patients and those with complex CHD. While the PumpKIN trial has had some delays, it is still encouraging to see that pediatric-specific mechanical support device development is possible. With improved collaboration between clinicians, industry, and governmental organizations, we hope to see this trend continue so that pediatric patients will not be limited to modifying adult devices and therefore not subject to the many inherent challenges unduly placed on children and their families. Nevertheless, new pediatric product development takes an immense amount of time and resources and has often been thwarted by unfavorable market and regulatory forces. Pediatric VAD providers must maximize the options that are available to them.

Additionally, as our field has begun to mature, we have seen that many pediatric patients can be well supported on ventricular assist devices and thus these devices no longer need to serve only as a means to transplantation but rather can be leveraged to optimize patient rehabilitation and improve and normalize the quality of life as much as possible for families and children with end-stage heart failure. While most infants and many small children are only able to be supported with paracorporeal VADs for which they must be hospitalized, we remain optimistic that further device development and improved management will allow for discharge to become a reality for even our smallest patients.

Many recent advancements have been galvanized by the Advanced Cardiac Therapies Improving Outcomes Network (ACTION), an innovative international learning network that brings together clinicians, researchers, parents, and patients from over 40 centers [40•]. Driven by a mission to improve outcomes for children and adults with heart failure, ACTION has formed unique collaborative relationships between all stakeholders to accelerate sharing of best practices and dissemination of all learning widely within the network and beyond. Given the steep learning curve, patient complexity, and limited numbers, it is not surprising that higher center volume has previously correlated with better outcomes [2••, 40•]. ACTION aims to level the playing field for all clinicians and patients, irrespective of geography, and dramatically improve knowledge and outcomes throughout its growing network. Soon-to-be-released data will show ACTION's impact on stroke rates and outcomes in pediatric VADs through working together on quality improvement initiatives. With an ever-growing network and clinical scope, ACTION brings a unique spirit of collaboration to the field of pediatric MCS and holds promise for spearheading future advances.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Ai D. Current state of pediatric cardiac transplantation. Ann Cardiothorac Surg. 2018;7(1):31–55.
2. •• Morales DLSRJ, VanderPluym C, Lorts A, Cantor R, St Louis JD, Koeh D, et al. Third Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Report: preimplant characteristics and outcomes. Ann Thorac Surg. 2019;107(4):993–1004

This study provides the most up-to-date analysis of the Pedimacs database, including data regarding pre-operative patient risk factors, complications and patient outcomes.

3. 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(1):70–7.
4. Huang JYMP, Massicotte MP, VanderPluym CJ. Antithrombotic therapies in children on durable ventricular assist devices: a literature review. Thormb Res. 2018;172:194–203.
5. Saeed OJR, Kargoli F, et al. Blood pressure and adverse events during continuous flow left ventricular assist device support. Circ Heart Fail. 2015;8:551–6.
6. Bennett MKAS. Blood pressure management in mechanical circulatory support. J Thorac Dis. 2015;7(12):2125–8.
7. Peng DMKD, Cantor RS, McMillan KN, Barnes AP, McConnell PI, Jordan J, et al. Outcomes of children with congenital heart disease implanted with ventricular assist devices: an analysis of the pediatric interagency registry for mechanical circulatory support (Pedimacs). J Heart Lung Transplant. 2019;38(4):420–30.
8. Miller JRLT, Eghtesady P. Current approaches to device implantation in pediatric and congenital heart disease patients. Expert Rev Cardiovasc Ther. 2015;13(4):417–27.
9. Miller JRLT, Callahan C, Abarbanell AM, Eghtesady P. An overview of mechanical circulatory support in single-ventricle patients. Transl Pediatr. 2018;7(2):151–61.
10. Poh CLCR, Zannino D, Brizard C, Konstantinov IE, Horton S, Millar J, et al. Ventricular assist device support in patients with single ventricles: the Melbourne experience. Interact Cardiovasc Thorac Surg. 2017;25(2):310–6.
11. Carlo WF, Villa CR, Lal AK, Morales DL. Ventricular assist device use in single ventricle congenital heart disease. Pediatr Transplant. 2017 Nov;21(7). https://doi.org/10.1111/petr.13031
12. • Lorts A, Eghtesady P, Mehegan M, Adachi I, Villa C, Davies R, et al. Outcomes of children supported with devices labeled as "temporary" or short term: a report from the Pediatric Interagency Registry for Mechanical Circulatory Support. J Heart Lung Transplant. 2018;37(1):54–60

This study evaluated the use of paracorporeal continuous flow VADs reported within the Pedimacs database. While initially these devices were used for short-term support, there was also longer term support noted. Additionally, despite the use in high acuity patients with complex anatomy, overall outcome was encouraging with 71% of patients experiencing a positive outcome.

13. Miera O, Kirk R, Buchholz H, et al. A multicenter study of the HeartWare ventricular assist device in small children. J Heart Lung Transplant. 2016;35:679–81.
14. Hetzer R, Alexi-Meskishvili A, Weng Y, Hubler M, Potapov E, Drews T, Hennig E, Kaufmann F, Stiller B. Mechanical cardiac support in the young wth the Berlin EXCOR pulsatile ventricular assist device: 15 years' experience. Semin Thorac Cardiovasc Surg Pediatr Card. 2006:99–108.
15. Stiller BHR, Weng Y, Hummel M, Hennig E, Nagdyman N, Ewert P, et al. Heart transplantation in children after mechanical circulatory support with pulsatile pneumatic assist device. J Heart Lung Transplant. 2003;22:1201–8.
16. Stiller BWY, Hubler M, Lemmer J, Nagdyman N, Redlin M, Lange PE, et al. Pneumatic pulsatile ventricular assist devices in children under 1 year of age. Eur J Cardiothorac Surg. 2005;28:234–9.
17. Fan YWT, Xiao YB, Huebler M, Franz N, Potapov E, Hetzer R. Outcomes of ventricular assist device support in young patients with small body surface area. Eur J Cardiothorac Surg. 2011;39:699–704.
18. Almond CSMD, Blackstone EH, et al. Berlin heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. Circulation. 2013;127:1702–11.
19. Almond CSBH, Massicotte P, Ichord R, Rosenthal DN, Uzark K, Jaquiss RDB, et al. Berlin heart EXCOR pediatric ventricular assist device investigational device exemption study: study design and rationale. Am J Heart. 2011;162:425–35.
20. Jordan LCIR, Reinhartz O, Humfl T, Pruthi S, Tjossem C, Rosenthal DN. Neurological complications and outcomes in the Berlin heart EXCOR pediatric investigational device exemption trial. J Am Heart Assoc. 2015;4:1429.
21. Jaquiss RD, Humpl T, Canter CE, Morales DL, Rosenthal DN, Fraser CD Jr. Postapproval outcomes: the Berlin Heart EXCOR pediatric in North America. ASAIO J. 2017;63(2):193–7.
22. Hetzer R, Kaufmann F, Delmo Walter EM. Paediatric mechanical circulatory support with Berlin Heart

EXCOR: development and outcome of a 23-year experience. Eur J Cardiothorac Surg. 2016;50(2):203–10.

23.•• Miera O, Morales DLS, Thul J, Amodeo A, Menon AK, Humpl T. Improvement of survival in low weight children on the Berlin Heart EXCOR ventricular assist device support. Eur J Cardiothorac Surg. 2019;55(5):913–9

This study compared the survival of children <10 kg supported on the Berlin EXCOR between a more recent cohort (2000–2017) to a historic cohort (2000–2012). Important findings include improved survival in children in children < 5 kg, as well as those between 5–10 kg. Further, no survival difference was noted between children between 5–10 kg and those >10 kg in the current era.

24. Kirklin JKND, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Miller MA, et al. Sixth INTERMACS annual report: a 10,000 patient-database. J Heart Lung Transplant. 2014;33:555–64.

25. LA Rossano JW, VanderPluym C, Jeewa A, Guleserian K, Bleiweis MS, Reinhartz O, et al. Outcomes of pediatric patients supported with continuous-flow ventricular assist devices: a report from the pediatric interagency registry for mechanical circulatory support (PediMACS). J Heart Lung Transplant. 2016;35(5):585–90.

26. Conway J, St Lous 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 Jan; 3(1): 70–7).

27. Mehra MRGD, Uriel N, et al. Two year outcomes with a magnetically levitated cardiac pump in heart failure. NEJM. 2018;378:1386–95.

28. Shugh SBRK, Morales DLS. Mechanical circulatory support in children: past, present and future. Transl Pediatr. 2019;8(4):269–77.

29. Nandi DMK, Bober CM, Rosenthal TM, Montenegro LM, Rossano JW, Gaynor JW, et al. Systemic atrioventricular valve excision and ventricular assist devices in pediatric patients. Ann Thorac Surg. 2018;105(1):170–4.

30. Lorts A, Mehegan M, Adachi I, Villa C, Davies R, Gossett JG, et al. Outcomes of children supported with devices labeled as temporary or short term: a report from the pediatric interagency registry for mechanical circulatory support. J Heart Lung Transplant. 2018;37(1):54–60.

31. Adachi I. Current status and future perspectives of the PumpKIN trial. Transpl Pediatr. 2018;7(2):162–8.

32. Amodeo AFS, Perri G, Iacobelli R, Adorisio R, Iodice F, Rizza A, et al. First human implantation of a miniaturized axial flow ventricular assist device in a child with end-stage heart failure. J Heart Lung Transplant. 2020;39(1):83–7.

33. Philip J, Reyes K, Ebraheem M, Gupta D, Fudge JC, Bleiweis MS. Hybrid procedure with pulsatile ventricular assist device for hypoplastic left heart syndrome awaiting transplantation. J Thorac Cardiovasc Surg. 2019;158(2):e59–61.

34. Bates A, Buchholz H, Freed D, MacArthur R, Pidborochynski T, Conway J. Bivalirudin experience in a heterogenous ventricular assist device population. ASAIO J. 2019 Nov 7. [Epub ahead of print].

35. Puri K, Tunuguntla HP, Humlicek TJ, Dreyer WJ, Denfield SW, Cabrera AG, Hui S, Hensch L, Price JF, Choudhry S, Adachi I, Teruya J. Use of bivalirudin in pediatric patients on ventricular assist device support. J Heart Lung Transplant. 2019: 38(4): S481

36. Medar SS, Hsu DT, Lamour JM, Bansal N, Peek GJ. Use of bivalirudin as a primary anticoagulant in a child during Berlin Heart EXCOR ventricular assist device support. Perfusion 2020; 35(2):172–176.

37.• VanderPluym CJ, Cantor RS, Machado D, Boyle G, May L, Griffiths E, Niebler RA, Lorts A, Rossano J, Sutcliffe DL, Lytrivi ID, Buchholz H, Fynn-Thompson F, Hawkins B, Conway J. Utilization and outcomes of children treated with direct thrombin inhibitors on paracorporeal ventricular assist device support. ASAIO J 2019 Nov 20 [Epub ahead of print]

This is a retrospective multicenter study of 43 children with paracorporeal VAD support who were treated with direct thrombin inhibitors for antithrombosis therapy. Overall results were encouraging with decreased adverse events of major bleeding and stroke compared to previously reported cohorts on other anticoagulation agents.

38. Adachi IKV, Hensch L, Chacon-Portillo MA, Teruya J. Management of hemostasis for pediatric patients on ventricular assist devices. Semin Thromb Hemost. 2018;44(1):30–7.

39. Rosenthal DRLC, McElhinney DB, Chen S, Stein ML, Lin A, Doan L, et al. Impact of a modified antithrombotic guideline on stroke in children supported with a pediatric ventricular assist device. J Am Coll Cardiol. 2017;36(11):1250–7.

40.• Peng DMRD, Zafar F, Smyth L, VanderPluym CJ, Lorts A. Collaboration and new data in ACTION: a learning health care system to improve pediatric heart failure and ventricular assist device outcomes. Transl Pediatr. 2019;8(4):349–5.

This paper explains the rationale and structure behind the creation of the ACTION learning network.

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