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CONGENITAL HEART DISEASE (RA KRASUSKI, SECTION EDITOR)

Heart Transplantation and Mechanical Circulatory Support in Adults with Congenital Heart Disease

John D. Serfas[1] · Priyesh A. Patel[1] · Richard A. Krasuski[1]

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Abstract

Purpose of Review To assess current management strategies for advanced heart failure in adults with congenital heart disease, including heart transplantation and mechanical circulatory support.

Recent Findings Current data demonstrate that adults with CHD generally experience higher short-term mortality after heart transplantation and MCS implantation, but enjoy superior long-term survival. Such patients are nonetheless less likely to receive a transplant than non-ACHD peers due to a variety of factors, including lack of applicability of current listing criteria to HF in ACHD. MCS is underutilized in ACHD, but provides similar quality of life benefits for ACHD and non-ACHD patients alike.

Summary Heart failure in ACHD is complex and difficult to treat, and both heart transplantation and mechanical circulatory support are often challenging to implement in this patient population. However, long-term results are encouraging, and existing data supports increasing use of MCS and transplant earlier in their disease course. Multidisciplinary care is critical to success in these complex patients.

Keywords Adult congenital heart disease · Heart transplantation · Mechanical circulatory support · LVAD · Failing Fontan

Introduction

Improved surgical and medical care of congenital heart disease (CHD) has resulted in an increasing number of patients with CHD surviving to adulthood, and there are now estimated to be more adults (~ 1.4 million) than children (~ 1 million) in the USA living with CHD [1]. As the adult CHD (ACHD) population has grown and aged, its comorbidity burden has increased, and heart failure has emerged as one of the most prevalent and ominous comorbidities. From 1998 to 2005, the rate of heart failure hospitalization among ACHD increased by 83% [2], and mortality following first heart failure hospitalization is high [3, 4]. Furthermore, heart failure is now the leading cause of death among adults with CHD [4]. As a result, referrals for heart transplantation have increased, but CHD patients and their physicians face several unique challenges when considering transplantation, including their diverse physiology, atypical presentations, allosensitization, prior sternotomies, aortopulmonary collaterals, and requirement for reconstructive surgery at the time of transplant [5••]. These challenges have led to higher waitlist mortality, longer wait times, and lower initial listing status for ACHD than for their non-ACHD counterparts [6••]. Similarly, mechanical circulatory support (MCS) is used less frequently among ACHD on the transplant list than non-ACHD patients [7], owing in part to anatomic challenges, uncertain benefit, and the lack of experience with MCS in this patient population. Controversy remains regarding the optimal use and timing of MCS and transplant in ACHD, as publications are largely limited to case reports, case series, and retrospective registry analyses. This review aims to summarize the available data on the use of cardiac transplant and mechanical circulatory support in this complex patient population.

Cardiac Transplantation

As adults with CHD and heart failure are generally younger and suffer from fewer comorbid conditions than their non-ACHD counterparts, cardiac transplantation is an appealing treatment option for those who require advanced support. However, according to United Network for Organ Sharing

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✉ Richard A. Krasuski
richard.krasuski@duke.edu

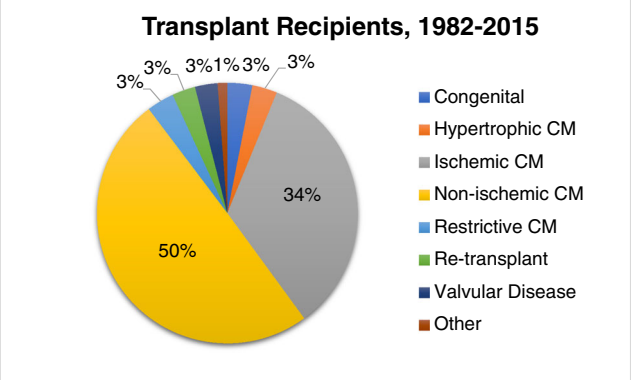
[1] Duke University Medical Center, Durham, NC, USA

(UNOS) data from 2005 to 2009, ACHD patients listed for transplant are less likely than their non-ACHD peers to receive a transplant (53% vs. 64%) and have longer wait times; in fact, ACHD patients were less likely to receive a transplant at every time interval after listing and for each priority tier (i.e., 1A, 1B, 2) than non-ACHD patients [8]. Outcomes while on the waitlist are sobering, as ACHD patients at status 1A have a higher incidence of death or delisting due to worsening clinical status [6••]. Furthermore, short-term (< 1 year) mortality post-transplant is higher among ACHD, although they enjoy superior long-term survival (see Fig. 1) [9, 10••].

Reasons for Long Waitlist Times

Perhaps the most fundamentally important explanation for prolonged waitlist times is the inability to identify, treat, and risk-stratify heart failure in the ACHD population. The pathophysiology and clinical presentations of heart failure in patients with CHD are myriad and atypical, and traditional prognostic markers in acquired heart failure have not been well established in CHD-associated HF [11]. Furthermore, current UNOS listing criteria for heart transplantation are highly dependent on the utilization of MCS or inotropes, both of which may be less effective and/or less desirable in certain ACHD populations. As a result, ACHD patients are more commonly listed as status 2 than their non-ACHD counterparts (59.4% vs. 40.9%) and less likely to be listed as status 1A (11.8% vs. 21.7%) or 1B (26.3% vs. 34%) [6••]. This represents a substantial disadvantage for ACHD patients, since they may not receive favorable priority for donor organs. Notably, upcoming changes to the heart transplant allocation criteria will not resolve this discrepancy. In addition, an increased frequency of prior blood transfusions and implanted materials related to prior palliative surgeries or catheter-based interventions can lead to significant allosensitization and limit the donor pool [12••].

Organ selection and procurement are also important factors when identifying a suitable donor organ. Recipient anatomy often requires greater length of donor tissue and vessels for the purposes of reconstruction [13]. This can substantially restrict the pool of possible donor hearts for these patients, particularly when donor lungs are also utilized, which limits the amount of great vessel and atrial cuff tissue that can be procured. Other important limiting factors include the availability of an experienced complex congenital heart disease surgeon for transplantation, and a general unfamiliarity with managing ACHD patients among cardiologists and surgeons without dedicated CHD training. Additionally, it is worth noting that most available data pertain only to ACHD patients already on the waiting list for transplant, and it is very difficult to ascertain how many ACHD patients are evaluated for transplant and not listed or who die from heart failure without formal heart failure evaluation. Our anecdotal experience is that many ACHD patients are either not referred for transplant evaluation or are referred too late, once end-organ damage has progressed to make transplant prohibitively risky or necessitate multi-organ transplantation.



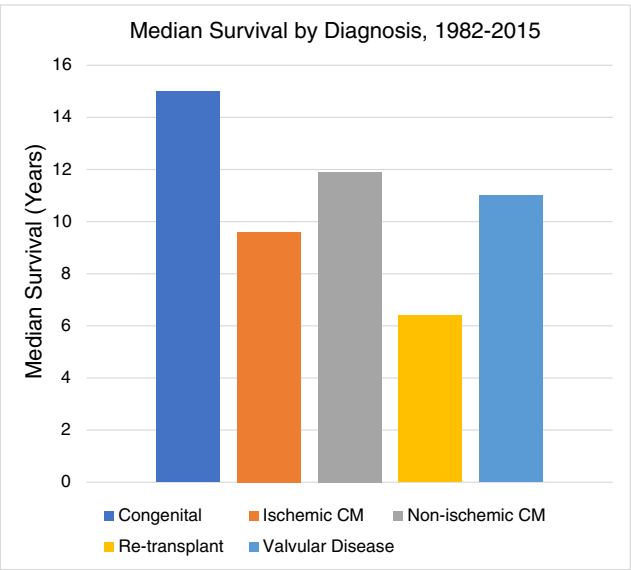


Fig. 1 Heart transplant recipient breakdown and median survival by diagnosis according to the 2017 Adult Heart Transplantation Report of the Registry of the International Society for Heart and Lung Transplantation. **a** The percentage of all heart transplant recipients by diagnostic category; CHD represents 3.1% of all transplant recipients. **B** Median survival of transplant recipients by diagnosis; CHD has the longest median survival of all groups at 15.0 years

Reasons for Increased Waitlist Morbidity and Mortality (see Table 1)

While long wait times may themselves contribute to worsening waitlist outcomes for ACHD patients, there are several other factors which could play a role. Many device-based therapies that have been demonstrated to improve outcomes in acquired heart failure, such as implantable cardiac defibrillators (ICD), cardiac resynchronization therapy devices (CRT), and left ventricular assist devices (LVAD), have not been validated in the ACHD population and are therefore used less frequently. For example, 75% of non-ACHD patients have an ICD at the time of listing for transplantation, compared with only 44% of ACHD patients. Despite the fact that

sudden cardiac death (SCD) accounts for 19% of ACHD mortality [4], ACHD patients often do not meet standard criteria for ICD placement as left ventricular ejection fraction may be normal or near normal despite advanced heart failure. Examples of this include tetralogy of Fallot, where sudden death risk is driven by adverse right ventricular remodeling, and Eisenmenger syndrome, where subaortic and even subpulmonic ventricular function may be preserved despite the presence of suprasystemic pulmonary pressures. Anatomic considerations often complicate the delivery of a standard ICD system, such as in Fontan repairs, which require the placement of an epicardial system. The further development and established efficacy of subcutaneous devices may provide a viable solution to the latter problem.

Similar to ICDs, MCS is utilized less frequently in the ACHD population than typical adult heart failure patients. In a recent study of the Scientific Registry of Transplant Recipients, 8.7% of ACHD patients received some form of MCS, compared with 24.8% of non-ACHD patients [6••]. In this study, VADs, which have been demonstrated in randomized trials to improve quality of life and outcomes in acquired heart failure [18–20], were used in 5.1% ACHD patients compared to 21.3% of non-ACHD patients. This is particularly relevant since increasing numbers of patients are being supported with MCS as a bridge to transplant (more recent data show that nearly half of adult patients are now transplanted off of MCS [10••]), which may put ACHD patients at a comparative disadvantage to the typical adult heart failure patient. For further discussion of MCS in ACHD patients, see the "Mechanical Circulatory Support" section below.

Other patient factors that may contribute to waitlist mortality include liver dysfunction related to congestive hepatopathy (so-called cardiac cirrhosis) and unique disorders which plague certain CHD patients, such as plastic bronchitis and protein-losing enteropathy in Fontan repairs [11]. Renal dysfunction (eGFR < 60 ml/min/1.73 m^2), malnutrition (albumin < 3.2 g/dl), and hospitalization at the time of listing have been associated with death or delisting due to clinical worsening [6••], and pulmonary hypertension with trans-pulmonary gradient > 12 mmHg has been associated with increased waitlist mortality, but interestingly not post-transplant mortality [14].

Reasons for Worsened Short-term Outcomes Post-Transplant (see Table 1)

ISHLT data have consistently shown higher 1-year mortality among patients with ACHD [9, 10••]. Among transplant recipients from 1985 to 2010, survival in ACHD patients at 1, 5, 10, and 15 years after transplant was 77%, 67%, 57%, and 53%, respectively, whereas survival among non-ACHD patients was 83%, 70%, 53%, and 37% [9]. Importantly, conditional survival beyond 1 year was consistently better in ACHD vs. non-ACHD patients throughout the 15-year follow-up period. Reasons for the higher early mortality risk include an increased risk of perioperative morbidity, including increased incidences of primary graft failure, multi-organ failure, stroke, post-transplant renal failure requiring dialysis, and reoperation or death from technical factors [21, 22]. This is not surprising, as ACHD patients are more likely to have received prior cardiac surgery (87.3% vs. 38.6% in one study [6••]) and have more complex anatomy requiring additional reconstruction at the time of transplant, which can lead to increased ischemic time and risk of bleeding [15]. Indeed, data suggest that ACHD patients who die post-transplant have longer ischemic times than those that survive transplant (3.6 vs. 3.1 h), and ACHD patients experience longer ischemic times than non-ACHD patients (3.5 vs. 2.9 h) [21].

The specific anatomy of the recipient can also impact post-transplant outcomes. In one study, the highest survival was observed in TGA patients, while the lowest was seen in AV canal defects. Having a prior Fontan procedure was strongly associated with early mortality, with a relative risk of 8.6 [15]. Single-ventricle physiology was found in a separate study to be associated with increased in-hospital mortality (23% vs. 8% in two-ventricle CHD) regardless of specific diagnosis;

Table 1 Factors associated with adverse outcomes on transplant waitlist, within 1 year after transplant, and after MCS implantation

Factors associated with adverse outcomes among ACHD with advanced heart failure		
Transplant waitlist mortality or delisting due to worsening	Early post-transplant mortality	Mortality after MCS implantation
• eGFR < 60 ml/min/1.73 m^2 [6••]	• Single-ventricle physiology [15, 16]	• BiVAD/TAH support [17••]
• Albumin < 3.2 g/dL [6••]	• AV canal defect [15]	
• Hospitalization at time of listing [6••]	• Elevated creatinine [9]	
• Trans-pulmonary gradient > 12 mmHg [14]	• Obesity [9]	
	• Age (peak mortality at 25–30) [9]	
	• Female gender [9]	
	• CMV-positive donor [9]	

AV, atrioventricular; *CMV*, cytomegalovirus; *BiVAD*, biventricular assist device; *TAH*, total artificial heart

notably, ACHD patients with biventricular physiology had similar in-hospital mortality to the general population [15, 16].

Additional predictors of early (< 1 year) mortality in ACHD from the ISHLT database include worsening creatinine, higher BMI, donor CMV seropositivity, female gender, and patient age, with a mortality peak at 25–30 years of age [9]. Though this peak is somewhat surprising, young patients are known to have a higher rate of death due to rejection after transplant and a lower rate of death due to infection, suggesting that the cause may be related to a more robust immune system [23] potentially combined with challenges of medication adherence at this age [24]. Moreover, ACHD transplant recipients are less likely to receive induction immunosuppression and maintenance steroid therapy than non-ACHD patients, which could further exacerbate risk of rejection and increase mortality [25]. Hence, we may be able to improve outcomes in the young adult ACHD transplant population with more aggressive immunosuppression and strategies that enhance compliance. Moreover, the increased mortality among the youngest ACHD may reflect a population enriched with particularly complex or single-ventricle anatomy, though this remains uncertain at present.

Single-Ventricle Physiology

Considering their inferior outcomes after transplant, patients with single-ventricle physiology are worthy of more detailed discussion, as they present several unique challenges and represent a rapidly growing proportion of ACHD referred for transplant. The mechanisms of failure in Fontan patients differ from those of patients with acquired heart disease, and patients can be broadly grouped into those with a failing ventricle and those with normal ventricular function but failing Fontan physiology (FFP). Preserved ventricular function has been associated with increased mortality in Fontan patients undergoing transplantation [26]. Unique issues encountered in this population include "hidden" pulmonary vascular disease, vascular collaterals, protein-losing enteropathy (PLE), plastic bronchitis (PB), and concomitant cardiac cirrhosis [27].

Pulmonary Vascular Resistance

The assessment of PVR even in non-CHD patients can be challenging; but in CHD patients, and particularly in single-ventricle physiology, it can be fraught with difficulty. Non-pulsatile, sluggish, and unevenly distributed pulmonary blood flow due to the formation of arteriovenous malformations and microemboli can make estimation of PVR difficult, if not impossible [27], leading to occasional underestimation. This can result in "unmasking" of PVR post-transplant with resultant right ventricular dysfunction [28, 29]. Multiple groups have reported success in overcoming this obstacle by oversizing donor hearts [13, 27].

Collateral Circulation

The formation of aortopulmonary or veno-venous collaterals in Fontan patients is common, can cause desaturation or hemoptysis, and importantly can result in increased intraoperative bleeding during transplant. Furthermore, if left untreated, collaterals can lead to high-output heart failure and graft dysfunction after transplant, and ideally should be occluded percutaneously prior to transplantation [30].

Protein-Losing Enteropathy and Plastic Bronchitis

PLE is a feared complication of Fontan palliation, involving loss of integrity of the lining of the gastrointestinal tract, causing excessive protein loss in the stool. The resulting hypoalbuminemia causes a decrease in oncotic pressure, leading to ascites, pleural effusions, malnutrition, coagulation abnormalities, and impairment in immune function. The associated mortality is high, but it consistently resolves after transplantation [27, 31]. However, it does confer additional perioperative risk [15], and so the decision to pursue transplantation should be carefully considered. When transplantation is pursued, strategies to enhance nutrition prior to surgery should be employed. Plastic bronchitis is quite rare, and is almost never encountered in adult Fontans [32]. One study of 14 patients demonstrated an association between PB and increased 30-day mortality, yet there was complete resolution of PB in all patients who survived to 30 days after transplant [33].

Hepatic Dysfunction

Liver disease is nearly universal in Fontan patients who reach adulthood, although it often remains sub-clinical and varies widely in severity and clinical presentation [34]. Its impact on transplant-related outcomes has not been well-established and requires further study [35]. Purported benefits of combined heart-liver transplantation over heart-only transplantation include fewer bleeding complications [36•] and reduction in rejection [37], although practice varies widely with regard to heart-only or combined heart-liver transplantation, with reported practices ranging from only 1 of 75 SV patients receiving combined heart-liver transplantation [27] to 100% of patients with Fontan physiology receiving both organs [36•].

Optimizing Outcomes

The above considerations make clear that many challenges remain for ACHD patients facing transplantation, yet there are significant reasons for optimism. The excellent rates of long-term survival after transplantation and the young age and relatively low burden of comorbid conditions in ACHD patients should provide ample motivation for working to optimize waitlist and short-term post-transplant outcomes. Many

single-center reports offer reassuring results, perhaps providing blueprints for achieving success. Mori et al. [38] report their experience with 12 consecutive ACHD patients (seven single ventricles) undergoing heart transplantation from 2005 to 2013, in whom they impressively achieved a 100% survival to hospital discharge. As expected, the postoperative courses were quite complicated, with half of patients requiring mechanical circulatory support, 3 patients requiring tracheostomy, and the majority experiencing other non-fatal complications. The authors postulate that their excellent outcomes are due in part to the expertise of a CHD-trained surgeon and postoperative care taking place at an adult rather than pediatric hospital, where more subspecialized technologies and subspecialty consultations are available to assist in convalescence. They surveyed 11 other programs and found their approach to be unique.

Menachem et al. [36•] also report impressive outcomes, with 100% 30-day and 1-year survival among 20 consecutive ACHD patients who underwent cardiac transplant. The authors detailed a multidisciplinary process by which ACHD patients with heart failure were evaluated and managed through the process of pre-transplant evaluation and all subsequent care. Some of the relevant details included bimonthly meetings of the ACHD team and heart transplant physician team to discuss complex patients, which led to earlier consideration of transplantation. Furthermore, there were joint presentations from the ACHD and transplant teams to the heart transplant committee at their institution, which led to careful and collaborative patient selection. Other important aspects of this partnership included aggressive use of applications for exception to prioritize patients to higher listing status in over 50% of listed patients, surgical collaboration between adult transplant surgeons and congenital surgeons, careful preoperative planning to minimize ischemic times, heart-liver transplantation for Fontan patients with liver fibrosis, and perioperative care provided at an adult hospital with high transplant volumes.

While neither of these reports is sufficient to determine causality, their impressive results underscore the importance of collaborative care with consistent and early involvement of practitioners with expertise in both CHD and heart trans plantation.

Mechanical Circulatory Support

As mentioned earlier, the use of MCS, both as a bridge to transplant and as destination therapy, has been shown to improve outcomes in acquired heart disease; consequently, its use in that population has substantially increased. Meanwhile, the use of MCS among ACHD has remained stagnant and low [39]. A recent analysis of INTERMACS data [17••] found that ACHD patients constitute less than 1% of all patients supported by durable MCS, with little increase in that proportion over time. And, as noted previously, a much smaller proportion of ACHD patients on the transplant waitlist are receiving MCS compared to non-ACHD patients [6••].

It is not difficult to imagine why MCS is utilized less frequently in ACHD; most forms of MCS were designed to support normal cardiac anatomy, and are not necessarily or easily adaptable to the many anatomic challenges that ACHD patients pose. Moreover, coexistent PLE, hepatic dysfunction, or other comorbidities may impair wound healing, increase infectious risk, and cause derangements of the clotting system [8], increasing hesitancy on the part of providers to use MCS. Overall experience with MCS in ACHD patients is also limited, with most centers only reporting one or two cases [17••], thereby restricting access to a limited number of centers with necessary expertise.

Systemic Right Ventricles

Patients with L-TGA or d-TGA with an atrial switch procedure have a morphologic right ventricle as the systemic ventricle. As can be imagined, the anterior location of the systemic right ventricle can pose anatomical challenges. Durable ventricular assist devices designed for left ventricular support may displace organs upon chest closure, compressing the heart or potentially causing liver or bowel injury. To minimize this risk, device placement has been described through the right chest wall, back-to-front, and shifted toward the midline [40•]. In addition, intraventricular anatomic considerations may also pose challenges. Standard cannulation strategies developed for left ventricular support often lead to malposition or even obstruction by the moderator band when utilized in a systemic RV [41]. Strategies used to overcome these problems include use of intraoperative echocardiography (epicardial and TEE) to optimize cannula placement, and resection of myocardial tissue and trabeculations at the time of VAD implantation (see Table 2). As the ACHD population continues to grow, design and investigation of durable mechanical support for systemic right ventricles are greatly needed.

Single-Ventricle Physiology

Patients presenting with single-ventricle physiology have a diverse array of anatomy and physiology, and published literature on MCS for these patients is limited to small case reports or model systems. Only 17 cases of MCS use in single-ventricle patients appear in the INTERMACS database [17••]. There have, however, been reports of successful implantation of mechanical support devices in the systemic ventricle [42, 43] as well as in the cavopulmonary position [44], and reports similarly exist regarding use of the total artificial heart (TAH) [45]. Careful device selection and placement is

Table 2 Anatomic considerations when considering MCS for complex CHD

MCS considerations in ACHD		
Systemic right ventricle		
Anatomic consideration	Possible consequences	Solutions
Anterior position of the right ventricle in the chest	• Cardiac compression by device • Liver or bowel injury upon closing the chest	• Alternate surgical approaches (i.e., via right thoracotomy) • Alternate device orientations (i.e., back-to-front, shifted toward the midline)
Unpredictable apical position	• Inflow cannula malpositioning • Cannula obstruction by moderator band or trabeculations	• Trans-esophageal or epicardial ultrasound • Resection of myocardial tissue at implant
Single ventricle/Fontan		
Mode of failure	Ejection fraction	Device position
Failing ventricle	• Impaired	• Systemic ventricle
Failing Fontan physiology	• Preserved	• Cavopulmonary

critical in single-ventricle patients, as the optimal strategy may depend heavily on the mode of Fontan failure; a device in the systemic ventricle seems most appropriate for patients with systemic ventricle dysfunction, whereas cavopulmonary support is likely optimal for patients with failing Fontan physiology but preserved ventricular function [46]. TAH should likely be reserved for cases in which there are no other options, given the additional complexity of the procedure.

Perioperative Outcomes with MCS

Outcomes for patients requiring MCS for CHD are expectedly worse than those for patients without CHD. Several reports identify increased perioperative mortality in ACHD compared with non-ACHD [12••, 17••, 40•], along with higher rates of morbidity including renal, hepatic, and respiratory dysfunction, infection, arrhythmias, and readmission. MCS strategy and severity of illness may underlie the discrepancy in outcomes, with patients that require BiVAD/TAH support having worse outcomes than patients needing LVAD only, whereas mortality in the latter group is indistinguishable from that of patients without CHD [17••]. Given this observation, perhaps the excess mortality seen in these patients may be related to late referral for MCS, which in turn leads to more advanced presentations of heart failure and end-organ dysfunction prior to and after surgery. Fortunately, as in non-ACHD patients, there has been a trend toward implanting MCS in lower-acuity ACHD patients.

Despite all the limitations noted above, there are reasons for optimism. Currently, the majority of MCS in ACHD is used as bridge to transplant (45%) or bridge to candidacy (38%), with only 16% destination therapy (compared with 38% in non-ACHD) [17••]. With increasing practitioner experience and comfort as well as reassuring data, we may see an increase in destination therapy MCS use in ACHD. For example, a recent analysis of INTERMACS showed that patients with CHD derived as much benefit from durable MCS as non-CHD patients, as assessed by change in 6MWD, gait speed, NYHA class, and measured quality of life [12••]. Another study of the Scientific Registry of Transplant Recipients found that ACHD supported with MCS had similar rates of post-transplant mortality compared with ACHD without MCS, despite having a higher risk profile and more comorbidities. Furthermore, with the exception of longer LOS and increased need for transfusion, there did not appear to be any significant downside [7].

Conclusion

Advanced heart failure in ACHD is common and portends a grim prognosis without transplant. While significant challenges exist when considering cardiac transplantation or MCS in these patients, there is a growing body of literature that suggests that transplantation and MCS can be safely and effectively utilized to improve morbidity and survival in carefully selected patients. Proper patient selection and collaborative multidisciplinary care are critical to the optimal management of these patients. Regular input from practitioners with expertise in adult congenital cardiology, congenital cardiac surgery, and adult cardiac transplant and MCS is essential with a critical need for subspecialty communication. Consideration should be given to atypical presentations of advanced heart failure for ACHD, with early referral for transplant evaluation and initiation of MCS when needed. We hope that the use of advanced therapies for ACHD will increase with time, and encourage new, prospective investigations to increase the effectiveness and safety of MCS and transplant for ACHD patients.

Compliance with Ethical Standards

Conflict of Interest John D. Serfas, Priyesh Patel, and Richard A. Krasuski declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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