AHA Scientific Statement

Transplantation and Mechanical Circulatory Support in Congenital Heart Disease
A Scientific Statement From the American Heart Association

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Dramatic evolution in the medical and surgical care of children with congenital heart disease (CHD) has led to a growing number of adults with late-onset complications, including heart failure (HF).[1] In parallel with an overall increase in hospital admissions for adults with CHD (ACHD) and HF,[2] CHD complexity has increased substantially in survivors over the past 2 decades.[3] Heart transplant (HTx) specialists face the challenge of determining eligibility for advanced HF treatments among an increasingly complex population of CHD patients in whom guidelines for HTx and mechanical circulatory support (MCS) are scant. The purpose of this review is to provide a state-of-the-art update on HTx and MCS in CHD.

Overview

HTx remains the surgical procedure of choice for eligible patients with severe advanced HF,[4,5] with little change in the number of transplants performed yearly over the past decade. The body of information related to transplantation for CHD is derived almost entirely from registry and single-center–based outcome data; no randomized clinical trial or meta-analysis data are available.

CHD presents additional challenges to successful HTx compared with HTx in patients with acquired HF. Many CHD patients require complex vascular reconstruction at the time of transplantation. The presence of antibodies to human leukocyte antigen (HLA) and ABO blood group sensitization are also impediments to timely transplantation. The ability of patients with single-ventricle physiology to survive during the waiting period is also limited by the additional burden of "outgrowing" their pulmonary blood flow and the resultant cyanosis. It is not surprising that CHD remains a risk factor during the waiting period and after transplantation. Therefore, although the management of the CHD patient with end-stage HF must include the option of HTx, its indication and timing are very different from that for acquired HF.

Patients with ACHD represent an increasing proportion of HTx recipients. Since 1999, the prevalence of HTx among adults with CHD has increased 41%.[6] Despite this, adults with CHD are less likely to receive implantable cardioverter-defibrillator therapy, more likely to be listed at lower urgency status, less likely to have a status upgrade, and less likely to receive a transplant at any given time after listing than patients without CHD.[7,8] Although there are limited outcome data, ACHD patients are also less likely to receive a ventricular assist device (VAD) as a bridge to transplantation. Moreover,

listed ACHD patients are more likely to experience cardiovascular death (including sudden death and death caused by HF) than adults with acquired HF.[7] There has been a significant increase in MCS use in patients with acquired HF as a bridge to transplantation (17%)[8]; however, there has been little change in MCS use in ACHD patients, with only 3% receiving a VAD at the time of transplantation[8] and a higher mortality in patients receiving MCS independent of the type of support.[9]

Status and Priority Listing Challenges

Organs available for transplant are a scarce resource, and the majority of patients who might benefit from a transplant will not be able to receive one. Criteria have been developed in both the adult and pediatric populations to prioritize organ allocation. These criteria differ between adults and children and among the international transplant organizations. The adult criteria were developed for patients with acquired HF, particularly left ventricular failure. Adults who receive a transplant because of acquired HF are predominantly male (76.3%), are older (average age 54 years), and have dilated (53.8%) or ischemic (37.1%) cardiomyopathy.[10] In some regions, transplantation as a status 1A candidate is the norm, particularly among recipients with blood type O. ACHD patients often do not meet standard adult 1A criteria, and as a result, they have a lower priority and longer wait times. If ACHD patients deteriorate and meet status 1A criteria, they are more difficult to support mechanically and more likely to die while on the waiting list than their typical HF counterparts. Sensitization from prior surgeries further adds to the long waits. ACHD patients often do not even meet 1B criteria, requiring a narrative for "exceptional" status for 1B listing.

In the United States, ACHD patients are more likely to be listed as status 2, which is concerning given recent United Network for Organ Sharing (UNOS) policy changes that may disadvantage those patients listed as status 2.[8] Specifically, since UNOS changed the allocation algorithm in 2006, transplant recipients were more likely to receive transplants as status 1A candidates (48% versus 37% before 2006), with an additional 40% receiving a transplant as status 1B candidates.[11] Allocation policies may further disadvantage the ACHD group because of the higher priority given to wait-listed patients on MCS, a therapy infrequently used in ACHD. In addition, when CHD patients deteriorate to the clinical acuity associated with status 1 listing, they may represent a "sicker" population at the time of transplantation, because VAD support to improve end-organ perfusion and allow for overall rehabilitation is rarely used.[8] ACHD patients wait longer on the list despite a higher percentage of time spent as status 1/1A/1B than their non-CHD counterparts.[9] The reasons for this are not entirely clear but may be related to a perceived need to find an ideal donor, the desire to reduce ischemic time by limiting distance of donor organ transport, the requirement for extra tissue at procurement for reconstruction, and a higher proportion of patients requiring a negative prospective crossmatch because of elevated panel reactive antibodies (PRAs).

The need for a transplant in children with end-stage CHD is traditionally well accepted. The UNOS pediatric heart allocation policy does take into account to some extent the fragile nature of neonates with unrepaired ductus-dependent circulation. Nevertheless, pediatric CHD patients have a unique set of challenges. Similar to adults, the number of pediatric transplants per year is limited by donor availability and has remained fairly constant, at 350 to 370, from 2006 to 2012 in the United States.[12] The number of new entrants to the wait list has increased to 500 per year, and thus, the transplant rate has decreased from a peak of 300 per 100 patient-years to 192 in 2012.[12] Currently, CHD is present in 54% of infants and ≈30% of older children undergoing HTx.[13] The clinical profile of those who received a transplant has remained the same except for the <1-year-old age group, for whom CHD diagnoses have decreased from 79% between 1988 and 1995 to 62% between 1996 and 2010. This is largely because of the success of palliative surgery in the treatment of infants with hypoplastic left heart syndrome (HLHS).[14] Long-term MCS is rarely used in children with complex CHD and carries a higher risk of mortality.[15] Aside from the adult indications for transplantation in CHD, HTx has also been used in children as treatment for complex heart disease that is not amenable to surgical repair or as a rescue operation after failed CHD surgery. Potential recipients in these categories require more urgent transplantation than those with chronic HF.

Use of a cardiac allocation score[16] has been suggested by some to improve allocation to those wait-listed HF patients at greatest need. It does not take CHD into account; moreover, no listing score has been developed that accounts for a CHD diagnosis. However, given challenges in the management of children with CHD who require a transplant, including a higher risk of death and longer waiting times, UNOS recently proposed revised criteria that are meant to address this subpopulation.[17] Specifically, inotropic support of pediatric patients with hemodynamically significant CHD will result in a status 1A listing, whereas pediatric patients with cardiomyopathy who are taking inotropic drugs will be listed at the next-lower priority status of 1B. Other countries have tried to address the high mortality of ACHD patients on the wait list by prioritizing patients with cyanosis, patients with high PRA, and patients awaiting heart-lung transplantation (HLTx).[18,19] Organ allocation policies must be evaluated carefully to ensure that CHD patients are not unnecessarily disadvantaged because of listing criteria or the limited application of MCS. Educational efforts must be made to ensure that the longer wait is not related to a risk-averse approach or discomfort in performing transplants in CHD patients.

Indications for Transplant

Patients with end-stage CHD have unique pathophysiology and comorbidities that require specialized care from CHD practitioners and HF/transplant subspecialists. Because guideline-directed medical therapy for HF in both pediatric CHD and ACHD is largely lacking, the decision to consider transplantation is often empiric, prompted when an attempt at medical or surgical treatment has failed. Nevertheless, difficult decisions arise on the timing of transplantation, such as whether to pursue transplantation before primary or additional repair and whether certain lesions or conditions make transplantation more favorable. These CHD-specific challenges were not addressed in either the 2009 or 2013 American College of Cardiology Foundation/American Heart

Association guidelines on the management of HF in adults or the International Society for Heart and Lung Transplantation guidelines for children or adults.[20–23] An overview of the approach to advanced HF in CHD is given in the Figure.

Pediatric-Specific Issues

General indications for transplantation in children with CHD overlap those for other population groups.[24] They include chronic dependence on inotropic therapy, mechanical ventilation, or MCS; malignant arrhythmias unresponsive to therapy; severe HF symptoms despite optimal medical/surgical therapy; and growth failure or unacceptable quality of life attributable to heart disease. A patient with active HF who resides at home without the need for continuous support also meets the indication if over time the patient has not improved to the point of qualifying for additional palliative/definitive surgery that will improve the quality of life or offer a survival advantage that is sustainable. For example, not being able to attend school in the older child or growth failure and enteral tube feeding dependence in the toddler are signs of poor quality of life resulting from chronic HF but do not necessarily indicate hemodynamic instability. The natural history of symptomatic CHD is typically progressive. Hence, if a lesion requires surgery but surgery is deemed too high risk to perform, a transplant may be necessary because the condition will typically progress (eg, valvular dysfunction, cyanosis, irreversible end-organ damage, cirrhosis, or pulmonary vascular disease).

Single Ventricle

The issue of when to pursue transplantation in a pediatric single-ventricle patient is important ("Hypoplastic Left Heart Syndrome"). It appears that the lowest mortality from transplantation resides within the bidirectional cavopulmonary connection stage.[25] In this report, transplantation 30-day survival was 100% for the bidirectional cavopulmonary shunt subgroup as opposed to 62% for the systemic-pulmonary shunt subgroup and 33.3% for the subgroup with Fontan failure (P=0.010). One reason for this is that a patient with a systemic-pulmonary shunt has cyanosis and excessive preload, which results in increased cardiac work and allows progression of myocardial disease, whereas the patient with a cavopulmonary shunt has cyanosis without an increase in preload or excessive work from left-to-right shunting. Although the applicability of the study's results must be considered preliminary because of the small sample size (n=26), there is a cautionary note here in that the timing of transplantation in relation to the stage of palliation is probably important. For example, if a stage 1 patient with ventricular dysfunction and active HF still has a good chance of experiencing success from palliation via a cavopulmonary connection, it may be worthwhile to attempt this palliation to stabilize the circulation in anticipation of a protracted waiting period in this infant population.

Patients who are able to reach the final stage of their single-ventricle palliation track are also at risk for both ventricular failure and circulatory failure that is isolated to the cavopulmonary side of their circulation. At the same time, the ability to complete a total cavopulmonary connection successfully has improved significantly in the past decade. Although it is a preselected group of patients who are accepted for Fontan completion, the consistently superb short- and long-term results from multiple centers argue against new stringent acceptance criteria being the reason for the improved results.[26–28] With the extracardiac Fontan as the cavopulmonary connection of
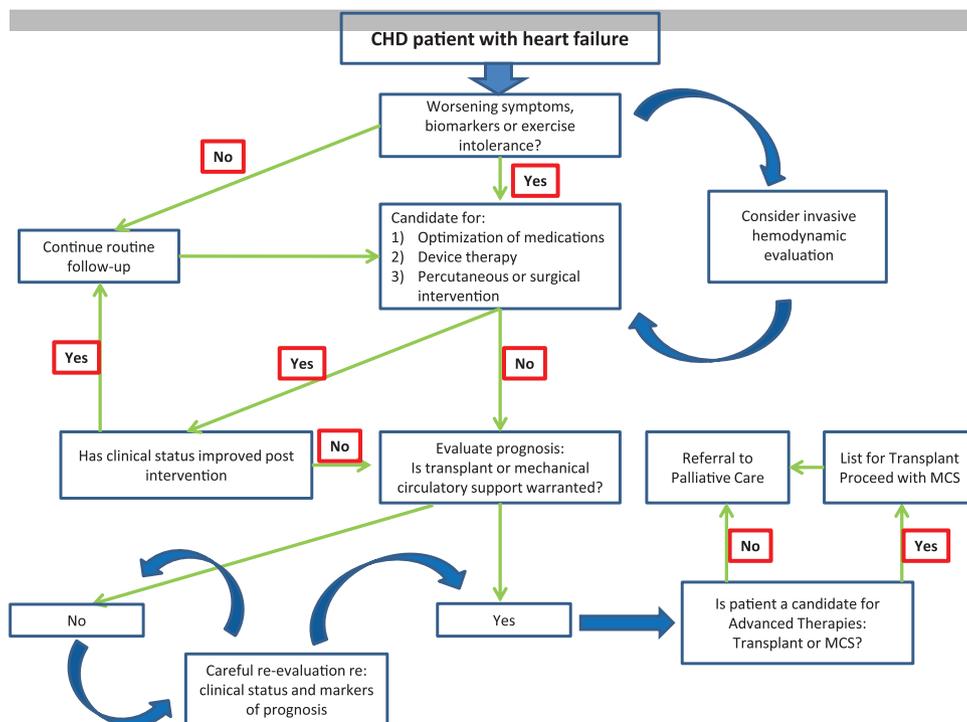

Figure. Overview of the approach to advanced heart failure in congenital heart disease (CHD). MCS indicates mechanical circulatory support.

choice, 10-year survival is typically >85%, noticeably better than the pediatric HTx outcome in the modern era.[13] Some of the traditional preoperative risk factors for early and late death continue to include pulmonary artery (PA) pressure, atrioventricular valve regurgitation, and common atrioventricular valve morphology, but no report specifies a firm and clearly defined set of exclusion criteria in the selection of suitable Fontan candidates. Also, no study has compared transplantation versus high-risk Fontan completion. With such good Fontan results in the modern era, perhaps the more appropriate comparison is in the overall survival between those who were listed for transplantation at the time of being rejected for Fontan palliation versus those who were rejected but preferred to delay listing for transplantation until further deterioration. Within this group, those who are hemodynamically unstable are unlikely to be accepted for a Fontan procedure (even with fenestration) and have no recourse but to be listed for transplantation immediately.

For those patients who develop late Fontan failure, the options include medical management, Fontan conversion, or transplantation. For those whose failure can be attributed to a significant residual anatomic defect, further repair is attractive, especially if the cavopulmonary connection can be "upgraded" to an extracardiac Fontan, given its superior short- and long-term results.[27–30] For example, in the absence of significant ventricular dysfunction, corrective surgical repair with or without Fontan conversion appeared to confer a low morbidity and mortality in a carefully selected group of patients.[31] If significant ventricular dysfunction is already present, it is questionable that correction of the anatomic defect to recover ventricular function will be an acceptable risk; however, if the defect is in conjunction with an atriopulmonary Fontan (less energy efficient but also uncommon in children in the current era) and atrial arrhythmia is a contributor to the dysfunction, some research would suggest that a Fontan conversion with surgical arrhythmia ablation plus correction of anatomic defects is an alternative to transplantation.[32,33] The data are too scarce to predict whether Fontan conversion for isolated ventricular dysfunction or for protein-losing enteropathy (PLE) or plastic bronchitis with the addition of a fenestration would be beneficial.

The decision to pursue transplantation is based on single-arm outcome studies. Of 97 pediatric Fontan patients who received a transplant between 1993 and 2001, pretransplantation survival was 78% at 6 months, no different from same-era cohorts with or without CHD.[34] Status 1 patients had a significantly higher risk of death while waiting for a transplant, particularly those who were listed soon (within 6 months) after their failed Fontan procedure (33% versus 11% [$P<0.0007$]). In a different study using the same registry, the time from palliation to listing (<6 months or >6 months) was not associated with mortality in the group that had undergone the Glenn procedure but remained a statistically significant risk factor in the Fontan group.[35] The overall actuarial survival during the waiting period was not different between the 2 groups, but the severity of hemodynamic compromise appeared to be an important risk factor. In the posttransplantation phase, Bernstein et al[34] reported a survival rate of 77% at 1 year, which was inferior to same-era cohorts with CHD (85%, P=NS) and non-CHD (91%, P=0.0004), with the attrition occurring mainly during the early postoperative period. In a single-center report of 43 Fontan patients who received a transplant between 1984 and 2007, including children and adults (median age 14.5 years), the 1-year transplant survival for Fontan patients was 62%, lower than the 80% in the CHD comparison group.[36] Smaller reports also describe a high mortality when Fontan patients receive transplants,[37] although excellent single-center results[38] and case series describing success using transplantation as rescue therapy for early failed Fontan patients[39] also exist. Importantly, transplantation as reported in the literature corrects PLE[34] and plastic bronchitis[40] in patients who survive beyond the early transplantation phase.

In summary, the data are not strong enough to offer a recommendation on the optimal timing of transplantation based on the stage of single-ventricle palliation alone. The decision should be based on an integrative appraisal of surgical expertise for further palliation/repair, the degree of compromise experienced by the patient, and the understanding that in general, the Norwood and Fontan procedures are higher-risk undertakings than the Glenn procedure, especially for those patients who are already being considered for organ replacement.

Hypoplastic Left Heart Syndrome

HLHS and its single-ventricle variants carry a high mortality risk over time. Since the 1980s to 1990s, with improved outcomes of the Norwood procedure and an increase in the number of neonatal candidates listed without a concomitant increase in donors,[12] primary transplantation, out of institutional or family preference, has become uncommon. For example, overall survival from listing to 5 years after transplantation was only 54% in a study that incorporated Pediatric Heart Transplant Study registrants from 1993 to 1998.[41] The wait-list mortality rate, not including those who crossed over to palliation, was 25%. In a cohort study from a similar era of Norwood-palliated patients, the overall 5-year mortality rate was 54%.[42] On the basis of more current data from the largest multicenter randomized clinical trial to date for Norwood palliation of HLHS, the 12-month survival rate was 64% for patients with a modified Blalock-Taussig shunt and 74% for those with a right ventricle (RV)–to-PA shunt.[43] In a follow-up study to 3 years, the transplantation-free survival rates were 61% and 67%, respectively.[44] Therefore, unless infant donor supply increases or new data support better pretransplantation management leading to better posttransplantation outcome, it is difficult to justify primary transplantation for the standard patient when Norwood and cavopulmonary connection outcomes continue to improve.

Akin to other single-ventricle patients for whom palliation fails in the short term, patients with HLHS undergoing rescue transplantation after a failed Norwood procedure experience significantly higher mortality than those undergoing transplantation as a primary treatment strategy (n=8 [50%] versus n=23 [13%], respectively; P=0.053[45]). A Pediatric Heart Transplant Study registry study supported these findings, showing a 52% postoperative mortality rate in those cases that crossed over from primary transplantation listing to an interim repair, some of which were presumably delayed Norwood repairs.[41] Rescue transplantation after the Norwood procedure

in another large surgical registry showed a postoperative mortality rate of 55%.[46] When only the posttransplantation phase was examined in a large registry-based study, young infants with HLHS who underwent surgical palliation before transplantation fared the worst in 1-year survival (70%) compared with those without surgery (79%).[47] What effect, if any, the application of hybrid techniques as a first-stage palliation will have on transplantation strategies remains to be seen.

Primary transplantation in select cases deemed too high risk for surgical palliation appears to be the typical approach. Examples of abnormalities that confer higher risk to the Norwood procedure and consideration for primary HTx include significant ventricular dysfunction, tricuspid regurgitation, pulmonary valve dysfunction, and left ventricle–coronary fistula; however, there is no standardization as to the extent of these abnormalities that would affect surgical decision making. Furthermore, randomized studies comparing the outcome between such high-risk patients selected for transplantation versus palliation have not been performed to permit a recommendation on which patients should have primary transplantation.

Because the management of care for high-risk patients is also likely to be more difficult before transplantation, stabilization of these patients can mitigate some of the attrition from HF during the waiting period and deserves some attention. Excellent results from centers that specialize in the management of infants with HLHS may yield better pretransplantation survival than centers in which such specialized diagnosis-specific care is lacking. One study using mostly medical therapy showed an 87% survival to transplantation, albeit the waiting time was not excessive at a median of 79 days.[48] An emerging option that demands more data is the use of the hybrid procedure to stabilize the ductus-dependent circulation without the use of cardiopulmonary bypass and circulatory arrest.[49] The hybrid procedure involves the creation of an adequate atrium-level shunt, which balances the distribution of systemic-to-pulmonary blood flow. It also involves PA banding and deployment of a large ductal stent to secure unrestricted systemic flow. The procedure does not reconstruct the aortic arch, and this additional step plus removal of the bands and stent must be undertaken at the time of transplantation. The procedure has been used by many centers but deployed preferentially over the Norwood procedure by only a few.[50] Most centers select the hybrid approach for high-risk Norwood candidates (those with prematurity, low birth weight, hemodynamic instability, or brain or other noncardiac conditions that could affect the safety of aortic reconstruction at birth) and for those who may be able to undergo a 2-ventricle repair later.[51] Some of these patients do eventually go on to receive a transplant.[50,52] Despite the fact that some high-risk Norwood candidates may be offered primary transplantation, no study to date has specifically described the use of the hybrid approach as a bridge to transplantation.

Other High-Risk CHD Lesions
Two distinct CHDs that deserve consideration for primary transplantation listing are pulmonary atresia with intact ventricular septum/RV–dependent coronary circulation and heterotaxy syndrome with single-ventricle physiology. Early

studies suggested a high incidence of death in patients with pulmonary atresia with intact ventricular septum/RV-dependent coronary circulation, particularly among infants early after surgery for creation of a systemic-to-PA shunt.[53,54] Lower mortality in the current era may reflect (1) better selection of patients to decompress and attempt a biventricular repair, (2) the recognition of overcirculation and coronary steal in the initial palliation, and (3) the incorporation of transplantation as one of the therapeutic options.[55–58] With the overall survival having improved, the most practical approach may be to study the coronary circulation on diagnosis of those with a small tricuspid valve annulus, because it is now apparent that an RV-dependent coronary circulation typically exists in the hypoplastic RV unsuitable for biventricular repair. If an RV-dependent coronary circulation exists in an asymptomatic patient with normal left ventricular function and wall motion, then a reasonable option is to proceed with palliative surgery with a systemic-to-PA shunt with postoperative management that minimizes overcirculation, followed by early placement of a bidirectional cavopulmonary shunt and a Fontan procedure. In the symptomatic patient with ventricular dysfunction or signs of ischemia at any time along the palliative pathway, listing for transplantation can be considered. In those with coronary atresia and severe or diffuse left coronary involvement, the threshold to list an asymptomatic patient for transplantation would be lower, although the data are clearly not sufficient to expand this beyond a consideration.

Patients with heterotaxy syndrome and single-ventricle circulation also represent a difficult decision as to whether to perform transplantation before ventricular dysfunction and HF develop. In a large single-center review of left atrial isomerism, patients who underwent 2-ventricle repair had 5- and 10-year survival rates of 71% and 66% compared with 61% and 53%, respectively, for those who had single-ventricle repair.[59] Such poor outcome is reminiscent of early debates over whether de novo transplantation for HLHS is warranted. In the case of left atrial isomerism, the attrition is more gradual and not concentrated between the first and second stage and may not be as much related to the surgical repair. There is also no report to show improvement between eras. A mortality rate of 18% was seen even in those without cardiac anomalies, which suggests multiple organ system involvement in this syndrome. Patients with right atrial isomerism did not fare better in a similarly large single-center review.[60] In this group of 98 patients, more complex cardiac malformations were seen, notably anomalous pulmonary venous return with stenosis. Many were not operable. The overall survival rate for those who had repair was 71% at 1 month and 35% at 5 years. Clearly, not all who were not operable or died after repair would be transplant candidates, but it does raise the question of whether consideration should be given to transplantation in those who are borderline repair candidates or who have HF despite an attempt at repair. Lodge et al[61] reported intermediate survival of ≈50% after repair of total anomalous venous return in the setting of single-ventricle circulation. In this cohort, 68 of 91 patients (75%) had heterotaxy syndrome. An increase in survival between eras was seen when transplantation was added to the treatment strategy, but only 5 patients received primary HTx. In the largest series of transplant recipients with heterotaxy

Table 1.   Possible Indications for Heart Transplantation in CHD

Patients with stage D HF refractory to medical therapy who will not benefit significantly from surgical, interventional, or electrophysiological intervention

CHD patients with associated near-sudden death or life-threatening arrhythmias refractory to all therapeutic modalities

Patients with stage C HF associated with reactive pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future

Stage C HF associated with systemic ventricular dysfunction in pediatric patients with previously repaired or palliated CHD when HF is associated with significant growth failure attributable to the heart disease

Pediatric patients with CHD with normal ventricular function when the following anatomic and physiological conditions are present and not amenable to surgical intervention:

    Severe stenosis (stenoses) or atresia in proximal coronary arteries

    Moderate-to-severe stenosis or insufficiency of the atrioventricular or systemic semilunar valve(s)

    Symptomatic arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction

    Persistent protein-losing enteropathy despite optimal medical-surgical therapy

Stage C HF in pediatric patients with CHD and severe limitation of exercise and activity

CHD indicates congenital heart disease; and HF, heart failure.

syndrome, Larsen et al[62] described 29 patients, all of whom had a high-risk anatomic phenotype (ventricular dysfunction, aortic atresia, or atrioventricular valve dysfunction), with 9 being primary transplant recipients, and showed 1-, 5-, and 10-year survival rates of 86%, 68%, and 50%, respectively. Right versus left atrial isomerism was not associated with outcome. Although outcomes were inferior to those of same-era cohorts with cardiomyopathy, one would still consider them satisfactory for this era (1989–2001) in a high-risk group of patients.

Other CHD lesions, repaired or de novo, can pose an increased risk to transplant outcome mainly because of the inadequacy of the pulmonary vasculature. These include intrinsically hypoplastic or diseased PAs such as in pulmonary atresia with major aortopulmonary collaterals, truncus arteriosus, transposition of the great arteries with ventricular septal defect, and anomalous or stenotic pulmonary veins. One must be cautious in assessing whether HTx alone will provide a good outcome.

Adult-Specific Issues

Transplantation for ACHD is often performed for patients with severe ventricular dysfunction, with a poor prognosis as a result of circulatory impairment (eg, Fontan failure), who have advanced symptoms and are unable to undergo further medical or surgical therapy. Specific indications are shown in Table 1.

Prognosis

Although there are many prognostic markers (Table 2[63–98]) that have been identified in ACHD, predicting outcome in an individual patient remains difficult, and hence, the timing of assessment and listing for transplantation is challenging. Brain natriuretic peptide (BNP) levels have been shown to predict mortality across CHD diagnosis (BNP >78 pg/mL),[83] specifically in Eisenmenger syndrome.[84,85] A large study of ACHD patients revealed that N-terminal pro-BNP levels differed by diagnosis, being the highest in patients with Fontan circulation and a systemic RV.[86] In a systematic review, BNP levels were increased in complex CHD, with a clear association between BNP levels and New York Heart Association functional class.[87] Overall, BNP levels that suggested increased risk were low and quite different from those seen in acquired HF. Biomarkers are potentially modifiable with appropriate medical therapy and may be volume dependent, which can result in fluctuations over time. The usefulness of single or serial BNP assessment to predict outcomes requires larger prospective study with risk thresholds defined on the basis of the specific ACHD anatomy.

As in acquired HF, exercise testing including formal cardiopulmonary testing can provide prognostic information in ACHD. In the most comprehensive cardiopulmonary exercise study to date (1375 consecutive patients, with a mean follow-up of 5.8 years), after adjustment for clinical parameters, a combination of peak $\dot{V}o_2$ and heart rate reserve provided the greatest predictive power across a broad range of CHD diagnoses.[90] Reference values for specific CHD subtypes have been suggested.[99] This should aid practitioners in comparing their patients' values to normative values categorized by anatomy.

Despite this breadth of knowledge, the above prognostic markers do not necessarily lend themselves to decisions regarding timing of referral for transplantation. Prognostication (taking into account surgical risk) that better predicts which patients will do better with a HTx than without one is still needed. In addition, further studies are needed to identify predictors of impending mortality to guide listing status (upgrade to 1A) in ACHD patients who do not meet traditional 1A criteria developed for acquired congestive HF or who are not suitable candidates for MCS.

Wait-List Mortality and Surveillance

Patients wait-listed for HTx need close and frequent reassessment, which should include monitoring of clinical status, laboratory evaluation, psychosocial support, and potential need for MCS as a bridge to transplantation. Strategies that improve or optimize the physiological status of wait-listed patients, including nutritional support and exercise where able, should be implemented. It is important to ensure no new comorbidities have developed that may preclude transplantation. Survival for children with end-stage CHD continues to lag behind that of children with cardiomyopathy. This is true during the waiting period[100,101] and after transplantation.[13,102,103] Neonates and infants with CHD also have to wait longer and have a higher mortality during the waiting period.[13,100] The survival disadvantage appears to reside solely during the waiting period and perioperatively.

In a review of the UNOS database of 41 849 patients >18 years of age listed for primary transplantation (1995–2009),[9] risk factors for wait-list mortality were described. Use of VADs in non-CHD patients was associated with lower wait-list mortality; however, ACHD patients had a higher risk with MCS regardless of device type. An albumin level <3.5 g/dL, male sex, and admission to the hospital outside the intensive

Table 2.   Prognostic Variables in CHD

Variable	Finding
Age	Interventions, the number and length of hospital stays, and survival were worse for older patients with ACHD (age ≥60 y) than for an age- and sex-matched comparison population[63]
	Older age at repair was associated with a higher risk of sudden death and atrial tachyarrhythmia in adults with repaired TOF[64]
Arrhythmias	Arrhythmias in ACHD patients are associated with a 1.5-fold increase in mortality risk and a >2-fold increase in risk of HF[65]
	Atrial tachyarrhythmia is an independent predictor of death and composite outcome of death/hospitalization in patients who have undergone a Fontan procedure[66]
	Atrial tachyarrhythmias are predictive of death and sustained VT in adults with repaired TOF[67]
	QRS duration ≥180 ms is a sensitive predictor of life-threatening ventricular arrhythmias in TOF[68]
	QRS duration ≥140 ms confers a >13-fold risk of sustained VT/sudden cardiac death in d-TGA patients after Mustard operation[69]
Hospitalization	ACHD patients admitted for HF had a 5-fold higher risk of mortality than patients not admitted[70]
Ventricular function	Ventricular dysfunction is predictive of death and sustained VT in adults with repaired TOF[67]
PH	PH increased the all-cause mortality rate in ACHD to >2-fold compared with patients without PH[71]
Pulmonary function	In ACHD, reduced forced vital capacity of at least moderate severity was an independent predictor of survival[72]
MRI	Extent of late gadolinium enhancement on MRI in TGA correlates with clinical events[73,74]
	Fibrosis on MRI in TOF is a marker of adverse outcome and arrhythmia[75]
Echocardiography	Pulmonary regurgitation is associated with increased risk of VT and sudden cardiac death in adults with repaired TOF[64]
	Longitudinal LV strain on echocardiography in repaired TOF is associated with a greater risk of sudden cardiac death/life-threatening ventricular arrhythmias[76]
	Longitudinal systemic RV strain in TGA is associated with adverse outcomes (symptomatic progression to New York Heart Association functional class ≥3, clinically relevant cardiac arrhythmia, or death)[77]
	Tricuspid annular plane systolic excursion, RV function, and RA area predict mortality in ES[78]
Biomarkers	
Serum sodium	Predictor of mortality in ACHD[79]
Anemia	In ACHD, patients with anemia have a 3-fold higher mortality risk than nonanemic patients[80]
Renal function	In ACHD, renal dysfunction had a propensity score–weighted hazard ratio of 3.25 impact on mortality[81]
Troponin	In CHD with PH, troponin, NT-proBNP, and RV function were determinants of death[82]
BNP/NT-proBNP	Associated with poor outcomes and increased mortality in ACHD, ES[82–87]

(Continued)

Table 2.   Continued

Variable	Finding
Exercise testing	6-Min walk distance in ES predicts mortality[88]
	Peak systolic blood pressure during exercise <180 mm Hg and increased RV end-diastolic volume index (>150 mL/m²) is associated with increased risk in systemic RV (death, vascular events, tricuspid regurgitation requiring surgery, worsening HF, and [supra]ventricular arrhythmia)[89]
	Peak $\dot{V}o_2$ across CHD diagnosis predicts an increased risk of hospitalization and death (Fontan operation, repaired TOF, and Ebstein anomaly)[90–94]
	Increased $\dot{V}e/\dot{V}co_2$ slope correlates with mortality risk in repaired TOF, noncyanotic ACHD, TGA (Senning or Mustard repair)[93,95,96]
	Abnormal heart rate reserve predicts mortality[90,94–97]
	Peak circulatory power (peak exercise oxygen uptake multiplied for peak mean arterial blood pressure) predicts increased mortality across ACHD diagnosis[98]

ACHD indicates adult congenital heart disease; BNP, brain natriuretic peptide; CHD, congenital heart disease; d-TGA, dextro transposition of the great arteries; ES, Eisenmenger syndrome; HF, heart failure; LV, left ventricular; MRI, magnetic resonance imaging; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; peak $\dot{V}o_2$, peak oxygen consumption; PH, pulmonary hypertension; RA, right atrial; RV, right ventricular; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; $\dot{V}e/\dot{V}co_2$, minute ventilation/carbon dioxide production; and VT, ventricular tachycardia.

care unit were univariate predictors of mortality in ACHD patients on the waiting list. In multivariable analysis, male sex, an albumin level <3.5 g/dL, and mechanically assisted ventilation were significant predictors of mortality 2 months after listing.

In pediatric Fontan patients undergoing transplantation, patients with Fontan physiology were at increased risk of dying while on the waiting list if they were <4 years of age, status 1 (including 1, 1A, 1B), or mechanically ventilated or if they had a shorter interval between the Fontan procedure and the listing date (<6 months).[34]

Contraindications

Possible contraindications to transplantation for ACHD patients include traditional risk factors for transplantation and ACHD-specific risk factors.[23] It is often not any individual risk factor that precludes transplantation but the additive risk of multiple relative contraindications. Patients with CHD are best evaluated at centers with multidisciplinary expertise, including surgical and medical expertise in HF, transplantation, and CHD.[104–107]

Sensitization: PRAs

There is a high prevalence of sensitization in ACHD patients because of prior surgeries with use of blood products and the use of homografts during surgery.[108–110] In these patients, a high PRA (>10%) was associated with poorer outcomes after transplantation.[108] Exposure to allograft tissue during a Norwood procedure was associated with long-term sensitization in 56% of patients.[111] Elevated PRA, defined as PRA >20%, was seen more commonly in pediatric Fontan patients (16.5%) than in pediatric CHD patients without Fontan circulation (12.8%)

or a contemporaneous cohort of non-CHD pediatric patients (2.3%) listed for transplantation.[34] Strategies to minimize exposure to sensitizing agents (eg, blood products and homografts) should be sought.

In a recent UNOS review of 8160 transplant recipients, PRA >25% before transplantation was associated with increased mortality after transplantation.[110] Similarly, the presence of anti-HLA antibodies was associated with worse long-term graft survival in pediatric patients undergoing HTx.[112] Preexisting or the development of de novo donor-specific antibodies has been shown to be associated with an increase in both cellular- and antibody-mediated rejection and cardiac allograft vasculopathy and to adversely affect graft function and survival.[113–117] Strategies to address elevated PRA include desensitization or virtual/real-time crossmatch and are beyond the scope of this article. There have been no randomized controlled trial data comparing these strategies in non-CHD or ACHD patients. Use of virtual crossmatch may impact wait times and access to viable organs.[118]

Pulmonary Vascular Resistance
Pulmonary hypertension (PH) deserves special attention because it is common in CHD,[119] its pathogenesis is likely to be different from PH secondary to acquired HF,[120] and it is an important contributor to posttransplantation morbidity and mortality. In ACHD patients, a pulmonary vascular resistance (PVR) exceeding 4 Wood units was associated with greater perioperative mortality risk (20%), but there was no difference in long-term survival based on pretransplantation PVR.[108] Hence, evaluation of PVR is important and may influence the timing and decision to pursue HTx.

When pulmonary vascular disease is incorporated in the evaluation of a potential transplant candidate, pediatric considerations include age and duration of unprotected overcirculation and PH. Although several studies have examined PH and posttransplantation outcome, they either purposely did not include patients with CHD or patients with CHD represented a minority of the cohort.[121–124] Furthermore, these studies included only those who were preselected to undergo transplantation. Therefore, no simple criteria exist to determine who is considered too high risk for orthotopic HTx. It is important to illustrate the anatomy of the pulmonary vascular tree (proximal and distal vessels) and identify pulmonary venous stenosis so that surgical correction can be undertaken at the time of transplantation.

Left-sided heart disease remains an important cause of PH in CHD, particularly in patients with significant left-sided obstructive or regurgitant lesions. Differentiation of left-sided heart disease from intrinsic pulmonary vascular disease is important to distinguish potentially reversible from irreversible disease in those being considered for HTx. Patients with RV outflow tract obstruction commonly also have elevated RV pressures. It is critically important to distinguish this from true PH. The involvement of a CHD specialist and complete hemodynamic assessment are particularly important for ACHD patients with suspected PH. Depending on the degree of PH, patients may ultimately require HLTx, which is associated with poorer outcomes than isolated HTx or lung transplantation (average life expectancy 3.3 years for HLTx

versus 10 years for HTx and 5.6 years for lung transplantation).[125] Overall, HLTx numbers are on the decline,[125] but it may be the only therapeutic option for some patients. In addition to CHD expertise, evaluation for HLTx should include a multidisciplinary team with expertise in both heart and lung transplantation.

There are increasing data on pulmonary hemodynamics in the risk assessment of HTx in adults and children with HF, although mainly in patients with dilated or ischemic cardiomyopathy. In CHD, however, not only the anatomic but also the hemodynamic conditions for pulmonary vascular remodeling are likely to be different. Instead of high filling pressure in the left atrium as the predominant contributor to PA pressure, cyanosis, volume overload, high sheer force, and abnormal development of the vasculature and lungs often contribute to pulmonary vascular disease. Accurate determination of PVR is not always possible because of shunting (which sometimes can occur at multiple levels and directions), vascular access, dependence on oxygen consumption measurement, and potentially, further loss of accuracy in a pumpless circulation (cavopulmonary connection). Indeed, Mitchell et al[126] showed an increase in transpulmonary gradient and an elevated PVR index in Fontan patients after HTx. Furthermore, the ability to accurately calculate derived values from direct measurements is less reliable. Thermodilution to measure pulmonary flow index is inaccurate in the presence of left-to-right shunts. Flow determined by the Fick principle requires accurate measurement of mixed venous and pulmonary saturation, which is not always straightforward in CHD. Lastly, real-time measurement of oxygen consumption is rarely obtained or reported. These inherent limitations must be considered in the assessment of individual patients.

Although hemodynamic values and pulmonary reactivity are important, other factors should be considered when determining their importance in consideration for transplantation. These include the accuracy by which they are obtained, the clinical history (such as type of CHD leading to PH), age, duration of HF, ability to unload the pulmonary vasculature before transplantation, donor selection, and available options to best support PH and RV failure after transplantation (eg, RV assist device, extracorporeal membrane oxygenation [ECMO], hemofiltration, pulmonary-specific vasodilators). The most practical approach to determining transplantability will require the synthesis of all these variables. The management of PH in CHD is outside the scope of this review.

Surgical Challenges: Complex Anatomy
Many ACHD patients have had prior surgical procedures, which can increase the risk of adhesions and bleeding, lengthen the operative procedure, and increase the need for reoperation.[9] PA reconstruction is commonly required, especially in Fontan patients (85.4% for Fontan patients versus 42.9% for other CHD diagnoses),[36] and is associated with increased mortality risk (odds ratio, 3.3).[103] ACHD patients with atrial switch/redirection procedures (ie, Mustard/Senning) often have calcified baffles and previous stents that need to be removed, which leaves less tissue for atrial anastomoses. Bicaval and pulmonary venous anastomoses are preferable in these situations. Systemic venous anomalies in patients with situs inversus or

heterotaxy require surgeons to use baffle techniques for directing systemic venous return from left-sided cavae to the donor right-sided atrium. Greater lengths of superior vena cava, innominate vein, and donor aorta may be required.

Increased ischemic times are seen in ACHD versus non-CHD patients,[6,9,108] and specifically in ACHD patients with >3 prior sternotomies versus those with 1 or 2.[102] The procurement team needs to be aware if any extra donor tissue or alternate material (eg, bovine) is required for reconstruction.[36] This can limit donor availability depending on the amount of donor tissue required, often resulting in restriction to non-lung donors. Approximately one-third of ACHD patients undergoing transplantation will require additional surgical procedures.[127] Longer surgical times are often associated with longer ischemic times and poorer operative survival.

Assessment for aortopulmonary and venovenous collaterals is important. When possible, coiling before transplantation is appropriate.[128] Percutaneous closure of collaterals will also enable more accurate determination of PVR before transplantation. By minimizing aortopulmonary collateral flow, coiling before transplantation may also assist with cardiopulmonary bypass. A potential disadvantage of coiling before transplantation is the resultant reduction in pulmonary blood flow, which may contribute to worsening hypoxia. A low threshold should be maintained for percutaneous closure of collaterals after transplantation, particularly in patients with unexplained high cardiac output.

Consideration should be given to peripheral cannulation for bypass if difficulties with initial dissection or challenges with anatomy are anticipated, or if there are concerns regarding bleeding. Patients should have vascular ultrasound performed before being listed for transplantation to ensure that the femoral/jugular vein and femoral/axillary artery can accommodate access for bypass.

Liver Disease

ACHD patients, particularly Fontan patients, are at increased risk of liver disease because of the presence of chronic elevations in systemic venous pressure, "right-sided" ventricular dysfunction and valvular heart disease, and an increased prevalence of hepatitis C. Chronically elevated venous pressures increase the risk of congestive hepatopathy, portal hypertension, and cirrhosis. In adults without CHD undergoing HTx, liver dysfunction before transplantation is associated with significant morbidity and an increased risk of posttransplantation mortality.[129] Moreover, the presence of cirrhosis has been associated with increased mortality and morbidity for coronary artery bypass surgery, regardless of the severity of liver dysfunction.[130] In contrast to non-CHD, little is known about the impact of liver disease on ACHD patients at the time of transplantation. The lack of ACHD-specific data and guidelines explains the significant institutional variation in the assessment and treatment of liver disease in this cohort at the time of transplantation. Although some centers would consider significant liver disease a contraindication to HTx, others now offer combined heart-liver transplantation.

The Model for End-Stage Liver Disease (MELD) score has been shown to stratify patients undergoing coronary artery bypass and tricuspid valve surgery (MELD >15) according to risk,[131] with higher scores predicting increased mortality. MELD scores have also been shown to predict mortality in HF patients being evaluated for transplantation,[132] undergoing transplantation (MELD and modMELD, which substitutes albumin for international normalized ratio),[133] or left VAD (MELD ≥17).[134,135] Assenza et al[136] used a modified MELD, MELD-XI (which excluded the international normalized ratio), in a retrospective study of Fontan patients and found that after a mean follow-up of 5.7 years, the baseline MELD-XI score was independently related to the composite end point of HTx, sudden death, or death caused by HF. Although MELD scores predict morbidity and mortality, the use of MELD scores to prospectively assess the candidacy of patients with CHD for MCS or HTx has not been evaluated.

All potential transplant candidates are screened for hepatitis. The presence of hepatitis C is associated with poorer outcomes after transplantation.[137] Hepatitis C appears to be common in ACHD patients (8.6%) who underwent surgical procedures before the introduction of routine blood product screening for hepatitis in 1992.[138] Although hepatitis C–seropositive HTx recipients had poorer survival than seronegative recipients, the relative risk did not reach statistical significance after correction for other donor and recipient factors, which suggests that hepatitis C should not preclude HTx.[137]

Although there are few systematic data to define thresholds of liver disease (which should preclude HTx), a recent consensus report provided guidance for the assessment of liver disease in renal transplant candidates.[139] Their recommendation suggested that patients with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient ≥10 mm Hg should not undergo isolated kidney transplantation but should be considered for simultaneous kidney and liver transplantation. In patients with noncardiac liver disease, an elevated hepatic venous pressure gradient (HVPG) has been associated with the development of esophageal varices,[140] histologic cirrhosis,[141] and risk of liver decompensation.[142] Ripoll et al[142] found that patients with compensated cirrhosis and an HVPG <10 had a low probability (10%) of developing clinically decompensated cirrhosis at a median follow-up of 4 years. Although not studied prospectively in HF, these studies support the use of HVPG <10 as a reasonable threshold to help define candidacy or risk for isolated HTx in patients with liver disease. However, in a small study, hepatic wedge pressures were not able to estimate portal vascular disease in Fontan patients with congestive hepatopathy and sinusoidal dilatation.[143]

In patients with chronically elevated venous pressures, a history of esophageal varices, other features of portal hypertension, or a history of hepatitis B, a liver biopsy and histologic evaluation for cirrhosis and determination of hepatic venous wedge pressure are appropriate. The presence of a normal hepatic venous wedge pressure and normal synthetic liver function suggests that these patients should not be turned down for transplantation on the basis of liver disease alone. However, patients with underlying liver disease (based on MELD, HVPG, cirrhosis, symptomatic portal hypertension, varices, or abnormal synthetic liver function) may face higher operative mortalities and must be evaluated carefully

by an experienced multidisciplinary team. Serial evaluation for wait-listed patients at increased risk of liver disease and hepatocellular carcinoma may help to monitor liver status and function.[144] Combined heart-liver transplantation in patients with combined end-stage HF and liver disease has been performed in small numbers (176 to date in the United States[145]). Cases of successful combined heart-liver transplantation in pediatric and adult CHD have been reported.[146,147]

Disease-Specific Issues

Fontan

Fontan circulation is associated with poorer outcomes after transplantation than other CHD diagnoses, with an 8.6-fold increase in relative risk of death.[102] Fontan patients presenting for transplantation with preserved ventricular function but failing Fontan physiology (eg, symptoms and signs of poor cardiac output, raised right atrial pressure, PLE, ascites, and edema) are at higher risk of dying than those who present with HF and reduced ventricular function.[148] Plastic bronchitis is also seen in single-ventricle physiology patients with a previous Fontan palliation. A recent small pediatric series showed increased risk early after transplantation; however, patients with plastic bronchitis had a 70% 5-year survival, which suggests that the presence of plastic bronchitis should not preclude transplantation.[40] Data in adults are lacking. Chronic venous hypertension, secondary to elevated systemic ventricular end-diastolic pressures, lymphatic drainage abnormalities, endothelial dysfunction, and possible venous thromboembolic disease, is common and may be difficult to accurately assess before transplantation, only manifesting as increased PA pressures or RV failure after transplantation. Sildenafil was found to reduce pulmonary resistance both at rest and with exercise in a small cohort of Fontan patients, which raises the possibility of using sildenafil in those patients with high PVR awaiting transplantation.[149] Fontan patients are more likely to require PA reconstruction and experience longer cardiopulmonary bypass times at transplantation.[36]

Chronic venous hypertension can lead to increased risk of PLE, cirrhosis, and renal dysfunction. Baek et al[150] performed a cross-sectional study assessing hepatic complications in 139 Fontan patients and found that 26% of patients had radiological features of liver cirrhosis, 3% had hepatic masses, and 28% had abnormal markers (thrombocytopenia or hyperbilirubinemia). In multivariate analysis, only the time since initial Fontan procedure was associated with hepatic complications. Importantly, Simpson et al[151] found in a small study of Fontan patients (mean age, 13 years) that computed tomography evidence of liver cirrhosis did not predict 1-year mortality after HTx. They did not systematically assess MELD scores, histology, or HVPG.

Most pediatric Fontan patients who die on the transplant list will do so within 6 months of listing.[34] Moreover, being wait-listed as UNOS status 1 (including 1, 1A, and 1B) was associated with a significantly higher risk of dying while waiting for a transplant.

After transplantation, Fontan patients showed a trend toward a higher risk of death attributable to graft failure, infection (possible increased risk related to malnutrition and PLE),

and bleeding (possibly secondary to liver/renal dysfunction and complexity of surgical dissection, as well as collaterals). Notably, the presence of PLE did not influence outcome after listing or transplantation[34] and resolved in almost all patients after transplantation.[34,148] When renal function allows, the coiling of large arterial-venous malformations and aortopulmonary collaterals before transplantation is worth considering.

Eisenmenger Syndrome

Adults with Eisenmenger syndrome constitute a small proportion (4%) of those seen in tertiary cardiac centers.[152] The role of HLTx remains controversial given the generally poor long-term outcomes of patients who have received transplants (63% 1-year survival[153]; average life expectancy 3.3 years, with a 10-year life expectancy conditioned on survival to the first year[125]; limited donor organ availability; and the need for effective use of the scarce donor resource). Patients with Eisenmenger syndrome are often referred for HLTx or lung transplantation with cardiac repair. Timing of transplantation in this heterogeneous group is difficult to predict. The 5-year survival rate in 229 medically treated adult patients with Eisenmenger syndrome was reported to be 77%,[154] comparable to the <60% 5-year survival rate with HLTx.[153] For Eisenmenger cases in which cardiac repair appears straightforward (atrial septal defect, patent ductus arteriosus, or perimembranous ventricular septal defect) and RV function is acceptable, lung transplantation with primary cardiac repair may be preferable[155]; however, HLTx appears to be the preferred treatment for Eisenmenger syndrome secondary to ventricular septal defect.[155] The relative stability of many patients with Eisenmenger syndrome, particularly on pulmonary vasodilator therapy,[154] is often considered preferable to the risks of HLTx.

Outcomes After HTx

Overall, ACHD patients account for 1.9% of HTx performed,[108] increasing to 3% in the International Society for Heart and Lung Transplantation registry report.[10] Survival early after transplantation is poorer in patients with ACHD than with other pretransplantation conditions,[6] with a higher incidence of primary graft failure[156] and a 2-fold increased relative risk of mortality over the first year.[157] This early risk is offset by a survival paradox seen in ACHD recipients, in which the high early mortality is counterbalanced by better long-term survival.[158] A diagnosis of ACHD carries an odds ratio of 4.18 for early in-hospital mortality after HTx in the recent risk-prediction model developed by Singh et al.[159] Graft failure is the leading cause of midterm and late mortality in ACHD recipients, which highlights the importance of tailoring immunosuppression regimens according to patient demographics and rejection risk.[158] However, late-term survival is better, such that the median life expectancy is better for ACHD patients than for all other pretransplantation diagnoses (13 years), and median survival conditioned on survival to year 1 is also superior to any other diagnosis (18 years). Data from the Nationwide Inpatient Sample show that the in-hospital mortality risk after transplantation in ACHD is much higher in patients with single-ventricle physiology (23% for 1 ventricle versus 8% for 2 ventricles).[160] Survival in 2-ventricle

ACHD patients was comparable to that of a contemporaneous UNOS sample of patients with acquired HF.[160] In pediatric CHD, conditional survival beyond 1 year after transplantation is no different and actually even better for young infants with CHD versus acquired HF, such that over time, their survival catches up with other groups who had higher rates of survival perioperatively.[13,103] On Cox regression analysis, independent risk factors for death after transplantation in ACHD patients included black race, ischemic time, and PVR >4 Wood units.[108]

Given their young age, more ACHD patients who undergo transplantation require retransplantation than non-CHD patients (4.7% versus 3.4%, *P*=0.09).[6] Emerging data on outcomes after cardiac retransplantation in ACHD patients have identified a 2.7-fold increase in the hazard ratio of mortality within 5 years, conditioned on survival to 1 year, for cardiac retransplantation compared with primary transplantation.[158] Further exploration of the factors associated with mortality in ACHD patients undergoing cardiac retransplantation, such as the time interval from primary transplantation and degree of sensitization in these patients, will be important.

ACHD patients have longer ischemic times and higher PVR and require postoperative dialysis and reexploration more frequently than non-ACHD patients after transplantation.[108] Moreover, they face a higher incidence of death caused by early hemorrhage. Careful attention must be paid to perioperative bleeding, RV dysfunction, liver and renal dysfunction, and the presence of residual left-to-right shunts (caused by aortopulmonary collaterals), which may cause high-output HF in the postoperative period. There is also a higher risk of infection.[108] Causes of death attributable to primary graft failure, multiorgan failure, and renal failure are significantly more common in patients with ACHD than in all other diagnoses.[108] Moreover, there is a trend toward increased death attributable to stroke in patients with ACHD.[108] A lower incidence of death attributable to malignancy was seen in ACHD patients.[158] Importantly, there is an additive effect on risk in ACHD between recipient age, donor age, and ischemic time, with hearts from donors >19 years of age demonstrating impaired results with ischemic times >5.5 hours.[161] Lamour et al[102] found that mortality risk increased from 15% to 40% in a 40-year-old ACHD recipient of a heart from a 50-year-old donor simply by increasing the ischemic time from 3 hours to >5 hours. This interaction of risks underscores the need to focus on donor age and acceptable ischemic times when this complex group of patients undergoes transplantation.

Mechanical Circulatory Support

Although overall use of MCS before transplantation has increased over the past decade,[162] it has not increased in ACHD patients. Moreover, MCS is associated with significant morbidity and uncertain long-term outcomes in ACHD patients. Careful evaluation and selection are important to determine whether the patient may be a candidate for other therapies. A variety of VADs have been used to assist the failing systemic RV both in the setting of patients with congenitally corrected transposition of the great vessels and in those with d-transposition after atrial switch operations.

For those patients who have undergone atrial switch procedures, the location and orientation of the systemic RV can provide additional complexity to placement of the inflow cannula, in particular for implantable devices in which the angle of the inflow cannula is short and somewhat restricted. However, for patients supported with paracorporeal devices, manipulation of the inflow and outflow cannulae can adjust for anomalies of cardiac situs or rotation.[163] Despite these issues, because of the difficulty of atrial inflow in the setting of Mustard or Senning baffles, an RV inflow cannula may be preferable. The systemic RV is vulnerable to inflow cannula occlusion because of abundant trabeculations. Accordingly, in most reported cases, muscle resection has been performed before inflow cannula placement.[164–166]

Future-generation devices, including catheter-based therapies[167] and smaller axial flow pumps,[168] may provide additional temporary and long-term support that may be more forgiving of size and orientation constraints. MCS for transposition of the great arteries has been reported with reasonable outcomes in small case series[164]; however, apart from case reports, MCS for Fontan patients[169] has not been widely adopted. In fact, for these complex congenital patients whose Fontan may "fail" at several levels, total cardiac replacement strategies may ultimately be the most effective. In a recent review of the Nationwide Inpatient Sample, ACHD patients with 2-ventricle physiology were far more likely to be bridged to transplant than those with single-ventricle physiology.[160] Evaluation at an experienced ACHD center is important before a patient proceeds with MCS, because medical therapy or surgical repairs may delay the need for transplantation or avoid the need for MCS.

In the most up-to-date guidelines for MCS,[170] 2 important considerations are raised regarding CHD. One is the need for assessment of full cardiac morphology (including location of great vessels, shunts, and collateral vessels, assessed before MCS). The other is that for those patients who are not candidates for left ventricular support, assessment for total heart replacement strategies is important. A multi-institutional MCS single-ventricle registry that better defines selection criteria for MCS is needed.[171]

MCS has been used in the pediatric population for a long time. The experience stems largely from the use of ECMO for postcardiotomy or fulminant myocarditis, such that this support is meant to be temporary until recovery. A subpopulation of these patients, as well as those with cardiomyopathy or CHD without postcardiotomy, may require longer-term support as a bridge to transplantation. ECMO may not be ideal for longer intervals of support, and thus, durable devices have been the focus of attention in the pediatric medical and surgical HF community. In an analysis of the Organ Procurement and Transplantation Network and Extracorporeal Life Support Organization registries combined, ECMO used as a bridge to transplantation for all-comers was associated with a 47% survival rate to discharge, specifically, recovery or transplantation.[172] Pretransplantation and posttransplantation survival were independently associated with CHD in patients bridged to transplant with ECMO, in whom survival to discharge was 44% for CHD with 2-ventricle physiology and 33% with single-ventricle anatomy, compared with 63% for cardiomyopathy. The need for durable support in children led to the

development and application of the Berlin Heart EXCOR (Berlin Heart, The Woodlands, TX), which is the device that has been studied the most extensively. The North American cohort study[173] included 19 patients with CHD (26%) and reported a mortality rate of 23% for the entire cohort, with a median duration of support of 1.6 months for those who received this therapy as an intentional bridge to transplantation. Subpopulation analysis of CHD was not available. In a later period that included patients enrolled under an investigational device exemption trial in the United States, survival at 12 months was 75%, including 64% who reached transplantation.[174] CHD accounted for 59 of 204 patients (28.9%), with 19 (9.3%) having single-ventricle physiology. Although CHD was not shown to be a univariable risk factor for death, lower weight and need for biventricular support were risk factors in the multivariable analysis, and many of the CHD patients were younger and smaller and required biventricular support. Of note, among 14 infants with CHD who weighed <5 kg, 13 died. Perhaps the most rigorously performed study that led to US Food and Drug Administration approval of the Berlin EXCOR was a single-arm prospective enrolment of patients bridged to transplant compared with a contemporary group of propensity score–matched ECMO patients.[175] Similar to previous pediatric studies, CHD patients made up a minority of the participants (9 of 46 patients). Survival was better with the Berlin EXCOR than for a historical ECMO cohort from the Extracorporeal Life Support Organization registry. Major adverse events were fairly common, with 29% experiencing a stroke and 92% experiencing some major adverse event in the small (body surface area <0.7 m^2) cohort. A recent study found the 12-month posttransplantation survival rate was 88.7% in the EXCOR group compared with 89.3% in the UNOS high-priority listed status 1A group and 60.3% in the ECMO-supported group.[176] Among the EXCOR patients, CHD (23 of 106 patients) was found to be a risk factor for posttransplantation mortality in the univariate analysis (26.1% versus 7.2% in non-CHD, P=0.02).

Support of patients with a cavopulmonary connection is considered to be more challenging. There are no large reports, probably because there are not many patients who have undergone the Glenn or Fontan procedures who are supported by durable assist devices. Weinstein et al[15] further reviewed the single-ventricle patients from the North American EXCOR experience. The authors described 26 patients with single-ventricle physiology supported with the EXCOR: 3 of 5 with total cavopulmonary connection, 7 of 12 with Glenn connection, and 1 of 9 after Norwood stage 1 procedures were successfully bridged to transplant. Although there was higher mortality than for 2-ventricle patients with CHD, the use of EXCOR in a cavopulmonary connection was possible. Isolated case reports of the application of various devices, including both newer continuous-flow assist devices already on the market and the total artificial heart, are beginning to emerge in the literature, but it is clearly too early to comment on their use.

Table 3. Future Areas of Transplantation and MCS Focus in CHD

Multicenter observational CHD lesion-specific studies to aid in predicting prognosis

Multicenter observational studies of MCS in lesion-specific CHD

Prospective cohort study comparing outcomes between high-risk patients with CHD selected for transplantation versus palliation

Identification of predictors of impending mortality to guide listing status (upgrade to 1A) in ACHD patients who do not meet traditional 1A criteria developed for acquired CHF or who are not suitable candidates for MCS

Strategies for reducing wait-list times for CHD patients to ensure equitable access to transplantation, including measures to address listing status

Evaluation of existing and emerging desensitization strategies for elevated panel reactive antibodies, both in acquired heart disease and in CHD

ACHD indicates adult congenital heart disease; CHD, congenital heart disease; CHF, congestive heart failure; and MCS, mechanical circulatory support.

Therefore, it remains unclear whether and when MCS or a specifically chosen device should be used for the pediatric patient with HF and CHD.

Summary

The prevalence of CHD patients with severe disease is increasing,[3] with increasing numbers of CHD patients who survive into adulthood[177] in need of advanced therapies, including transplantation and MCS. Although much progress has been made over the past decade, there are many questions, and there is much work still to be done (Table 3). Inclusion of palliative care is important for all patients with end-stage CHD, regardless of decisions regarding transplantation or mechanical support. Although patients with CHD are at higher risk early after transplantation, long-term outcomes for CHD patients are superior to those for patients who undergo transplantation for other reasons. Prediction of prognosis in CHD patients is difficult, and further studies are needed. The role of biomarkers and survival scores for CHD patients with HF has not been addressed. More longitudinal data on risk and predictive models of risk may aid prognostication. CHD patients face a longer time on the wait-list and higher wait-list mortality. The diagnosis and management of CHD patients are complex. These patients need multidisciplinary and interdisciplinary evaluation and care, both before and after transplantation. Hence, it is important that patients with CHD and HF be referred early for consideration of advanced therapies. Current evidence supports HTx, lung transplantation with cardiac repair, or HLTx in appropriately selected ACHD patients. ACHD anatomy-specific issues, PH, renal and liver disease, and the presence of anti-HLA antibodies require appropriate pretransplantation assessment and may identify patients at greater risk of perioperative events. Use of registry data to better understand the role of conventional MCS in CHD is imperative. Moreover, development and evaluation of disease-specific MCS devices is needed to aid the large numbers of ACHD patients whose anatomy precludes traditional MCS support.

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*Modest.

†Significant.

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Significant.

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