Challenges and Opportunities in Pediatric Heart Failure and Transplantation

Changing Indications for Pediatric Heart Transplantation
Complex Congenital Heart Disease

Daphne T. Hsu, MD; Jacqueline M. Lamour, MD

Since the first heart transplantation procedure was performed almost 50 years ago, heart transplantation has undergone a startling transformation from an experimental, high-risk intervention to being offered as standard of care for children and adults with heart failure refractory to medical and surgical therapy.1,2 The potential for heart transplantation to treat complex congenital heart disease was recognized early in the transplantation experience. In 1967, the first heart transplantation procedure in the United States was performed in an infant with Ebstein anomaly and subvalvular right ventricular outflow tract obstruction.3 Shortly thereafter, heart transplantation was adopted to treat the most complex forms of congenital heart disease in the most critical situations.4–9 Over the past 3 decades, the indications for transplantation in adults and children have evolved as new medical and device therapies have been developed, the number of available donors has plateaued, and risk factors for better and worse outcomes have been identified.10,11

In the 1980s, survival after heart transplantation was significantly better than survival after the Norwood procedure, and un repaired hypoplastic left heart syndrome was the major indication for infant heart transplantation.12–15 As survival after the Norwood procedure improved to >80% and the shortage of infant donor hearts continued to result in a high incidence of death while waiting (20%–25%), the indications for transplantation in the neonate with hypoplastic left heart syndrome have narrowed to the point where transplantation is rarely considered in the initial management of this lesion.16–18 This has resulted in a significant decrease in the proportion of infants with the diagnosis of congenital heart disease undergoing transplantation, as shown in Figure 1.18,19

A corresponding shift in the demographics of heart-transplanted patients has resulted from the successful palliation of complex heart diseases such as hypoplastic left heart syndrome, with an increasing population of adolescents and young adults referred for heart transplantation because of acute-onset or worsening heart failure.20–22 New medical and device therapies developed for adult patients with heart failure have not proven to be broadly efficacious for the treatment of heart failure in patients with complex congenital heart disease.23,24–26 Thus, heart transplantation is often the only option for patients with congenital heart disease and heart failure unresponsive to conventional medical therapy. The majority of these patients have undergone palliation for single-ventricle physiology with either a Fontan or bidirectional Glenn/hemi-Fontan.27–36 Enthusiasm for the use of transplantation in this population has been tempered by relatively high transplantation-related morbidity and mortality, with 1-year mortality ranging between 20% and 25%.37–42

Establishing indications for transplantation is a complex process that includes determining the benefits of the procedure for the patient, optimizing donor longevity, and ensuring equitable allocation of organs within the society.43 In heart transplantation, the limited donor supply and the desire to maximize the usefulness of the donated heart have led to benchmarking of transplantation outcomes by comparison of results among centers.44 The United Network of Organ Sharing has mandated public reporting of transplantation activity by all centers approved by the Centers for Medicare and Medicaid Services. The semiannual reports include deaths on the wait list and deaths and graft loss after transplantation. Since 2012, all programs with an observed 3-year patient or graft survival lower than expected undergo review, and depending on the results of the review, programs may be required to develop a corrective action plan and to submit to closer monitoring.45 The goals of improving an individual patient’s situation, ensuring the best use of the donor heart, and achieving equitable donor allocation may not always be concordant. Situations have arisen in which conflicts among these goals have extended into the public realm, and the result has been direct clashes between United Network of Organ Sharing policy and legal opinion.46

Although an in-depth examination of the bioethical issues surrounding the goals of achieving the maximal benefit of heart transplantation to the patient and to society is beyond the scope of this discussion, understanding the survival benefits of transplantation for an individual patient and comparing survival results among patients are important steps toward developing evidence-based indications for transplantation and ensuring the best use of the donor heart. The following sections outline the scope and outcomes of advanced heart failure in congenital heart disease and highlight ways in which risk stratification and outcome data can be used to evaluate the potential benefit of transplantation in this challenging population.

Heart Failure in Complex Congenital Heart Disease
The types of congenital heart lesions found in patients who develop advanced heart failure are skewed, not unexpectedly,
The causes of low cardiac output in the congenital heart disease are protein-losing enteropathy, intra-atrial reentrant tachycardia, and systemic venous congestion can lead to complications such as heart failure and chronic effusions. These complications all decrease the ability of the heart to pump blood efficiently.

Among patients with congenital heart disease undergoing transplantation, single-ventricle lesions are the most common (36%), followed by systemic right ventricles (20%; Table 1).

The causes of low cardiac output in the congenital heart disease patient extend beyond systolic ventricular dysfunction to include hemodynamic abnormalities specific to the underlying heart defects. Severe volume overload from an intracardiac shunt or regurgitant valve or pressure overload resulting from stenosis of the right or left ventricular outflow tract can cause heart failure with normal ventricular function or can exacerbate heart failure in the patient with depressed ventricular function. Although less common, heart failure can occur with preserved ejection fraction resulting from diastolic function abnormalities in patients with left ventricular outflow tract obstruction. In patients with Fontan physiology, chronic heart failure and long-term exposure to passive systemic venous congestion can lead to complications such as protein-losing enteropathy, atrial reentrant tachycardia, and chronic effusions. These complications all decrease venous return to the systemic ventricle and can result in a low-cardiac-output state.

The presence of cyanosis, tachyarrhythmias, or bradyarrhythmias is common in patients with congenital heart disease and can worsen symptoms of heart failure. Table 2 lists common causes of heart failure in patients with congenital heart disease.

The onset of heart failure in patients with congenital heart disease ranges from early infancy to adulthood. The prognosis of heart failure varies widely, depending on the cause of the heart failure and the age at presentation. In infancy, heart failure may be present at the time of diagnosis, is often related to the pathophysiology of the defect, and may be exacerbated by impaired oxygen delivery resulting from cyanosis. Ventricular dysfunction can be present even at birth and, if moderate or severe, may be a contraindication to surgical intervention, particularly in the most complex lesions such as single-ventricle lesions. Myocardial dysfunction that occurs in the early postoperative period has a high mortality (>50%), particularly if it is persistent or mechanical support is required.

Although overall survival after congenital heart surgery has been improving steadily, mortality in patients with single-ventricle physiology remains high. In a large multicenter study of infants after the Norwood procedure, mortality in the first 3 years of life was 30%. In this cohort, the most common cause of death was heart failure.

In older children, adolescents, and young adults with congenital heart disease, heart failure is an important cause of late morbidity and mortality. Ventricular systolic dysfunction is a common occurrence, particularly in the patient with a systemic right ventricle or a single ventricle. Symptomatic heart failure requiring admission to the hospital is associated with 3% to 5% mortality during hospitalization and a 24% incidence of death within the first year after admission. Among deaths occurring in the adult congenital heart disease population, heart failure is the cause in 30% to 50%, and sudden death resulting from ventricular arrhythmias accounts for another 20%. Patients at highest risk for death as a result of heart failure are those with single-ventricle physiology or systemic right ventricular anatomy; however, patients with left-sided obstruction or chronic volume overload of the right ventricle are also at a higher risk than the general population.

### Table 1. Major Diagnostic Categories for Patients With Congenital Heart Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>% (of 488)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single ventricle</td>
<td>176</td>
<td>36</td>
</tr>
<tr>
<td>d-Transposition of the great arteries</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Right ventricular outflow tract lesions</td>
<td>49</td>
<td>10</td>
</tr>
<tr>
<td>Ventricular/atrial septal defect</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>Left ventricular outflow tract lesions</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>l-Transposition of the great arteries</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>Complete atrioventricular canal defect</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>53</td>
<td>11</td>
</tr>
</tbody>
</table>

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### Indications for Heart Transplantation

In the United States, universal guidelines for transplantation have not been adopted for pediatric heart transplantation, and transplantation programs are mandated to develop centerspecific criteria. Several groups have published indications for heart transplantation in children, developed by expert consensus because evidence is lacking. They are written primarily from the perspective of the individual patient, with the goal of improving survival by weighing the risks and benefits of medical, surgical, or catheterization-based therapies against the risks and benefits of heart transplantation. Although written to be applicable to the general population of children referred for transplantation, several indications specific to the congenital heart disease population are included in these recommendations.

A recent scientific statement from the American Heart Association contains a comprehensive overview of the current state of pediatric heart transplantation and presents recommended indications that are based on expert consensus developed by a pediatric heart transplantation specialists.
this document, class D heart failure, defined as symptomatic heart failure at rest requiring continuous inotropic support, mechanical ventilation, or mechanical device support, was considered a Class I indication. Transplantation was also recommended in children with class C heart failure (present or past history of symptomatic heart failure) who were at risk for sudden death or pulmonary hypertension. The application of these recommendations to the congenital heart disease population can be difficult. Defining symptomatic heart failure in congenital heart disease patients is challenging. Patients with complex congenital defects often accommodate their lifestyle to lower levels of activity gradually, making symptoms more difficult to elicit. Exercise performance after palliation of complex congenital heart lesions such as the atrial switch procedure or the Fontan procedure is impaired, with a maximal oxygen consumption of 60% of predicted in asymptomatic patients. A lower maximal oxygen consumption has been associated with worse outcomes in patients with a Fontan procedure. A maximal oxygen consumption <50% of the expected for the congenital heart lesion has been proposed as an indication for listing. In some circumstances, this may result in a maximal oxygen consumption value lower than the 15-mL·kg⁻¹·min⁻¹ maximal oxygen consumption commonly used as an indication for transplantation in the adult heart failure population.

Identifying the patient with congenital heart disease at risk for pulmonary hypertension or sudden death can also be challenging. Patients with congenital heart disease have a predisposition to pulmonary hypertension, particularly those with diastolic dysfunction or chronic volume overload. Risk factors and the time course for development pulmonary hypertension in the congenital heart disease patient have not been identified. Sudden death is an important cause of death in adult patients with congenital heart disease. Risk factors for sudden death in this population have not been well defined; thus, quantifying the degree of risk for the sudden death in a potential recipient can be difficult.

Since the earliest days of heart transplantation in children, it has been recognized that to develop indications for transplantation in patients with complex congenital heart disease, the outcomes of surgical intervention and medical therapy must be considered. In 1993, Boucek and colleagues reported a risk-adjusted algorithm for transplantation in infants with congenital heart disease designed to maximize the success of transplantation and to achieve results comparable to those of palliative surgery. This algorithm considered the presence of potential risk factors for death on the wait list and death after transplantation and emphasized the importance of taking into consideration mortality before and after transplantation when comparing results for transplantation with results for palliative surgery. More recently, Singh et al reported an analysis of the United Network of Organ Sharing database that assessed the benefits of transplantation by evaluating the ability of heart transplantation to lower the risk of death. Their model compared mortality with and without transplantation in the first year after listing. They found that although patients with a higher mortality risk on the wait list also had a higher risk of death after transplantation, the improvement in survival with transplantation was also greater in the higher-risk patients. Patients with the diagnosis of congenital heart disease were often in the group with a higher risk of mortality on the wait list and as a result had a greater potential for transplantation benefit.

### Outcomes in Children After Heart Transplantation

Data from the Registry of the International Society of Heart and Lung Transplantation demonstrate that between 2006 and 2012 congenital heart disease was the cause of heart failure in 54% of infants and 30% of older children who were transplanted. Ten-year survival was 10% lower in patients with congenital heart disease compared with those with cardiomyopathy. The majority of the mortality difference could be attributed to the early posttransplantation period because conditional survival in patients who were alive 1 year after transplantation was no different between the patients with cardiomyopathy and those with congenital heart disease.

### Risk Factors for Mortality in Pediatric Heart Transplantation

Risk analysis using data available from donor registries and prospective databases has identified several factors that negatively affect survival after transplantation. These include renal failure, the need for extracorporeal membrane oxygenator support, mechanical ventilation, the presence of anti-HLA antibodies, and infection within 2 weeks of transplantation. The use of extracorporeal membrane oxygenation before transplantation had a hazard ratio of 2.65, and 1-year posttransplantation survival was 64%. Mortality on the wait list for sensitized patients who express anti-HLA antibodies is reported to range between 19% and 22% because a negative prospective HLA cross-match is often a prerequisite to accepting the donor heart. Survival after transplantation is also worse in sensitized compared with nonsensitized patients, 73% versus 90%, respectively. Anti-HLA antibodies are common in patients with complex congenital heart disease who have had allograft material such as conduit or aortic

<table>
<thead>
<tr>
<th>Table 2. Causes of Chronic Heart Failure in Congenital Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic ventricular systolic or diastolic dysfunction</td>
</tr>
<tr>
<td>Single-ventricle physiology</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>d-Transposition of the great arteries s/p atrial switch procedure</td>
</tr>
<tr>
<td>i-Transposition of the great arteries</td>
</tr>
<tr>
<td>Atrioventricular canal defect with chronic mitral regurgitation</td>
</tr>
<tr>
<td>Post–cardiopulmonary bypass</td>
</tr>
<tr>
<td>Pulmonary ventricular dysfunction</td>
</tr>
<tr>
<td>Tetralogy of Fallot with pulmonary or tricuspid insufficiency</td>
</tr>
<tr>
<td>Complications of the Fontan procedure</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
</tr>
<tr>
<td>Intra-atrial reentrant tachycardia</td>
</tr>
<tr>
<td>Chronic effusions</td>
</tr>
<tr>
<td>Cyanosis</td>
</tr>
</tbody>
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arch patch implanted. The reported incidence of anti-HLA antibody formation was 50% by 1 year after congenital heart surgery that included implantation of allograft material.\textsuperscript{81–88} Patients with congenital heart disease often have >1 risk factor present, and the presence of multiple risk factors has a cumulative effect on mortality. In an analysis of the United Network of Organ Sharing database, the presence of a higher number of risk factors increased the 30-day mortality after transplantation from 8% in patients with 1 risk factor to 25% in patients with 3 risk factors.\textsuperscript{78}

Outcomes of Heart Transplantation in Patients With Dilated Cardiomyopathy

Overall survival in children with dilated cardiomyopathy after listing and after transplantation has improved as a result of better risk assessment, advances in medical management of advanced heart failure, and the availability of mechanical ventricular assist devices. Ventricular assist devices capable of longer-term support have the potential to decrease the incidence of recipient comorbidities such as renal dysfunction, mechanical ventilation, and malnutrition. Mortality on the wait list may differ by type of cardiomyopathy, with some series reporting that children with nondilated cardiomyopathy have a higher risk of death while waiting (15%).\textsuperscript{89} Current outcomes after transplantation for dilated cardiomyopathy in children are outstanding, with a 98% 1-month and 94% 1-year survival.\textsuperscript{89}

Risk Factors for Mortality Unique to Patients With Congenital Heart Disease

The majority of factors associated with death on the wait list and death after transplantation in infants with congenital heart disease are similar to those reported for all children undergoing transplantation and include the need for extracorporeal membrane oxygenation support, mechanical ventilation, and renal dysfunction. Risk factors specific to the infant congenital heart disease population such as lower weight and the need for prostaglandin support have also been identified.\textsuperscript{17,18,80} Although results in infants transplanted for unrepaired complex congenital heart disease are similar to those for transplanted infants with dilated cardiomyopathy,\textsuperscript{18,89} outcomes of transplantation in young infants as a rescue therapy for failed hypoplastic left heart syndrome are worse compared with those for patients with cardiomyopathy (1-year survival, 70% versus 89%, respectively).\textsuperscript{81,91}

Older children and young adults with congenital heart disease have additional risk factors affecting their outcome after listing and transplantation compared with children with cardiomyopathy. Patients who were listed for transplantation within 6 months of the Fontan procedure were more likely to die while waiting for a heart than patients who were listed >6 months after the procedure (33% versus 11%, respectively).\textsuperscript{32} Congenital heart disease itself has consistently been identified as a risk factor for early and midterm mortality after transplantation compared with patients with cardiomyopathy.\textsuperscript{10,20,32,35,39,40,42,92–99} The increased mortality occurs soon after transplantation and is likely the result of a combination of factors, including the debilitated state of the recipient, longer donor ischemic times, baseline renal insufficiency, a higher incidence of HLA-sensitized patients, and immune system dysfunction. In the Fontan patient, chronic hepatic congestion has been found to lead to fibrosis and ultimately cirrhosis.\textsuperscript{100,101}

The type of congenital heart disease also affects survival after transplantation. Patients who have undergone the Fontan procedure have a higher posttransplantation mortality than patients with other types of congenital heart disease, with one series reporting a hazard ratio of 8 for early mortality.\textsuperscript{29,35,37,98,105} In a report from 2006, 1-year posttransplantation survival was 77% in patients with a Fontan procedure, 85% in patients with other types of congenital heart disease, and 91% in those with cardiomyopathy.\textsuperscript{12} One-year posttransplantation survival in patients who have undergone repair of corrected transposition of the great arteries, an atrial switch procedure, or an aortopulmonary shunt ranges between 80% and 100% in several small series.\textsuperscript{63,93}

Despite increased early and midterm mortality seen in patients with congenital heart disease, data from the International Society for Heart and Lung Transplantation registry demonstrate that adult patients with congenital heart disease have the best conditional survival and the highest overall survival compared with patients with all other underlying causes (Figure 2).\textsuperscript{109} An overall survival benefit was not seen in pediatric patients with congenital heart disease compared with those with cardiomyopathy because of the significantly higher mortality (20% versus 10%) in the peritransplantation period.\textsuperscript{107} Conditional survival was not different in the patients with congenital heart disease compared with children with the diagnosis of cardiomyopathy.\textsuperscript{12,107}

Alternatives to Transplantation in Patients With Congenital Heart Disease

The potential for new medical therapies to alter the course of children and young adults with heart failure caused by congenital heart disease is uncertain because the underlying mechanisms and genetic substrates differ substantially from those of the adult population. In the aging adult population, the development of mechanical support devices that will provide up to 10 years of support is increasingly within reach and, once achieved, will offer an excellent alternative to orthotopic transplantation.\textsuperscript{108} On the other hand, the use of mechanical devices as destination therapy in children and young adults poses major challenges. Reports of the use of ventricular assist devices to support patients with congenital heart disease are rare and limited to case reports or small series. Morbidity and mortality are high, and survival to transplantation can be challenging.\textsuperscript{109–111} A recent article summarizing the experience with the Berlin EXCOR device in infants and small children with a single ventricle reported a mortality of 42% on the device and a survival to heart transplantation rate of 42%.\textsuperscript{23}

The technical challenges of developing long-term destination devices to support growing children include the need for adjustable pumps with small volumes that can be increased...
over time and the need for pump housing and cannula that are small enough to be implanted internally with the capacity to lengthen over time. Patients with complex congenital heart disease pose additional design challenges because hypoplasia of the cardiac chambers and abnormal positioning of the systemic veins, arteries, atria, and ventricles require flexibility in cannula and pump placement. Thus, in the foreseeable future, the use of ventricular assist device support as a bridge to transplantation or as destination therapy in pediatric and adult patients with congenital heart disease will be limited.

### Donor Shortage
The lack of suitable donor hearts is a major limiting factor in the application of heart transplantation to all who would potentially benefit. Approximately 15% to 20% of children who are listed for a transplant die without receiving a heart, and children with congenital heart disease are more likely to die while waiting for a heart. In 2013, heart transplantation was performed in 2147 adult and 404 pediatric patients in the United States. Between 2006 and 2012, 10% of the adult patients transplanted between the ages of 18 and 39 years had the diagnosis of congenital heart disease. The number of children transplanted in the United States has remained relatively stable over the past 10 years, whereas the overall proportion of adult patients transplanted with congenital heart disease has increased from 1.8% to 2.9% over the past 20 years, reflecting the growing population of late survivors of complex congenital heart disease surgery.

### Changing Indications of Heart Transplantation in Complex Congenital Heart Disease
The indications for transplantation in children with complex congenital heart disease have evolved over the past 3 decades from a primary indication for treatment of neonates with unrepaired hypoplastic left heart syndrome to the treatment of heart failure in the adolescent and young adult with palliated congenital heart disease. Currently, transplantation is indicated in patients with complex congenital heart disease who have acute decompensated heart failure, are refractory to medical therapy, and are not acceptable candidates for reparative or palliative surgery. Prevention of modifiable risk factors such as sudden death, pulmonary hypertension, renal dysfunction, and progression of disease to severe heart failure is an important goal of the pretransplantation management these patients; however, evidence on the best treatment protocols is lacking, and the impact of specific risk factors on overall outcome has not been studied.

The decision of when to offer transplantation to the patient with chronic heart failure and congenital heart disease presents unique challenges. A gradual deterioration in functional status may be more common than an episode of acute decompen- satory heart failure, and careful serial assessment of a patient’s functional ability may be the best and most timely indication of worsening heart failure. Frank discussions of the risks and benefits of transplantation between the transplantation team, the patient, and the family include the need to weigh the excellent long-term survival that occurs in adolescents and young adults with congenital heart disease against the higher risk for morbidity and 20% risk of mortality in the first year after transplantation. This potential “short-term pain for long-term gain” raises the importance of shared decision making among the patient, family, and medical providers when considering whether to move forward with transplantation.

### Future Challenges
The lack of alternative therapies to treat end-stage heart failure in patients with complex congenital heart disease makes the shortage of donor organs a particularly pressing issue for this population. Regulatory bodies monitoring transplantation center activity are becoming increasingly sophisticated in defining success and in the future must be prepared to consider longer-term outcomes than 1- and 3-year survival when evaluating center results and implementing donor allocation policies. It is important to ensure that patients who would benefit in the long term are not disadvantaged in the short term because benchmarking is linked to short-term outcomes. Further research optimizing the design of mechanical assist devices to enable them to support patients with complex congenital heart anatomy has the potential to lessen peritransplantation risk. Until acceptable long-term mechanical support is available, it could be argued that the optimal use of a donor heart would be implantation in a patient with chronic heart failure and complex congenital heart disease who has no other treatment options. Recently, pediatric donor allocation
policies were changed to give preference to patients <18 years of age with congenital heart disease who require isotropic support over those with cardiomyopathy. This policy has not yet been implemented, but the hope is that it will result in better outcomes after listing in all patients, including those with congenital heart disease.\textsuperscript{11} As transplantation centers and regulatory bodies move toward standardizing indications for transplantation, the need to make decisions on equitable allocation of donor hearts will require both better data to predict outcomes more accurately and the wisdom of Solomon to achieve an equitable solution.

Disclosures

None.

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