Review Board (RB) Guidance for Adult Congenital Heart Disease (CHD) Exception Requests

The OPTN/UNOS Board of Directors recently approved the Thoracic Organ Transplantation Committee's Modification *to the Adult Heart Allocation* proposal during their December 2016 meeting in St. Louis, MO. One of the major components of the new allocation system was the creation of three additional medical urgency statuses, for a new total of six. This new six-status system stratifies heart transplant candidates according to waiting list mortality.

During the development of the adult heart allocation policy, the Committee received feedback from the heart transplant community that adult congenital heart disease (ACHD) candidates may be disadvantaged by the new system, as they are a very heterogeneous candidate group and they may not always be optimal candidates for devices or inotropes.

The Committee acknowledged that some ACHD candidates may have higher waiting list mortality. The new allocation policy includes hemodynamic criteria in addition to criteria based on levels of support. Measurement of hemodynamics among patients with CHD can be complicated by altered anatomy and rendered meaningless. In addition, ACHD patients may not be candidates for the inotropic or mechanical support options. Thus CHD candidates may have difficulty meeting criteria for higher status according to policy, despite waitlist mortality equivalent to other candidates at higher status. Instead, the exception and review process will continue to accommodate these candidates, who can still apply for an exception at any status as their medical urgency and potential for benefit would warrant, including status 1, short-term. The Committee drafted this guidance with the goal of helping review board (RBs) standardize decision-making for ACHD exception requests.

Review Board (RB) Guidance for Adult Congenital Heart Disease (CHD) Exception Requests

Background

The majority of adult heart transplants occur for candidates diagnosed with ischemic cardiomyopathy. Heart failure in such candidates is often treated with inotropes or mechanical support, and the need for these support modalities is an important predictor of survival while waitlisted for an organ. Candidates without predominant systolic heart failure, including those with congenital heart disease (CHD), hypertrophic, or restrictive cardiomyopathies (HCM, RCM) are often poorly served by these types of support. Since the listing status of heart transplant candidates may be dependent on the utilization of mechanical support or inotropes, this subgroup of patients may have limited access to higher urgency statuses using standard criteria.

Overall mortality for ACHD places them clearly within status 4 of the new allocation system, so this allocation scheme does acknowledge that on average, these candidates have higher waiting list mortality than candidates with dilated cardiomyopathy.[1] But, there are likely subsets of candidates with CHD in status 4 who will have worse outcomes and merit listing at a higher urgency. Despite a detailed review of available OPTN data, as well as results from the thoracic simulation allocation model (TSAM) that informed the modifications to the adult heart allocation system, the Committee was unable to classify specific ACHD candidates into higher urgency statuses based on reliable, objective hemodynamic or other data in a nationwide sample. Therefore, the Committee recognized that these candidates may need to be handled through the exception pathway and review board (RB) system. In evaluating exception requests, the RBs are tasked with determining whether the "candidate has an urgency and potential for benefit comparable to that of other candidates at the requested status."[2] While this provides a measure of individual assessment for each candidate, there is the risk that it will also result in unintended variation and disparate listing criteria based on the region of listing rather than the severity of heart failure. Accordingly, the Committee believes that an attempt to define broad groups of CHD candidates who are likely to have higher mortality and merit higher urgency listing would assist the review boards in their assessments and improve the consistency across the entire review process.

Recommendations

The following guidelines are intended to broadly classify ACHD candidates and, based on a comprehensive review of the current literature, suggest appropriate status upgrades under specific clinical circumstances. As part of its review, the Committee acknowledges that while the recommendations are, to the extent possible, based on published, peer-reviewed data as well as Scientific Registry of Transplant Recipients (SRTR) modeling, there is also a component of expert consensus that is not as robust. Therefore, these recommendations should not be interpreted as stringent as policy but more so a guide for each individual candidate. The Committee expects that the RBs will play an important role in objectively assessing medical urgency and potential for benefit in individual candidates by placing candidates within a status that corresponds to their most likely level of waiting list mortality as compared with other candidates in that status.

Adult candidates with CHD who are listed for transplant are a particularly heterogeneous group. They represent a small proportion of adults listed for transplant (approximately 2% in any given year), and have a range of diagnoses, including single ventricle circulation at various stages of palliation, failed two ventricle circulations, and failure not directly attributable to altered systolic function.[3] Each diagnosis may have drastically different predictors of waiting list mortality; for example, Fontan candidates with protein-losing enteropathy (PLE) may have normal filling pressures and normal cardiac output, but have a high risk of infection and decompensation, while a candidate with tetralogy of Fallot may have a combination of

[1] First proposal/TSAM
[2] OPTN/UNOS Policy 6.3: Adult and Pediatric Status Exceptions.
[3] Davies RR, Russo MJ, Yang J, Quaegebeur JM, Mosca RS, Chen JM. Listing and transplanting adults with congenital heart disease. *Circulation.* 2011;123:759–767.

biventricular failure and arrhythmia risk. The task of the RBs is to attempt to estimate the medical urgency and potential for benefit in each candidate, something that is particularly challenging in this population, and may be made more challenging by the relative lack of experience with these diagnoses among many adult heart failure practitioners. While reliance on objective measures of heart failure severity, including hemodynamics and laboratory values, is intuitively attractive, there is little data (especially in single ventricle candidates) to support the use of objective measures in predicting waiting list mortality among ACHD. The inability to reliably predict survival among candidates with Fontan failure remains a critical challenge in choosing when to list these complex candidates. Clearly, waiting for non-cardiac end organ injury, including renal failure or profound liver insufficiency, results in poor post-transplant outcomes and indicates that listing and transplant have occurred too late.[4] Therefore, reliance on the occurrence of end-organ dysfunction may not be appropriate in evaluating candidates for higher listing urgency.

In order to provide some standardization to the analysis of these candidates, the Committee recommends two broad category groupings based on the number of ventricles:

- Single ventricle heart disease candidates
- Dual ventricle heart disease candidates

Each category is discussed more fully below. It is important to note that in all cases, candidates must be admitted to the transplant hospital that registered the candidate on the waiting list to be eligible for exceptions to status 1-3.

Category 1: Single ventricle heart disease

Most candidates, in the absence of the conditions below, are appropriately categorized in status 4 or status 2 (when supported by a ventricular assist device). Table 1 provides useful guidance for RBs asked to approve upgraded listing urgency by exception for ACHD with single ventricle physiology.

[4] Davies RR, Sorabella RA, Yang J, Mosca RS, Chen JM, Quaegebeur JM. Outcomes after transplantation for “failed” Fontan: A single-institution experience. *J Thorac Cardiov Surg*. 2012;143:1183–1192.e4.

Table 1: Recommended criteria for ACHD status exceptions

If the candidate meets this criteria:	Then the candidate is eligible for:
Is admitted to the transplant hospital that registered the candidate on the waiting list and is experiencing complications of their VAD (limited to VAD complications indicated in *Policies 6.1.A-6.1.C*: life-threatening ventricular arrhythmia, hemolysis, pump thrombosis, right heart failure, device infection, mucosal bleeding, and aortic insufficiency). Note single-ventricle VADs are currently classified into status 2 in policy[5]	Status 1 exception

Is admitted to the transplant hospital that registered the candidate on the waiting list and meets *any* of the following:
• Supported by *one* of the following:
  ▪ A continuous infusion of at least one high-dose intravenous inotrope:
  ▪ Dobutamine greater than or equal to 7.5 mcg/kg/min
  ▪ Milrinone greater than or equal to 0.50 mcg/kg/min
  ▪ Epinephrine greater than or equal to 0.02 mcg/kg/min
  ▪ A continuous infusion of at least two intravenous inotropes:
  ▪ Dobutamine greater than or equal to 3 mcg/kg/min
  ▪ Milrinone greater than or equal to 0.25 mcg/kg/min
  ▪ Epinephrine greater than or equal to 0.01 mcg/kg/min
  ▪ Dopamine greater than or equal to 3 mcg/kg/min
• Intolerance to maximally-tolerated inotropic dosages, as evidenced by hemodynamic instability (e.g. hypotension, vasodilation, hemodynamically unstable atrial or ventricular arrhythmias)
• Mechanically ventilated
 	
Continuous monitoring of hemodynamic data, including cardiac output, with a pulmonary artery catheter or other device, is *not* required in these candidates.
	Status 2 exception

Is admitted to the transplant hospital that registered the candidate on the waiting list and is experiencing complications related to their congenital heart disease (including but not limited to: protein-losing enteropathy, plastic bronchitis, or circuit thrombosis), without regard for change in the candidate's cardiac support	Status 3 exception

Adult single ventricle candidates are nearly all candidates with Fontan circulation, but smaller subsets may also be palliated through other stages, including a superior cavopulmonary connection (bidirectional Glenn procedures, hemiFontan procedures) or volume-loading palliative surgeries such as aortopulmonary shunts or pulmonary artery bands.

[5] Policy notice

Some of these candidates will have “typical” heart failure symptoms, whether primarily diastolic, systolic, irreparably valvular, or combined. While the hemodynamics in these candidates, with low ejection fractions or higher filling pressures, may appear superficially similar to non-ACHD candidates with dilated cardiomyopathy, single ventricle candidates are exceptionally fragile, may not respond favorably to initiation of inotropic support, and are at substantially higher risk of death if they receive mechanical circulatory support, or they may not be candidates for mechanical circulatory support at all. In candidates without mechanical circulatory support options, mechanical ventilation may be used as a treatment for heart failure, but mechanical ventilation is an important risk factor for higher mortality in children with Fontan palliation, and this likely applies to adults as well.[6]

In addition to “typical” heart failure candidates, all candidates with palliated single-ventricle circulations are at-risk for extra-cardiac complications not directly related to ventricular or valvular dysfunction. In most of these cases, traditional treatments for systolic heart failure (including inotropes and mechanical circulatory support) provide limited benefit and may be harmful.[7,8] On the other hand, recent data suggests that as a group, Fontan candidates with preserved ventricular function may have worse outcomes that those with impaired ventricular function.[9] Protein-losing enteropathy is associated with relatively high mortality, and much of this excess mortality is attributable to infectious and other non-hemodynamic complications.[10] Specific and clear predictors of mortality in the complex and heterogeneous group of candidates with extra-cardiac complications and preserved ventricular function are not available in the literature, although candidates with high pulmonary vascular resistance (PVR), elevated cavopulmonary circuit pressures, and low cardiac output are likely at increased risk.[11] However, there is a broad spectrum of severity in most of these diseases processes, especially protein-losing enteropathy and plastic bronchitis, and normal PVR or filling pressures does not exclude a high risk of poor outcomes. In addition, these candidates have a lower quality of life due to the extra-cardiac manifestations of cavopulmonary circuit failure. They may be at lower short-term risk of mortality on the waiting list, but they do not respond to inotropes, and mechanical circulatory support is often not helpful in treatment. Optimal timing of listing and transplantation remains elusive, but it does appear that many candidates are transplanted late in their disease course and the onset of end-organ function suggests the window for successful transplantation may have already passed.[12,13] Continued deterioration during long listing times (proneness to infection, malnutrition, deteriorating lung function, coagulopathy, etc.) contributes to their higher peri-transplant mortality.[14] However, because of the spectrum of manifestations, the presence of a complication (e.g. protein-losing enteropathy) alone likely does not merit listing at a higher urgency status than the currently assigned status 4. Conversely, where complications require hospitalization (e.g. for ongoing albumin infusions or monitoring of severe cyanosis and polycythemia), higher urgency is likely justified.

[6] Kovach JR, Naftel DC, Pearce FB, Tresler MA, Edens RE, Shuhaiber JH, Blume ED, Fynn-Thompson F, Kirklin JK, Zangwill SD. Comparison of risk factors and outcomes for pediatric patients listed for heart transplantation after bidirectional Glenn and after Fontan: An analysis from the Pediatric Heart Transplant Study. *J Heart Lung Transpl*. 2012;31:133–139.
[7] Gewillig M and Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart* 2016; 102: 1081-1086.
[8] John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. *J Amer Coll Cardiol*; 64: 54-62.
[9] Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, del Nido P. Evaluating failing Fontans for heart transplantation: predictors of death. *Ann Thorac Surg*. 2009;88:558–63.
[10] John
[11] Ibid.
[12] Davies, *Outcomes after transplantation*
[13] Kovach
[14] Davies, *Outcomes after transplantation*

Category 2: Dual ventricle heart disease

The following may be useful guidance for RBs asked to approve upgraded listing urgency by exception.

Most candidates, in the absence of the conditions below, are appropriately categorized in status 4 (where all CHD candidates are currently categorized).

For a candidate to be considered eligible for a status 3 exception, a candidate must be admitted to the transplant hospital that registered the candidate on the waiting list and meets *any* of the following criteria:

- Has heart failure with risk factors for VAD support including a systemic right ventricle, failing pulmonary ventricle, heterotaxy syndrome or multiple previous sternotomies
- Is supported by *on*e of the following:
    - A continuous infusion of at least one high-dose intravenous inotrope:
        - Dobutamine greater than or equal to 7.5 mcg/kg/min
        - Milrinone greater than or equal to 0.50 mcg/kg/min
        - Epinephrine greater than or equal to 0.02 mcg/kg/min
    - A continuous infusion of at least two intravenous inotropes:
        - Dobutamine greater than or equal to 3 mcg/kg/min
        - Milrinone greater than or equal to 0.25 mcg/kg/min
        - Epinephrine greater than or equal to 0.01 mcg/kg/min
        - Dopamine greater than or equal to 3 mcg/kg/min
- Intolerance to maximally-tolerated inotropic dosages, as evidenced by hemodynamic instability (e.g. hypotension, vasodilation, hemodynamically unstable atrial or ventricular arrhythmias)

Candidates with two-ventricle CHD include those with a systemic right ventricle (e.g. congenitally corrected transposition of the great arteries, [ccTGA], transposition of the great arteries [TGA] following an atrial switch procedure) as well as those with systemic left ventricles (e.g. tetralogy of Fallot, repaired double-outlet right ventricle, major coronary anomalies [such as anomalous left coronary artery from the pulmonary artery, ALCAPA], Ebstein's anomaly, etc.). Most candidates in these categories have heart failure as the consequence of ventricular dysfunction. Therefore, they may superficially resemble the "typical" adult heart failure candidate with dilated or ischemic cardiomyopathy. However, the use of either temporary or durable mechanical circulatory support in these populations is associated with significantly higher risks. Among the factors resulting in high-risk are: anatomy (including heterotaxy syndrome), the presence of a systemic right ventricle (associated with technical challenges during implant and likely poorer outcomes), multiple previous sternotomies, and often multiple previous aortic procedures.[15] Each of these make VAD implantation more challenging and increase the risk of subsequent complications.

Conclusion

Some adult candidates with CHD may represent a higher risk group awaiting heart transplantation when compared to candidates with dilated cardiomyopathy. They qualify for status 4 based entirely on the etiology of heart failure. However, they often have limited options (or higher risk options) for mechanical support. Attainment of higher urgency status through standard criteria (which require both impaired two-ventricle hemodynamics and specific levels of either inotropic or mechanical support) may be restricted. Unfortunately, there are no clear hemodynamic or laboratory data that indicate candidates at high risk. When non-cardiac end organ injury (such as renal or liver failure) has occurred, transplantation is extremely high-risk and may be prohibitive. Obtaining higher urgency status for candidates prior to the occurrence of such injury should guide RBs.

RB members should consult this resource when assessing exception requests for ACHD candidates. Adult heart transplant programs should also consider this guidance when submitting exception requests for adult candidates with CHD. However, these guidelines are not prescriptive of clinical practice.

[15] Peng E, O'Sullivan JJ, Griselli M, Roysam C, Crossland D, Chaudhari M, Wrightson N, Butt T, Parry G, MacGowan GA, Schueler S, Hasan A. Durable ventricular assist device support for failing systemic morphologic right ventricle: early results. *Ann Thorac Surg*. 2014;98:2122–2129.