OPTN | UNOS

Briefing Paper

Review Board Guidance for Adult Congenital Heart Disease Exception Requests

OPTN/UNOS Thoracic Organ Transplantation Committee

Prepared by: Kimberly Uccellini, MS, MPH
UNOS Policy Department

Contents

Review Board Guidance for Adult Congenital Heart Disease Exception Requests

Affected Policies: *N/A*
Sponsoring Committee: *Thoracic Organ Transplantation*
Public Comment Period: *July 31, 2017 – October 2, 2017*
Board of Director's Date: *December 4-5, 2017*

Executive Summary

The OPTN/UNOS Board of Directors recently approved the Thoracic Organ Transplantation Committee's (Committee) Proposal to Modify the Adult Heart Allocation System during its December 2016 meeting.[1] During the development of the proposal, the Committee received feedback from the heart transplant community during both rounds of public comment voicing concerns that adult congenital heart disease (ACHD) candidates may be disadvantaged by the proposed policy.[2] The Committee considered the implications of the new policy on ACHD candidates:

- Higher urgency statuses are device-driven and ACHD candidates are often not eligible for devices
- Variability in review board decision-making for ACHD exception requests
- Challenging to objectively quantify severity of illness

The Committee acknowledged that some ACHD candidates may have higher mortality and may not be candidates for mechanical support options, but ultimately did not change proposed policy due to lack of objective data to support these assumptions. In the short-term, the exception and review process will accommodate these candidates, who can apply to the RB for an exception in any status as their medical urgency and potential for benefit would warrant. The Committee recognized that ACHD expertise may be inconsistent across the RBs, thus potentially making evaluation and award of ACHD exception requests vulnerable to variability. To help mitigate these inconsistencies, the Committee created guidance for the RBs with the goal of outlining objective criteria to standardize the evaluation and decision-making of ACHD exception requests.

This proposal aligns with the OPTN strategic goal of improving equity in access to transplant by providing objective criteria to RBs, potentially making evaluation and award of exception requests for ACHD candidates more consistent, especially for those boards that lack a CHD expert. In addition, developing standardized exception criteria creates an intelligible pathway for more medically urgent ACHD candidates to obtain access to higher urgency statuses, under which they may be transplanted more quickly, thereby potentially reducing waitlist mortality for those candidates.

[1] OPTN/UNOS Policy Notice. *Proposal to Modify the Adult Heart Allocation System*. Accessed June 27, 2017. https://optn.transplant.hrsa.gov/media/2028/thoracic_policynotice_201612.pdf .
[2] OPTN/UNOS Board Briefing. *Proposal to Modify the Adult Heart Allocation System*. Accessed June 27, 2017. https://optn.transplant.hrsa.gov/media/2006/thoracic_brief_201612.pdf.

What problem will this resource address?

The OPTN/UNOS Board of Directors recently approved the Thoracic Organ Transplantation Committee's (Committee) Proposal to Modify the Adult Heart Allocation System during its December 2016 meeting.[3] During the development of the proposal, the Committee received feedback from the heart transplant community during both rounds of public comment voicing concerns that ACHD candidates may be disadvantaged by the proposed policy.[4] The Committee considered the implications of the new policy on ACHD candidates:

- Higher urgency statuses are device-driven and ACHD candidates are often not eligible for devices
- Variability in review board decision-making for ACHD exception requests
- Challenging to objectively quantify severity of illness

Higher urgency statuses are device-driven
For both anatomic and physiologic reasons, these candidates are less frequently helped by mechanical support, and are at higher risk when mechanical support is used than non-CHD candidates.[5,6]

Variability in review board decision-making for ACHD exception requests
The evaluation and award of exception requests for ACHD candidates may vary from region to region because there is variable, limited, and inconsistent congenital heart disease (CHD) expertise on review boards (RBs).[7]

Challenging to quantify severity of illness
Because of limited data and challenges in reproducibly quantifying the severity of disease in a highly heterogeneous population, a variety of ACHD candidates (likely with different mortality risks) have been grouped together within the new policy.

The Committee acknowledged that some ACHD candidates may have higher mortality and may not be candidates for mechanical support options, but ultimately did not change proposed policy due to lack of objective data to support these assumptions. In the short-term, the exception and review process will accommodate these candidates, who can apply to the RB for an exception in any status as their medical urgency and potential for benefit would warrant. The Committee recognized that ACHD expertise may be inconsistent across the RBs, thus potentially making evaluation and award of ACHD exception requests vulnerable to variability.

Why should you support this resource?

To help mitigate these inconsistencies, the Committee drafted guidance for the RBs with the goal of outlining objective criteria to standardize the evaluation and decision-making of ACHD exception requests. Evidence-based assessment of waitlist mortality drove the assignment of particular criteria into statuses in the new allocation policy. While the Committee acknowledges the community's consternation with ACHD candidates' assignment to status 4, the historical waitlist mortality of ACHD patients was consistent with other populations within status 4.[8] Improved data collection envisioned within the new policy should result in better assessment of whether specific subpopulations of ACHD are disadvantaged by the status 4 assignment and may, in the long term, result in policy changes to address any disadvantages. As an interim measure, the Committee determined guidance to the RBs was an

[3] OPTN/UNOS Policy Notice. *Proposal to Modify the Adult Heart Allocation System.*
[4] OPTN/UNOS Board Briefing. *Proposal to Modify the Adult Heart Allocation System*. https://optn.transplant.hrsa.gov/media/2006/thoracic_brief_201612.pdf .
[5] Peng, Griselli, O'sullivan, Crossland, Chaudhari, Wrightson, Butt, Roysam, Parry, Macgowan, Schueler, and Hasan. "Mechanical Circulatory Support for Failing Systemic Right Ventricle Using Left Ventricular Assist Device - An Option To Decide and Bridge?" *The Journal of Heart and Lung Transplantation* 33, no. 4 (2014): S58-59.
[6] Villa, Chet R., and David L. S. Morales. "The Total Artificial Heart in End-Stage Congenital Heart Disease." *Frontiers in Physiology* 8 (2017): Frontiers in Physiology, 2017, Vol.8.
[7] OPTN/UNOS Heart Regional Review Board (RRB) Guidelines for Reviewing Adult and Pediatric Heart Status 1A- and 1B-Exception Cases. 2010. Accessed November 8, 2017.
[8] Scientific Registry of Transplant Recipients. "*HR2015_01: Data Request from the Heart Subcommittee of the OPTN Thoracic Organ Transplantation Committee". Inferential Data Analyses. Prepared for the Heart Subcommittee, 2015.*

appropriate step to address the heart transplant community's concerns while additional data collection is ongoing and the impact of the new policy is assessed.

This guidance suggests objective criteria to define a pathway to the higher urgency statuses for ACHD. The transplant community explicitly requested such criteria during both rounds of public comment. Per the community's concerns, this guidance provides:

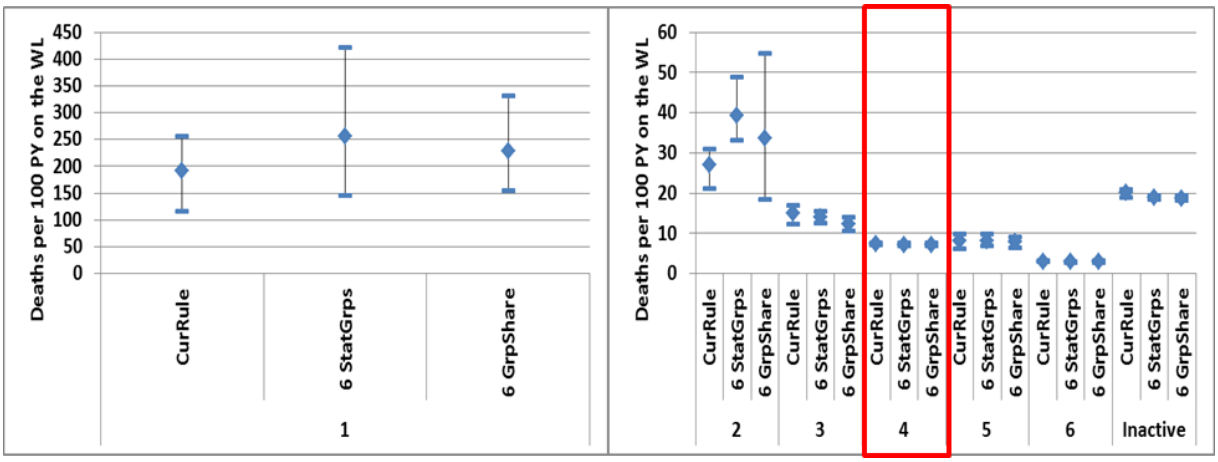
- Guidelines regarding which statuses would be appropriate for specific conditions
- Rationale and context that justify the recommendations, potentially helping RBs without an ACHD expert
- Specific, objective criteria the RBs can use in evaluating exception requests, potentially increasing standardization of decision-making

If utilized, the RBs should be able to recognize more medically urgent ACHD candidates requesting exceptions and can grant access to the higher urgency statuses. Therefore, they may be transplanted more quickly.

How was this resource developed?

During public comment in response to the proposed changes to the adult heart allocation system, the Committee received feedback that ACHD candidates face unique challenges and warrant a higher status due to limited eligibility for mechanical and inotropic therapies. The Committee took these concerns seriously. Ultimately, after considering whether to alter policy, the Committee re-committed to the adult heart allocation proposal's primary goal of reducing waiting list mortality rates. Therefore, it made a conscientious decision to keep candidates stratified in the same statuses originally proposed, as supported by evidence and the thoracic simulated allocation model (TSAM) (Figure 1)[9]. It important to note that status 4 is not limited to ACHD candidates. Specific CHD diagnoses were not stratified in the TSAM cohort analyzed but are included in status 4. The TSAM results showed waitlist mortality rates were similar under current rules and under allocation by statuses.[10]

Figure 1: Waitlist mortality rates by simulation and new status groups, adult candidates



However, the Committee agreed to consider drafting guidance for RBs to standardize the evaluation of CHD exception requests and define objective clinical criteria that would provide a pathway for these candidates to access higher urgency statuses.

The Heart Subcommittee (Subcommittee) discussed the advantages and disadvantages of developing guidance, in advance of the implementation of the heart allocation policy changes. During public comment, several commenters requested guidance specifically, or questioned how exceptions for ACHD candidates would be handled. The Committee understood that the RBs have requested more "guidance" in the past to standardize decision-making, especially because of the often limited ACHD expertise on the

[9] Scientific Registry of Transplant Recipients. HR2015_01, 2015.
[10] SRTR. *HR2015_01,* 2015.

RBs. Guidance may help reduce the number of approved exceptions because RBs may help make more informed decisions. Conversely, the Committee recognized that one of the goals of the modifications to the adult heart allocation policy proposal was to reduce exceptions by better stratifying candidates according to medical urgency. It concedes that the exception process continues to be an important way for ACHD candidates to access the higher urgency statuses (which will not be unique to this patient population). As with all guidance, these recommendations are voluntary and do not carry the weight of policy, and therefore may not change behavior as much as a policy change.

The Subcommittee considered expanding the scope of this guidance to include hypertrophic and restrictive cardiomyopathy (HCM/RCM) and amyloid candidates, also assigned to the new status 4. However, there was a consensus that the candidate populations differ markedly and the required expertise for these disparate patient groups was distinct. Therefore, this guidance is specific to ACHD candidates; a separate workgroup is addressing guidance for HCM/RCM candidates.

As there were only a few pediatric specialists on the Subcommittee, a pediatric congenital heart disease physician was recruited to bolster expertise and provide an external perspective. These members formed a small workgroup (ACHD workgroup). The group identified several professional societies and advocacy groups to engage during public comment, including the International Society for Heart and Lung Transplantation, the Adult Congenital Heart Association, and the Heart Failure Society of America. In addition, the Committee sought additional perspective and support from the OPTN/UNOS Pediatric Transplantation Committee.

Workgroup members were not aware of any standard classification system for ACHD transplant candidates proposed by professional societies, thus the ACHD workgroup performed literature searches to find evidence in peer-reviewed journals to support its recommendations. It also met via teleconference with the Subcommittee on multiple occasions to reach clinical consensus on questions that may not be explicitly answered by data or literature alone. Finally, in the absence of conclusive evidence in literature or in data, the workgroup reached clinical consensus based on expertise to determine its final recommendations.

The ACHD workgroup began to draft the guidance document language by first evaluating draft criteria composed by an ad hoc workgroup from Region 5. This ad hoc workgroup was formed during the fall 2016 regional meetings in response to concerns raised during the pre-plenary thoracic breakout session and consisted of three CHD experts (from one adult and two pediatric heart transplant programs). It drafted criteria for ACHD candidates based on clinical consensus regarding the severity of illness. These criteria categorized CHD diagnoses into three broad categories: 1. single ventricle disease with extra-cardiac complications; 2. single ventricle disease with pump failure; and 3. dual ventricle disease. Pathways qualifying for higher status were proposed for each category.

Table 1: Region 5 Workgroup's Strawman of RB Guidelines for Stratifying CHD Candidates

Category		Suggested Status	Rationale
Category 1	Single ventricle heart disease with protein losing enteropathy, plastic bronchitis, excessive cyanosis, or other extra-cardiac chronic complication not directly related to ventricular or valvular function, but potentially cured by heart transplant.	• Propose these patients should be status 4 by default. • Propose that these patients, if admitted to the listing institution for complications of their illness, would be suitable for status 3, without regard for change in their cardiac support.	Many of these listed patients have single ventricle heart disease, and poor quality of life, but may be at lower risk of dying while listed (compared with single ventricle patients with heart failure). However, they do not respond to inotropes, and MCS is not a helpful option for their treatment. Their continued deterioration during long listing times (proneness to infection, malnutrition, deteriorating lung function, coagulopathy, etc) contributes to their higher peri-transplant mortality.
Category 2	Single ventricle heart disease with failing pump function (myocardial or valvular heart disease not amenable to surgical correction).	• Propose that these patients should be status 4 by default. • This group would fit with status 3 if prescribed dischargeable inotropic support. • This same group should be allowed to be status 2 if on multiple inotropes as an inpatient (and Swan Ganz Monitoring should not be required, as it is frequently irrelevant and often complicated by thrombosis).	This definition can be refined to refer to those single ventricle heart disease with "typical" failure, whether primarily diastolic, systolic, irreparably valvular, or combined. These patients are exceptionally fragile, may not respond favorably to initiation of inotropic support, and are at substantially higher risk of death if they receive MCS (if they are candidates for MCS at all).

Category		Suggested Status	Rationale
Category 3	Failing dual ventricle heart disease (e.g. Tetralogy of Fallot, congenitally corrected transposition of the great arteries (CCTGA), repaired double outlet right ventricle (DORV), coronary anomalies, Ebstein's anomaly, etc. *Propose using the same definition of congenital heart disease used in the newest version of the pediatric listing system.*	• Propose that these patients should be status 4 by default, unless meeting additional criteria.	These patients, when listed for heart transplant, are generally high-risk candidates for temporary or durable MCS. While a patient with 2-ventricle CHD on oral therapies may be suitable for status 4 due to risk stratification, further increases in the listing criteria can be similar to other patients without congenital heart disease.

This categorization formed the starting point for the guidance document workgroup.

Granularity versus Simplicity

Initial draft modifications included further subdividing the dual ventricle patients into those with a systemic right or a systemic left ventricle. While it was felt that this might provide more granular guidance, there was a countervailing concern that the guidance was becoming too detailed and prescriptive, and that review board members may interpret the guidance too stringently. The Subcommittee expressed concern that an overly complex guidance might not be as helpful. The workgroup agreed that simplifying the guidance may be the best strategy.

In addition, the workgroup discussed a concern that the distinction between single ventricle patients with and without pump failure was clinically difficult, often subjective, and likely beyond the expertise of the review boards. This simplification did prompt concerns from some Subcommittee members that the guidance might become insufficiently helpful to RBs that lack a CHD specialist. As a compromise, the workgroup members agreed to collapse the categories to condense the guidance, but to keep examples and rationale to help educate RB members. All workgroup members and members of the Subcommittee supported this strategy.

The Subcommittee presented draft criteria to the Committee during the March 23, 2017 full committee meeting. The Committee acknowledged the challenges in further stratifying this group by waitlist mortality or medical urgency due to lack of data, but recommended the criteria be more specific, similar to previous guidance drafted by the Subcommittee.[11] The Subcommittee deliberated over the Committee's recommendation to make the guidance more specific and therefore, potentially more helpful to RBs. While this would better standardize how review boards evaluate exceptions for these candidates, members of the Subcommittee reiterated that it was difficult to select hemodynamic criteria or laboratory testing to make the guidance any better than originally proposed. The group reconsidered whether the guidance was specific enough to resolve the problems it was meant to address: variability in RB decision-making, leading to inequitable access, and physicians not trained in ACHD determining ACHD exception requests. After making minor adjustments to the criteria, the Subcommittee was satisfied with the changes, as outlined below.

Exception Request Guidance for Single Ventricle ACHD Candidates

The Subcommittee proceeded to evaluate the guidance initially proposed to ensure there was consensus that the suggestions would be appropriate for all *single ventricle* patients:

[11] OPTN/UNOS Thoracic Organ Transplantation Committee*. "Guidance Regarding Adult Heart Status 1A(b) Device-Related Complications*". Accessed June 29, 2017. https://optn.transplant.hrsa.gov/resources/guidance/guidance-regarding-adult-heart-status-1a-b-device-related-complications/.

Table 2: Draft RB Guidance for Single Ventricle CHD Exception Requests

If a candidate meets this criteria:	**Then the candidate is eligible for:**
• Has complications of his/her VAD (single-ventricle VADs are currently classified into Status 2 in the new policy)	Status 1 exception
• Admitted to the transplant hospital that registered the candidate on the waiting list and either: o Is on multiple inotropes o Is mechanically ventilated Continuous monitoring of hemodynamic data, including cardiac output, as with a pulmonary artery catheter or other device, is not required in these patients, because it is often not relevant and may be complicated by thrombosis or infection.	Status 2 exception
• Admitted to the transplant hospital that registered the candidate on the waiting list and is experiencing complications of his/her illness, without regard for change in his/her cardiac support OR • Has dischargeable inotropic support	Status 3 exception

Status 1 Exception Criteria
The CHD workgroup and Subcommittee agreed unanimously that single ventricle patients experiencing complications of their VAD have no other options and are equally as urgent as other candidates in status 1.[12,13,14] Single ventricle patients with VADs are currently assigned to status 2 in the approved policy.[15]

Status 2 Exception Criteria
The Subcommittee debated whether ACHD candidates on multiple inotropes (a status 3 criterion) are as medically urgent as other candidates in status 2 and whether it would be sufficient for the guidance to simply note that pulmonary artery catheters are not indicated in single ventricle patients. Ultimately, the Subcommittee concluded that (1) this was a very small group of patients, and (2) they are exceptionally fragile and often may not respond favorably to initiation of inotropic support.[16] However, in order to limit overuse of this pathway, the Subcommittee agreed to add the specific inotropes and dosages to be consistent with policy language. In addition, the Subcommittee proposed adding mechanical ventilation as a criterion for higher status because single ventricle patients are often higher-risk for VADs, making mechanical ventilation an appropriate, if sub-optimal, treatment for heart failure in this population.

[12] Mackling, Tracey, Tejas Shah, Vivian Dimas, Kristine Guleserian, Mahesh Sharma, Joseph Forbess, Monica Ardura, Jami Gross-Toalson, Ying Lee, Janna Journeycake, and Aliessa Barnes. "Management of Single-Ventricle Patients With Berlin Heart EXCOR Ventricular Assist Device: Single-Center Experience." *Artificial Organs* 36, no. 6 (2012): 555-59.
[13] Vanderpluym, Rebeyka, Ross, and Buchholz. "The Use of Ventricular Assist Devices in Pediatric Patients with Univentricular Hearts." *The Journal of Thoracic and Cardiovascular Surgery* 141, no. 2 (2011): 588-90.
[14] Brancaccio, Gianluca, Fabrizio Gandolfo, Adriano Carotti, and Antonio Amodeo. "Ventricular Assist Device in Univentricular Heart Physiology." *Interactive CardioVascular and Thoracic Surgery* 16, no. 4 (2013): 568-69.
[15] OPTN/UNOS Thoracic Organ Transplantation Committee*. "Guidance Regarding Adult Heart Status 1A(b) Device-Related Complications*"
[16] Nakano, Nelson, Sucharov, and Miyamoto. "Myocardial Response to Milrinone in Single Right Ventricle Heart Disease." *The Journal of Pediatrics* 174 (2016): 199-203.e5.

Status 3 Exception Criteria
The Region 5 workgroup initially included "dischargeable inotropic support" as a status 3 exception criterion in their proposed criteria, but the Subcommittee opted to eliminate it because, as per the approved policy, (1) a candidate must be admitted to the transplant hospital that registered the candidate on the waiting list for all status 1, 2 and 3 exception requests, and (2) all patients with single-ventricle CHD and a VAD are already status 2.[17]

Exception Request Guidance for Dual Ventricle ACHD Candidates
The Subcommittee then vetted the categorization of dual ventricle patients. Members agreed to adopt the same approach to simplify the dual ventricle categories as was done with the single ventricle categories and collapse them into a single category. The Subcommittee agreed the following guidance would be appropriate for all dual-ventricle patients:

- Most two-ventricle candidates *are generally not eligible* for an exception to a higher status and are appropriately classified in Status 4 (where all CHD candidates are currently categorized)
- A candidate that meets either of the following criteria is eligible for a Status 3 exception:
    - Failing biventricular heart disease with either a systemic right ventricle or other risk factors for VAD support including heterotaxy syndrome or multiple previous sternotomies
    - Admitted to the transplant hospital that registered the candidate on the waiting list **and** is on multiple inotropes

These candidates are generally high-risk candidates for temporary or durable mechanical circulatory support. While the original Region 5 workgroup proposed that most of these candidates are appropriately assigned to status 4 per new policy, there was consensus on the CHD workgroup that patients are both higher risk for complications or lack of stabilization on mechanical support and may have difficulty meeting the stringent hemodynamic and other sub-criteria required to qualify for Status 3 in the new policy.

While the guidance restates policy in some cases and may be redundant, the new allocation policy is complex and its application to ACHD patients may not be immediately evident. Public comment for the heart allocation proposal continued to indicate confusion regarding how policy applies to ACHD patients. RBs may therefore get exception requests for scenarios already captured within the new policy language. Therefore, the guidance reiterates how policy applies to ACHD candidates and includes policy citations in the guidance document as reference.

The Subcommittee reviewed the draft guidance during their April 27th meeting, made some additional clarifications to the guidance document narrative, and voted (10-yes, 0-no, 0-abstentions) to recommend to the full Committee that this guidance go out for public comment. The Committee made several clerical changes to the guidance narrative and voted (15-yes, 0-no, 0-abstentions) to send the proposal out for public comment in July 2017.

How well does this resource address the problem statement?

This proposal is informed primarily by clinical consensus, due to the lack of data to support elevating this diverse patient population to higher urgency statuses, as well as the lack of data regarding specific clinical, hemodynamic, or laboratory data that might assist with identifying a higher risk population. The RBs operate based on medical judgment and clinical consensus; hence, guidance developed via clinical consensus for a body whose decisions are made by clinical consensus is reasonable. When relevant, OPTN descriptive analyses and TSAM results referenced in the modifications to the adult heart allocation system proposal were considered, as well as current peer-reviewed literature. In addition, the Subcommittee reviewed relevant feedback pertaining to this patient population from both public comment cycles.

Higher urgency statuses are device-driven

[17] OPTN/UNOS Policy Notice. *Proposal to Modify the Adult Heart Allocation System.* Accessed June 27, 2017. https://optn.transplant.hrsa.gov/media/2028/thoracic_policynotice_201612.pdf .

This resource suggests specific medical criteria that, if met, would convey a program's ACHD candidate has an urgency comparable to that of other candidates at the requested status.

Variability in review board decision-making for ACHD exception requests

This resource provides rationale and context to justify the recommendations, potentially helping review boards without an ACHD expert. It offers specific, objective criteria the RBs can use in evaluating exception requests, potentially increasing standardization of decision-making.

Challenging to objectively quantify severity of illness

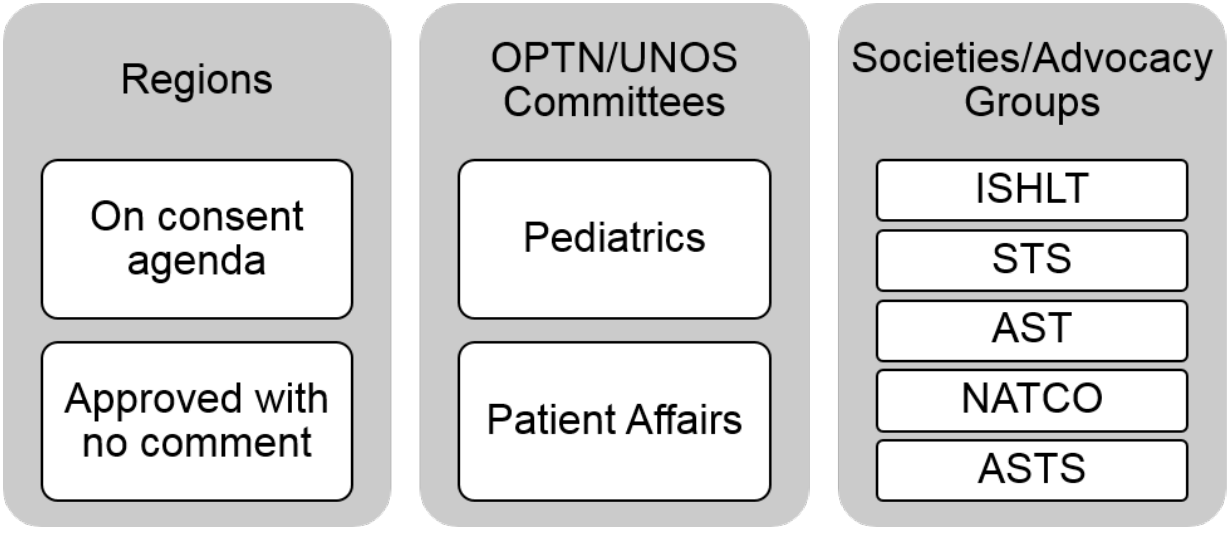
This resource provides more discrete recommendations for specific CHD conditions, therefore recognizing more medically urgent CHD diagnoses groups and those with limited therapeutic options.

While this guidance addresses some of the community's concerns, it does not carry the weight of policy. It also may diminish the Committee's original goal of reducing the number of exceptions, especially for this patient population, as it may encourage more exception requests.

Was this proposal changed in response to public comment?

This proposal represents the work of a diverse group of heart transplant professionals, including cardiologists, cardiothoracic surgeons, and congenital heart disease specialists. Public comment was generally favorable with various recommendations suggested. Figure 2 illustrates the different types of commenters.

Figure 2: Public Comment Overview



The proposal was on the non-discussion agenda at the regional meetings and passed in all regions. In Region 5 during a thoracic breakout session, attendees agreed the guidance appropriately addressed their original concerns expressed during the fall 2016 Region 5 meeting regarding how this population was stratified in the adult heart allocation statuses and endorsed the guidance. Both the Pediatric Transplantation and Patient Affairs Committee supported the proposal unanimously with a few comments, which are detailed below. In addition, five professional societies commented and generally supported the proposal. The following themes emerged from all the feedback:

1. Nature of guidance
2. Exception requests
3. National specialty or pediatric review board
4. Further stratification of ACHD subgroups

The Committee's discussion and response to each of these themes is included below.

1. Nature of Guidance

A chief concern was the nature or interpretation of guidance generally:

- Limitations of guidance (versus policy)
- Interpretation of guidance as de facto policy

Commenters noted the limitations of guidance as being voluntary and not enforceable. Specifically, the Patient Affairs Committee (PAC) questioned whether RBs would use it if utilization is voluntary. If the guidance is not adopted, the PAC asked how effectively this proposal addresses the heart transplant community's initial concerns. The Committee noted that OPTN-developed guidance tended to be readily adopted by the thoracic community; for example, the guidance developed for status 1A device complications helped standardize the award of exception requests for those conditions and ultimately was incorporated into the new adult heart allocation policy.[18] In addition, apart from actually changing policy, the community asked for instruction on how these candidates might access higher urgency statuses.

In contrast, other commenters were concerned that RBs would interpret this guidance as de facto policy. The ISHLT noted that even though guidance documents do not carry the weight of policy, transplant physicians do rely on them to guide listing decisions, and they influence the decisions of RB members. The STS, ASTS, and ISHLT expressed concern that if review boards interpret the guidelines as stringently as policy, ACHD candidates who do not meet the specific criteria outlined may be negatively impacted. The Committee felt that the dedicated education RBs would receive during implementation of the adult heart allocation policy changes would be the best opportunity to reinforce that guidance serve as recommendations, and that RBs may continue to grant exceptions to candidates seeking access to higher statuses who do not meet the suggested criteria. As long as the RB agrees that the transplant program has provided compelling evidence that their candidate has an urgency and potential for benefit comparable to that of other candidates at the requested status, it is within its purview to grant (or deny) any exception. Ultimately, the Committee determined not to modify the guidance itself, but to address concerns through education and training.

2. Exception requests

Another prevalent theme was around CHD exception requests generally:

- Increase in exception requests
- Data collection around exception requests

There were several comments about whether this guidance (or perhaps the adult heart allocation policy changes itself) could have unintended consequences and lead to an increase in exception requests for this patient population. Members noted that the need for exceptions would be a smaller subset of the overall adult CHD group; every adult CHD candidate should not require an exception. The STS and ASTS advised robust data collection to monitor program behavior in terms of the frequency of the exception requests and acceptances. The Committee discussed this feedback. While there could possibly be a temporary increase in the number of exceptions as the community becomes acquainted with the adult heart allocation policy changes, members acknowledged that the Committee cannot predict at this time whether that effect would persist. Members were not convinced the guidance in and of itself would cause an increase in exceptions. The Committee confirmed that it will track exception data as part of the monitoring plan, but that information may also inform other future projects, such as a national review board.

3. National specialty or pediatric review board

Several commenters called for the Committee to consider a national pediatric or specialty (CHD) review board. Such a board may resolve the problem in the variability in the evaluation and award of exception requests for ACHD candidates region to region due to limited or inconsistent congenital heart disease or general pediatric expertise on RBs. While the Committee strongly supports this suggestion, it

[18] OPTN/UNOS Thoracic Organ Transplantation Committee*. "Guidance Regarding Adult Heart Status 1A(b) Device-Related Complications*".

acknowledged that such a change was clearly beyond the scope of this proposal. This national board could include specialty boards for specific diagnoses or for pediatrics, similar to the national liver review board. It is the Committee's intent to pursue such a project (a national heart review board) in the near future. Consequently, the word "regional' was struck from the guidance document.

4. Further stratification of ACHD subgroups

Finally, several societies critiqued the fact the guidance failed to stratify the ACHD patient population into more granular high risk subgroups. ISHLT commented that the guidance failed to capture the complexities of risk assessment in this patient population. The Vice Chair shared that the Committee grappled with this very subject while modifying the adult heart allocation policy, and similarly, the workgroup didn't feel they could get much more specific based on currently available data, even data from small, single-center studies. The Committee considered keeping the guidance as proposed during public comment or attempting to further stratify this population by waitlist mortality. The Committee noted that no suggestions on how to further categorize this population were offered, and there was some concern that attempting to do so post-public comment could lead to substantive changes. The Committee was not confident it could incorporate more specificity into the guidance without changing it significantly, and determined not to modify the guidance.

Although not identified as a theme, there was a comment from the ISHLT that there seemed to be an emphasis placed on treatment decisions that are subjective (i.e., the decision to treat a patient in the hospital vs. as an outpatient and the decision to start a patient on inotropes). The Committee confirmed that hospitalization is required for all status 1-3 exceptions, and a policy change to alter that is beyond the scope of this project[19]. The ISHLT also raised concerns that the proposed requirements for specific inotropes and dosages for status 2 exceptions for single ventricle ACHD candidates are arbitrary for this group, and it is possible that they may not benefit and may even potentially be harmed by the use of high-dose inotropes. In an early draft submitted to the Heart Subcommittee, inotropes were included as criteria but dosages not specified. The Subcommittee recommended including the specific dosages from the adult heart allocation policy as a matter of consistency, and to mitigate concerns around gaming, especially as the guidance does not require continuous hemodynamic monitoring via pulmonary artery catheter or other invasive device. The Committee debated whether to adjust or remove the inotrope dosages, or keep the guidance as proposed during public comment. Members did not suggest modifying the inotrope dosages, but advised adding an "or" caveat to the effect of requiring evidence of intolerance to maximally-tolerated inotropic dosages. The Committee agreed to add this verbiage to both the single and dual ventricle criteria.

There was consensus that VAD complications, as referenced in the status 1 exception criteria for single ventricle candidates, should be specifically defined. The Committee agreed that for consistency, VAD complications would be limited to those specified in the new policy.

The Committee voted unanimously (16-yes, 0-no, 0-abstentions) to approve the guidance with the minor modifications specified and to send to the Board of Directors for consideration. It was noted this guidance will not be utilized by RBs until the adult heart allocation policy changes are fully implemented.

Which populations are impacted by this resource?

As of June 30, 2017, there were 161 ACHD candidates on the waitlist.[20] Table 4 shows the number of adult (defined as listed at age 18 or greater) registrations on the waiting list for a heart with a diagnosis recorded on the transplant candidate registration form (TCR) in the CHD category by waiting list status and whether or not the status 1A and 1B candidates were waiting with exceptions.

Table 4: Heart CHD Registrations by Status and Exception

[19] Policy notice
[20] United Network for Organ Sharing Research Department. *Heart CHD Registrations by Status and Exception.* OPTN/UNOS Descriptive Data Analyses. Prepared for the Heart Subcommittee. July 5, 2017.

Status	1a or 1b Exception	N
Status 1a	**No**	**6**
Status 1a	**Yes**	**9**
Status 1b	**No**	**58**
Status 2	**No**	**55**
Inactive	**No**	**33**
Total		**161**

This guidance will affect ACHD candidates whose transplant programs request exceptions under the new adult heart allocation policy.

How does this resource impact the OPTN Strategic Plan?

1. *Increase the number of transplants:* There is no impact to this goal.
2. *Improve equity in access to transplants*: This guidance provides objective criteria to RBs, potentially making evaluation and award of exception requests for ACHD candidates more consistent, especially for those boards that lack a CHD expert.
3. *Improve waiting listed candidate, living donor, and transplant recipient outcomes*: Developing standardized exception criteria creates an intelligible pathway for more medically urgent ACHD candidates to obtain access to higher urgency statuses, under which they may be transplanted more quickly, thereby potentially reducing waitlist mortality for those candidates.
4. *Promote living donor and transplant recipient safety*: There is no impact to this goal.
5. *Promote the efficient management of the OPTN*: There is no impact to this goal.

How will the OPTN implement this resource?

If the Board approves this proposal, the OPTN/UNOS will publish this guidance to the resources section of both the OPTN and other websites concurrently to when the policy changes to the adult heart allocation system are fully implemented. UNOS staff will work with the Committee to develop a training pertaining to the new heart allocation policy, specific to RB representatives and alternates. The content of this guidance will be included as part of that training. This proposal will not require programming in UNet^{SM}.

How will members implement this resource?

Review board members should consult this resource when assessing exception requests

Transplant Hospitals

Heart programs should consider this guidance when submitting exception requests for their adult congenital heart disease candidates. However, these guidelines are for voluntary use by members and are not prescriptive of clinical practice.

Will this resource require members to submit additional data?

No, this proposal does not require additional data collection.

How will members be evaluated for compliance with this resource?

Guidance from the OPTN does not carry the weight of policies or bylaws. Therefore, members will not be evaluated for compliance with the guidance in this document.

How will the sponsoring Committee evaluate whether this resource was successful post implementation?

Adult CHD patients and any such exceptions will be monitored with other exception requests in concert with the post-implementation monitoring of the heart allocation proposal. In monitoring the new allocation policy, the Committee will monitor pre- and post-transplant outcomes as well as access to transplant for specific sub-populations of transplant candidates including ACHD patients every six months for 2-3 years as the Committee sees fit.

Guidance Document

RESOLVED, that the guidance document entitled "Review Board (RB) Guidance for Adult Congenital Heart Disease (CHD) Exception Requests," as set forth below, is hereby approved, effective pending implementation and notice to OPTN members.

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.[21] 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."[22] 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.[23] 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

[21] First proposal/TSAM
[22] OPTN/UNOS Policy 6.3: Adult and Pediatric Status Exceptions.
[23] 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.[24] 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.

[24] 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[25]	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.

[25] 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.[26]

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.[27,28] 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.[29] Protein-losing enteropathy is associated with relatively high mortality, and much of this excess mortality is attributable to infectious and other non-hemodynamic complications.[30] 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.[31] 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.[32,33] Continued deterioration during long listing times (proneness to infection, malnutrition, deteriorating lung function, coagulopathy, etc.) contributes to their higher peri-transplant mortality.[34] 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.

[26] 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.
[27] Gewillig M and Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart* 2016; 102: 1081-1086.
[28] 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.
[29] 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.
[30] John
[31] Ibid.
[32] Davies, *Outcomes after transplantation*
[33] Kovach
[34] 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 *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)

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.[35] 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.

[35] 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.

181 #