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Comparison of Listing Strategies for Allosensitized Heart Transplant Candidates Requiring Transplant at High Urgency: A Decision Model Analysis

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Abstract

Allosensitized children who require a negative prospective crossmatch have a high risk of death awaiting heart transplantation. Accepting the first suitable organ offer, regardless of the possibility of a positive crossmatch, would improve waitlist outcomes but it is unclear whether it would result in improved survival at all times after listing, including post-transplant. We created a Markov decision model to compare survival after listing with a requirement for a negative prospective donor cell crossmatch (WAIT) versus acceptance of the first suitable offer (TAKE). Model parameters were derived from registry data on status 1A (highest urgency) pediatric heart transplant listings. We assumed no possibility of a positive crossmatch in the WAIT strategy and a base-case probability of a positive crossmatch in the TAKE strategy of 47%, as estimated from cohort data. Under base-case assumptions TAKE showed an incremental survival benefit of 1.4 years over WAIT. In multiple sensitivity analyses, including variation of the probability of a positive crossmatch from 10-100%, TAKE was consistently favored. While model input data were less well suited to comparing survival when awaiting transplantation across a negative virtual
crossmatch, our analysis suggest that taking the first suitable organ offer under these circumstances may also be favored.

INTRODUCTION

Historically, allosensitized children requiring heart transplantation were commonly listed with a requirement for a negative donor cell crossmatch prior to transplantation [1]. Consequently waitlist survival for this group has been poor because fewer donor organs are “acceptable” for such patients [1, 2]. However, data from 2 recent case series suggest that transplantation across a positive donor-specific crossmatch (DSXM) can be achieved with early post-transplant survival comparable to transplantation across a negative DSXM [3, 4]. This has led to an ongoing multicenter, NIH-funded study of the outcomes after listing and after transplantation for candidates with a positive donor cell crossmatch compared to those without [5]. Whether this strategy actually improves survival of allosensitized candidates or merely achieves transplantation at the cost of shifting mortality from the pre- to post-transplant phase is unknown and a direct comparison of survival from the time of listing for these two competing waitlist strategies is unlikely to ever be performed due to multiple logistical, and potentially ethical, concerns. Thus we sought to analyze this question using decision analysis - a quantitative, probabilistic method for modeling problems under situations of uncertainty. Decision models are used commonly in business and finance to inform decision making and are also used in evidence-based medical decision making where there is a specific decision that must be made and a tradeoff involved in the decision [6 - 8]. A key aspect of decision modelling is the ability to perform sensitivity analyses in which the “base-case” model result is reassessed after varying input data across a range of estimates. Thus, even if the base-case data are somewhat uncertain, sensitivity analyses can show whether or not that uncertainty affects the model’s findings and to what extent.

In this study we created a Markov model which used national transplant registry data to compare survival after listing for heart transplantation between two competing waitlist management strategies for allosensitized, status 1A (highest urgency) pediatric candidates: listing with a requirement for a negative prospective crossmatch (WAIT) vs. acceptance of the first suitable organ offer (TAKE). We hypothesized that the TAKE strategy would result in a net survival benefit (i.e. at all times after listing, including post-transplant) and thus be favored over the WAIT strategy.

METHODS

Decision Model Overview and Model Parameters

Markov modeling uses a tree representation of discrete health states and probabilities of transitioning from one state to another to compare outcomes subsequent to the choice of a management strategy [9]. These models also incorporate time, such that after a decision on management strategy is made, the occurrence of subsequent model events can vary over a predefined number of model cycles. Event probabilities can be programmed to vary according to the number of model cycles that have elapsed. Outcomes for each strategy, expressed as estimated survival from the time of model entry, are calculated based on model
input data. By convention, the ‘favored’ strategy is the one with the greatest survival and model results are commonly expressed in terms of the incremental survival benefit of the favored strategy relative to the non-favored strategy.

The Markov decision model we created is shown in figure 1. After assignment to either the TAKE or WAIT strategy, the hypothetical model candidate can remain in the waitlist phase of the model for up to 2 years, during which in each model cycle he/she can receive a transplant, die awaiting transplant, or be delisted as either too sick or too well. The probability of these events was varied with each cycle (defined as 1 month in our model) according to Organ Procurement and Transplant Network (OPTN) data on the occurrence of these events among children (age <18 years) who were listed status 1A between January 21, 1999 and December 2009 (n=2,937). For the TAKE strategy we used event probabilities derived from candidates in the OPTN dataset who were never listed with a prospective crossmatch requirement (PXMR) during the entirety of their listing (n=2,650) and for the WAIT strategy we used event probabilities from candidates who were listed with a PXMR throughout the entirety of their listing (n=109). Data on candidates who had a PXMR at some point during their listing were not used in the model because the duration, and thus impact, of their PXMR varied on a case-by-case basis and therefore was not reflective of either model strategy.

In the post-transplant phase of the model, recipients had a risk of death that varied according to the model cycle (monthly during the first 2 years, then annually to a maximum of 10 years after model entry). Time-dependent probabilities of death after transplantation across a positive DSXM and a negative DSXM that were used in the model were derived from the OPTN dataset from recipients who had a positive DSXM by any technique (n=239) and those with a negative DSXM (n=1,243), respectively. Crossmatch techniques reported in OPTN dataset were “anti-globulin”, “NIH/extended”, “wash/extended”, “flow”, “other,” and “not reported.” We assumed no patient in the WAIT arm could have a positive DSXM whereas in the TAKE arm we assumed the probability of a positive DSXM was 47% for our base-case analysis. This was based on the mean pre-transplant PRA of patients who were listed with a PXMR throughout the entirety of their listing that were common to both the OPTN and Pediatric Heart Transplant Study (PHTS). This was necessary because PRA data are collected by OPTN only for transplant recipients whereas the PHTS collects PRA information on all candidates.

Sensitivity Analyses

To account for potential uncertainty of our model input data we performed a series of sensitivity one-way sensitivity analyses [10] in which we varied the probability of a positive DSXM from 10 to 100%, the annual probability of death after transplantation across a positive DSXM from 4 to 40%, and each of the waitlist event probabilities from 0.5 to 1.5 times the base-case estimate. We also performed two-way sensitivity analysis on selected variables and a probabilistic sensitivity analysis [11] where the model outcome was determined for 5000 iterations in which each of the model input variables were varied simultaneously and randomly across a range of values. We used the 95% confidence
intervals of the time-dependent pre- and post-transplant event probabilities and a probability of a positive DSXM of 10 to 100% as the boundaries in this analysis.

We also performed supplemental analyses to assess the impact of regional differences in waitlist durations on our findings. For these analyses we determined the median time to heart transplantation for status 1A children in each UNOS region from 1999 to 2009 and then repeated the base-case analysis twice, substituting waitlist outcomes data from the UNOS regions with the shortest and longest waiting times.

Lastly, we attempted to define a cohort from the OPTN dataset that represented the experience of candidates listed with a virtual crossmatch requirement. For this supplemental analysis we identified all status 1A children listed with “unacceptable antigens” in the OPTN dataset from 1999-2009 (n=64) and substituted this group's waitlist event probabilities into the WAIT arm of the model. Of note, the OPTN dataset contains only the date and time of unacceptable antigen additions but not the occurrence or timing of removal of unacceptable antigens. Thus we were unable to determine the duration for which the unacceptable antigen stipulation (i.e. virtual crossmatch requirement) was in effect during each of these candidates’ waiting times.

**Data Sources and Data Analysis**

The OPTN data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States (US), submitted by the members of the OPTN, and has been described elsewhere \[12\]. The Health Resources and Services Administration, US Department of Health and Human Services Administration, provides oversight to the activities of the OPTN contractor. The PHTS is an organization of more than 40 centers in North America and the United Kingdom that contribute data about children from the time of listing and throughout the post-transplant period to a centralized, prospective, multicenter, event driven database \[13\]. Study centers require institutional review board (IRB) approval to participate in the PHTS, confirmation of which is kept on file at the PHTS data collection center.

Data were analyzed with SAS v9.2 (SAS Institute Inc, Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). Decision modeling was performed using TreeAge Pro Suite 2009 (TreeAge Software, Inc, Williamstown, MA). This study was conducted with the approval of the University of Pittsburgh IRB, OPTN, and PHTS.

**RESULTS**

**Base-case analysis**

Characteristics of patient cohorts used in the model are shown in table 1. Waitlist competing outcomes and post-transplant survival data that were used in the model are shown graphically as cumulative event curves in figure 2. Under base-case assumptions our model predicts survival for the TAKE strategy is 5.9 years versus 4.5 years for the WAIT strategy. Thus the TAKE strategy was favored over WAIT with an incremental net survival benefit of 1.4 years.
Sensitivity Analyses

Varying the probability of a positive DSXM for the TAKE group from 10 to 100% did not affect model outcome (i.e. TAKE strategy remained favored). Similarly, the TAKE strategy was also favored when each of the waitlist monthly event probabilities were varied from 0.5 to 1.5 times their base-case estimates. When we adjusted the model so that waitlist probabilities of death and delisting were equal for both strategies while maintaining the lower probability of transplantation associated with the WAIT strategy, the TAKE strategy remained slightly favored with an incremental net benefit of 0.3 years. Thus, even after multiple adjustments of model input data, including lessening the risk of waitlist death for the WAIT strategy, our model still predicted that the TAKE strategy was favored. One-way sensitivity analysis of post-transplant survival also resulted in the TAKE strategy being favored except when the probability of death after transplantation across a positive DSXM was >33% per year (equivalent to a median post-transplant survival of ≤1.8 years). Table 2 shows the relationship between the annual probability of death after transplant and median post-transplant survival.

Figure 3 shows a two-way sensitivity analysis in which we varied both the probability of a positive DSXM and the probability of death after transplantation across a positive DSXM. The WAIT strategy was never favored when the probability of a positive DSXM was <43% and even under the extreme assumption of 100% probability of a positive DSXM in the TAKE strategy, the probability of death after transplantation across a positive DSXM had to exceed 13% per year (equivalent to median post-transplant survival of <5 years) for WAIT to be favored (table 2). In the probabilistic sensitivity analysis, which performed 5000 model iterations while drawing randomly from specified ranges for model input variables during each iteration, the TAKE strategy was four times more likely to be favored than the WAIT strategy.

When we examined the effect of regional differences in waitlist durations on strategy preference, the TAKE strategy remained favored over WAIT (table 3). As shown in figure 4, there were similar cumulative incidences of death for the TAKE strategy in UNOS regions with the longest and shortest median times to transplantation. However for the WAIT strategy, a greater proportion died in the regions with the shortest times to transplant as compared to regions with the longest times to transplant.

Finally, we substituted waitlist outcomes of candidates listed with unacceptable antigens into the WAIT strategy and found that WAIT was slightly favored over TAKE with an incremental survival benefit from listing of 0.4 years.

DISCUSSION

Our model predicts that taking the first suitable organ offer, regardless of the potential for a positive DSXM, results in greater survival at all times after listing (including post-transplant) for allosensitized pediatric heart transplant candidates who are listed with high urgency and a requirement for a negative prospective donor cell crossmatch. It appears that the TAKE strategy was favored because the inferior survival observed after transplantation across a positive DSXM was more than offset by enhanced waitlist survival. The TAKE
strategy was favored across a broad range of variations in sensitivity analyses that accounted for many plausible, and some less plausible, clinical scenarios. Though our supplemental analysis found that WAIT was minimally favored over TAKE for candidates listed with unacceptable antigens, this analysis almost certainly under-represents the true severity of the waitlist experience for those in whom a negative virtual crossmatch is required. This is because the occurrence and timing of changes in unacceptable antigen requirements could not be factored into our supplemental model cohort. With any removal of unacceptable antigens or of the virtual crossmatch requirement entirely, the cohort becomes less reflective of the WAIT strategy and more reflective of the TAKE strategy. Assuming that outcomes for candidates with a virtual crossmatch requirement lie somewhere between those estimated by the unacceptable antigen cohort in the supplemental analysis and the PXRM cohort in the base-case model, it is reasonable to consider that taking the first suitable organ offer would be favored for patients with a virtual XM requirement.

With the emergence of highly sensitive and specific antibody detection assays \cite{14}, virtual crossmatching has become increasingly more commonly utilized in pediatric heart transplantation \cite{15}. Thus, the ideal dataset to compare these strategies would not only contain the specificities of unacceptable antigens but also the timing of all changes in these unacceptable antigens, which make up the virtual crossmatch requirement. To the best of our knowledge these data do not exist and so we have used surrogate data to provide insight into this significant and timely issue.

We believe our findings are important because they provide support for reconsideration of the historical paradigm with respect to listing highly allosensitized pediatric heart transplant candidates. This paradigm was established after Patel and Terasaki showed in 1969 that a positive prospective crossmatch is highly predictive of early graft loss following renal transplantation \cite{16}. While this approach improved post-transplant outcomes across multiple organ transplant types by minimizing the prevalence of graft loss and death from hyperacute rejection and antibody-mediated rejection, it relegated many allosensitized candidates to death because of insurmountable waiting times or outright exclusion from candidacy \cite{1, 2, 17}. In an era when peri-operative management was not as well developed and acute cellular rejection, infection, and malignancy/post-transplant lymphoproliferative disease were more significant causes of death after transplantation, the avoidance of additional risk/complexity seemed appropriate. However our data show that from at least 1999, a strategy of waiting for a negative prospective donor cell crossmatch over taking the first good donor organ offer results in inferior survival for status 1A, allosensitized pediatric heart transplant candidates from the time of listing. This finding held even after marked diminishment in the pre-transplant risk of death for the WAIT strategy.

While our supplemental analysis on the basis of shorter vs. longer regional waiting times did not alter our findings with respect to favored strategy, we did find that for the WAIT strategy a greater proportion died in the regions with the shortest times to transplant as compared to regions with the longest times to transplant. One possible explanation for this may be that centers in UNOS regions where waitlist durations are typically shorter are less accustomed to sustaining patients who endure longer waitlist durations, such as those who require a negative prospective crossmatch. Alternately, there may be a selection bias to list sicker...
patients (e.g. those urgently placed onto ECMO) because of the expected short wait time. In centers with longer expected waiting times these cases may be considered “hopeless” and are never listed, rather than being delisted for deterioration within a week or two if a heart does not become available.

The perspective from which organ transplantation is viewed is also critically important. From that of any high-risk, urgent-need candidate, even a small chance at meaningful post-transplant survival with a reasonably good quality of life would make transplantation desirable. However, costs of pediatric heart transplantation are substantial [18] and the demand for donor organs far exceeds supply [19]. From a societal perspective, decisions made about transplant candidacy must not only consider risk and benefit for each individual candidate relative to others, but must also be made within the framework of societal expectations for opportunity and bearable costs [20]. Assessment of the opportunity cost of transplantation of positive DSXM patients and other high risk candidates is important but is beyond the scope of Markov decision modeling and requires more intricate modeling techniques, such as discrete event simulation [21].

There are several important limitations to our analysis to consider, such as the use of registry data, which may be incomplete. We believe this potential bias is unlikely to affect waitlist outcomes and PXMR data given that these data originate directly from the clinical process of listing and delisting, rather than from retrospective reporting of these events. Post-transplant survival data and DSXM results are reported in the latter fashion and thus may be at a somewhat great risk of inaccuracy. Because we considered any reported positive crossmatch in the OPTN dataset as positive, including flow cytometry, we may have overestimated positive DSXM group survival and biased the model in favor of the TAKE strategy. To address this possible bias we reanalyzed post-transplant survival after excluding candidates in the OPTN dataset whose only positive crossmatch result was by flow cytometry and found no substantial change in favored strategy (predicted survival for TAKE was 0.15 years less than base-case). Likewise to address possible bias in our base-case model due to censoring of candidates who were reported too sick or too well for transplant, we reanalyzed the model with the assumption that candidates who were delisted too sick had died and found no substantial difference (predicted survival for TAKE was 0.1 years less than base-case).

It is important to reiterate that our findings are relevant to only urgent transplant candidates. Thus the application of our findings to candidates with less urgency may not be applicable. Also it should be noted that our decision model relied on event probability estimates and other assumptions. While the relative difference in survival between the strategies is meaningful, model survival estimates incorporate death on the waiting list as well as after transplantation and are thus not as clinically meaningful as median post-transplant survival. We feel confident our model parameters were derived from the best possible data available and the consistency we observed in our results after multiple sensitivity analyses also argues in favor of this. Further supporting our model conclusions are data from two pediatric case series showing only slightly inferior early post-transplant survival after transplantation across a positive crossmatch as compared to those with a negative DSXM [3, 4]. However, even with our effort to use the best quality data available and employ multiple sensitivity
analyses to compensate for possible gaps and assumptions in the model input data, we acknowledge that our model estimates may not be consistent with the results of a prospective assessment of these competing waitlist strategies.

In summary, our model predicts that taking the first suitable organ offer for allosensitized status 1A pediatric heart transplant candidates results in greater survival after listing, including post-transplant, as compared to waiting for a transplant across a negative donor cell crossmatch. This is because the inferior survival after transplantation across a positive crossmatch is more than offset by enhanced waitlist survival in taking the first suitable organ offer. Data which fully describe the waitlist experience for candidates listed with a virtual crossmatch requirement are lacking, however our sensitivity and supplemental analyses suggest that even for these candidates a strategy of taking the first suitable organ offer could result in a net survival benefit from the time of listing. The broader implications of these conclusions with respect to utilization of a precious, limited resource (i.e. donor organs), is a very important consideration that involves not only the transplant community but society as a whole.

ACKNOWLEDGEMENTS

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Abbreviations

DSXM  donor-specific crossmatch
IRB  institutional review board
OPTN  Organ Procurement and Transplantation Network
PRA  panel reactive antibodies
PXMR  prospective crossmatch requirement
UNOS  United Network for Organ Sharing
US  United States

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Figure 1.
Markov decision model of survival after listing for two competing waitlist management strategies of allosensitized pediatric heart transplant candidates. Following assignment to either the WAIT or TAKE strategy, the hypothetical model cohort was at risk each month for transition from the “Awaiting Transplant” state to any state directly connected by an arrow. Waitlist probabilities for transition (p₁ through p₆) varied monthly and were derived from OPTN data on waitlist outcomes of candidates who were listed with a prospective crossmatch requirement throughout the entirety of listing (WAIT strategy) or who never had a prospective crossmatch requirement (TAKE strategy). For the WAIT strategy there was no probability of transitioning to transplant across a positive DSXM state (i.e. p₆=0). Post-transplant survival was also modeled using OPTN data on mortality after transplantation across a positive DSXM (p₈) or negative DSXM (p₉) and varied (monthly until 2 years, then annually). Note p₄ = [1-(p₁+p₂+p₃+p₅+p₆)], p₈ = 1-p₇, and p₁₀ = 1-p₉. Tx, transplant.

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Figure 0002
Figure 0003

Graphical representation of OPTN outcomes data on status 1A pediatric heart transplant candidates (1999-2009) that were used to derive model probabilities of waitlist outcomes and post-transplant survival. Upper competing risk graphs depict waitlist outcomes for candidates who (A) maintained a requirement for a prospective crossmatch (PXMR) throughout listing (WAIT strategy) and (B) never had a PXMR during listing. Lower graph (C) depicts post-transplant survival for status 1A recipients, stratified by DSXM result.

Figure 2.

Negative DSXM
Positive DSXM

P<0.0001

No at risk: 1243
239
767
135
505
84
311
53
161
28
54
10

Time after transplant (years)
Figure 3.
Two-way sensitivity analysis of the probability of death after transplantation across a positive DSXM and the probability of a positive DSXM (for the TAKE strategy). The TAKE and WAIT strategies are favored within the color-coded boundaries depicted. The dashed line indicates the boundary between TAKE and WAIT strategies when the probability of a positive DSXM for the TAKE strategy is 100%. Thus even when a positive DSXM is guaranteed, the WAIT strategy is only favored when the annual probability of death after transplant across a positive DSXM is >13% (equivalent to a median post-transplant survival is <5 years).
Figure 4.
Competing risk graphs depicting waitlist outcomes for status 1A candidates in the UNOS regions with the longest (A and B) and shortest (C and D) median time to transplantation. Waitlist outcomes for candidates who maintained a requirement for a prospective crossmatch throughout listing (i.e. WAIT strategy) in the longest and shortest regions are shown in figures A and C. Waitlist outcomes for candidates in the longest and shortest regions who never had a PXMR during listing (i.e. TAKE strategy) are shown in figures B and D.
Table 1

Cohort characteristics used to estimate base-case waitlist and post-transplant outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Weight (kg) $^a$</th>
<th>Age</th>
<th>Female</th>
<th>Race</th>
<th>Listing diagnosis</th>
<th>Inotropes at listing</th>
<th>Ventilator at listing</th>
<th>ECMO at listing</th>
<th>VAD at listing $^b$</th>
<th>Primary payer $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PXMR During Listing “TAKE” (n=2650)</td>
<td>19.0 ± 22.9</td>
<td>4.1 ± 5.7</td>
<td>1184 (45)</td>
<td>White</td>
<td>1304 (49)</td>
<td>1738 (66)</td>
<td>1082 (41)</td>
<td>470 (18)</td>
<td>177 (9)</td>
<td>Public/gov’t insurance</td>
</tr>
<tr>
<td>PXMR Throughout Listing “WAIT” (n=109)</td>
<td>26.5 ± 25.9</td>
<td>6.4 ± 6.6</td>
<td>50 (46)</td>
<td>Black</td>
<td>1316 (50)</td>
<td>70 (64)</td>
<td>42 (39)</td>
<td>25 (23)</td>
<td>14 (17)</td>
<td>Private insurance</td>
</tr>
<tr>
<td>Negative DSXM (n=1243)</td>
<td>23.5 ± 25.7</td>
<td>5.2 ± 6.2</td>
<td>560 (45)</td>
<td>Hispanic</td>
<td>486 (18)</td>
<td>70 (64)</td>
<td>358 (29)</td>
<td>135 (11)</td>
<td>175 (18)</td>
<td>Other</td>
</tr>
<tr>
<td>Positive DSXM (n=239)</td>
<td>22.9 ± 23.3</td>
<td>5.2 ± 5.9</td>
<td>91 (38)</td>
<td>Other</td>
<td>157 (6)</td>
<td>7 (6)</td>
<td>41 (13)</td>
<td>30 (13)</td>
<td>41 (23)</td>
<td>Public/gov’t insurance</td>
</tr>
</tbody>
</table>

CHD, congenital heart disease; ECMO, extra-corporeal membrane oxygenation; gov’t, government; ReTx, re-transplant; Tx, transplant; VAD, ventricular assist device.

$^a$TAKE n=2647, WAIT n=105

$^b$TAKE n=1948, WAIT n=83, Negative DSX n=971, Positive DSX n=1240, Negative DSX n=239.

$^c$TAKE n=2648, WAIT n=109, Negative DSX n=971, Positive DSX n=1240, Negative DSX n=239.
### Table 2

Relationship between Annual Probability of Death and Median Survival

<table>
<thead>
<tr>
<th>Annual probability</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>17</td>
</tr>
<tr>
<td>13%</td>
<td>5</td>
</tr>
<tr>
<td>22%</td>
<td>2.8</td>
</tr>
<tr>
<td>31%</td>
<td>1.9</td>
</tr>
<tr>
<td>40%</td>
<td>1.4</td>
</tr>
</tbody>
</table>
### Table 3

Median time to heart transplantation by UNOS region and results of regional waiting-time sensitivity analyses.

<table>
<thead>
<tr>
<th>UNOS Region</th>
<th>“shortest”</th>
<th>“longest”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Days to HTx</td>
<td>28 30 33 37.5 39 40 51 50 49 48 47</td>
<td></td>
</tr>
</tbody>
</table>

Incremental survival benefit of TAKE relative to WAIT

| | HTx, heart transplant; UNOS, United Network for Organ Sharing | 1.6 years | n/a | 0.8 years |