

OPTN/UNOS Histocompatibility Committee
Meeting Summary
August 11-12, 2014
Chicago, Illinois

Dolly Tyan, Ph.D., Chair
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Discussions of the full committee on August 11-12, 2014 are summarized below and will be reflected in the committee's next report to the OPTN/UNOS Board of Directors. Meeting summaries and reports to the Board are available at <http://optn.transplant.hrsa.gov>.

Committee Projects

1. Expanding HLA Typing Requirements

In the fall of 2013, the Committee released a comprehensive rewrite of all the OPTN Policies governing histocompatibility. During this time, the Committee identified several problems with the current HLA typing requirements. The Committee spent several months gathering feedback from the OPO and organ specific committees and put together a proposal to address the numerous problems. UNOS staff presented an overview of the changes proposed by the Committee, followed by the public comments received.

UNOS staff presented to the Committee three different programming options:

1. Add DQA and DPB fields only in DonorNet
2. The addition of DQA and DPB in DonorNet only (but required for kidney, kidney pancreas, and pancreas donor offers. Also, make the HLA-A, HLA-B, HLA-Bw4, HLA-Bw6, and HLA-DR fields required for pancreas islet registrations.
3. The addition of DQA and DPB fields in DonorNet only (but required for kidney, kidney pancreas, and pancreas donor offers, make the HLA-A, HLA-B, HLA-Bw4, HLA-Bw6, and HLA-DR fields required for pancreas islet registrations, and add DQA and DPB fields in Waitlist as unacceptable antigens.

The Committee voted unanimously to recommend approval of the proposal, without changes, to the Board of Directors for the November 2014 meeting. The Committee unanimously agreed the proposal should be programmed to include DQA and DPB fields in DonorNet and DQA and DPB fields in Waitlist as unacceptable antigens.

2. Bylaws Rewrite Phase II

UNOS staff updated the Committee on the status of its Bylaws Rewrite Phase II proposal. In November of 2013, the Board of Directors approved several new changes to the OPTN Bylaws governing histocompatibility laboratories. The Committee is now in the second phase of the comprehensive review of the Bylaws. The second phase of the Bylaws rewrite contains changes dealing with education, certification, and experience requirements for laboratory key personnel and performance indicators that will trigger a mandatory performance review of a laboratory. On June 26, 2014, the Committee unanimously voted to recommend to the Executive Committee that the proposal be

distributed in the fall 2014 public comment. This proposal was also presented to the Membership and Professional Standards Committee (MPSC) and received no opposition.

The Policy Oversight Committee (POC) and Executive Committee will review the Bylaws Rewrite Phase II public comment proposal and make recommendations in mid-September.

3. Addressing HLA Typing Errors

As part of the histocompatibility comprehensive policy rewrite that was approved in June 2014, the Committee considered policy changes to address HLA typing errors that are reviewed by the Discrepant HLA Typing Subcommittee, but decided to delay sending those changes to the Board of Directors. The Committee discussed preventative and disciplinary solutions for HLA typing errors at its August 2014 in person meeting. The Committee addressed the disciplinary aspect by including in the Bylaws Rewrite Phase II proposal a provision for MPSC review of a laboratory. The MPSC may review a laboratory if one or more HLA typing errors or reporting errors on a donor results in an incompatible transplant or the re-allocation of an organ to someone other than the intended recipient.

After development of the disciplinary aspect, the Committee thought it necessary to discuss solutions to prevent HLA typing errors from occurring prior to allocation or to detect them prior to transplant. Leadership explained two possible solutions to prevent HLA typing errors:

1. Require second person confirmation for reporting HLA
2. Require recipient laboratories to re-type deceased donors

The Committee determined uncertainty exists with respect to the magnitude of HLA typing errors on organ allocation and explored limitations of the current data on HLA typing errors.

The Committee concluded that the extent of problem is not yet fully known and tasked the Discrepant HLA Typing Subcommittee with gathering data to fully understand the scope of the problem in order to narrowly tailor a solution. The Discrepant HLA Typing Subcommittee will meet in the fall to discuss the Committee's requests and recommendations.

4. CPRA and Priority for Kidney Candidates Undergoing Desensitization

The Committee discussed CPRA prioritization for kidney candidates undergoing desensitization. Under the Kidney Allocation System, highly sensitized kidney candidates who undergo desensitization lose allocation points associated with their CPRA score, thereby reducing their opportunity for kidney offers. Previously, a workgroup decided the most effective step for moving forward was to conduct a survey of kidney transplant programs to learn whether more programs would utilize desensitization for highly sensitized candidates if these candidates could keep the prioritization associated with their CPRA score for a period of time.

The Chair provided an overview of this project and update on the survey design. A series of draft survey questions were presented and reviewed by the Committee. The Committee recommended the KAS Desensitization Workgroup refine the survey questions for eventual distribution.

Committee members discussed the possibility of future simulation modeling. SRTR responded that they will need to obtain more information from the Committee to determine what type of simulation modeling, if any, can be done.

The KAS Desensitization Work Group will meet in the fall to discuss the Committee's request and recommendations.

5. Enhancing Prioritization for DR Matching in Deceased Kidney Allocation

In fall 2013, the DR Mismatch Subcommittee met to review data aimed at addressing two issues:

1. To assess the impact of lower level of HLA-DR mismatch on kidney graft survival;
2. To test the hypothesis that lower levels of HLA-DR and –DQB mismatch is superior to lower DR mismatch alone with a secondary goal of assessing whether HLA-DQB matching should be considered as an additional element in organ allocation

The Vice Chair presented a summary of results and conclusions drawn from the data. The Committee agreed with subcommittee's conclusion that based on data shown to date, there is no added value to adding priority points for DQB matching in addition to those already assigned for HLA-DR matching in kidney allocation. The Committee members also agreed the DR Matching Subcommittee should focus on whether the current point allocation for lower levels of DR mismatch is appropriate or whether additional priority should be given to those patients.

The Committee directed the DR Matching Subcommittee to request at their next meeting multivariable analysis to determine if lower DR mismatch levels are associated with better deceased donor kidney graft survival after adjusting for other facts that affect survival (different donor, recipient and transplant characteristics including CPRA value, induction, cold ischemia time). The DR Matching Subcommittee will specify several factors to be included in the model and will consult SRTR in suggesting additional variables.

The Committee discussed a request for simulation modeling to analyze the outcome if an increased number of points was given for a lower level of DR mismatch during deceased donor kidney allocation. The Committee ultimately decided to wait until they review the results of multivariable analysis and then revisit this request. The Committee is aware that they will need to involve the Kidney Committee prior to requesting simulation modeling.

6. Histocompatibility Guidance Document

In an effort to update the histocompatibility policies the Committee proposed numerous changes to Policy 4. In June 2014, the Board of Directors approved the histocompatibility comprehensive policy rewrite proposal. As part of this rewrite, the Board of Directors voted to move 28 sections of policy to a guidance document. Although these 28 sections do not contain member requirements, the Committee determined they are nonetheless useful to members for conversion into a guidance document.

The Committee decided to create a subcommittee to develop the proposal for the Committee's review. UNOS staff reminded the Committee that when the policy rewrite was sent out for public comment AST and ASTS made a formal request to see the guidance document before it is forwarded to the Board of Directors.

7. CPRA Manuscript

The goal of this manuscript is to describe the changes in CPRA distribution that have occurred since the CPRA replaced PRA for kidney allocation based on analysis performed for the Committee. This manuscript is the final step in CPRA monitoring done by the Histocompatibility Committee. The POC specified this project has a deadline at the end of this year. The lead member on this project described the structure of the manuscript and indicated a draft will be distributed in September for revisions and circulation before a final submission.

8. Programming Allele Level Typing in UNet

Current histocompatibility testing allows for the identification of allele level types of HLA and unacceptable antigens. These allele level types are a more exact indication of a patient's HLA and antibody level. However, there is no structure in UNet for laboratories to enter allele level typing. Instead, the laboratory staff must convert the allele level type into one of the existing antigens listed. This increases the likelihood for mistakes, especially since conversion of an allele level type to an antigen is not possible for all alleles. In addition, the inability to list allele level antibodies disadvantages candidates in the screening process because, when only antigens can be entered, candidates are screened from donors from whom they could safely accept an organ.

UNOS staff explained that the Executive Committee views all committee projects from a standpoint of OPTN/UNOS's resources. Resources are limited and due to the complexity and volume of the Committee's other projects, this project falls on the lower end of the Committee's prioritization list, unless the Committee is willing to re-prioritize their current project list. UNOS staff reiterated the importance of advancing current projects through the policy process before beginning new projects.

This project will require a re-evaluation after current projects advance through the policy process. Members indicated instead of programming all of the alleles to program the most common alleles.

Implemented Committee Projects

9. Monitoring Changes of CPRA Calculation

Changes to CPRA calculation were implemented on December 5, 2013. Those changes included updating HLA and ethnic frequencies used to calculate CPRA for kidney, kidney-pancreas, and pancreas registrations on the waiting list and adding HLA-C into calculation. On March 20, 2014, "Tested for anti HLA antibodies" question was added to the waiting list to better interpret 0% CPRA value. The committee members reviewed changes in CPRA values immediately after December 2013 implementation and asked to revisit monitoring these changes, once more time has passed after implementation.

During the August 11-12 meeting in Chicago, the Committee discussed continuing monitoring of implemented changes and had several data questions. The goal of the request is to monitor the update of HLA and ethnic frequencies used to calculate CPRA and addition of HLA-C into the calculation and "Tested for anti HLA antibodies" question on the waiting list.

Review of Public Comment Proposals

10. Kidney Paired Donation (KPD) Histocompatibility Guidelines to Policy

The Kidney Transplantation Committee's Kidney Paired Donation (KPD) Histocompatibility Testing Policies proposal and public comments were presented to the Histocompatibility Committee for feedback. The Histocompatibility Committee offered the following feedback:

Crossmatching

The Committee recommended requiring a review between the physician/surgeon and the HLA laboratory director (to discuss sensitization history, the possible need for additional screening or crossmatch) if the transplant doesn't occur within 60 days of the original physical crossmatch.

Frequency of Antibody Screenings

In response to the specific request for feedback regarding the requirement to perform antibody screenings on all candidates every 90 days, the members of the committee were somewhat split in opinion. Half of the committee indicated support for leaving the requirement as is. This half of the committee did not agree that there should be a longer timeframe for candidates who are/were unsensitized on previous screenings, because a longer timeframe (180 days was used, for example) could mean that they would proceed to transplant on what they considered to be very old test results (100 days or more).

The other half thought that it would be more productive to require the collection of sera every 30 days (monthly) instead of specifying the frequency for antibody screenings. This half of the committee said that having a recent sample to perform the tests is the most important key in this instance and that the frequency of screenings should be left as a center specific practice.

Other members of the Committee did not agree that this should be left to the center to decide as a protocol, reasoning that many programs are involved in the same match run

and they are just as dependent on the outcome as other centers, so consistency is key for KPD.

Inactivation Due to Unacceptable Positive Crossmatch

The Committee did not specify a particular option as to whether UNOS or the transplant program should be responsible for inactivating the candidate. They did, however, express the hope that the review/reporting turnaround time would be quick so that the candidate is not disadvantaged by not being eligible for match runs for significant periods of time. There will be many instances where the crossmatch is unacceptable because of low level antibodies and the unacceptable antigens are not going to change with the review between the surgeon/physician and the HLA laboratory director.

Members of the Committee suggested that the Kidney Committee consider an additional requirement in these instances – that the program pre-refuse that particular donor for the candidate for subsequent match runs.

As a side note (unrelated to the policy changes), one member asked if the OPTN KPD program allowed for exploratory crossmatches similar to other KPD programs.

11. Presentation from Thoracic Committee

UNOS staff presented a report provided to the Heart Subcommittee of the Thoracic Committee in March of 2014 that described unacceptable antigen reporting on the waiting list for heart candidates and recipients. The Heart Subcommittee has discussed possible modifications to adult donor heart allocation, with the primary focus being on revisions to the prioritization tiers. The Heart Subcommittee identified sensitization as a critical issue for inclusion in a new allocation system, but is still discussing the best mechanism for incorporation. The Heart Subcommittee was interested in available information on reporting of unacceptable antigens for heart candidates on the waiting list and if that information could be used to identify patients who are sensitized for incorporation into an allocation system. These data were presented to the Histocompatibility Committee for recommendations on the definition of sensitization and how to prioritize patients that are defined as sensitized.

The Histocompatibility Committee recommended the Heart Subcommittee review the existing data, identify the transplant centers that reported unacceptable antigens, and determine how many patients they have in their transplant center. Afterwards, the Heart Subcommittee can analyze the distribution for the frequency of the sensitization or listing.

The Histocompatibility Committee was also asked to define highly sensitized heart candidates. The Committee responded that kidneys now have an approved sliding scale based on CPRA values and the Thoracic Committee may consider whether a sliding scale can be incorporated into the modeling for hearts so there is recognition that the patient is sensitized but at a higher value of sensitization, patients are given incrementally higher priority.

Other Significant Items

12. Presentation from Vascularized Composite Allograft Committee

The Board of Directors accepted the first OPTN policies and standards for vascularized composite allograft (VCA) transplantation, effective July 3, 2014. The requirements will be in effect for 18 months, allowing public comment in the fall of 2014. The Vascularized Composite Allograft Transplantation Committee will continue development of other aspects of VCA policy. Priorities include refining allocation policy, data requirements and data collection procedures for VCAs.

Histocompatibility Committee members were particularly interested in addressing highly sensitized patients. The Committee encouraged the VCA Committee to begin contemplating the requirement for testing of HLA antibodies and typing so that after gaining experience the VCA Committee can later analyze the data to determine what policies are appropriate for these transplants. The VCA chair concurred and stated that one of the largest restraints for VCA is an absence of data.

A member asked whether the VCA Committee intends on adding a histocompatibility specialist to the VCA Committee. The VCA chair explained that after the basic issues are resolved, and as the VCA Committee moves forward with in depth questions, an ad hoc histocompatibility expert should attend the meetings. The VCA chair further stated that as the numbers increase and the competition for organs increases, histocompatibility will be a very important issue.

13. Presentation on Kidney Allocation System (KAS)

The new Kidney Allocation System (KAS) will become effective on December 4, 2014. The Chair discussed what laboratories need to do to prepare and the tools available for implementation of the new system. To prepare OPOs, transplant programs, and HLA laboratories for the upcoming changes to the kidney allocation system, a podcast, recorded webinars, and a toolkit for professionals has been provided. These resources are located on the OPTN website or on Transplant Pro.

14. OPTN Policy Development Process Improvement

UNOS staff explained key upcoming changes to the OPTN policy development process. In the fall 2014 public comment cycle, the Executive Committee will distribute a proposed new pathway to allow expedited consideration and action on rare issues that must be addressed more quickly than the usual process allows. Under the proposed pathway public comment would be sought after an initial Board of Directors approval. If significant concerns or questions are raised during the public comment, the policy would be referred back for additional consideration and action under the standard policy development process. In addition, UNOS developed a revised schedule of meetings and public comment cycles to allow more timely action on policies and bylaws. The new calendar will schedule Board meetings in June and December.

Upcoming Meeting(s)

- TBD