OPTN/UNOS Histocompatibility Committee
Report to the Board of Directors
November 16-17, 2009
Orlando, Florida

Summary

I. Action Items for Board Consideration

- None

II. Other Significant Issues

- Policy 3.5.11.3 Calculated Panel Reactive Antibody (CPRA) was fully implemented on October 1, 2009. (Item 1, Page3)

- Potential for a Committee Sponsored Variance for kidney transplant candidates on a desensitization protocol. (Item 2, Page 4)

- Potential policy proposal to modify Policy 3.5.11.3 (Calculated Panel Reactive Antibody (CPRA)) to award sensitivity points on a sliding scale. (Item 3, Page 4)

- Potential policy proposal which would require deceased donor HLA typing be performed by DNA methods. (Item 5, Page 6)

- Potential updates to Policy Appendix 3A. (Item 6, Page 6)

- The Committee developed histocompatibility guidelines for programs participating in the National Kidney Paired Donation Program. (Item 7, Page 6)

- The Thoracic Organ Transplantation Committee has asked the Histocompatibility Committee to cosponsor a proposal to require HLA typing of deceased donors prior to the match run. (Item 10, Page 10)

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Michael Cecka, Ph.D., D (ABHI), Chair
Nancy Reinsmoen, Ph.D., D (ABHI), Vice Chair

The following report presents the OPTN/UNOS Histocompatibility Committee's deliberations and recommendations on matters considered during its October 25, 2008, and February 2, 2009, conference calls, and its July 15, 2009, meeting.

1. Calculated Panel Reactive Antibody (CPRA). As a review, in December 2006, the Board of Directors approved modifications to Policies 3.5.11.3 (Panel Reactive Antibody) and 3.8 (Pancreas Allocation) to replace current and peak Panel Reactive Antibody (PRA) with calculated Panel Reactive Antibody (CPRA) for kidney, kidney-pancreas, and pancreas allocations. Due to the complexity of these changes, they would be introduced in three phases.

    - **Phase One:** Allocation will continue to be based on traditional PRA; however, OPOs, transplant centers, and HLA laboratories will be able to calculate and see CPRA on the Waitlist[sm]. Members can access the CPRA calculator on the OPTN and UNOS Web sites.
    - **Phase Two:** Allocation based on CPRA will be initiated, although OPOs, transplants centers, and HLA laboratories will be able to enter and see traditional PRA on the Waitlist[sm] if desired.
    - **Phase Three:** Allocation will be based on CPRA. Traditional PRA information will no longer appear on the Waitlist[sm].

    Phase One was implemented in December 2007. On the March 2008 conference call, it was announced that there would be a delay in the implementation of Phase Two due to programming challenges at UNOS. This pushed implementation of Phase Two back to the third quarter of 2009.

    In the meantime, the Committee has followed the use of CPRA within the existing kidney system. Analyses were presented to the Committee during conference calls held on October 2008 and February 2009. The Committee requested ongoing updates of these analyses until phase two of CPRA was implemented.

    At the July 15, 2009, meeting, the Committee reviewed CPRA data from the kidney waiting list registrations as of June 12, 2009, and compared those to the PRA data. The Committee reviewed the percentage of registrations with a CPRA and the number of candidates who could potentially lose their sensitization points if CPRA were implemented today.

    As of June 12, 2009, 27,503 registrations (32.4%) on the kidney waiting list had at least one unacceptable antigen entered, allowing the calculation of a CPRA. This was an increase from the number observed on June 13, 2008 (23,009). A small number of centers (11/256) had not

entered any unacceptable antigens for their candidates. Most of these centers (8/11) had fewer than 10 kidney candidates.

Phase Two of the CPRA policies were implemented October 1, 2009. Because of the long delay in the implementation of phase two, phase three was also applied at this time. Therefore, as of October 1, 2009, allocation of kidney, kidney/pancreas, and pancreas, will be based on CPRA. The traditional PRA information no longer appears on the Waitlist[sm].

At the July 2009 meeting, the Chair of the Committee, asked the Committee to discuss a potential problem that may surface with this implementation. He asked if there should be a way to show if a candidate was sensitized to HLA antigens, but had a CPRA of 0. He asked if a check box could be added on the waitlist that would signify that the candidate did indeed have HLA antibody, but not at levels high enough to list them as unacceptables. The Committee was told that such a revision at that time would delay implementation of the CPRA policy. The Committee therefore agreed to let implementation proceed as scheduled in the third quarter of 2009.

However, the Committee may propose an addition to the candidate waitlist form depending on whether the need becomes evident with the implementation of phase two of CPRA. The proposed addition to the waitlist form is:

> *Add a check box query to waitlist form…"Were any anti-HLA antibodies detected? Yes/No/Not done/blank", the CPRA would default to 0 if yes or no is indicated. If the CPRA field is blank, that would indicate that the test was not done.*

2. Committee Sponsored Variance. Also at the July meetings, the Vice-Chair, expressed concern that kidney candidates on a desensitization protocol would be disadvantaged with the implementation of CPRA. She said this is because the CPRA is directly linked to the unacceptable antigens listed. If a candidate took part in a desensitization protocol, that candidate could receive a kidney from a donor to which he had previously had donor specific antibody (DSA) listed as unacceptable. If these unacceptable antigens were removed so the candidate would not be screened from the list from those donors, their CPRA level would fall, and potentially so could their place on the list. Therefore she proposed and the Committee supported the following Committee sponsored variance:

   > *Programs that submit an IRB-approved desensitization protocol can apply for a variance that will permit a desensitized patient's CPRA to remain at pre-desensitization levels for one year after reactivation even though unacceptable antigens may be removed.*

   The Committee will confer with the Kidney Transplantation Committee and the American Society of Histocompatibility and Immunogenetics (ASHI) in the winter of 2009 with the goal of having a proposal ready for public comment in March 2010. The Committee's objective would be to have a final proposal complete to be presented to the Board of Directors in November 2010.

3. Sliding Scale for Sensitization Points. Current policy grants four points to those kidney candidates with a PRA of 80% or higher. When CPRA is implemented, policy will grant kidney candidates with a CPRA of 80% or higher 4 points. Policy does not grant any points to those candidates with a PRA/CPRA level of 79% and lower. The members of the Histocompatibility Committee, as well as those from the Kidney Transplantation Committee,

have expressed a concern that this policy was not fair because all sensitized candidates are disadvantaged to some degree.

At the July 2009 meeting, the Committee discussed proposing a change to policy that would grant the number of points received by sensitized candidates on the waiting list during deceased kidney allocation process based on a sliding scale. The Committee realized that the points granted should not follow a linear progression because that is not how candidates are disadvantaged. Therefore, the Committee requested data on transplant rates by sensitization level to be presented at their next meeting.

The Committee will review this data at their meeting in October 2009 and finalize the proposal language. The potential proposal to modify Policy 3.5.11.3 (Calculated Panel Reactive Antibody (CPRA)) to award sensitization points to sensitized candidates on a sliding scale (to be determined.)

The Committee will than share this potential proposal with the Kidney Transplantation Committee and ASHI in the winter of 2009 to gain their feedback. These comments will be incorporated into a formal proposal with the possibility of having it ready for public comment in March 2010. The Committee's goal would be to have a final proposal to be presented to the Board of Directors in November 2010.

4. Discrepancy report. As background, at the July 2007 meeting, the Committee discussed the UNet[sm] Discrepant HLA Typing report, as referenced in Policy Appendix 3C. This report will flag centers that provide HLA on the waitlist, the donor histocompatibility form (DHF), and/or the recipient histocompatibility form (RHF) if the typing provided differs. The policy goes on to say "The Laboratory Director(s) or their designee(s) shall contact the other Laboratory Director(s) or their designee(s) to resolve these discrepancies."

   A brief analysis indicated that 2,787 donor records and 2,079 recipient records were unresolved at that time. It also showed that the report was not working as intended, and that it was not being used by many laboratories. Several Committee members said that they did not know the report existed. Given the high number of unresolved discrepancies shown, the Committee opined that the programming problems within the report should be resolved. The Committee also agreed that once the UNet[sm] report has been modified, laboratories should be notified that they are to resume using the report. UNOS IT staff corrected the report in May 2008. On May 9, 2008, a system notice was sent to all UNet[SM] users stating that "The OPTN/UNOS Histocompatibility Committee will be reviewing the Discrepancy Report for all OPTN/UNOS member laboratories annually."

   The Committee reviewed an updated report in July 2009 using current data from the discrepant HLA typing report in UNet[sm.] The report showed that over all, the percentage of resolved cases increased from September 2007 to June 2009.

   The discussion on this topic included a number of possible explanations for discrepant typings and indicated some of the difficulties that may bias the report. The Committee discussed the possibility of developing a threshold for these errors, and suggested that laboratories that went over this threshold should be reported to accrediting agencies as alerts for inspection.

The Committee opined that the primary goal of the discrepancy report is to provide accurate data. They said the report alerts laboratories that there are conflicting data that has been recorded and that these discrepancies need to be resolved and the data corrected. Regional representatives were urged to relay this information to the laboratory directors in their regions. The Committee felt strongly that laboratories with high levels of unresolved discrepancies should be made aware that they have a high percentage of discrepant typings and that they may be held accountable.

The Committee also stated that discrepancies between match run and donor forms may be a key measures of laboratory performance. A subcommittee was appointed to review and evaluate the specific discrepancies between the donor match run and DH Form to determine whether this is a good indicator of laboratory performance or merely reflects sloppy reporting.

5. Potential Proposal to Modify Policy 3.5.9.1 Essential Information for Kidney Offers. The Committee opined that the time had come to require a level of testing for all deceased donors that was uniform and therefore would eliminate many discrepancies. The Committee said that most errors in donor HLA typing are due to continued use of serological tests. A new policy that would require the use of molecular tests would improve safety for candidates, speed allocation, and reduce costs of repeat typing. Therefore, at its July 2009 meeting, the Committee unanimously approved the following:

   Potential Proposal to modify Policy 3.5.9.1 (Essential Information for Kidney Offers) to require deceased donor typing be performed by DNA methods and must identify splits of HLA-A,-B,-Cw,-DR and -DQ antigens.

   The Committee will confer with the Kidney Transplantation, Pancreas Transplantation, and OPO Committees, and ASHI in the winter of 2009 with the goal of having a proposal ready for public comment in March 2010. The Committee's objective would be to have a final proposal complete to be presented to the Board of Directors in November 2010.

6. Update Appendix 3a as required by policy. A subcommittee was formed to update Appendix 3A (equivalence tables) as required by policy. The Committee asked for supporting data that it will need to update the table; specifically they wanted antigen counts for A, B, Bw4/6, Cw, DR, DR51, DR52, DR53 and DQ for deceased donors and candidates during 2007-2008 by DNA and serology separately.

   Potential Policy Proposal: Update Appendix 3a as required by policy.

   The Committee will gain feedback from the Kidney Transplantation Committee and ASHI in the winter of 2009 with the goal of having a proposal ready for public comment in March 2010. The Committee's objective would be to have a final proposal complete to be presented to the Board of Directors in November 2010.

7. Guidelines for Kidney Paired Donation (KPD) The Committee wrote the first draft of these guidelines in 2005 and submitted them to a subcommittee of the Kidney/Pancreas Transplantation Committees, which was working on paired donation. That project was put on hold until the government confirmed that paired kidney donation did not violate NOTA. Permission to proceed with paired kidney donation was received in the fall of 2007. In June 2008, the Board of Directors approved a national KPD pilot program. The Scientific Affairs Committee of ASHI was then charged by its Board to prepare guidelines for appropriate

histocompatibility testing for a national paired donation program. ASHI asked the Histocompatibility Committee to appoint members from the Committee to collaborate on a set of guidelines for paired kidney donation. The Histocompatibility Committee shared its 2005 guidelines as a starting point. Then, a joint ASHI/Histocompatibility subcommittee worked to update these guidelines. The Committee reviewed this document and made specific suggestions in January and March 2008. These suggestions have been incorporated into the document.

The amended version of the document was presented to the Committee on the October 2008 conference call. The real challenge was to design a set of guidelines that would establish a kind of virtual crossmatch because a high number of unexpected positive crossmatches could "kill" the fledgling KPD program. For that reason, the members of the Committee said every risk of a positive reaction should be in the database, and that the listing of unacceptable antigens must be complete, rigorous, and stringent.

After much discussion, the Committee voted to include a requirement for molecular typing with the inclusion of HLA-A, B, Cw, DRB1, DRB3, 4, 5, DQB, and DP into the document.

A Committee member questioned a clause in the document which stated if a particular lab had a large number of unexpected positive crossmatches; it should be required to use another laboratory for antibody testing. The member was assured this requirement was not meant to be punitive, but educational.

This document separated the unacceptable antigens and all other HLA antigens to which the patient was sensitized. The document states "Sensitized patients must have unacceptable HLA-A,-B,-Cw,-DR,-DQ and DP antigens listed that include those antigens to which the patient is sensitized and would preclude transplantation at the candidate's center with a donor having any one of those antigens". Therefore, unacceptable antigens would be avoided in all match run pairings.

The document also requires that sensitized patients have all other antigens to which antibodies were detected listed. These would include HLA antigens to which the patient is sensitized, but which may not cause a positive crossmatch by themselves. The Committee suggested that if a match is made with a donor with such an antigen, discussions between the center and HLA laboratories involved must take place within 72 hours. This would assure that the center is serious about considering this match for transplant before the recipient and donor are removed from the system.

The Committee noted for all this to work as anticipated, there must be a strong educational component in place. The Histocompatibility Committee would provide a detailed report with examples of how the KPD match program could work for the transplant community; this document should stress the importance of doing all that is possible to prevent unexpected positive crossmatches because they could totally derail the system.

A copy of this document is attached as **Exhibit A**.

8. Issues from the Membership and Professional Standards Committee (MPSC). The MPSC asked the Committee to review the number of laboratories that one individual could reasonably direct. A research request showing exactly how many directors supervise multiple laboratories was made on the February 2009 conference call and the results were reviewed by the Histocompatibility Membership Subcommittee in April of 2009. The Subcommittee came

to the conclusion that the issue was too complex to be dealt with by the Histocompatibility Committee alone and recommended that UNOS rely on the agencies which have deemed status to accredit laboratories: the American Society of Histocompatibility and Immunogenetics (ASHI) and the College of American Pathologists (CAP) to make that determination. However, the Subcommittee recommended a new format for the membership ballot. The full Committee reviewed and approved this new format at the July 2009 meeting. To clarify, this ballot is a document prepared by UNOS Staff. The ballot summarizes information concerning progress made in the approval process for applicant HLA laboratories and laboratory personnel. This information is provided by the agencies which have deemed status with UNOS to accredit laboratories, ASHI and CAP. The Committee reviews this document periodically and makes recommendations to the MPSC as to whether these changes should be approved for UNOS membership. The Histocompatibility Membership Subcommittee requested a new format for this ballot because they said the Committee needed more information about the impending approval to make a decision. The Subcommittee was particularly concerned with the number of laboratories one individual could direct and the significant amount of time required for some laboratories to gain final approval. The Committee opined that if the accrediting agency had approved an interim plan for a laboratory while it was going through the approval process, the Committee could recommend to the MPSC that the laboratory be approved for membership. The Committee also said that if a laboratory received approval under an interim plan, the Committee should be updated every three months on the laboratory's status until the laboratory reaches final approval.

The Committee reviewed key personnel changes in member laboratories with the new ballot format and made recommendations which were presented to the Membership and Professional Standards Committee (MPSC) July 21, 2009, meeting.

The Committee also discussed two other MPSC-referred issues.

1. It was reported that there continue to be complaints about insufficient amounts of tissue used for typing being sent with organs for transplant. This issue was first brought to the MPSC in January 2008. The MPSC suggested a policy change and passed this suggestion on to the Histocompatibility Committee for consideration. In response, the Histocompatibility Committee reviewed Policy 2.5.5 which defines the minimum tissue typing material requirements. The Committee noted the existing policy was adequate and the issue was one of compliance. Because the Committee was not sure how often or prevalent this problem actually was, it developed a survey that was given to fellow Committee members to fill out. (Most regional representatives to the Committee are also HLA Laboratory Directors.) The Committee members tracked the amount of typing material received with all import organs for three months.

   Preliminary results from this survey show that there may indeed be a compliance issue that should be addressed by the MPSC. The results suggested up to 6% of imported kidneys were shipped with inadequate typing materials or were improperly labeled. The Committee opined that there should be a way to track these findings and a mechanism should be developed for centers to report this problem to the Committee and ultimately the MPSC.

   The complete results of the informal survey were not available to present by the July 2009 meeting date. However, it was suggested that such incidents could be reported

on UNet under Patient Safety –Safety Issues. All incidents reported in this manner are investigated and could be reported to the MPSC.

2. The second issue from the MPSC was asking for assistance with the development of clear responsibilities and guidelines for individuals serving as a data coordinator in a HLA Laboratory. It was noted that current bylaws provide similar information for other positions. The Committee developed the following proposed definition of a Laboratory Data Coordinator:

   Laboratory Data Coordinator. All laboratories should identify one or more staff members who will be responsible for coordinating data entry, checking and validation of histocompatibility information reported on UNet[sm] and DonorNet forms. The data coordinator will work with laboratory staff to insure complete and accurate data reporting to the contractor. The data coordinator must be familiar with laboratory and transplant program information systems and other sources of patient and donor histocompatibility test results as needed to fulfill these functions. Specific responsibilities should include, but are not limited, to:

   1. *Waitlist form*
      a. *Assures the accuracy of HLA typing and sensitization data entered on the waitlist form, whether these data are entered by the laboratory, transplant program or other personnel.*
      b. *Assures unacceptable antigens and CPRA are updated when needed.*
   2. *Donor histocompatibility form*
      a. *Completes donor histocompatibility forms within 30 days of donor testing if this is performed by the laboratory.*
      b. *Corrects HLA typing data when discrepancies are noted and resolved.*
      c. *Verifies donor histocompatibility data.*
   3. *Recipient histocompatibility form:*
      a. *Completes recipient histocompatibility forms within 30 days of transplantation.*
      b. *Corrects HLA typing data when discrepancies are noted and resolved.*
      c. *Verifies donor histocompatibility data.*

9. Histocompatibility Forms. The Committee discussed changes to the UNet[SM] histocompatibility forms on Tiedi. It was proposed that all of the fields under HLA antibody screening and crossmatch on the recipient histocompatibility form be eliminated. The Committee said these data fields were extremely complex, and it was unclear what sort of research questions could be addressed using them. The Committee recommended the following changes:

   a. Donor form
      1. Remove thymoctes, cell lines/clonal cells and solid matrix as options for target source for class I and class II typing.
      2. Remove 1 and 2 designations for antigen locus for class I and class II types (to be consistent with recipient form).
      3. Eliminate 0.5 and 1.5 haplotype match options.

b. Recipient form
    1. Prefill CPRA and unacceptable antigens in recipient information box (values at time of transplant).
    2. Eliminate section II - HLA antibody screening.
    3. Eliminate section III – crossmatch.
    4. Remove thymocytes, cell lines/clonal cells, solid matrix as target cell sources for class I and class II donor retyping.

10. Thoracic Transplantation Committee. The Thoracic Committee has asked the Histocompatibility Committee to cosponsor a proposal to require HLA typing of deceased donors prior to the match run. The Committee supports this proposal and agreed to form a subcommittee that would work jointly with the Thoracic Committee toward that end.

HISTOCOMPATIBILITY COMMITTEE		JULY 1, 2009 – JUNE 30, 2010
	MONTH	JULY
	DAY	15
	FORMAT	In Person
NAME	COMMITTEE POSITION	
J. Michael Cecka, PhD	Chair	x
Nancy Reinsmoen, PhD	Vice Chair	x
Dean Sylvaria, BS,CHS	Regional 1 Rep.	x
William Ward, PhD	Regional 2 Rep.	x
Karen Sullivan, PhD	Regional 3 Rep.	x
Jerry Morrisey, PhD	Regional 4 Rep.	x
Lee Ann Baxter-Lowe, PhD	Regional 5 Rep.	x
Paula Wetzsteon	Regional 6 Rep.	x
David Maurer, PhD	Regional 7 Rep.	x
Steve Geier, PhD	Regional 8 Rep.	x
Char Hubbell, M.T.	Regional 9 Rep.	x
A. Bradley Eisenbrey MD, PhD	Regional 10 Rep.	x
John Schmitz, PhD	Regional 11 Rep.	x
Dawn Brims, B.S.N.,RN	At Large	x
Douglas Keith, MD	At Large	x
Brad Kornfeld	At Large	
Emily Messersmith	SRTR Liaison	x
Alan Leichtman, MD	SRTR Liaison	x
Lori Gore	Committee Liaison	x
Anna Kucheryavaya	Support Staff	x
Jory Parker	Support Staff	By Phone