OPTN/UNOS Histocompatibility Committee
Report to the Board of Directors
June 21-22, 2010
Richmond, VA

Summary

I Action Items for Board Consideration

- None

II Other Significant Items

- Proposed modifications to update UNOS Policy Appendix 3A. (Item 1, page 3)

- Proposed modifications to Policies and bylaws which would require deceased donor HLA typing be performed by DNA methods and identify the HLA -A, -B, -Cw, -DR and -DQ antigens before making any kidney, kidney-pancreas, pancreas, or pancreas islet offers. (Item 2, page 3)

- The Committee continues to work on an approach to provide access to candidates undergoing desensitization. (Item 3, page 4)

- The Committee continues to work on a potential policy proposal to modify Policy 3.5.11.3 (Calculated Panel Reactive Antibody (CPRA)) to award sensitivity points on a sliding scale. (Item 4, page 5)

- The Committee continues to monitor the Discrepant Typing Report. (Item 6, page 7)

- The Committee responded to a memo from the Membership and Professional Standards Committee (MPSC) asking for guidance in its consideration of the maximum number of laboratories that may be appropriate for one person to direct. (Item 7, page 7)

- The Committee suggested updates to the Histocompatibility OMB forms (Histo recipient and donor forms.) (Item 8, page 8)

- The Thoracic Organ Transplantation Committee has asked the Histocompatibility Committee to cosponsor a proposal to require HLA typing of deceased donors prior to a thoracic match run. (Item 9, page 8)

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J. Michael Cecka, Ph.D., D (ABHI), Chair
Nancy L. 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 February 2, 2010 conference call and all subcommittee conference calls made between November 2009 and the present.

Currently the Histocompatibility Committee has two proposals being reviewed for public comment. The public comment period closes July 16, 2010.

1. Updates to Policy 3, Appendix A. The first proposal is an update to Policy 3, Appendix A (Appendix 3A). The Histocompatibility Committee is required to update the tables within this appendix every 2 years. The tables must be updated periodically to reflect changes in HLA typing practice and to improve the utility of the unacceptable antigens. Appendix 3A includes 2 tables; one listing HLA antigen designations that should be considered equivalent for purposes of matching kidney candidates and donors for the HLA-A,-B, and –DR antigens (HLA Antigen Values and Split Equivalences) and a second for determining which donor HLA antigens are unacceptable based on the unacceptable HLA-antigens listed for a sensitized candidate (HLA A, B, C, DR, and DQ Unacceptable Antigen Equivalences). The Committee sought and received support for this proposal from the Kidney Transplantation and the Pancreas Transplantation Committees. The proposal in its entirety can be viewed in Exhibit A. It was distributed for public comment on March 19, 2010 and the Committee will review the proposal and comments at its next meeting.

2. Proposed modifications to Policies and bylaws which would require deceased donor HLA typing are performed by DNA methods with additional antigens before making any kidney, kidney-pancreas, pancreas, or pancreas islet offers. The second proposal requires OPOs and their associated laboratories to perform HLA typing of deceased donors by DNA methods and identify the HLA-A, -B, -Cw, -DR and -DQ antigens before making any kidney, kidney-pancreas, pancreas, or pancreas islet offers. This would affect Bylaws Appendix B Attachment IIA - Standards for Histocompatibility Testing D HLA Typing D1.000; UNOS Policies 3.5.9.1 Essential Information for Kidney Offers, and 3.8.2.2 Essential Information for Pancreas Offers.

   This proposal would extend the HLA typing requirements for deceased donors to include the identification of HLA-A, -B, -Cw, -DR and -DQ antigens. These additional requirements would align the deceased donor HLA types with the unacceptable antigens that can be listed for sensitized candidates. The proposal further requires HLA testing of deceased donors to employ molecular methods. These modifications will increase accuracy and precision of the HLA typing and should reduce the number of predictably crossmatch incompatible offers for sensitized candidates. The full content of this proposal can be viewed in Exhibit B.

   The Committee sought and received support for this proposal from the Kidney Transplantation and the Pancreas Transplantation Committees. The Committee also asked the OPO Committee for feedback. The OPO Committee noted the following concerns:

- The proposal would extend the time for a complete donor work up from 6 hours to approximately 18-20 hours.
- The proposed testing would be extremely expensive compared to the current process.
- The OPO Committee was concerned that most of the information gained would be HLA-C locus data which has not been proven to be of use for predicting renal transplant outcomes.

The chair replied to the OPO Committee on February 17, 2010. He reported that in at his laboratory in Los Angeles, HLA typing is completed and reported prior to organ procurement in >95% of cases. The use of molecular methods speeds up rather than delays typing because supplemental testing is rarely required. More importantly, DNA typing can be performed on donor peripheral blood, even when lymphocyte counts are low, and is easily completed in 5-7 hours.

It was noted that 95% (98/103) of laboratories already perform DNA typing on deceased donors. Because nearly all laboratories report DNA typing, the infrastructure for this testing platform already exists in all but a few labs. Therefore, the cost of DNA testing would not be more than serology.

The OPO Committee was reminded that the purpose of the proposal is to align the donor typing requirements with antigens that can be listed as unacceptable for sensitized candidates. This was the reason for adding -Cw and -DQ antigen typing to the requirement. HLA-Cw and -DQ antigens are already typed for 84% and 98% of deceased donors, respectively, and that the quality and precision of typing for these antigens using serology tests is poor resulting in inappropriate allocation to candidates who have -Cw or -DQ antigens listed as unacceptable. This may cause delays in placement, require retesting the donor at the recipient laboratory and involves some risk for the patient.

Members of the transplant community have shared with members of the Histocompatibility Committee that they cannot switch to DNA technologies because UNOS does not require it. It was the opinion of the Committee that if it were to become a requirement, the necessary funds would be appropriated. Many on the Committee opined that this proposal is not a large change in what is currently being done, but it should have an important impact on reducing errors in HLA typing and it should help laboratories that are currently blocked from acquiring these modern techniques.

The letters from the OPO Committee and the Committee response can be viewed in Exhibit C.

The Committee will review comments received during the public comment period on these two proposals at their July 13, 2010 meeting. It is the Committee's objective to have the final proposals presented to the Board of Directors in November 2010.

3. <u>An approach to provide access to candidates undergoing desensitization</u>. The Committee has also tried to develop an approach to provide access to candidates undergoing desensitization. The problem is that sensitized candidates waiting for a deceased donor kidney who undergo desensitization have been disadvantaged since the implementation of CPRA on October 1, 2009. This is because CPRA and the allocation points assigned to broadly sensitized candidates (80+% CPRA) are directly linked to the unacceptable antigens (UA) listed. When a candidate undergoes desensitization, unacceptable antigens may become acceptable because the corresponding antibodies are reduced or eliminated by the desensitization protocol. However, when these antigens are removed as unacceptables on the waitlist, the CPRA may fall below 80% and the patient's waitlist rank may fall, reducing the patient's opportunities for kidney offers. (Prior to October 1, 2009, programs could remove unacceptable antigens without a change in PRA, sensitization status or waitlist rank.)

The Committee discussed development of a "national variance." Programs that actively desensitize broadly sensitized candidates awaiting a deceased donor kidney transplant could apply to take part in such a "variance." It would permit a desensitized patient's CPRA to remain at pre-desensitization levels until an immunologically acceptable donor is identified or for six months after desensitization even though unacceptable antigens may be removed.

The goal of this proposed variance would be to preserve the waitlist rank of a sensitized renal transplant candidate who participates in a desensitization protocol. This change would affect Policy 3.5.11.3. (This policy awards 4 points to kidney candidates who have a CPRA of 80% or higher.)

This variance would be an important option for programs that attempt to desensitize broadly sensitized candidates so that they may be transplanted with a deceased donor kidney. These desensitization protocols are expensive, but may provide the only chance for a broadly sensitized individual to be transplanted with an immunologically compatible deceased donor kidney.

In researching the need for such a variance, the Committee inquired how many programs are currently using desensitization protocols for use with deceased donors. (There are many programs throughout the country that are routinely using such protocols on candidates who are receiving a graft from a living donor and these candidates would not be affected by this variance.)

While it was an informal survey, the Committee became aware of at least 10 specific programs in California, Maryland, Minnesota, Ohio and Oregon that use desensitization protocols. Together these programs have treated 100-150 candidates in the past year. It is the feeling of the Committee that this number will increase with the success of such protocols and the increased availability of funding.

The Committee is aware that there may be objections to this proposed variance based upon whether it would be open to "gaming" and whether it would be fair to non sensitized or less sensitized candidates. It should be noted that this proposal does not give a patient with $\geq$80% CPRA any donor access advantage, unless desensitization works and UAs are removed.

However, this proposal is not yet ready to be distributed for public comment pending additional decisions by the Committee and UNOS. Such a policy must specify conditions and qualifying criteria that affected programs and candidates must meet; finalizing these components of the proposal is ongoing. It has been noted that other proposed revisions to kidney allocation policy are also ongoing, including the development of a sliding scale for awarding CPRA points. Multiple revisions to kidney allocation policy are planned for simultaneous implementation once all components of the new kidney allocation policy have been developed and approved. It is thought that an approach to provide access to candidates undergoing desensitization could be built into this new kidney allocation system.

Until then, an alternate, more manual plan may need to be implemented on a local scale rather than a national one. As long as only a few candidates are affected, local priority agreements might prevent loss of rank or give priority for candidates undergoing desensitization with specific limits and conditions set by other transplant centers within the DSA whose candidates would be affected. The OPTN would have to agree to allow some out-of-sequence transplants for candidates undergoing desensitization. The Committee will discuss this temporary option at its July2010 meeting.

4. Sliding scale for CPRA. Current policy grants four points to those kidney candidates with a CPRA of 80% or higher. Policy does not grant any points to those candidates with a 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.

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. The Committee requested data on the number of deceased donor transplants by sensitization level to be presented at its next meeting.

Broadly sensitized renal transplant candidates currently are awarded 4 allocation points if their CPRA is 80% or above. This provides them with the equivalent of an extra 4 years waiting time and improves their access to transplantation. However candidates with 79% CPRA or less currently receive no sensitization points even though they are similarly disadvantaged in proportion to their level of sensitization. Since the implementation of CPRA on October 1, 2009, candidates are not offered kidneys from donors who express any unacceptable HLA antigens, which are used to calculate the CPRA. Thus, sensitized candidates receive fewer offers than unsensitized candidates in direct proportion to their CPRA value. To compensate for this biological disadvantage, candidate with CPRA values between 20-95% would receive up to 4 allocation points (from 0 at 20% to 2.0 at 55% to 4.0 at 95%) on a sliding scale in addition to wait or ESRD time points. Candidates with >95% CPRA will have few compatible donors and should be given the highest priority when a compatible donor finally becomes available.

The Committee reviewed the data on transplant rates by sensitization level and tried to finalize proposal language that would modify Policy 3.5.11.3 (Calculated Panel Reactive Antibody (CPRA) to award sensitization points to sensitized candidates on a sliding scale. The Committee could not develop a proposal for how points should be granted at this time because CPRA has only been in effect for such a short time. Therefore, the proper modeling for a proposal could not be done. It was noted that multiple revisions to kidney allocation policy are planned in the near future. It might be most cost effective to implement all of these changes at the same time. Therefore, the sliding scale for CPRA points may be built into the new kidney allocation system. The Committee plans to work with the Kidney Transplantation Committee for simultaneous implementation once all components of the new kidney allocation policy have been developed and approved.

5. Calculated Panel Reactive Antibody (CPRA). 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. These changes were fully implemented in October 2009.

   The Committee has followed the use of CPRA within the existing kidney system. Further analyses will be presented to the Committee at its July 2010 meeting.

   At the July 2009 meeting, the Committee discussed a potential problem with the implementation of CPRA. The Committee asked if there should be a way to show if a candidate was sensitized to HLA antigens, but had a CPRA of 0. They 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 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.

6. Discrepancy report. The July 2009 meeting, the Committee discussed the UNet[sm] Discrepant HLA Typing report, as referenced in UNOS Policy 3 Appendix C (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 states "The Laboratory Director(s) or their designee(s) shall contact the other Laboratory Director(s) or their designee(s) to resolve these discrepancies." This 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. 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 measure of laboratory performance. A subcommittee was appointed to review and evaluate the specific discrepancies found within the "HLA Discrepant Typing Report" in UNet[sm] to determine whether this is a good indicator of laboratory performance or merely reflects sloppy reporting. This subcommittee will report its findings at the July 2010 meeting.

7. Issue from the Membership and Professional Standards Committee (MPSC). In January 2009, 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.

   The Committee sent a letter to the MPSC stating the above on November 4, 2009.

   Because of this issue, the histocompatibility membership subcommittee requested a new format for its membership ballot because they said the Committee needed more information about the impending approval to make a decision. 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 two agencies that 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 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 membership subcommittee reviewed key personnel changes in member laboratories with the new ballot format and made recommendations which were presented to MPSC at their January 25, 2010, and March 23, 2010 meetings.

8. Histocompatibility Forms. The Committee discussed changes to the UNet[SM] histocompatibility forms in 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 thymocytes, cell lines/clonal cells and solid matrix as options for target source for class I and class II typing.
        2. Change dropdowns for DP antigens.
        3. Eliminate haplotype match currently collected for recipients of living donors.

    b. Recipient form
        1. Prefill CPRA and unacceptable antigens in recipient information box (values at time of transplant) for recipients of all organs.
        2. Change dropdowns for DP antigens.
        3. Replace fields in section II - HLA antibody screening with:
            - Were any HLA antibodies detected by Cytotoxicity?
            - Were any HLA antibodies detected by Solid Phase?
            - Was there current donor specific HLA antibody?
            - Was there historical donor specific HLA antibody?
        4. In section III – crossmatch:
            - Eliminate all fields except date of the most resent crossmatch serum and autocrossmatch results subsection.
            - Add cell source (Peripheral Blood, Lymph Nodes, Spleen).
            - Add a question on which crossmatch tests were performed (Cytotoxicity No AHG: Cytotoxicity AHG; Flow Cytometry; Solid Phase).
        5. In section IV – donor retyping remove target cell sources for class I and class II.

    The Policy Oversight Committee (POC) reviewed all proposed changes and recommended keeping PRA values and crossmatch results on the Recipient Histocompatibility form.

9. Thoracic Organ Transplantation Committee (Thoracic Committee). The Thoracic Committee 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 work jointly with the Thoracic Committee toward that end.

The OPO Committee has expressed opposition to any proposal to include HLA with thoracic offers. For the most part, the OPO Committee has said that obtaining HLA typing for thoracic donors before performing a match-run could be burdensome operationally to some OPOs.

Dr. Cecka represented the Histocompatibility Committee, along with Maryl Johnson, M.D., Chair of the Thoracic Committee at the April 20, 2010 OPO Committee meeting in an effort to gain a better understanding of the OPO Committee's concerns.

The issue with prospective HLA typing for thoracic offers, according to the OPO Committee, was how to permit allocation when the HLA could not be completed. They recognized the goal of HLA typing of thoracic donors was to facilitate sharing for sensitized patients, but said many thoracic candidates are not sensitized and sometimes procurement must be done urgently. They were fearful that if HLA typing became a requirement, thoracic organs may be needlessly discarded.

The group discussed that there is limited knowledge of which OPOs could or could not readily provide HLA data for thoracic donors. It was agreed that UNOS staff would prepare a survey that would be sent to all OPOs and laboratories that serve those OPOs to better understand the national practice of obtaining HLA typing on deceased thoracic organ donors.

The Histocompatibility Committee will discuss the findings of this survey at their next meeting in July 2010.

HISTOCOMPATIBILITY COMMITTEE		2010
	MONTH	February
	DAY	2
	FORMAT	Conference Call
NAME	COMMITTEE POSITION	
J. Michael Cecka, PhD	Chair	x
Nancy Reinsmoen, PhD	Vice Chair	x
Dean Sylvaria, BS,CHS	Regional 1 Rep.	-
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.	-
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.	-
Dawn Brims, B.S.N.,RN	At Large	-
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	x