OPTN/UNOS Histocompatibility Committee
AMENDED Report to the Board of Directors
November 8-9, 2010
St. Louis, MO

Summary

I. Action Items for Board Consideration

- 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)

II. Other Significant Items

- The Committee voted unanimously to include the HLA antigen Cw in the CPRA algorithm. Plans are being made distribute this proposal for public comment in the spring of 2011. (Item 3, Page 6)

- 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 4, Page 7)

- The Committee continues to work on an approach to provide access to candidates undergoing desensitization. (Item 5, Page 8)

- 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 6, Page 8)

- The Committee suggested updates to the Histocompatibility OMB forms (recipient and donor forms).(Item 7, Page 9)

- The Committee continues to monitor the use of the Calculated Panel Reactive Antibody (CPRA) within the transplant community. (Item 8, Page 11)

- The Committee continues to monitor the Discrepant Typing Report. (Item 9, Page 12)

- 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 10,Page 12)

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Nancy Reinsmoen, Ph.D., (ABHI), Chair
Lee Ann Baxter-Lowe, Ph.D., (ABHI), Vice Chair

The following report presents the OPTN/UNOS Histocompatibility Committee's deliberations and recommendations on matters considered during its February 5, 2009, and May 27, 2010, conference calls, and its July 13-14, 2010, meeting.

1. Modifications to Policy 3 Appendix A – HLA A, B and DR Antigen Values and Split Equivalences Table.

The purpose of this proposal is to update the tables in Appendix 3A 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 discussed and approved the attached modifications to Policy 3 Appendix A – HLA A, B and DR Antigen Values and Split Equivalences Table, and a proposal was distributed for Public Comment in March 2010.

Thirty-three responses were submitted to UNOS regarding this policy proposal. Twenty eight (84.84%) supported the proposal, one (3%) opposed the proposal, and four (12.12%) had no opinion. Of the twenty nine who submitted with an opinion, 96.55% were in favor of the proposal. The Committee was encouraged with the comments, and responded to a few suggestions given. An itemized response to all comments and changes appears in **(Exhibit A).** The Committee recommends the following resolution for consideration by the Board:

> ****RESOLVED, that the modifications to Appendix 3A – HLA A, B and DR Antigen Values and Split Equivalences set forth in (Exhibit A), shall be approved, effective pending notice and programming.**
>
> (Committee Vote: 15 for, 0 against, 0 abstentions)

2. Proposal to Require That Deceased Donor HLA Typing Be Performed by DNA Methods and Identify Additional Antigens for Kidney, Kidney-Pancreas, Pancreas, and Pancreas Islet Offers.

UNOS policy for kidney, pancreas, and kidney/pancreas offers requires donors to be typed for the HLA-A,-B.–DR, Bw4 and Bw6 locus antigens only. Many patients have antibodies directed against HLA-Cw or -DQ locus antigens that are listed as unacceptable but are not screened from matches from donors that express Cw or DQ antigens because the donor was not typed or because the results of typing these antigens were not reported prior to the match run. This proposal would require that OPOs and their associated laboratories 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. These additional requirements would align the deceased donor HLA types with the unacceptable antigens that can be listed for sensitized patients.

The proposal further requires HLA testing of deceased donors to employ molecular methods. The molecular technologies are currently in use by 98 of the 103 member laboratories that reported deceased donor types. Most deceased donors had HLA-Cw antigens (84%) and HLA-DQ antigens (98%) reported on donor histocompatibility forms during this period. 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 proposal addresses two problems: first, the high discrepancy rate associated with HLA typing by older, serological methods and second, the need for the typing of antigens encoded by additional HLA loci that will identify crossmatch incompatible donors. The availability of accurate donor HLA typing prior to the match run is necessary because these HLA antigens affect the allocation of deceased donor kidneys and pancreata, as well as other solid organs.

The strength of this proposal is that it will align the HLA-typing requirements in policy with the current technologies for identifying HLA antibodies, offering better protection and access for sensitized patients and improving organ allocation.

A potential weakness of the proposal is that it may require a few laboratories to acquire equipment to perform molecular testing and may require training of technologists to perform this testing on deceased donors. We have determined that 95% (98/103) of affected laboratories already have the infrastructure to perform this testing. Others have suggested that they would require the policy in order to obtain this infrastructure from their hospital or agency that controls their budgets.

This proposal affects all sensitized kidney, kidney-pancreas, pancreas, and pancreas islet transplant candidates and may affect sensitized candidates awaiting thoracic organs (hearts and lungs) and intestines in the near future. (The Thoracic Organ Transplantation Committee (Thoracic Committee) approached the Histocompatibility Committee to support a proposal to require HLA typing of thoracic donors prior to allocation at the July 15, 2009, committee meeting.)

The intended results of this proposal are to improve organ allocation by increasing the accuracy of HLA typing for deceased donors and to provide more complete typing that will avoid predictably crossmatch incompatible offers to sensitized patients. The long range results will include fewer errors in HLA types used for ranking candidates for deceased donor kidneys and pancreata and better access for sensitized patients to crossmatch compatible organs. Transplant coordinators, physicians and laboratory personnel will spend less time evaluating organ offers for histocompatibility. Costs may be reduced because repeated or supplemental donor HLA testing may be reduced. Broader geographic sharing of extra renal organs will result from more accurate virtual crossmatching.

An unintended consequence of this policy might be an increase in reporting broad HLA antigens, since the molecular nomenclature differs slightly from the serological nomenclature and requires conversion. All laboratories should be capable of correctly converting molecular types. However, in cases when typing results are entered by non-laboratory personnel, some training may be required.

The Committee discussed and approved the attached modifications to Policies 3.5.9.1 (Essential Information for Kidney Offers), 3.8.2.2 (Essential Information for Pancreas Offers), and UNOS Bylaws Appendix B Attachment IIA - Standards for Histocompatibility Testing D HLA Typing D1.000. A proposal was sent out for Public Comment in March 2010 **(Exhibit B)**.

Fifty-two responses have been submitted regarding this proposal. Thirty-eight (73.08%) supported the proposal, three (5.77%) opposed the proposal, and eleven (21.15%) had no opinion. Of the forty-one who submitted with an opinion, 92% were in favor of the proposal. The Committee was gratified with the resultant comments, both pro and con. An itemized response to all comments appears in **(Exhibit B)**.

Two of eleven regions did not approve of the proposal at their respective regional meetings. One region said it was unclear in the proposal language if serology typing could be used as an adjunct to the molecular methodology to obtain the best typing or whether donors must be molecularly-typed alone. The Committee responded that serology could be used as an addition to molecular typing if needed.

Several regional and individual comments questioned the inclusion of the C-locus as mandatory. The Committee wants to emphasize that there is no policy that requires the listing of any unacceptable antigen. However, currently there are close to 10,000 kidney candidates listed with at least one C antigen as an unacceptable. Therefore, it only makes sense to align the HLA requirements of the donor with that of the candidates. The Committee added that while the clinical relevance of these antibodies is only now beginning to be documented, it has been established that antibodies to HLA-C can cause positive crossmatches. And that it is imperative that we continue to collect the data to demonstrate the significance of this antigen for organ allocation as well as graft survival.

The original proposal contained the language that asked HLA-A, -B, -Cw, -DR and -DQ antigens be identified for all kidney, kidney/pancreas and pancreas offers. However, there was some confusion, mentioned in the regional public responses as to which exact antigens were required to be reported. A subcommittee suggested the following change to the policy language to clarify: HLA-A, B, Bw4, Bw6, C (including identified splits of HLA□A, □B, C) □DR, (including DRB1, DRB3/4/5), and □DQB antigens. The full Committee will review this suggestion on its fall 2010 meeting. It must be emphasized that this is not a change in the requirement, only a clarification in the language.

For the most part those who did not did not approve of the proposal noted that it was because they were concerned that this requirement may extend cold ischemic time and increase costs. The following is an excerpt from a letter from J. Michael Cecka, Ph.D., the immediate past chair of the Committee, sent to the OPO Committee on February 17, 2010. The letter in its entirety can be reviewed as **(Exhibit C)**.

"Because nearly all laboratories report DNA typing, the infrastructure for this testing platform already exists in all but a few labs. In that case, the cost of DNA testing is not more than serology. 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. In Los Angeles, HLA typing is completed and reported prior to organ procurement in >95% of cases. This speeds up rather than delays typing because supplemental testing is rarely required. "

Finally, the Committee has suggested a grace period of 6 months from the time this proposal is approved to the time of full implementation to ensure that all member laboratories can comply.

The Committee is confident that it has answered the questions created by this proposal and would therefore recommend the following for the BOD for consideration:

****RESOLVED, that the following modifications to policies 3.5.9.1 (Essential Information for Kidney Offers), 3.8.2.2 (Essential Information for Pancreas Offers), and UNOS Bylaws Appendix B Attachment IIA - Standards for Histocompatibility Testing D HLA Typing D1.000 are hereby approved effective June 1, 2011:**

3.5.9 Minimum Information/Tissue for Kidney Offer.
3.5.9.1 Essential Information for Kidney Offers. The Host OPO must provide the following information to the potential recipient center with each kidney offer:
(i) Donor name and Donor I.D. number, age, sex, and race;
(ii) Date of admission for the current hospitalization;
(iii) Diagnosis;
(iv) Blood type;
(v) ~~HLAA, B, Bw4, Bw6, and DR antigens~~ ~~HLA-A, B, Bw4, Bw6, C (including Identified splits of HLA-A,-B, ,-C)-DR, (including DRB1, DRB3/4/5), and -DQB antigens~~ HLA A, B, Bw4, Bw6, C, DR and DQB antigens. When reporting DR antigens, DRB1 and DRB3/4/5 must be reported. The lab is encouraged to report splits for all loci as shown in Appendix 3A;
(vi) . . .

3.8.2.2 Essential Information for Pancreas Offers. The Host OPO or donor center must provide the following donor information, with the exception of pending serologies, to the recipient center with each pancreas offer:…..

15. Familial history of diabetes; and
~~a. HLAA, B, Bw4, Bw6, and DR antigens.~~ ~~HLA-A, B, Bw4, Bw6, C (including Identified splits of HLA-A,-B, ,-C)-DR, (including DRB1, DRB3/4/5), and -DQB antigens~~ HLA A, B, Bw4, Bw6, C, DR and DQB antigens. When reporting DR antigens, DRB1 and DRB3/4/5 must be reported. The lab is encouraged to report splits for all loci as shown in Appendix 3A

Bylaws Appendix B Attachment IIA - Standards for Histocompatibility Testing
D HLA Typing D1.000 ~~The laboratory must be able to define HLA-A, B, -Bw4,Bw6, -C, -DR and -DQ antigens at a level that is appropriate for solid organ transplantation~~ The laboratory must be able to define ~~HLA-A, B, Bw4, Bw6, C (including Identified splits of HLA-A,-B, ,-C)-DR, (including DRB1, DRB3/4/5), and -DQB antigens at a level that is appropriate for solid organ transplantation.~~ HLA A, B, Bw4, Bw6, C, DR and DQB antigens. When reporting DR antigens, DRB1 and DRB3/4/5 must be reported. The lab is encouraged to report splits for all loci as shown in Appendix 3A. Laboratories that perform deceased donor typing to be used in kidney, kidney-pancreas, pancreas, or pancreas islet allocation must report molecular typing results (at the level of serological splits) for all required antigens prior to organ offers.