OPTN/UNOS Histocompatibility Committee
Report to the Board of Directors
June 28-29, 2011
Richmond, Virginia

Summary

I Action Items for Board Consideration

- None

II Other Significant Items

- The Committee reviewed with the implementation of the updates to Policy 3, Appendix 3 that were approved by the BOD in November 2010. (Item 1, page 3)

- The Committee continues to monitor the use of the Calculated Panel Reactive Antibody (CPRA) within the transplant community. This includes deidentified center and lab related differences in CPRA and transplantation of sensitized patients, as well as offers declined because of a positive crossmatch. (Item 2, page 5)

- The Committee is moving ahead with a proposal in Fall 2011 (proposed BOD date in June 2012) that would update CPRA. These updates should include the HLA frequencies used to calculate CPRA, and the addition of the antigen C to the calculation. (Item 3, page 6)

- The Committee continues to consider updates to the Histocompatibility standards in policy and bylaws. (Item 4, page 7)

- The Committee will continue to work with the Kidney Transplantation and Pancreas Transplantation Committees to develop an approach to provide fair access to candidates undergoing desensitization, and to award sensitivity points on a sliding scale. (Item 5, page 7)

- The Committee reviewed the operation of HLA Discrepant Typing Report as it is now functioning in Tiedi and is reviewing whether changes in policies and bylaws be proposed in view of ongoing changes in the field of histocompatibility testing. This will be done in conjunction with monitoring compliance with the requirement of molecular typing that was passed by the BOD in Nov. 2010 and goes into effect June 1, 2011. (Item 6, page 8)

REPORT OF THE
OPTN/UNOS HISTOCOMPATIBILITY COMMITTEE
TO THE
BOARD OF DIRECTORS

Richmond, Virginia
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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 January 19, 2011, and May 20, 2011, conference calls.

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

Updates to OPTN Policy 3, Appendix A, HLA Antigen Equivalences, were approved by the OPTN/UNOS Board in November 2010. (Such modifications are made biannually and are made to reflect changes in HLA typing practice.) These updates are implemented in two phases:

- Phase 1 was implemented March 16, 2011, and is reflected in the updated tables found within Policy 3 Appendix A.
- Phase 2 will be implemented at a later date.

This is the first time that these tables have been updated since the full implementation of CPRA. Because of this, there have been some unforeseen consequences to the CPRA of some kidney, kidney/pancreas, and pancreas candidates.

UNOS staff began to receive inquiries soon after the updates to the tables were made asking if the tables were working correctly. Most of the questions involved candidates that had a DQ antigen marked as unacceptable. For example, a candidate's CPRA with DQ 4, 6, 8, marked as unacceptable jumped from 45% to 78%.

Analysis established that the differences in CPRA values were resulting from changes in the HLA antigen equivalences made in the updated table that were not supported by the HLA frequencies used to calculate the CPRA. CPRA is currently calculated using frequencies that reflect the level of HLA typing performed in 2003-2004. At that time, broad antigen level assignments were being reported more frequently than that of the antigen splits. In some case, i.e. DQ5, the updates to the tables within Appendix 3A added a broad antigen to a split antigen, making some CPRA values artificially elevated.

For example, in the previous version of Appendix 3A, DQ5 was equivalent only to DQ5. If the recipient had DQ5 marked as unacceptable, that person would be screened from all match runs where the donor had the antigen DQ5. When that person's CPRA was calculated it would use only the frequency of donors with DQ5. One of the suggested changes to the Appendix was to add DQ1 as an equivalent to DQ5. This is because the Committee wanted to make sure that if a candidate had DQ5 marked as an unacceptable; the candidate would be screened from match runs where the donor had DQ1 as an antigen. Now when that candidate's CPRA is calculated using the updated table, the frequencies for both DQ5 and DQ1 are used. The frequency reported for DQ1 was much higher in 2003-2004 than it is today.

Therefore, because the CPRA will now be calculated using the frequencies of both DQ5 and DQ1 as they were reported in 2003-2004, the estimated probability of a positive crossmatch occurring may be incorrect.

The use of Appendix 3A will likely become obsolete with the implementation of the requirement of molecular typing of donors (which will go into effect in June 2011). After June 2011, no donors should be marked as DQ1. But in the meantime, the Committee asked what the magnitude of the problem is. UNOS staff shared data that showed how the implementation of the updates to Appendix 3A affected candidates:

- A total of 32,162 kidney registration CPRA values changed
- 26,997 registrations had increasing CPRA values. Of these, 15,523 registrations had increases that were so small that they could not be recorded as a change in CPRA (Meaning that the increase was less than 1% point.)
- 9,563 registrations had increases in CPRA values of 1-10% points
- 1,471 registrations had increases in CPRA values of 11-20% points
- 407 registrations had increases in CPRA values of 21-30% points
- 32 registrations had increases in CPRA values of 31-40% points
- Only 1 registration had an increase of over 40% points in its CPRA value
- 5,165 registrations had decreasing CPRA values, but for almost all of these (5,141) the changes were less than 1% point
- Only 24 registrations had noticeably decreasing CPRA values (all changed by 1% point).

The Committee was concerned about how many of these candidates fell at the key threshold points of 20% and 80%. UNOS staff later reported to the subcommittee that:

- 251 kidney registrations going from less or equal to 20% to greater than 20%
- 679 kidney registrations going from less than 80% to greater than or equal to 80%
- 5 kidney/pancreas registrations going from less or equal to 20% to greater than 20%
- 15 kidney/pancreas registrations going from less than 80% to greater than or equal to 80%
- 7 pancreas registrations going from less or equal to 20% to greater than 20%
- 27 pancreas registrations going from less than 80% to greater than or equal to 80%

The Committee concluded that the impact of the new equivalences on CPRA values was minimal, noting that only a small number of disadvantaged sensitized candidates are affected in a way that may unfairly benefit them. Implementation of more recently derived HLA frequencies, which reflect significantly reduced entry of broad HLA antigens, would resolve this issue. However, the programming cannot be changed at this point and the frequencies cannot be updated before going out for public comment. The plan for the future is that a proposal will come from the Committee in Fall 2011 to update CPRA. These updates will include updating the frequencies used to calculate CPRA and the addition of HLA-C to the calculation. If this proposal went out for public comment then, it would go to the BOD for approval in June 2012. The subcommittee noted that the full Committee should also discuss how to approach Appendix 3A in the future and if they want to limit the use of broad antigens.

2. CPRA Update

The Histocompatibility Committee has been charged by the BOD to monitor the use of CPRA, which was fully implemented in UNet^{SM} on October 1, 2009. At the July 13-14, 2010, meeting the Committee reviewed waiting list and transplant data 6 months before and after policy implementation. Preliminary data showed an increase in the number of unacceptable antigens reported on the waiting list and a dramatic drop in the number of positive crossmatches reported as a reason for organ refusal. Transplant rates decreased for non sensitized patients (0% CPRA) and stayed about the same moderately sensitized registrations (21-79%). The transplant rate increased for broadly sensitized registrations (80 %+), but this increase wasn't statistically significant.

During the October 13, 2010, conference call, the Committee requested an update of these analyses comparing data one year before and after policy implementation to be presented during this call. Anna Y. Kucheryavaya, UNOS research liaison, presented the data to the Committee. A summary the results are as follows:

- There was an increase in the number of unacceptable antigens that were reported on the waiting list and a decrease in the number of kidney refusals due to positive crossmatch.
- The percentage of non sensitized registrations increased and the percentage of low sensitized registrations decreased. The percentage of very broadly sensitized registrations (>95% PRA/CPRA) also increased.
- After initial decline, transplant rates for none and low sensitized patients seem to return to prepolicy implementation level. Transplant rates for broadly sensitized patients significantly increased.

The Committee was pleased with the results. Several members asked for a further analysis to be presented at the July 2011 meeting in Chicago. They thought it would be important to monitor the way different centers list unacceptable antigens for their candidates. The concern is that some centers may be in essence "delisting" their candidates by over assigning unacceptable antigens listed for their candidates.

The Committee understands that OPTN cannot provide specific policy for assigning unacceptable antigens. That is up to the center and is based on their practice. Each lab and center will need to do define how they assign unacceptable antigens and still transplant their sensitized patients. However, the Committee believes that the transplant community as a whole could use some guidance as to how to use CPRA in the best interests of the patient, especially because its use is still relatively new. The Committee hopes that by reviewing procedures in place across the country, they may identify some best practices that they could pass on to the transplant community.

The Committee requested an update of the analyses of CPRA with several additional analyses to be presented during their July 2011 meeting.

The Committee requested data on:

- The use of unacceptable antigens (UAs)
- CPRA distribution for kidney registrations listed on 03/31/2011 compared to the PRA distributions for kidney alone registrations listed on 03/31/2008 and 09/30/2009, stratified by ethnicity
- CPRA distribution of kidney alone registrations on 03/31/2011 by center stratified by gender and ethnicity

- CPRA distribution of kidney alone registrations waiting for retransplant on 03/31/2011 by center
- A comparison of the CPRA values for kidney patients who are multiply listed
- A comparison of the CPRA values for kidney patients transferred to a different center
- The number of positive crossmatches reported as a reason for organ refusal for kidney matches during 04/01/2008-09/30/2009 and 10/01/2009-3/31/2011. They want this further stratified by the candidate's sensitization level (0, 1-20, 21-79, 80+).
- The number of deceased donor kidney transplants performed for adult recipients during 04/01/2008-12/31/2008, 01/01/2009-09/30/2009, 10/01/2009-06/30/2010 and 07/01/2010-03/31/2011, stratified by recipient's sensitization level (0, 1-20, 21-79, 80+) and HLA-ABDR mismatch level (0ABDR mismatch vs. non 0ABDR mismatch).
- Transplant rates per 1,000 patient years for adult kidney alone registrations on the waiting list during 04/01/2008-12/31/2008, 01/01/2009-09/30/2009, 10/01/2009-06/30/2010 and 07/01/2010-03/31/2011, stratified by allocation PRA/CPRA (0, 1-20, 21-79, 80+).

The Committee said it is time to look at the graft survival rates for the sensitized candidate. The Committee believes that these rates have improved given the use of solid phase testing. They also asked for the graft survival rate for kidney deceased donor transplants performed in 2001-2003, 2004-2006, 2007-9/30/2009, 10/01/2009-03/31/2010 stratified by recipient's sensitization level (0, 1-20, 21-79, 80+).

3. Proposal to Update CPRA

In October 2009, Policy 3.5.11.3 was implemented which effectively replaced a Panel Reactive Antibody (PRA) value with a Calculated Panel Reactive Antibody (CPRA) value for Kidney, Kidney/Pancreas, and Pancreas and significantly changed kidney and pancreas allocation. (The CPRA is defined as the frequency of incompatible donors an individual may encounter while waiting for an organ offer.)

Based on post-implementation data analyzed by the Histocompatibility Committee, the policy has been very effective and has yielded many benefits. However, the CPRA is based on the donor HLA typing done by older technology; to maximize its effectiveness some major updates should be made, including:

- Updating the HLA frequencies used calculate CPRA. CPRA was fully implemented in October 2009 with HLA frequencies generated by M. Sue Leffell, Ph.D., from Johns Hopkins University in Maryland based on deceased kidney donors entered into OPTN registry from January 1, 2003 through December 31, 2004. These frequencies should be updated to a more recent time frame so that the CPRA truly reflects the probability of an incompatible match with the current donor pool.
- The Addition of C to CPRA Algorithm.-the CPRA calculation itself includes the frequencies for A, B, Dr and DQ. The HLA antigen C was considered at that time of implementation but ultimately not included because there was not enough data available on the frequency of C in donors. That has since changed; updated frequencies using data from January 1, 2007 through December 31, 2008 contain enough data to generate the C frequencies. Currently more than 10,000 kidney registrations are listed with at least one C antigen as unacceptable. These candidates are screened from lists but receive no CPRA value for their increased potential of a positive crossmatch because C is not part of the CPRA calculation. Also, currently candidates can be sensitized to the antigen C and look to the UNet^{SM} system as being completely unsensitized because their CPRA would be zero. Adding C to the CPRA calculation would mark these candidates as sensitized, and could possibly raise the candidate's CPRA to over 80%, enabling the candidate to receive 4 points.

The Committee was informed that there would be no programming of new policy during the Chrysalis Project. This would include the Committee's desire to update the HLA frequencies used to calculate CPRA and the incorporation of the antigen C into the CPRA algorithm. This concerned the Committee greatly. They said this could greatly disadvantage a number of candidates. The Committee asked for the following data points to try to determine how many candidates will be disadvantaged:

- The number and percentage of adult kidney alone registrations with 0% CPRA and at least one unacceptable antigen (excluding C locus) entered on the waiting list on 03/31/2011.
- The number and percentage of adult kidney alone registrations with 0% CPRA and at least one C locus unacceptable antigen entered on the waiting list on 03/31/2011.

4. Rewrite of the Histocompatibility standards within OPTN/UNOS Policy and Bylaws

Currently, the UNOS Bylaws, the OPTN Bylaws and the OPTN Policies that govern HLA laboratories need revision. They are not in a central location, large portions are obsolete, several are contradictory, and the level of detail is inconsistent. These documents must become more succinct, and to reflect current laboratory practices.

HLA laboratories are not accredited or monitored directly by UNOS, but through agencies that have deemed status with UNOS (American Society of Histocompatibility and Immunogenetics, ASHI and the College of American Pathologists, CAP). Our contracts with these agencies require that a crosswalk be done biannually to make sure our standards and their standards are equivalent. Such a comparison has not been done since 2003. A new cross walk that would reflect the current state of affairs cannot be initiated until our standards are in order.

Furthermore, the MPSC depends on the information given to it by ASHI and/or CAP to validate if histocompatibility standards are being met. For the first time in UNOS history, the MPSC is beginning to look into complaints pertaining to HLA laboratories. It must rely on the data supplied by these agencies to make their determinations. Therefore, the contracts with these agencies must be current.

The Bylaws Plain Language Rewrite Phase I project is currently reorganizing the laboratory requirements in the Bylaws and identifying content to move to Policy. However, substantive changes are not part of the Phase I rewrite, so the Committee has began to examine the HLA lab content of the Bylaws and Policy to identify inaccuracies, inconsistencies and superfluous information. The Committee hopes to have these revisions ready for public comment soon.

5. Ongoing work with the Kidney and Pancreas Committees to develop an approach to provide access to candidates undergoing desensitization and to award sensitivity points on a sliding scale.

These issues are of great concern to the Histocompatibility Committee and they plan to work with the Kidney Transplantation and Pancreas Transplantation Committees in the upcoming year to assure they are addressed in the new allocation systems.

The Committee has proposed that a "Committee Sponsored Variance" be used to help candidates that have undergone a desensitization protocol. They believe this represents an important option for programs that attempt to desensitize broadly sensitized patients so that they may be transplanted with a deceased donor kidney. This is because these candidates may have been disadvantaged since the implementation of CPRA on October 1, 2009. CPRA and the allocation points awarded broadly sensitized patients (80+% CPRA) are directly linked to the unacceptable antigens listed. When a candidate undergoes desensitization, unacceptable antigens become acceptable when the corresponding antibodies are reduced

or eliminated by the desensitization protocol, but when these antigens are removed, the CPRA may fall below 80% and the patient's waiting list rank may also fall. (Prior to October 1, 2009, programs could remove unacceptable antigens without a change in PRA, sensitization status or waitlist rank.) A Committee sponsored variance would allow the CPRA of a candidate to remain the same as they go through the protocol.

The Committee would like to award sensitivity points to candidates on the kidney waiting list on a sliding scale. This is because 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 patients receive fewer offers than unsensitized patients in direct proportion to their CPRA value. To compensate for this biological disadvantage, the Committee proposes candidates with CPRA values between 20-90% receive up to 4 allocation points (from 0 at 20% to 2.0 at 55% to 4.0 at 90%) on a sliding scale in addition to wait or ESRD time points. The Committee realizes that the points granted should not follow a linear progression because that is not how candidates are disadvantaged. Then because candidates with >90% CPRA will have few compatible donors, they should be given an absolute priority such as a regional or national share. The Committee has requested data on the number of deceased donor transplants by sensitization level in an effort to determine what the scale should look like and at what point a candidate should receive an absolute priority. This data will be presented to the full Committee in July 2011 and shared with the Kidney Transplantation Committee on a future date.

6. Discrepancy Report

The Histocompatibility Committee annually reviews data from the Discrepant HLA Typings Reports in UNet^{SM}, as referenced in Appendix C to Policy 3. This report shows how often donor HLA (A, B and DR) is different from donor HLA reported on the Recipient Histocompatibility forms in Teidi®. The Committee feels that it is important for laboratories to know how many HLA discrepancies they have had during the most recent 12 months and how they compare to other laboratories. The Committee asked that a letter be sent to all laboratories stating what the particular lab's discrepancy rate is and how it compares to the national average. They stated that laboratories with a higher number of discrepancies might change their practices and report fewer discrepant HLA typings in the future. The Committee expects the number of these discrepancies to diminish with the implementation of the requirement to type kidney, kidney/pancreas, and pancreas donors using molecular methods.

The Committee reviewed donor HLA and typing methods reported on the donor histocompatibility forms (DHFs) for deceased donors recovered in 2007-2008 while writing the public comment document for this policy. The Committee also requested updated data to be presented at the July 2011 meeting to monitor changes in typing practices and reporting of broad antigens. This data will also be used to monitor and evaluate the DNA typing requirement once it has becomes effective.

Committee Attendance

NAME	COMMITTEE POSITION	01/19/2011	5/20/11
J. Michael Cecka, PhD	ex officio (past chair)	x	x
Nancy Reinsmoen, PhD	Chair	x	x
Lee Ann Baxter-Lowe, PhD	Vice chair	x	x
Massimo Mangiola, PhD	Region 1 Rep.	x	x
Dimitri Monos, PhD	Region 2 Rep.	x	x
Karen Sullivan, PhD	Region 3 Rep.	x	x
Jerry Morrisey, PhD	Region 4 Rep.	x	
Dolly Tyan, PhD	Region 5 Rep.	x	x
Paul Warner, PhD	Region 6 Rep.	x	
David Maurer, PhD	Region 7 Rep.	x	
Sara Dionne, PhD	Region 8 Rep.	x	x
Char Hubbell, M.T.	Region 9 Rep.	x	x
A. Bradley Eisenbrey MD, PhD	Region 10 Rep.	x	x
John Schmitz, PhD	Region 11 Rep.	x	x
Dawn Brims, B.S.N.,RN	At Large		
Douglas Keith, MD	At Large	x	
Brad Kornfeld	At Large	x	x
Howard Gebel	SRTR Liaison	x	x
Adrine Chung	SRTR Liaison	x	x
Lori Gore	Committee Liaison	x	x
Anna Kucheryavaya	Support Staff	x	x
Jory Parker	Support Staff	x	x
James Bowman	Ex officio (HRSA)	x	x