OPTN/UNOS HISTOCOMPATABILITY COMMITTEE

Teleconference
May 27, 2010
1:00-3:00 (EDT)

Lori Gore, Committee liaison, began the meeting by thanking the Committee members for their valuable contributions over the past two years. She particularly thanked those members who will be rotating off the Committee at the end of June 2010 (Drs. Bill Ward, and Steve Geier along with Mr. Dean Sylvania and Ms. Paula Wetzsteon.)

The draft of the Board report for the June 21, 2010 meeting was unanimously approved (Committee vote: 13 for, 0 against, 0 Abstentions)

<u>The Committee reviewed the proposals that are currently out for public comment.</u>

1. Proposed Ohio Alternative Local Unit (ALU) (Liver and Intestinal Organ Transplantation Committee)
2. Proposed One Legacy Split Liver Alternative Allocation System (Liver and Intestinal Organ Transplantation Committee)
3. Proposed Region 2 Split Liver Alternative Allocation System (Liver and Intestinal Organ Transplantation Committee)

   The Committee did not have a comment about these first three proposals. They felt these proposals did not have any impact on histocompatibility issues.

4. Proposal to Develop an Efficient, Uniform National Pancreas Allocation System (Pancreas Transplantation Committee)

   The Committee unanimously supported this proposal.

5. Proposal to Modify OPO and Transplant Center Requirements for Screening, Communicating and Reporting All Potential or Confirmed Donor-Related Disease and Malignancy Transmission Events (Ad Hoc Disease Transmission Advisory Committee)

   The Committee unanimously supported this proposal.

6. Proposal for the Placement of Non-Directed Living Donor Kidneys: (Living Donor Committee)

   The Committee unanimously supported this proposal.

7. Proposal to Require Reporting of Non-utilized and Redirected Living Donor Organs (Living Donor Committee)

   Brad Kornfeld, an “at large” Committee member who is an organ donor, said this proposal was a good idea. The Committee unanimously supported this proposal.

10. Proposal to Require Use of a Standardized, Internal Label that is Distributed by the OPTN and that Transplant Centers Notify the Recovering OPO when they Repackage an Organ (Organ Procurement Organization (OPO) Committee)

The Committee unanimously supported this proposal.

Review of the Proposals from the Committee. The Committee then reviewed the comments for the proposals currently out for public comment from the Committee. The Committee first discussed the reaction they received when presenting the proposals at their individual regional meetings. A. Bradley Eisenbrey PhD, Jerry Morrisey PhD, and Dr. Geier all reported their regions approved both proposals (regions 10, 4 and 8 respectively.)

Dean Sylvania and Char Hubbell had a different experience in regions 1 and 9 (respectively). Ms. Hubbell said basically the same thing happened in both regions. She said an influential member of the region was against the proposals and the regions voted with that individual. The substance of these individual's opposition was that the requirement of molecular typing would cost too much money and add too much cold time to organs. They also doubted the efficacy of requiring Cw and DQ antigens for all donors. Dr. Cecka was confident we could answer those objections.

The Committee then reviewed the individual comments that have been received so far on line. The first comments discussed had to do with the proposal to update UNOS Policy 3, Appendix A.

The only opposed comment said "*Wouldn't be fair to candidates who have been on the list for many years, and may not have splits identified. May require retyping of those patients, which is costly and inconvenient.*"

The Committee said that programs should be updating their candidates HLA anyway. Ms. Hubbell agreed to write a response to this comment. Dr. Cecka will write responses to the other comments which all approved of the updates.

The Committee then discussed the one "opposed" comment to the molecular typing proposal. It said:

"Your proposal indicates only 6 labs aren't using molecular typing. Their typing error rate is 4% vs. the 2% error rate of molecular testing. Thats seems a pretty inconsequential difference and hardly seems to provide sufficient justification for the costs. The 6 labs would need to pay for the switching to molecular for all typing. All of us would have to pay if molecular typing for the minor HLA is required. Generally it takes another molecular tray or two to accomplish these typings. And if you have a limited number of cyclers, you just doubled the time to get a typing with the consequence of delaying allocation. Or you can buy more cyclers which would cost many labs a lot more money. I believe the expanded typings and the use of molecular testing are good recommendation. However, you have not justified (to me) the costs and the likely impact on testing time by many laboratories. Your comment that molecular typing labs should know serologic equivalents made me laugh. Having to figure out the serologic equivalent to less common alleles of B15 or B40 in the middle of the night is not fun. Whether or not this policy is approved, I would suggest UNOS allow typing entry using molecular nomenclature. That would help correct the

errors that are not obvious in your current formats."

The Committee thought that this problem may be addressed with some education. They thought the Committee should contact the offending labs (those labs that continue to use broad antigens) by letter and ask them why they did. The thought was that just sending the letter may help. The Committee tabled the discussion for our July meeting.

Dr. Baxter-Lowe agreed to write the response for the support comments. Dr. Cecka agreed to write the response to the last support comment which had to do with DP.

A copy of all the comments is attached as exhibits A-1 and A-2 on pages 8 and 9.

Report from Discrepant Typing subcommittee. Paula Wetzsteon, chair of the subcommittee gave this report. First she gave a brief history of the project. On May 9, 2008, a system notice was sent to all UNetSM users stating that "The OPTN/UNOS Histocompatibility Committee will be reviewing the Discrepancy Report for all OPTN member laboratories at their meeting in July 2009. Therefore, we encourage you to access the discrepancy report in Tiedi™ and to resolve as many of your discrepancies as possible."

During the July 2009 meeting the Committee received an update on the Discrepant HLA Typing report in UNetSM. A subcommittee was formed to review and evaluate recent discrepancies. Ms. Wetzsteon, along with Ms. Char Hubbell and Dr. Steve Geier volunteered to be part of this subcommittee.

Ms. Wetzsteon then gave a summary of the findings of this subcommittee. She first said she was pleased that several patterns of discrepancies could be identified. She said the goal of this report should be to decrease future discrepancies by bringing these patterns to the attention of the directors of all UNOS laboratories.

She suggested that the Committee send a follow up communication to each laboratory. In it, each laboratory director will be sent a list of their laboratory's discrepancies and their relative ranking among laboratories reporting discrepant typings. The directors would then be expected to assess their laboratory's discrepant typings and implement appropriate action plans. The Committee thought this would be a good idea.

Ms. Wetzsteon then gave a more detailed description of the data. She said two data sets were reviewed. One data set listed the discrepancies between the recipient types on the waiting list and the types on the recipient histocompatibility form submitted at the time of transplant. The other data set lists the discrepancies among laboratories typing the same donor.

What follows are the results for the discrepancies between the waiting list and the recipient histocompatibility forms: (Please note the following is copied from a data report given to the subcommittee by Ms. Anna Kucheryavaya, research liaison to the Committee. The report was based on recent (2007-2009) HLA discrepancies.):

- Overall there are 701 recipient discrepant typings associated with 108 laboratories. Number of discrepancies per laboratory ranges from 1 to 64.
- For comparison 69,665 Recipient Histocompatibility forms with recipient HLA typing were submitted by 154 laboratories for recipients transplanted during 2007-2009.

- Out of 701 discrepancies 349 (50%) remain unresolved. In some cases a laboratory provided a reason for discrepancy only on waiting list or Recipient Histocompatibility side. Discrepancy is not resolved until it is resolved on waiting list and Recipient Histocompatibility sides.

Results for the discrepancies among laboratories typing the same donor:
(Please note the following is copied from a data report given to the subcommittee by Ms. Kucheryavaya. The report was based on recent (2007-2009) HLA discrepancies.):

- Overall there are 576 donor discrepant typings associated with 126 laboratories. Number of discrepancies per laboratory ranges from 1 to 51.

- For comparison 23,797 Donor Histocompatibility forms were submitted by 114 laboratories for all deceased donors recovered during 2007-2009. Total of 134 laboratories reported retyping at least one of these donors on the Recipient Histocompatibility form. For deceased donors recovered in 2007-2009 there were 141 laboratories which submitted at least one Donor Histocompatibility form or reported retyping a donor on at least one Recipient Histocompatibility form.

- Out of 576 discrepancies 184 (32%) remain unresolved. If a laboratory provided a reason for a discrepancy then it is considered resolved by this laboratory. Discrepancy is not resolved until it is resolved by all involved laboratories.

Ms. Wetzsteon then reported her conclusions**:**

Recipients:
- 62 records were excluded because they were clearly transcription or sampling errors and not typing errors.
- BW4/6 discrepancies accounted for 70.8% of the discrepant records
- The remaining discrepancies were a combination of parent splits, e.g., DR3 vs. DR17, splits, e.g., A23 vs. A24 and different antigens entirely.

Donors:
Ms. Wetzsteon explained that each donor HLA discrepancy is listed under each involved laboratory which makes it much harder to analyze. Therefore, one will not be able to give an accurate percent of BW4/6 discrepancies or any other category.

Ms. Wetzsteon then made the following recommendations for the Committee:
- Have all or no parent splits considered discrepancies, i.e., not just a subset
- Determine if the way BW4/6 are entered can be changed so it is less prone to entry errors.
- Establish stronger incentives for reporting splits instead of the parent antigens or disincentives for reporting parent antigens instead of splits.
- Clarify "resolved" which currently means reviewed.
- Consider an entirely new system with turnaround times in weeks.
- If current system is kept, then revamp reason codes, e.g., one for each antigen.
- Ensure the most likely correct type is the type sent to outcomes research.

All in all, Ms. Wetzsteon expressed that the overall typing was extraordinarily good. She felt if we could take care of the above suggestions, the discrepancy rate may be lowered to less than 1%. She said that the Committee could easily review these "frank discrepancies" in real time which would improve the efficiency of allocation. Ms. Hubbell, a member of the subcommittee agreed to take over as chair and will report to the full Committee in July.

The Committee agreed that in addition to resolving HLA discrepancies, laboratories should also change HLA antigens on Histocompatibility Forms when incorrect typings are indentified. Therefore, the Committee asked for the number of resolved discrepancies where HLA data were changed on the Histocompatibility Forms after discrepancies were reported and resolved. These data will be presented at the next subcommittee call.

Update on proposed changes on OMB forms.

Ms. Kucheryavaya gave the Committee a summary of the OMB form changes to the Histocompatibility Forms (Donor Histo Form DHF and Recipient Histo form RHF).

She reminded the Committee that in 2009 they had reviewed the Donor and Recipient Histo forms and recommended some changes. She went on to say that all of those recommendations were reviewed by Policy Oversight Committee (POC) Ad Hoc Data Management Group and then POC in late 2009 – early 2010. All of the Histocompatibility Committee's recommendations were approved by the POC except for deleting the fields pertaining to PRA values and deleting Crossmatch and Autocrossmatch results from the Recipient Histo Form.

She then reported that all the finalized proposed changes went for out Public Comment in the spring of 2010. The Histo forms with the proposed changes are attached as exhibits B, page 10 (DHF) and C, page 12 (RHF). Please keep in mind the attachment fields outlined in red are the ones which were proposed for deletion by the Committee but kept on the form because of the POC's decision.

The public comment ended in April. As a whole, UNOS received such strong opposition to all the proposed changes on the OMB forms (other than the Histo and Deceased Donor Registration (DDR) forms) that it was decided to put the project on hold to give the UNOS and the Committees time to reevaluate. However, there were very few comments concerning the changes proposed by the Histo Committee, so it was decided that the RHF and the DHF could be finalized.

During Public Comment period there was only one comment on changes to DHF and RHF. It came from ASHI, page 15 (exhibit D). Note that operational changes (label changes, drop down changes, etc) were not part of the public comment document so ASHI was not aware that Committee already asked to use "DP" instead of "DPW" and eliminate the option "Solid Matrix" from the drop down for Target Source. The Committee was asked to respond to ASHI's comments.

The Committee first discussed ASHI's comment that it would be helpful to have the ability to add DQ alpha and DQ beta to the Histo forms. A couple of the Committee members agreed. But Dr. Cecka cautioned the Committee that to do so and to go along with ASHI's suggestion to use allele level molecular nomenclature may cause greater problems further down the road. He also thought such a major change may require another public comment. After much discussion, the Committee supported ASHI's recommendations in principle but thought they would need more

thought into how it could be done. Therefore, the discussion was tabled and will be discussed in more detail at out July meeting.

Ms. Kucheryavaya reminded the Committee of a discussion about DP antigens during a full Histo Committee conference call in February. She asked if based on these discussions the Histo Committee might also want to consider changing dropdown for DP antigens on both Histo Forms and adding "Other, specify" text boxes for DP antigens. The Committee decided to propose changing dropdown menu for DP antigens on Histo Forms to 1, 201, 202, 3, 401, 402, 5, 6, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30. After some discussion the Committee decided not to propose adding "Other, specify" text boxes for DP antigens.

The Committee then discussed the four PRA fields that will remain on the RHF because of POC's decision. (The Committee had recommended that those fields be eliminated.)

Ms. Kucheryavaya said the POC voted to keep these fields on the RHF in part because the PRA value for SRTR's Heart Program Specific Reports comes from RHF. Also, the Thoracic Committee voiced the concern that they do not currently use CPRA, and many programs still rely heavily on PRA when accessing candidate/donor risk.

The committee said that many of them no longer did PRA tests for their kidney candidates and voiced that keeping the fields was not justified. Ms. Kucheryavaya reminded the Committee that the fields for PRA could be marked not done, missing, or unknown. The Committee asked if they could change the business rules to make the PRA appear on the RHF for thoracic recipients only. The Committee also asked that if we were going to collect a peak PRA that maybe we could collect a peak CPRA as well. Ms Kucheryavaya said she would look into it and asked for a volunteer to write a rational as to why this would be helpful. Dr. Cecka said he would.

The POC had also voted to keep the crossmatch and autocrossmatch fields on the RHF against the Committee's recommendation. The Committee voiced that there was no reason to keep the auto crossmatch field. They asked to remove auto crossmatch results and incorporate into the instructions that a crossmatch which is positive due to autoantibodies be reported as negative.

The Committee remained skeptical of the value of the crossmatch fields given that each program has a different definition of what constitutes a positive cross match and as Dr. Cecka pointed out, these forms are only generated after the transplant. And, as Dr. Cecka reminded the Committee, whatever the result, the program elected to go ahead with the transplant.

Based on previous discussions with members of the Committee Ms. Kucheryavaya suggested that maybe we could change the form of the results, which could make the data collected more valuable. She suggested that the results be linked to the test that was done. She shared this format with the Committee, page 17 (exhibit E). The Committee agreed that this would be an improvement.

In addition to removing auto crossmatch results members of the Committee asked that the fields identifying the type of cross match be changed to say T cell cross match and B cell crossmatch.

The final recommended changes to the Forms suggested by the Committee are attached as exhibit F-1, page 18(DHF) and F-2, page 20 (RHF).

Annual Goals. Ms. Gore discussed the Histocompatibility Annual goals with the Committee. She reported that she would be sharing these goals with the UNOS executive Committee the next week. With that the meeting was adjourned.

HISTOCOMPATIBILITY COMMITTEE		2010
	MONTH	May
	DAY	29
	FORMAT	Conference Call
NAME	COMMITTEE POSITION	
J. Michael Cecka, PhD		x
Nancy Reinsmoen, PhD	Vice Chair	x
Dean Sylvaria, BS,CHS	Regional 1 Rep.	x
William Ward, PhD	Regional 2 Rep.	0
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.	0
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.	0
Dawn Brims, B.S.N.,RN	At Large	x
Douglas Keith, MD	At Large	x
Brad Kornfeld	At Large	x
Emily Messersmith	SRTR Liaison	0
Alan Leichtman, MD	SRTR Liaison	x
Lori Gore	Committee Liaison	x
Anna Kucheryavaya	Support Staff	x
Jory Parker	Support Staff	x