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Walter Graham, Executive Director

July 21, 2008

VIA CERTIFIED MAIL / RETURN RECEIPT REQUESTED

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President, American Society of Transplant Surgeons
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RECEIVED 7/25/08

Dear Dr Roberts,

The UNOS Histocompatibility Committee appreciates your sharing the concerns of members of the ASTS about the implementation of the calculated PRA (CPRA), which was approved by the UNOS Board of Directors in December 2006. Phase 1, during which the waitlist displays both conventional PRA and CPRA but allocation points are awarded based on conventional PRA, was implemented December 5, 2007. Phase 2, during which allocation points are to be awarded based upon the CPRA, was scheduled for implementation in Spring 2008,but has been delayed due to UNOS programming conflicts and implementation is not expected until Spring 2009. Thus, transplant centers and laboratories will have additional time to familiarize themselves with the calculation and to compare the CPRA values with those obtained by other methods during this period before CPRA is used for allocation. The effectiveness of CPRA will depend upon ongoing and clear communications between histocompatibility laboratories and the transplant centers they serve to insure that patients are not disadvantaged by the criteria used to identify unacceptable HLA antigens.

It is important to point out that CPRA is based upon unacceptable antigens (not on antibody determination by single-antigen beads). Unacceptable antigens are assigned by the transplant centers in collaboration with their laboratories) as antigens that would be considered to be associated with a high risk of graft failure or post transplant complications and that would not be acceptable in a potential donor. Guidelines for assessing the risks of donor-specific antibodies can be found in Appendix 3D of the UNOS Policies, and include consideration of the patient's immunological history, previous exposure to alloantigen through prior grafts, pregnancies or transfusions and antibodies detected by the crossmatch test used for donor selection. At least one solid-phase test must be included in the identification of anti-HLA antibodies because these tests employ purified HLA antigens and are less subject to false positive reactions than other methods.

With regard to your specific concerns about the single-antigen bead tests (which are applicable to all the solid phase tests), the Histocompatibility Committee offers the following:

1.1-3. There is variability in antigen density on beads between antigens, vendors and lots of beads from the same vendors.

The vendors use monoclonal monomorphic anti-HLA antibody (reactive with an epitope shared by all class I HLA antigens or with an epitope shared by all class II HLA antigens to estimate

antigen density on the beads. There is some variability in densities as you note, however, because these are complex antigens with many epitopes and because patients do not produce antibodies of uniform specificity or affinity, it is unlikely that the sort of standardization we would like would be possible.

Despite variability in antigen densities, the solid-phase tests (and particularly the single-antigen bead tests) have proven remarkable tools for identifying specific HLA antigen targets for the antibodies in complex patient sera, as evidenced by the concordance among laboratories in proficiency tests administered by the American Society for Histocompatibility and Immunogenetics (ASHI) and by the College of American Pathologists (CAP), which are now reaching 100%. This level of agreement was never achieved prior to the introduction of solid-phase testing and demonstrates the robustness and reproducibility of these tests.

The level of median fluorescence intensity (MFI) required for a positive reaction is not standardized. Until there is standardization, we believe this test should not become part of a national allocation system

Each vendor provides a method of ascertaining a "positive" reaction that is based upon comparisons between test serum reactions on each bead, non-specific reactions on one or more negative control beads, and reactivity with a positive control bead. Each vendor provides criteria for rejecting test results based upon patterns of reactivity with these beads. However, these methods are statistical and indicate that the reactions observed are different from reactions when no anti-HLA antibodies are present. A positive reaction can be standardized in these terms, but laboratories may differ in what degree of positivity they consider clinically important, and these differences may be based on other considerations including patient history and correlation with other tests results. The Histocompatibility Committee is working with members of ASHI and CAP in collaborative studies to define clinically relevant antibody levels.

1.4. *There is debate in the literature if maximum MFI to a single bead is most relevant to outcome or whether the sum of all MFI's is more relevant.*

Single-antigen beads are highly artificial because they have a high density of a single HLA antigen on their surface and may selectively bind antibodies of lower affinity than beads containing a mixture of different HLA antigens each at lower density, or cells with a mixture of HLA antigens at even lower density. Some laboratories have noted that correlations between MFI and channel shift in the flow cytometry crossmatch are better with beads coupled with a phenotype of HLA antigens (i.e. all class I or class II HLA antigens purified from cells from a single individual) than beads coupled with recombinant single HLA antigens. The individual contributions of HLA-specific antibodies to the risk of graft damage are under investigation. The debate re-emphasizes the need to use multiple tests and additional criteria to define unacceptable HLA antigens.

2.1 *If there is no standardization, there may be variation in the number of patients who have a PRA over 80% and are eligible for extra points. The system will be open for gaming*

The CPRA was implemented precisely to address this concern. There was no previous standard for PRA determination for waitlisted patients and a variety of tests are now employed by laboratories (even within laboratories) that provide a "percent panel-reactive antibody" value, ranging from lymphocytotoxicity tests with or without AHG using T-, B- or unseparated lymphocyte targets to solid-phase tests using ELISA, flow cytometry or Luminex platforms. These tests have varying sensitivities and variable representations of HLA antigens. The CPRA

was designed to provide a measure of uniformity for the transplant community that also reflects the probability of finding a compatible donor for sensitized patients. CPRA utilizes HLA frequencies derived from the OPTN/UNOS donor registry and, therefore, provides consistency in CPRA values that is not possible under the current system where PRA values are derived by numerous methods. When the point system was developed in the 1980's most laboratories were using cytotoxicity tests to measure PRA and these tests correlated with the crossmatch tests that were used to select compatible donors. Broadly sensitized patients tested in this way would be crossmatch incompatible with a high percentage of donors and 4 points were given those who would be incompatible with 80+% of donors. With the introduction of flow cytometry and solid-phase tests, there was no established correlation between PRA and crossmatch compatibility and the PRA was disconnected from probability of a positive crossmatch.

Since the CPRA is based on unacceptable antigens, the price of getting extra points is a decrease in donor offers, making the system more difficult to manipulate than the previous system.

2.2 *Patients with a PRA >80% based on antiglobulin testing can have a limited number of unacceptable antigens and be crossmatched against more donors.*

It will be possible to ignore some or even most HLA-specific antibodies and not list the corresponding unacceptable antigens during Phase 1 of CPRA implementation. Broadly sensitized patients often have accumulated considerable waiting time because few donors are crossmatch compatible and centers may elect to forgo listing unacceptable antigens for such patients in favor of performing crossmatches. However, this practice will impair the efficiency of organ allocation by contributing to avoidable, positive crossmatches. Patients may also be disadvantaged unless the center routinely crossmatches all of their broadly sensitized patients against blood-group compatible donors, which is costly. Complete listing of unacceptable antigens provides an advantage to sensitized patients because any kidney offer will have a high probability of crossmatch compatibility and false negative crossmatches will be minimized.

2.3 *Since there is no standardization, a multiply listed patient could have different PRAs depending on the center and the center's laboratory.*

The Kidney and Pancreas Transplant Committees, the Policy Oversight Committee, and the Histocompatibility Committee all considered that each Transplant Center has the inherent right and responsibility to determine its own criteria for determining what constitutes an unacceptable antigen. Because transplant centers differ in the level of acceptable risk presented by candidate sensitization, no standard test or acceptable antibody level is feasible. What is achievable and recommended is for each center to define unacceptable antibody levels in accordance with their transplant protocols. Histocompatibility laboratories have been sent guidelines on how they may correlate antibody test results with crossmatch outcomes.

If your members need information about how unacceptable antigens are assigned for their patients, UNOS requires that histocompatibility laboratories have written agreements with the transplant programs they serve that explain which tests are employed for their patients and how unacceptable antigens are assigned. We encourage all transplant programs to review their laboratories practices, particularly with regard to the criteria for defining unacceptable antigens and how unacceptable antigens are managed for waitlisted patients.

The Histocompatibility Committee has been monitoring the usage patterns of CPRA since Phase 1 was implemented last December and will continue to monitor its effectiveness. Currently, 28.5% of active waitlisted kidney candidates have unacceptable antigens listed that permit

calculation of CPRA and entry of these antigens has increased since December. Only 13 of 258 transplant centers have no unacceptable antigens listed and many of these are smaller centers. We have not seen a large increase in patients with CPRA values of 80% or above when compared with the conventional PRA values, so it does not appear that centers are listing unacceptable antigens beyond what they were listing as conventional PRA. Because CPRA includes both HLA class I and class II unacceptable antigens, which is not possible with PRA, the CPRA values for many patients are higher than with traditional PRA. About one-third of laboratories represented by Histocompatibility Committee members are already listing the PRA calculated from unacceptable antigens as the PRA to be used for allocation because it is the most rational and meaningful representation of the patient's sensitization status and probability of crossmatch compatibility among the many options for PRA that currently are available.

The Committee hopes we have addressed your concerns regarding the planned implementation of CPRA into the allocation system and that you agree that this represents a major step forward for the field.

Sincerely,

J Michael Cecka, Chair
Nancy Reinsmoen, Vice Chair
On behalf of the UNOS Histocompatibility Committee

Enclosures

cc: Robert S.D. Higgins, M.D., OPTN/UNOS President
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