

Explanation of CPRA for Professionals

Background:

Patients with preformed antibodies against donor HLA antigens may experience hyperacute or accelerated acute antibody-mediated rejection. You can determine the presence of HLA specific antibodies by testing patient sera against cells from a panel of HLA typed donors or against solubilized HLA antigens attached to solid supports. The results have historically been used to estimate the panel reactive antibodies (PRA) or percentage of likely cross-match incompatible donors. Nearly a third of the OPTN renal transplant wait list is sensitized patients with a PRA of 10% or more. These candidates wait significantly longer than non-sensitized patients do and once transplanted suffer a greater risk of graft loss from rejection. Recognizing these disadvantages, the current renal allocation system awards sensitized patients with PRAs ≥ 80 an additional 4 points to increase their access to potentially compatible donors. The Histocompatibility Committee began examining the PRA listing practices in 2004 in response to concern raised by the Kidney and Pancreas Transplantation Committee over the variability of PRA results. The committee identified several problems with the existing system, which include both the definition of PRA and the way professionals apply it.

Defining PRA

Using current methods, the degree of sensitization represented by PRA is highly variable and inconsistent. The value of PRA depends both upon the panel composition and the technique used for antibody detection. The composition of the antigen panel varies considerably with the use of different commercially available kits or locally procured cell panels which often do not represent the potential donor population. Additional variability arises from the use of tests with differing sensitivity in detecting HLA antibodies. Depending upon the assay method, the amount of antibody detected also can vary significantly. Detection methods range from the relatively insensitive complement dependent cytotoxicity tests to highly sensitive solid phase immunoassays. Because of these variables, PRA does not provide a realistic measure of how difficult it will be to find a compatible donor. PRA is also not a consistent means for comparing the relative degrees of sensitization among patients on the renal wait list.

Applying PRA in Allocation

There are several problems with the application of PRA in renal allocation. The cutoff value for PRA points is arbitrarily set at 80, but patients with lower levels of sensitization who are also disadvantaged receive no extra allocation benefit. Moreover, centers can choose to use either a peak or current PRA to determine whether the patient is eligible for extra PRA points. As of 12/31/04, among the 64,335 kidney registrations on the wait list, 44.3% of transplant centers use the current PRA to determine PRA points, while 55.7% use the peak serum PRA (1). Using assays with different levels of sensitivity to detect antibodies also contributes to the wide range in the proportion of highly sensitized patients among transplant centers. The Histocompatibility committee determined that 10% of centers (25/ 249) had a high proportion of their wait list composed of candidates with PRAs ≥ 80 . These proportions ranged from nearly twice to 4.2 times the national proportion of highly sensitized candidates, which is 7.9% (1). The use of more sensitive antibody assays can be an issue, if a crossmatch technique with the same level of sensitivity is not used, since more donors will be crossmatch compatible than the PRA would indicate.

In addition to the problems with PRA definition, the listing of unacceptable antigens for sensitized patients is inadequate. The transplant community began entering unacceptable antigens to help facilitate renal allocation. This approach eliminated patients from consideration with donors who possessed one or more HLA antigens to which the patient was known to be sensitized. The Histocompatibility Committee's review of the kidney registrations on 12/31/04 demonstrated substantial disparity in the listing of PRA and unacceptable antigens. Only 59.6% of patients with PRA ≥ 80 had at least one unacceptable antigen listed and only 44.2% of those with PRAs from 20-79, had an unacceptable antigen listed. Twenty-one % (54/249) of centers did not list unacceptable antigens in any PRA category and 31.7% (79/249) did not list unacceptable antigens for their highly sensitized patients (PRA ≥ 80). In the past, when the cytotoxicity assay was the sole means for defining HLA antibodies, it was often difficult to identify all the antibodies that a highly sensitized patient might have. The development of solid phase immunoassays that use solubilized HLA antigens as targets have greatly increased the ability to detect and identify HLA specific antibodies (2-4). Additionally, as shown in Table 1, these methods show excellent correlation with predicted positive crossmatch outcome (5). When no unacceptable antigens are listed for highly sensitized patients, crossmatches may be performed for patients with known HLA specific antibodies that could have been avoided. Given the scarcity of deceased donor organs and the impact of prolonged ischemia time on graft outcome, these predictably positive crossmatches should be eliminated to improve the allocation process.

Policy Timeline

- Policy 3.5.11.3 modified to require listing of unacceptable antigens sufficient to justify the PRA level. OPTN Board of Directors approved in June 2005.
- The Histocompatibility Committee proposed that PRA in the current renal allocation system be replaced with a “**calculated PRA**” (CPRA) based on the **unacceptable antigens** listed for patients. The CPRA will be determined using an established algorithm (6, 7) and HLA frequencies derived from the HLA phenotypes of more than 12,000 donors recently entered into the OPTN registry (8). OPTN Board of Directors approved in December 2006.
- State of Tennessee applied to keep their alternate system of awarding sensitization points. OPTN Board of Directors approved in June 2007. At same meeting, changes to Appendix 3a were made to accommodate CPRA.

CPRA Implementation

We will implement CPRA in three phases.

Phase 1: Depending upon the completion of programming, the first phase will occur during November 2007. During this phase, we will continue to base allocation on the traditional PRA, but the match runs will also list the CPRA. You will be able to access a CPRA calculator through UNET and patients can access this calculator from the Transplant Living Web site. We anticipate the first phase to last 3-6 months.

Phase 2: We will base allocation on CPRA, but you will still be able to enter and view the traditional PRA for comparison.*

Phase 3: We will base allocation on CPRA and the traditional PRA will no longer appear on the wait list.

*We will determine the implementation dates for phases 2 and 3 after analyzing the results of phase 1.

During all three phases, a joint committee made up of members from the Histocompatibility, Kidney Transplant and Pancreas Transplant committees will review listings of unacceptable antigens, comparisons of PRA and CPRA, and the incidence of unexpected crossmatch results (phases 2 & 3). This joint committee will identify and investigate any problems and recommend a course of action to the OPTN/UNOS Executive Committee.

CPRA calculator

When you enter unacceptable antigens for a patient, the calculator will automatically determine a CPRA value. If you add any additions or deletions to the patient's unacceptable list, the value will automatically recalculate. **The OPTN/UNOS Histocompatibility subcommittee derived and validated the necessary HLA frequencies for this calculation.** The calculated frequency of incompatible donors will provide consistency in listing since each center will determine the CPRA values in the same way.

Establishing criteria for listing unacceptable antigens

Centers will determine their own criteria for unacceptable antigens, which may include other factors, such as repeat mismatches. These criteria should reflect what is considered as a contraindication for transplantation for each candidate. For example, some centers may not want to list antigens for which their patient only has very low levels of antibody and who would be crossmatch compatible by their protocols with a donor having those antigens. However, not listing some unacceptable antigens will also reduce a candidate's eligibility for the extra points awarded when the CPRA is 80 or greater. It is important to note that the intent of awarding the extra points is to move patients who will only be compatible with 20% or less of donors to the top of the match list when a suitable donor becomes available. If center protocols permit acceptance of donors when there may be low levels of sensitization, those candidates will have access to a larger proportion of donors and should not, therefore, receive the extra CPRA points.

The algorithm is a more representative measure of sensitization, not only because of the use of more accurate HLA frequencies, but also because it accounts for sensitization to both HLA class I and II antigens. The calculated frequency also has been shown to give increased benefit to racial/ ethnic minority candidates who are sensitized to HLA antigens that are relatively common in the deceased donor population (9).

References:

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Table 1. Predictability of positive crossmatch results with solid phase assays shows excellent correlation with flow cytometric crossmatch tests. Results from a multi-center collaborative study (5).

Target Cells	Ab ¹ Detection Method	# Tests	% Correct Predictions
T Lymphocytes	ELISA ²	137	86.1
	SAB ³ by Flow Cytometry	580	93.8
B Lymphocytes	ELISA	145	91.0
	SAB by Flow Cytometry	698	97.9
	Multi-Ag ⁴ Beads - Flow or Luminex	16	93.8

¹ Ab = antibody

² ELISA = enzyme-linked immunosorbent assay

³ SAB = single antigen beads

⁴ Ag = antigen