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HLA compatibility assessment and management of highly sensitized patients under the new kidney allocation system (KAS): A 2016 status report from twelve HLA laboratories across the U.S.

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ABSTRACT

Twelve HLA laboratories were surveyed to assess the methods and operational issues involved to define highly sensitized patients and to assess HLA compatibility under the new kidney allocation system (KAS) in the U.S. All laboratories used single antigen bead assays both pre- and post-KAS to define both broad and allele-specific HLA antibodies. The methods and threshold used to list HLA unacceptable antigens in UNet for virtual crossmatch (vXM) and the criteria used for determining HLA compatibility varied among laboratories. Laboratories reported several limitations of the current assays including the accuracy of quantifiable antibody fluorescence values, inadequate coverage of common alleles on the bead panels, and challenges in calibrating the vXM. The new KAS has resulted in a significant surge of deceased donor organ offers requiring vXM evaluation under tight time constraints. In the post-KAS period, eight of twelve laboratories (67%) indicated that their center did not proceed to transplant based on vXM without a prospective lymphocyte crossmatch. In conclusion, HLA laboratories play a critical role in deceased donor allocation for highly sensitized patients under the new KAS. Significant opportunities exist to improve the methods used in the assessment of HLA compatibility to safely transplant highly sensitized patients.

1. Introduction

Deceased donor kidney allocation was restructured in the United States in December, 2014 to promote equitable and efficient utilization of deceased donor kidneys and to address the problem of the long waiting time for highly sensitized patients; these patients were given increased priority and, as expected, many were transplanted rapidly. Kidney utilization and recipient outcomes were recently described [1,2]. Overall, 6-month graft (95.3%) and recipient (97.6%) survival after implementation of the new kidney allocation system (KAS) are excellent, though slightly lower than pre-KAS [2]. The long term impact of the new KAS on clinical outcomes and efficient utilization of deceased donor kidneys remains to be determined.

One of the most significant technological breakthroughs in histocompatibility testing during the last decade is the identification of anti-HLA antibody specificities using single antigen microbead assays [3]. The ability to define HLA antibody specificities in a timely manner has allowed HLA laboratories to successfully perform a virtual crossmatch (vXM) using donor center HLA typing information. A negative vXM is typically defined as the absence of donor specific anti-HLA antibodies (DSA) as determined by single antigen bead assays [4–6].

Abbreviations: cPRA, calculated panel reactive antibody; CDC, complement dependent cytotoxicity; XM, crossmatch; DD, deceased donor; DSA, donor specific antibodies; KAS, kidney allocation system; MFI, mean fluorescence intensity; PCR, polymerase chain reaction; RT-PCR, real-time PCR; SSO, sequence specific oligonucleotide; SSP, sequence specific primer; UA, unacceptable antigen; UNOS, United Network for Organ Sharing; vXM, virtual crossmatch.

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The implementation of the new KAS has led to significant challenges for HLA laboratories, which include operational and technical issues regarding the assessment of HLA compatibility by vXM, and expanded workload due to an increase in the number of imported deceased donor organs [1,2].

Although vXM is routinely performed in many laboratories, there are still many questions regarding the most reliable and accurate means of assessment of vXM in patients with very high calculated panel reactive antibody (cPRA). For example: How are weak antibodies defined? How does a laboratory deal with allele specific antibodies if they cannot be listed in UNet? How does a laboratory determine if a recipient has antibodies to a donor allele that is not present on the single antigen bead set? Can user friendly software be applied to reliably predict donor:recipient compatibility? These questions, coupled with the implementation of the new KAS, led us to perform a comprehensive survey to determine the current state of HLA compatibility testing of highly sensitized patients and quality management in HLA laboratories under the new KAS. Here, we present a 2016 status report from twelve laboratories across the U.S. highlighting areas of accomplishment and opportunities for improvement.

2. Materials and methods

During 2016, twelve HLA laboratories were surveyed to assess the methods, logistics and operational issues involved to define and monitor highly sensitized patients and to assess HLA compatibility. The survey covered the first 16 months post-KAS, ending April 29, 2016, and consisted of multiple questions with explanatory material (Supplementary Material, Table S1). Survey questions asked: 1) which methods were used for deceased donor HLA typing, including the level of resolution that was obtained; 2) which methods were used for antibody detection and analysis; 3) what threshold was used to define the HLA unacceptable antigens listed in UNet; 4) what procedures were used for vXM; 5) what criteria were used to assess HLA compatibility; 6) which (or whether) lymphocyte-based crossmatches were applied; 7) the frequency and cause of vXM failures, and 8) questions related to operations and logistics.

In addition to the main survey questions, the following additional four questions were sent at a later date to all laboratories in order to better understand how laboratories were interpreting their data: 1) How (if at all) does your laboratory define "weak" DSA, especially those directed to DQA and DPB antigens; 2) Do you accept or not accept organ offers (local vs. import) in situations when weak DSA are present? Do you rely only on the VXM or do you proceed with a cell based prospective crossmatch for local donors? Same question for import donors; 3) How do you handle the interpretation of the virtual crossmatch when patients have HLA antibodies that cannot be listed as unacceptable antigens in UNET (i.e., allele specific antibodies, antibodies against HLA-DPA); 4) How do you handle the interpretation of the VXM when patients have DP antibodies and the donor is positive for specificities not represented on the solid phase platform?

The laboratories that participated in this survey were: Histocompatibility Laboratory at Georgetown University Hospital; Histocompatibility and Immunogenetics Laboratory, Comprehensive Transplant Institute at the University of Alabama at Birmingham; Histocompatibility and Molecular Immunogenetics Laboratory at Emory University Hospital; Immunogenetics Laboratory at Johns Hopkins University School of Medicine; Transplant Immunology, Indiana University Health Methodist; Bloodworks Northwest's Immunogenetics/HLA Laboratory; Immunogenetics and Transplantation Laboratory at the University of California, San Francisco; HLA laboratory at the University of Michigan; Histocompatibility and Immunogenetics Laboratory at the University of Pennsylvania; HLA laboratory at Washington University School of Medicine; Willis-Knighton Histocompatibility Laboratory at Shreveport, LA; and Histocompatibility and Immunogenetics Laboratory at Southwest Immunodiagnostics, Inc.

3. Results

3.1. HLA donor typing methods

Laboratories used a number of molecular assays to perform HLA typing on deceased donors including SSP, SSOP and increasingly, real time PCR (RT-PCR) with its shorter turnaround time (Supplementary Material, Table S2). Eight laboratories (67%) used RT-PCR, either exclusively or in part post-KAS. Six laboratories (50%) made no changes to their typing methodology after implementation of the new KAS, 5 laboratories (42%) added to their existing typing methodology, and 1 laboratory (8%) changed its methodology post-KAS. At the onset of the new KAS, typing and reporting of donors for HLA-DQA and -DPB antigens, and inclusion/exclusion of donors for highly sensitized candidates with HLA-DQA or HLA-DP antibodies was strictly voluntary; not all centers performed such typing. UNOS later mandated HLA-DQA and HLA-DP typing requirements for deceased donors, and all laboratories in this survey have reported this data since January 2016.

3.2. HLA antibody detection methods

All laboratories (100%) used single antigen bead (SAB) assays pre- and post-KAS to define both broad and allele-specific HLA antibodies. The distribution of laboratories that used mixed beads, and/or phenotype (PRA) beads in addition to SAB is shown in the Supplementary Material (Table S3). Post-KAS, the majority (9 of 12, 75%) of laboratories made no changes to their methodologies. Seven laboratories (58%) did not change their antibody screening interval post-KAS while the remaining 5 laboratories (42%) increased the frequency of antibody screens for highly sensitized patients (Supplementary Material, Table S4).

Laboratories were questioned as to whether any software programs to identify epitopes were utilized in order to determine the specificity of the antibodies that were reported. Pre- and post-KAS, the split between laboratories regarding use of software for epitope analysis remained the same: 5 laboratories (42%) do not use software, while the remaining 7 (58%) do. For labs that use epitope analysis, the data collected for this survey did not offer sufficient transparency to ascertain what criteria were used to list HLA unacceptable antigens (UAs).

3.3. Assessment of HLA compatibility

Cutoff values used by the 12 different HLA laboratories participating in this survey to list HLA class I (HLA-A, -B, and -C) and class II (DRB1, DRB3/4/5 and DQB) antigens as unacceptable in UNet were not uniform. Additionally, it is noteworthy that the ability to list HLA-DQA and HLA-DP specificities as unacceptable was not available at the onset of the new KAS; it became available only on January 21, 2016. Post-KAS, four of twelve laboratories (33%) modified their strategies for listing UAs in UNet (Table 1). Four laboratories commented that their cutoffs were guidelines, not absolutes and were determined on a case-by-case basis.

Many transplant centers experienced a surge in deceased donor organ offers, which required vXM evaluation under tight time constraints. Consequently, 10 out of 12 laboratories (83%) saw an increase in the number of virtual crossmatches post-KAS (range: 10–300%). The majority of laboratories (83%) had remote access