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Kidney Transplantation of Highly Sensitized Recipients Under the New Kidney Allocation System: A Reflection from Five Different Transplant Centers Across the United States

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Abstract

Deceased donor kidney allocation was reorganized in the United States to address several problems, including the highly sensitized patients disadvantaged with large, diverse repertoires of antibodies. Here, five transplant surgeons review their center's experience with the new allocation changes: highlighting areas of accomplishment, opportunities for improvement and, in some cases, stark differences in practice. Across these five centers the highly sensitized patients (CPRA ≥ 98%) range from 5.5 to 9.2% of the 12,364 candidates on their collective waitlist. All centers reported greater rates of kidney transplantations in highly sensitized patients (12.4–27%). Three of the programs (Emory, UCSF, UW) relied upon the virtual crossmatch prior to organ acceptance in a majority of cases (70–86%)—the mere presence of antibody on HLA antibody screen was sufficient to exclude the donor in most cases at Emory and UCSF. Penn and UAB relied upon the physical flow crossmatch in almost all cases prior to proceeding with transplantation. Current or historical donor-specific antibody was occasionally crossed in certain cases at UW and UAB necessitating IVIG/plasmapheresis and/or B cell depletion perioperatively. Some authors raised concerns for cost efficiency given the increased need for organ/specimen transportation, and extensive use of hospital resources and ancillary services. In general, we found that the new allocation system has successfully achieved one of its primary goals—increased kidney transplantation in the disadvantaged, highly sensitized patients; the long-term outcomes in all patients and the cost ramifications of these changes will require continued reassessment and clarification.

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Keywords

crossmatch; allocation; kidney transplantation; HLA; sensitization

Introduction

On December 4, 2014, the US kidney allocation algorithm changed significantly, as the new Kidney Allocation System (KAS) was implemented. KAS was designed to improve access to kidney transplantation for ethnic minorities and highly sensitized candidates (increase equity), as well as ensure that the highest quality kidneys were preferentially transplanted in the youngest, most healthy candidates (enhance utility)[1, 2]. Specifically, dialysis time prior to listing was credited to transplant candidates as accumulated waiting time, the best kidneys as defined by kidney donor profile index (KDPI) <20% were preferentially allocated to the healthiest 20% of candidates, defined by Estimated Post Transplant Survival (EPTS) score, and candidates with calculated panel reactive antibody (cPRA) <98% were given increased priority[3]. However, changes to allocation policy can have unintended consequences and may vary significantly by transplant center and donor service area. Potential KAS consequences that warrant further attention include impact on: cold ischemic time, delayed graft function rates, zero antigen mismatch transplant rate, pediatric transplant access, logistical complexity, and rate of organ discard[4] (see Wang, *et al* in this issue). Important graft and patient survival data are still under collection and will be scrutinized closely over time – reporting this at 1-2 years after policy implementation may not give a fair or final view of the impact of the policy change on post-transplant survival. The financial implications for the KAS remain unclear—for example the increased costs associated with organ transportation across larger distances, and the transplantation of patients with greater complexity.

Overall, we find that while the revised KAS increased organ equity (dramatically, for highly sensitized patients, see Table 1), it introduced short-term challenges and unmet objectives that create uncertainty about long-term outcomes. The United Network for Organ Sharing (UNOS) Kidney Transplantation Committee and national transplantation societies are actively engaged in clarifications and improvements to the KAS through public discussions and negotiation. As an adjunct to that effort we present five institutional experiences after the change in allocation and provide feedback to foster future dialogue toward even better kidney allocation.

University of Alabama, Birmingham

Approximately 4.8 million people live in the state of Alabama, comprising only 1.5% of the US population[5]; yet, Alabama has the highest incident and prevalent cases of ESRD[6]. Not surprisingly, the need for kidney transplantation among Alabamians is great, and as a result, UAB has the third largest kidney transplant waiting list in the US. Approximately 3,000 candidates are listed at UAB, 9.2% of waitlist candidates have a cPRA >98% and 74.8% are considered an ethnic minority. Given the waitlist demographics at UAB,

implementation of KAS has impacted our center in several significant ways: 1) surge in organ offers; 2) changes in donor kidney origin; and 3) changes in recipient risk profile.

We have experienced a 2.29-fold increase in the number of organ offers since implementation of KAS (1yr pre-KAS: 322 vs. 1yr post-KAS: 738). Prior to implementation of KAS, list maintenance required approximately 200 waitlist candidates to be transplant-ready at any given time. Since implementation of KAS, this number has risen to more than 580, and has placed strain on the evaluation and re-evaluation process. To account for workflow issues, we have implemented rapid inpatient evaluations and hired physician extenders to increase throughput in our outpatient clinics. These changes have added cost in terms of provider time and hospital resources (testing, ancillary services), yet our kidney transplant volumes pre and post KAS have remained static.

Prior to implementation of KAS, 92.7% of deceased donor kidneys came from donors within our local donor service area; post-KAS 78.7% of deceased donor kidneys come from our local donor service area ($p < 0.0001$). This represents a 15% decline in kidneys from local donors, and has increased logistical complexity due to the increase in imported kidneys. Despite increased utilization of deceased donor kidneys outside our donor service area, compared to the year prior to KAS implementation cold ischemia time (CIT) has only increased 2 hours in the post-KAS era, and in fact, rates of delayed graft function (DGF) have significantly declined likely related to more stringent selection criteria for import kidneys.

Median waitlist time has decreased across all blood groups in the post-KAS era. Moreover, blood group B recipients, of which minorities represent a larger proportion, have a median waiting time 3.2 years less in the post-KAS era compared to the year prior to KAS implementation (4.0yrs vs. 7.3yrs, $p = 0.01$). The mechanism for this decreased waiting time among blood group B candidate remains unclear, but likely reflects a bolus effect from transplanting highly sensitized patients as we have performed few A2-to-B kidney transplants. Highly sensitized patients (cPRA 98%) have also been transplanted at a higher rate after implementation of KAS (11.0% vs. 2.7%, $p = 0.01$), and while not statistically significant the proportion of recipients with a history of previous transplant increased post-KAS (11.6% vs. 10.3%). Given the abrupt change in recipient risk profile, particularly the significant increase in volume of transplants among highly sensitized patients, we have implemented additional processes designed to identify allograft dysfunction early to afford the opportunity for swift intervention and preservation of function. Specifically, our algorithm for highly sensitized recipients involves: 1) avoidance of repeat mismatches with prior donors; 2) pre-treatment with rituximab in the setting of a past positive, current negative crossmatch (XM) and history of prior transplant; 3) donor specific antibody (DSA) surveillance on post-operative days 3, 7, 14, 21 and 30; 4) protocol biopsies at reperfusion, 1 month, 6 months, 1 year; 5) pre-transplant initiation of tacrolimus and mycophenolate mofetil for DSA+ / XM negative transplants; and 6) avoidance of positive flow and cytotoxic XM transplants.

Emory University

At the Emory Transplant Center (ETC) our experience with the new kidney allocation system (KAS) has, with a few notable exceptions, mirrored the national experience[7]. To date the KAS has had a tremendously positive impact on our highly sensitized candidates (HSC, defined here as cPRA 98-100%) as our ability to successfully transplant these patients has increased dramatically.

Prior to the implementation of the KAS, the HSC constituted approximately 14% of our active waitlist (vs. ~8% nationally) as our waitlist has a large demographic of patients who have developed HLA antigen reactivity (most commonly multiparous, African American women). Our listing approach for the HSC was the same before KAS implementation as after. Prior to the KAS, the ETC transplantation rate for the HSC approximated the infrequent national levels of 2-3%[7]. The KAS “out of the gate” reports demonstrate an initial “bolus effect” of almost 18% of all transplants to HSC nationally, which then receded down to 12.6% by July of 2015[8]. We are transplanting HSC at a rate of ~32%[9].

Our success with transplanting HSC is multifactorial but begins and ends with ability of our HLA laboratory to perform vXM upon donor hospital typing information. We define a negative vXM as the absence of DSA, as determined by single antigen bead testing (One Lambda, Inc.), from a serum sample collected within 30 days of transplantation. We typically hold a cutoff MFI for our vXM less than 2000 for HLA A, B, DR, DQ, DP and less than 5000 for the C locus. For all vXM cases, a physical XM is performed using flow cytometry. HLA antibody assessment and a vXM using a serum collected within the past 30 days (monthly serum samples are routinely collected on patients with cPRA 98%) has permitted our team to confidently accept organ offers and proceed directly to transplantation without a prospective physical XM.

A few factors unique to the ETC are important to mention with regard to our success under the KAS. First, our general approach to the HSC is to avoid desensitization with medical therapy. We encourage all of our HSC to seek live donation. For the HSC with a living donor we will aggressively pursue paired donor exchange via the National Kidney Registry. For HSC who have exhausted their live donation options we will accept deceased donor kidneys that fit within our criteria for HLA compatibility. Second, at the ETC important logistical tasks for managing organ offers after implementation of the KAS have been instituted to maximize our ability to transplant the HSC. We make every effort to communicate clearly with the donor hospital prior to organ offer acceptance. In cases where possible DSA is present and pre-operative donor material is not available before organ acceptance and no local back up is permitted then we would typically decline the offer.

With the increased number of organ offers to HSC with multiple HLA antibodies the KAS has undoubtedly generated greater workloads for our HLA lab, stressing the limits of our system. Our HLA lab has been able to rise to the challenge. Since the KAS implementation ~86% of our HSC were transplanted from import offers and ~70% of these were performed based on a vXM (Table 1)[9].

Outcomes under the KAS are closely followed at the ETC and scrutiny at the national level will undoubtedly ramp up as more data is gathered. We have noted that still over half of the transplants are going to recipients < 50 years of age, that more transplants are going to long dialysis duration recipients, and that rates of delayed graft function have increased (although the increase may be related to more longer-dialysis-time patients)[7]. In terms of the HSC, we have seen early success with these patients receiving our standard belatacept-based immunosuppression regimen. Belatacept, basiliximab, corticosteroids will be given intra-operatively. Post-operatively, patients receive tacrolimus, mycophenolate mofetil and corticosteroids. Steroids are rapidly tapered to 5mg prednisone daily. We give monthly 10mg/kg belatacept for the first four doses and 5mg/kg monthly thereafter and begin tacrolimus wean at month 9 with eventual discontinuation by month 11. We have not noted any increase in acute rejection, cellular or antibody-mediated, since the institution of the KAS—however this is a topic of continued investigation. We generally pursue for-cause biopsies rather than protocol biopsies, unless patients fall with a clinical trial that requires scheduled biopsies. DSA is checked regularly at 1, 6, and 12 months and we have not seen any concerning changes in DSA levels post KAS.

Overall, the KAS has brought tremendous opportunity to a large segment of our waitlist that previously experienced poor access to transplantation, especially the HSC. The success of the KAS at the ETC will require a group effort between the HLA lab and the transplant team to facilitate ongoing benefit for our inherently disadvantaged HSC.

University of Wisconsin

The number of highly sensitized patients listed at our center has not significantly changed since the implementation of KAS. Currently, approximately 9% of our waitlist is highly sensitized (cPRA 98-100%). Our general approach to the highly sensitized patient depends largely on whether they have a suitable living donor. If there is a suitable living donor and the sum MFI for DSA is < 4000, then we will consider desensitization. This however is not an absolute MFI cutoff, rather it is made on a case by case basis, taking into account the overall antibody profile and likelihood of response to desensitization. If these patients are not candidates for desensitization then they will be considered for kidney exchange (national, regional or internal). Additionally, even if the MFI seems amenable to desensitization, we first opt for a trial in a paired exchange first if the antibody profile is indicative of finding a rapid match via exchange (but this is typically more for patients that are not broadly sensitized). If they do not find a match in 6-12 months, then we will revisit desensitization. Lastly if there is no suitable living donor available we do offer waitlist desensitization in select cases. Currently there is no standard of care regimen at our center. Instead, desensitization is usually incorporated into a clinical trial or is approached using IVIG and plasmapheresis +/- targeted B lymphocyte/plasma cell therapy.

In regards to deceased donors, when our center receives an offer for a highly sensitized patient, our HLA lab performs a vXM. If the vXM suggests a positive cell based flow XM we decline the offer. Of note our threshold sum MFI to suggest a positive T and/or B cell XM is around 2500 whereby our sum MFI value considers each donor antigen only once, regardless of how many beads that antigen may be represented on. In cases where an antigen

is represented on more than one bead, we will use the bead that corresponds to the donor's allelic typing. If we expect a weakly positive flow XM based on the vXM results, we may consider the offer with the plan to perform a pre-transplant final XM. If in fact it is only weakly positive we may move forward with transplant in conjunction with plasmapheresis, IVIG and T and B lymphocyte depleting induction. To help facilitate this logistically we often ask that blood be sent ahead of time to perform a flow XM ahead of the kidney procurement if possible. If blood cannot be sent ahead of time we often still accept the organ if the vXM suggests a negative or weakly positive flow XM. For both of the cases we try to obtain local back up if possible. For patients where the vXM that is run on a recent sample with no recent sensitizing events and is found to be negative we will proceed with transplant waiving a prospective flow XM. These patients will get a retrospective flow XM however. In patients with measurable DSA based on the vXM that is below our threshold for HLA incompatibility on a recent sample with no recent sensitizing events we will occasionally proceed with transplant waiving a prospective flow XM to shorten cold ischemic time.

We currently have limited granular data for our deceased donor experience for the 6 months pre and post KAS for patients with a cPRA $\geq 80\%$. Overall we did not see a significant increase in the number of patients transplanted with a cPRA $\geq 80\%$, 25% (20/80) in the pre-KAS cohort compared to 23% (17/74) in the post-KAS cohort ($p=0.36$). However, when examining only patients with a cPRA $\geq 98\%$ there was a significant increase from 8.8% (7/80) pre-KAS, compared to 23% (17/74) post-KAS, ($p<0.001$). Therefore, the new KAS seems to have led to a significant increase in patients transplanted with a cPRA $\geq 98\%$, however, it has also been accompanied by a significant reduction in patients transplanted with a cPRA between 80% and 98%. Additionally, there was a significant increase in the number of imported kidneys for highly sensitized patients, from 25% (5/20) in the pre-KAS cohort to 88.2% (15/17) in the post-KAS cohort, $p<0.001$. Two additional imported kidneys in the post-KAS cohort were not transplanted due to a positive cross-match (due to anti-HLA antibodies) and instead went to non-sensitized, back up recipients. The increase in imported kidneys was associated with an increase in the average cold ischemic time (CIT) from 15.5 ± 6.1 hrs pre-KAS to 21.7 ± 6.48 hrs post-KAS, ($p=0.01$). This was not, however, associated with an increase in delayed graft function (DGF), ($p=0.28$). Furthermore, there was no difference in the kidney donor profile index (KDPI) between the two groups, $30 \pm 22\%$ pre-KAS and $27 \pm 15\%$ post-KAS for patients with cPRA $\geq 80\%$ ($p=0.74$). Additionally, there was no difference in KDPI for cPRA $\geq 98\%$ ($30 \pm 25\%$ pre-KAS and $30 \pm 19\%$, $p=0.92$) Importantly, no graft losses or patient deaths were observed in either the pre or post KAS group. We currently do not have complete data on rejection outcomes but preliminarily there does not appear to be an obvious difference. This may be due to the fact that we tend to increase our immunosuppression for highly sensitized patients, favoring T-lymphocyte depleting antibodies, higher tacrolimus trough levels (8-10 ng/ml), and a prolonged steroid taper compared to our non-sensitized recipients. In summary our initial experience with the new KAS from a transplant center perspective has been positive overall. Despite a higher percentage of imported kidneys with longer CIT and higher PRA, we report excellent short-term outcomes in the post-KAS. Certainly, more study is needed to determine the long-term outcomes of extremely sensitized patients transplanted within the new KAS.

Given that we are a single center OPO, we have OPO level data on the impact of the new KAS. For the 11 months since the implementation of the new KAS, 171 kidneys were procured by the OPO. Of these, 22.2% (38/171) were exported to transplant centers outside the OPO donor service area. The majority of these exported kidneys were exported for high PRA (99-100% PRA) patients (19/38, 50%). The remaining kidneys were exported for 0 mismatch (1/38, 2.6%), directed donation (2/38, 5.3%), other allocation points (11/38, 29%) and liver share 35 (5/38, 13.2%). Importantly, of the kidneys designated for highly sensitized patients, 17/19 (89.5%) went into the intended recipient. For the remaining 2 kidneys exported for highly sensitized recipients: 1 went into a local backup recipient secondary to a positive cross-match, and the disposition of the other kidney is currently unknown. These exported kidneys for highly sensitized recipients were shipped, on average, 1059 ± 657 miles with 63.2% (12/19) going to transplant centers on the east or west coast. Additionally, the average KDPI for exported kidneys for highly sensitized kidneys was 31.0%, 63.2% (12/19) had a KDPI <25. In summary, from an OPO perspective, the new KAS has been associated with the majority of exported kidneys exported for high PRA recipients. These kidneys had a relatively low KDPI and incurred long shipping distances. Most of these kidneys were successfully transplanted into the intended high PRA recipients despite extreme sensitization. The graft outcomes of these exported kidneys are not fully known, however nearly all exported kidneys went into the intended highly sensitized recipient.

University of California, San Francisco

By US standards, University of California San Francisco has a large waiting list. With approximately 5,500 patients awaiting kidney transplantation, the list comprises approximately 5.3% of the national waiting list. 11.4% of the patients on the waiting list have a cPRA between 85-100%, which translates into 620 patients with a cPRA over 85%, and 301 who qualify for national sharing with a cPRA of 99-100%. The KAS has influenced our practice, and some of the effects of the changes were difficult to foresee. These changes have impacted every step of our process from listing, to waitlist management, and transplantation. The most profound change after the KAS was a reshuffling of the list, leading to less predictability about who would be getting organ offers. When the KAS was implemented all local variances were eradicated. Our donor service area had a variance for kidney allocation that eliminated points for HLA(DR) matching. Therefore, the variance in our donor service area allowed for a highly predictable calculation for the time to transplantation prior to KAS because waiting time was the dominant element influencing the offer sequence in our recipients. Removal of the variance, and the introduction of matching with KAS resulted in a variability in the time of transplantation for patients at the top of the list. Learning to better predict the time to organ offer has been a work in progress, and has influenced our approach to listing.

Historically, our listing approach has been liberal, to give as many patients with end stage renal disease the opportunity to undergo a transplant as possible. We listed patients after our initial clinic visit as long as the patient could reasonably be expected to be a candidate for transplant 6-8 years in the future. Patients with reversible impediments to transplant were given the opportunity to overcome these obstacles because we were confident in our ability to predict when patients on the waiting list would start to draw organ offers. Very little

testing was done at the time of listing as transplant specific testing generally would need to be repeated. Patients with potential living donors were tested when the living donor was cleared. For patients without a living donor option, we calculated a rough estimate for the likelihood of receiving a 0-MM offer. This estimation was done using available, historic, UNOS data of HLA frequency in donors applied to each recipient. Patients estimated to have a high probability of a 0-MM offer were tested earlier after listing, as were patients accepting ECD, PHS high-risk, and HCV+ donors. Patients were given the course of their waiting time (6-10 years) to demonstrate their candidacy for transplant. Many patients were listed but found not to be a candidate when they were re-seen years later, and were removed from the list. Candidates dropped off the list because of death, becoming too sick for transplant or had co-morbidities that resulted in the patient remaining inactive.

Because of the highly predictable time to organ offer prior to the KAS implementation and variance removal, candidates could be re-seen in clinic as they approached the top of the deceased donor waiting list. For a great majority, this process played out over a predictable timetable, and re-see appointments could be reliably scheduled a year before an organ offer. During that era, we readied approximately 300 patients for transplant at any time. That group of 300 patients had up to date cardiopulmonary testing, antibody testing, clinic visits and contact with our coordinators. After the KAS changes and removal of variances, the likelihood of a recipient receiving an organ offer was much less predictable. Under the new system, a patient added to the waiting list with 1-2 years' worth of DR points is placed in front of several hundred patients. Therefore, in the current era we keep approximately 900 patients ready for transplant. Readyng the additional 600 patients for transplant, and keeping them ready, has required significant process changes. We added pre-transplant coordinators, restructured the timing and frequency of testing, and applied more scrutiny to the patient's candidacy prior to listing.

We have also seen effects of the KAS that probably were expected, and are not unique to UCSF. We are transplanting more highly sensitized patients as KAS provides greater access to high PRA patients with a national share for patients with PRA of 99 and 100%. As an estimate, for a 99% cPRA patient, 1 in 100 donors would be expected to be a potential match. There are about 8000 national donors annually, each offering 1-2 kidneys. Therefore, it would be expected that a matching donor would arise 80 to 160 times per year. This advantage is evident for patients with these cPRAs immediately after listing.

In the three years leading up to the allocation changes approximately 6% of our recipients had a cPRA over 85%, and only 3% had a cPRA of 99-100%. Fourteen percent of our recipients in the first year after the KAS changes had a cPRA between 85-97%, and 27% had a cPRA of 99-100%. In fact, the transplantation of patients with cPRA of 99-100% has continued to increase after the 1-year period captured in this manuscript.

Compared to the three years before KAS, we are transplanting more female recipients (52% versus 38%, respectively, $p=0.001$). Our recipients are younger in the current era (49 versus 53 years of age, respectively, $p=0.009$). Twenty-four percent of the patients we have transplanted after KAS had a previous kidney transplant (versus 12%, $p=0.0001$). Patients with diabetes appear to have less access to transplant, as 20% of our recipients have type-2

diabetes currently, compared to 28% ($p=0.03$) in the three years before the changes. Our recipients with blood group AB have improved access to transplant (12% versus 5%), while our blood group A patients have less (29% versus 36%).

In patients without a living donor, the UCSF strategy for highly sensitized patients has favored waiting for a compatible match over desensitization. We use the extensive waiting list, paired exchange programs, and encourage recipients to consider PHS high risk and/or high KDPI donors, to transplant with a compatible organ. The KAS changes have greatly facilitated finding the “needle in the hay stack.” The surgeon, in communication with the HLA lab director at the time of the offer determine the need for a XM based on the current and historic sensitization data with respect to the donor in question. We list as unacceptable any antibody with a MFI $>1,000$, therefore we are confident in our vXM and do not perform a XM. One exception is DP antibodies. Many highly sensitized patients are broadly sensitized against DP antigens, but these antibodies do not seem to increase the risk of accelerated rejection to the same degree. We do not list DP antibodies at any MFI as unacceptable. If donor DP typing is not available, we perform the DP typing and XM prospectively if the recipient has high levels of DP antibodies. We move forward with transplant if the B flow XM MCS is <200 no matter how high the MFI of the DP DSA.

A vXM alone is sufficient in 86% of our transplants, even in highly sensitized patients, minimizing shipping of blood across the country. We suspect that using a vXM minimizes the need for late reallocations because we rarely have a XM in process while a kidney is being transported. In cases where no XM is done (86%), kidneys are only reallocated after arrival if a recipient issue is identified in the hours before surgery. We do not request a back-up recipient when a highly sensitized patient is being transplanted with a vXM. This is important because we have imported many more kidneys into our donor service area in the year after KAS compared to the three years leading up to the changes (131 versus 74, 86 and 95, respectively).

As a result of the increased number of transplants in highly sensitized recipients we have expanded the protocol for post-transplant DSA monitoring. Recipients with any pre-transplant DSA, and/or CPRA $>80\%$ have DSA checked at 1 week, 1 month, 3 months, 6 months, and 1 year after transplant. Protocol biopsy is done at 6 months. Additional testing is performed if memory response or rejection is suspected due to graft dysfunction. If a DSA develops with MFI $>1,000$, or an existing DSA (a known DSA from the pre-transplant testing, or a DSA developed de novo after transplant) increases by $>50\%$, a biopsy is performed to rule out antibody mediated rejection. If there are known low-level DSA from 0 - 2,000 MFI, or DP antibodies based on the vXM, we give 1-2 doses of IVIG at the time of transplant, and perform a retrospective XM in the early post-operative period to guide immune suppression, in addition to our routine DSA monitoring. If the retrospective XM is positive, we have a lower threshold for biopsy.

The increased access to transplantation for very highly sensitized patients meant that a number of patients listed for many years were finally getting organ offers. These patients may not have made urine for a decade, resulting in very small bladders creating technical challenges. Despite the immunologic, logistic and technical challenges, it is clear that the

new system has provided the opportunity for transplantation in a significant population that was previously excluded from transplant.

University of Pennsylvania

Our center exists in a competitive region with fifteen kidney programs in our OPO and a high volume of donors due to an aggressive and active procurement organization. Our adult kidney transplant list currently encompasses 1095 patients and we have a complex mix of patients listed with 13% re-transplant candidates. At the time of certification for the new KAS in December 2014, we certified 108 patients with PRA 99-100% (10% of our list). Over the course of the first calendar year after KAS implementation, we transplanted 26 of these patients (24% of the listed patients with PRA 99-100%) and listed another 19 patients in the 98-100% PRA category (Table 1). Additionally, we transplanted one patient with a PRA 98%, which qualifies for local priority in the new KAS.

Our center approach to transplantation did not change with the KAS implementation. We pursue live donor transplantation for those rare 98-100% PRA patients with compatible donors, kidney paired exchange (KPE) for incompatible living donor pairs, and compatible deceased donor transplantation for those who lack live donor options. We have not pursued desensitization as a general strategy. We have only registered one patient in this high PRA group for paired exchange (with a PRA of 100%) since KAS implementation and this patient has yet to be transplanted. Our general approach to immunosuppression has included thymoglobulin induction (7.5mg/kg over 5 doses in this PRA range) followed by steroid taper to maintenance 5mg daily, mycophenolate 500mg twice daily, and tacrolimus with initial trough targets of 10-12mg/dl. We have not employed B cell-directed approaches for compatible recipients barring evidence of rejection.

Upon being notified of a potential donor offer, the HLA lab performs a vXM to assess feasibility and then blood samples are sent for confirmatory flow cytometry cell-based XM. By center approach, we have considered antibodies with MFI ≥ 3000 to be compatible if flow XM has been negative [3]. On rare occasions we have transplanted patients with a weakly reactive flow XM (Delta MSEF values for the T and B cell XM $<1,500$ and $<2,500$ respectively) and if there are no DSA to mismatched antigens from prior transplants. Our center only performs biopsy for cause and generally defer biopsy to 3-4 weeks after transplant if there is remaining delayed graft function, as we have rarely seen early rejection even in this cohort under the coverage of thymoglobulin. Over the course of the first year after KAS adoption, 8 of 26 patients (31%) with PRA 98-100% were biopsied for cause (4 of these were biopsied twice) and of these, none were diagnostic of cellular or antibody-mediated rejection and none were positive for C4d on immunohistochemistry.

When offers are coming from a significant distance, we vigorously attempt to pursue having a donor sample sent in advance for a cell-based flow XM, especially if the organ quality is not optimal – this decreases cold ischemia time and prevents the need to XM backup patients. If samples are not sent in advance, we XM unsensitized backup patients at the same time as the XM for the intended sensitized recipient in case the sensitized patient XM is incompatible. Over the first year after KAS adoption, 6 of 26 patients were transplanted with

local OPO organs, 7 from regional sharing, and 13 from national shares. Of the organs accepted, only 3 had to be diverted from the primary recipient to a compatible backup due to XM incompatibility – one local, one regional, and one national share. For the other incompatible donors, flow XM were done prior to organ transportation and the organ transport was aborted. Thirteen out of 103 patients in the 99-100% PRA category experienced 17 total incompatible cell-based XM despite vXM presumed compatibility over the course of the calendar year after KAS introduction. Of these, 6 were due to DP antibodies, 3 were due to class II allele specific antibodies, 6 were due to multiple weak class I and/or class II antibodies, 1 was due to high levels of DSA that was present in historic sera, and in 1 case the B cell XM reactivity was not consistent with the profile of the anti-HLA antibody detected by the luminex antibody screening assay. Based on described other center protocols, it is possible there would have had been an indication for a prospective XM in the protocols employed by the other centers or been deemed incompatible due to lower MFI thresholds.

In the cohort of patients transplanted with PRA 98-100% in the first year after KAS allocation, some of which are still in the first year of graft survival, there were no identified episodes of acute cellular rejection (ACR) or antibody mediated rejection (AMR). 1/26 patients (4%) experienced primary graft non-function but the remaining 25 patients are alive with functioning grafts at end follow-up and the median 30-day creatinine for these grafts was 1.45mg/dl. The median KDPI was 30% (1-85) and the median EPTS was 45% (4-85). Fourteen of 26 (54%) of patients had a prior transplant and 4/26 (15%) had multiple prior transplants. Sixteen of 26 (62%) of patients had prior blood transfusions and 5/26 (19%) were female patients with no prior transfusion or transplant history but with personal history of pregnancy (1-7 pregnancies). Three of 26 patients (12%) were transplanted prior to dialysis exposure but the median dialysis exposure of the remaining patients was 1449 days (50-3166) and median waiting time for all recipients transplanted in this PRA category was 1411 days (50-3621).

DSA after transplant was assessed at 1 month, 3, 6, 12 months, and then annually per protocol. Eight of 26 patients (31%) developed DSA in the first year after transplant and of these eight, two spontaneously resolved. Of these eight patients, five developed class I DSA alone (1 resolved), 1 developed class II DSA alone, and 2 developed class I and II DSA (1 resolved). To be considered to be positive for DSA, there is both a rise in MFI of greater than 50% from pre-transplant value and an absolute MFI of greater than 1000. DSA development without graft dysfunction was not an indication for biopsy – three of these eight patients underwent a for-cause biopsy and none demonstrated C4d positivity. We have concern that these eight patients are at heightened risk of graft dysfunction but we have no evidence of this at this time.

Our center provides transplant surgical care for the Children's Hospital of Philadelphia as well and we should note that waiting times for pediatric deceased donors increased significantly in the year after KAS implementation (mean 604 days prior and 984 days after KAS). The KAS places cPRA 98 -100% and zero antigen mismatch adult patients categorically ahead of pediatric recipients and although the policy change now places pediatric recipients categorically ahead of less sensitized adults (as was not the case

previously) for kidneys with KDPI \geq 35%, we speculate that the high volume of these highly sensitized transplants has overall reduced pediatric access to deceased donor grafts at least in the first year after KAS implementation[4] (See Wang et al, this issue).

Conclusions

One of the major objectives of the new KAS has been to increase access to kidney transplantation in groups that have previously been disadvantaged. To achieve a more equitable playing field the new KAS made several modifications. The most impactful changes were 1) counting wait time for a kidney from the date the patient started dialysis, rather than from the date the patient joined the kidney transplant list, and 2) increasing priority on the wait list for highly sensitized patients.

In this manuscript we explored the center-level impact on the highly sensitized patients. The new KAS incorporated two approaches for prioritizing sensitized patients: 1) a sliding scale for assigning allocation points based on CPRA and 2) a local, regional and national priority for candidates with a cPRA of 98, 99 and 100%, respectively. Nationally, it appears that this two pronged approach has achieved its goal such that in the first year since KAS implementation, candidates with a calculated panel reactive antibody (CPRA) of 99 or 100% have been transplanted at nearly six times the rate they were under the prior allocation policy[6].

To explore the differential center level effects of this modification further we presented the experience of 5 transplant centers, and it is clear that despite variability in practice patterns and patient populations, many more highly sensitized patients have been transplanted as a result of the new KAS (Table 1). The approach to these patients does vary considerably depending on transplant center regarding type of immunosuppression, optimal use of kidney exchanges, and utilization of desensitization, induction therapy, MFI levels to consider the corresponding antigens as unacceptable and whether to list HLA antigens from a prior transplant as unacceptable (Table 1). Without a prospective trial utilizing standardized methodology across centers, it is difficult to assess which process is will yield the best results and at the most acceptable costs but this is a question that would clearly be illuminated with a clinical trial. These variations in approach have yielded short-term outcomes are similar to those seen in less complex recipients. Long term outcomes are not yet known and the details of whether patients declined by vXM alone might be acceptable for transplantation with a negative flow XM (or the converse) is unknown.

Moving forward as a community, many unanswered questions do remain concerning the most efficacious and cost effective approach to these patients. Balancing these issues of cost while preserving excellent outcomes will likely play a larger factor in the future. Additionally, it will be important for regulatory bodies to appropriately stratify risk for these immunologically complex patients so that centers transplanting them are not held to an unattainable outcomes standard. Another important consideration is what happens to the prioritization of highly sensitized patients undergoing waitlist desensitization. Currently there is no way to preserve this priority for patients that are successfully desensitized. However, the OPTN/UNOS Kidney Transplantation and Histocompatibility Committees are

discussing the issue and considering whether to recommend a policy change that would allow patients undergoing desensitization to keep their CPRA prioritization points (even while some unacceptable antigens are removed) for a period of time. Moreover, based on center-level experiences the threshold of HLA-incompatibility requiring desensitization varies considerably, as the same antibody risk profile may be considered compatible by some and incompatible requiring desensitization by others. This controversial aspect of desensitization merits further studies. Furthermore, we acknowledge that this report encompasses the experience of geographically and regionally diverse centers but typically large transplant centers with a large share of transplants in their OPOs and regions. These centers may have a greater number of highly sensitized patients and this experience may not translate well to smaller transplant centers.

In sum, what is clear from these five experiences is that the new KAS has been largely effective in increasing access for highly sensitized kidney transplant recipients. Additionally, it is evident that the care of these immunologically complex patients requires great coordination and thoughtfulness across various kidney transplant stake-holders including surgery, nephrology, pathology, HLA laboratory and OPO's. This increased complexity likely is increasing costs directly or indirectly and such costs are not well-accounted for in the system of transplantation reimbursement. The increased access for highly-sensitized patients is not leading to increased deceased donor volumes and thus is likely resulting in diminished access in certain groups – here we report lower transplant rates for highly sensitized patients just below the 98% cPRA broader sharing threshold and a lower transplant rate among pediatric recipients. This is an expected outcome as none of these allocation policies have directly increased the overall size of the donor pool. These reports merit further study at the national, regional, and OPO level. Desensitization strategies and efficient paired exchanges remain viable options for providing access to kidney transplantation for all highly sensitized patients beyond the current allocation improvements.

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Table 1

	Emory Transplant Center	University of Alabama	University of California San Francisco	University of Pennsylvania	University of Wisconsin
Adult waitlist and transplant center characteristics:					
Number of centers in OPO	3	1	3	15	1
Current waitlist size	1813	2979	5,461	1091	1020
Percentage of very highly sensitized (cPRA>98%) wait list candidates (n)	9.1% (164)	9.2% (275)	5.5% (301)	7.0% (76)	8.7% (89)
Cross-matching of completed transplants since KAS:					
Virtual crossmatch only (%)	0%	5%	0%	0%	0%
Physical crossmatch (%)	30%	95%	14%	100%	17%
Virtual crossmatch and retrospective physical crossmatch (%)	70%	0%	86%	0%	83%
Approximate MFI Cutoff below which a virtual crossmatch is sufficient	< 2,000 MFI	< 1,500 MFI	< 1,000 MFI	None	< 1,000 to 2,000 MFI
Crossmatching notes	All donors now undergo DP typing prior to transplantation. Anti-DP antibodies carry the same MFI cut off as other antibodies	All donors now undergo DP typing prior to transplantation. Anti-DP antibodies carry the same MFI cut off as other antibodies	< 6,000 -7,000 MFI for antibodies to DP	All donors now undergo DP typing prior to transplantation. <3,000 MFI with negative flow XM is generally accepted as compatible	All donors now undergo DP typing prior to transplantation. Anti-DP antibodies carry the same MFI cut off as other antibodies
Induction and post-op immune suppression:					
Induction for sensitized recipients	Basiliximab, Solumedrol	Thymoglobulin(6mg/kg),Solumedrol	Thymoglobulin(6mg/kg),Solumedrol	Thymoglobulin (6-7.5mg/kg) ,Solumedrol	Campath or Thymoglobulin, Solumedrol
Standard immune suppression for recipients considered low risk of rejection	Belatacept, Tac, MMF, Pred (wean Tac at 9-12 mo)	Tac, MMF, Pred (Pred only if simulect induction)	Tac, MMF, Pred (Pred withdrawal or Belatacept when appropriate)	Tac, MMF, Pred	Tac, MMF, Pred (Tac trough goal 6-8)
Standard immune suppression for recipients considered high risk of rejection	Belatacept, Tac, MMF, red (wean Tac at 9-12 mo)	Tac, MMF, Pred	Tac, MMF, Pred	Tac, MMF, Pred	Tac, MMF, Pred(Tac trough goal 8-10)

	Emory Transplant Center	University of Alabama	University of California San Francisco	University of Pennsylvania	University of Wisconsin
Deceased donor kidney recipients who underwent desensitization before and after KAS	none	Before: 5 After: 0	none	none	Before: 2 After: 6
Sensitization in recipients of a deceased donor kidney 1 year before and 1 year after KAS:					
Recipient s with cPRA 85-97%	Before: 7.6% After: 4.6%	Before: 7.5% After: 6.6%	Before: 5.1% After: 14.3%	Before: 7.2% After: 4.7%	Before: 11.1% After: 0.0%
Recipient s with cPRA 98%	Before: 2.5% After: 1.3%	Before: 0.0% After: 0.8%	Before: 0.5% After: 2.2%	Before: 1.1% After: 0.5%	Before: 1.3% After: 0.0%
Recipient s with cPRA 99-100%	Before: 3.4% After: 16.8%	Before: 4.2% After: 12.4%	Before: 1.9% After: 26.8%	Before: 1.7% After: 12.7%	Before: 7.5% After: 23.0%
Recipient s with a previous kidney transplant	Before: 7.0% After: 12.1%	Before: 10.8% After: 13.2%	Before: 11.8% After: 24.1%	Before 12.0% After 16.0%	Before: 22.5% After: 20.2%