Incompatible Live-Donor Kidney Transplantation in the United States: Results of a National Survey

Jacqueline M. Garonzik Wang,* Robert A. Montgomery,* Lauren M. Kucirka,* Jonathan C. Berger,* Daniel S. Warren,* and Dorry L. Segev†

Summary
Background and objectives Use of incompatible kidney transplantation (IKT) is growing as a response to the organ shortage and the increase in sensitization among candidates. However, recent regulatory mandates possibly threaten IKT, and the potential effect of these mandates cannot be estimated because dissemination of this modality remains unknown. The goal of this study was to better understand practice patterns of IKT in the United States.

Design, setting, participants, & measurements Directors from all 187 unique active adult kidney transplant programs were queried about transplantation across the following antibody barriers: positive Luminex, negative flow crossmatch (PLNF); positive flow, negative cytotoxic crossmatch (PFNC); positive cytotoxic crossmatch (PCC); and ABO incompatible (ABOi).

Results Responses from 125 centers represented 84% of the live-donor transplant volume in the United States. Barriers of PLNF, PFNC, PCC, and ABOi are being crossed in 70%, 51%, 18%, and 24%, respectively, of transplant centers that responded. Desensitization was performed in 58% of PLNF, 76% of PFNC, 100% of PCC, and 80% of ABOi using plasmapheresis and low-dose intravenous Ig (IVIg) in 71% to 83% and high-dose IVIg in 29% to 46%.

Conclusions A higher proportion of centers perform IKT than might be inferred from the literature. The rapid dissemination of these protocols despite adequate evidence of a clear advantage of IKT transplants argues for the creation of a national registry and randomized studies.


Introduction
Live kidney donation is safe and offers the recipient the best chances for survival, yet it is estimated that thousands of patients with kidney failure are relegated to the deceased-donor waiting list because of HLA or ABO incompatibilities even with a healthy, willing live donor (1–4). In an effort to transplant these patients, centers are increasingly turning to creative modalities such as incompatible kidney transplantation (IKT) with desensitization, kidney paired donation (KPD), or list paired donation (LPD). Advances in immunosuppression, desensitization, and KPD have enabled some centers across the country and throughout the world to transplant across immunologic barriers (5–17).

We define IKT as live-donor kidney transplantation with known donor-specific antibody (DSA). Despite what appear to be growing IKT practices, there is currently no systematic nationwide method of collecting data on the use of this modality or its associated outcomes. Therefore, all inferences about IKT dissemination are limited by publication bias, with reports from only a handful of relatively high-volume centers. Because of limited knowledge about IKT practices or outcomes in the United States, relevant factors are not currently accounted for in the Scientific Registry of Transplant Recipients (SRTR) risk adjustment models. Specifically, current SRTR models do not adjust for transplantation against HLA or ABO barriers, and they do not account for desensitization practices. Although they adjust for panel reactive antibody (PRA), this metric accounts for breadth of sensitization rather than the strength of antibody specifically against a donor.

In attempt to better understand the use of IKT in the United States, we surveyed directors from all active adult kidney transplant programs. We asked detailed questions about transplantation across immunologic barriers and desensitization practices including the use of immunosuppressive regimens, plasmapheresis, and rituximab. The goals of this study were to characterize national IKT practices as a first step toward improved reporting of outcomes and further standardization of protocols and best practices.

Materials and Methods
Using publically available data, we identified 196 transplant centers within the United States that per-
formed at least one adult (≥18 years) live-donor kidney transplant in 2008 or 2009. These centers were contacted via phone to obtain the identity and contact information of their current kidney transplant director, defined as the person listed with the United Network for Organ Sharing as the primary responsible transplant surgeon. If multiple centers in one geographic location shared a director, we combined those into one center so that the director would only complete one survey. Of the resulting 187 centers, we then contacted each director via e-mail and provided a link to an online electronic survey using Survey Monkey (www.surveymonkey.com). We also provided a hard copy of the survey if requested, of which 17 were returned and included in the study. If the director whom we initially contacted believed that a different faculty member was a more appropriate respondent (for example, a nephrologist or transplant surgeon who directed the IKT program at a given center), we contacted the alternative person provided.

Two response rates are reported. First, we report the absolute proportion of centers that returned our survey; in other words, the number of responses divided by 187. Second, we report the proportion of live-donor kidney transplant volume represented by our responses. For this estimate, we summed the number of live-donor transplants performed in 2008 at the centers that completed our survey and divided this sum by the total number of live-donor transplants performed in the United States in that year.

Respondents were asked if their centers performed any of the following types of incompatible kidney transplants: transplants with evidence of DSA by Luminex, but with negative flow cytometric crossmatch (PLNF); transplants with positive flow cytometric crossmatch, but negative cytotoxic crossmatch (PFNC); transplants with positive cytotoxic crossmatch (PCC); and transplants that were ABO incompatible (ABOi). Respondents were also asked if desensitization was used at their center for each of the above incompatibilities and, if so, they were asked to describe their desensitization protocols. Specific questions were asked about the use of plasmapheresis and low-dose intravenous Ig (PP/IVIg), high-dose intravenous Ig (IVIg), and pretransplant anti-CD20 antibody (rituximab). Finally, centers were questioned about what assays they used to determine levels of incompatibility and what titers they considered safe to proceed with transplantation.

The estimated prevalence of IKT use is reported as the proportion of respondents reporting transplantation across a given IKT barrier. However, although response rates were high (67%), responses were clearly not obtained from all eligible transplant centers. Two assumptions (at opposite extremes) were used to inform the “possible range” of prevalence estimates. One assumption was that centers not responding to the study simply did not perform IKT and as such either (1) had no interest in the study or (2) assumed that responding would be noninformative. Under this assumption, the lower bound of a prevalence estimate was determined as the number of centers performing IKT divided by the total number of eligible centers that were contacted. The other extreme assumption, albeit far less likely, was that all centers not responding to the study did indeed perform IKT, so the upper bound of a prevalence estimate was determined as the number of centers reporting that they performed IKT plus the number of nonresponders, all divided by the total number of eligible centers. Statistical analysis was performed using Stata 11/MP for Windows (Stata Corporation, College Station, TX).

**Results**

**Performance of Incompatible Kidney Transplants**

Responses were obtained from 125 centers, representing 67% of kidney transplant centers and 84% of the volume of live-donor kidney transplants in the United States. Ninety-three centers (74% of respondents, possible range 50% to 83% of US centers) performed at least one kind of IKT. Eighty-six centers (70%, possible range 46% to 80%) performed kidney transplants with PLNF. This type of incompatibility was the most widely disseminated (Figure 1). Sixty-three centers (51%, possible range 34% to 69%) performed IKTs with a PFNC, 22 centers (18%, possible range 12% to 46%) performed kidney transplants with PCC, and 30 centers (24%, possible range 16% to 50%) performed ABOi kidney transplants.

**Use of Desensitization/Preconditioning**

Use of desensitization varied across the four types of incompatibility (Table 1). Fifty-eight percent of centers performing PLNF reported desensitizing these patients, compared with 76% of centers performing PFNC and 100% of centers performing PCC. Among centers desensitizing for HLA barriers (PLNF, PFNC, and PCC), all centers indicated at least one specific modality (PP/IVIg, IVIg, or other) and approximately 35% to 40% indicated using more than one modality; 71% to 82% reported using PP/IVIg, 36% to 46% using IVIg, and 23% to 29% using other modalities. Among centers performing ABOi transplants,

![Figure 1. Proportion of transplant centers in the United States performing incompatible kidney transplants by level of incompatibility.](image-url)
PP/IVIg, plasmapheresis and low-dose intravenous Ig; IVIg, high-dose intravenous Ig; PLNF, positive Luminex, negative flow crossmatch; PFNC, positive flow, negative cytotoxic crossmatch; PCC, positive cytotoxic crossmatch; ABOi, ABO incompatible.

*aNumbers represent the percent on the basis of those from the overall cohort who answered the given question. For example, there were 86 centers that performed PLNF transplants, representing 70% of the 123 centers that responded to the set of questions about PLNF transplants.

*bNumbers represent the percent on the basis of those who reported performing the given modality. For example, of those 86 centers that performed PLNF transplants, 50 of 86 (58%) used preoperative desensitization in that situation.

*cNumbers represent the percent on the basis of those who reported using desensitization. For example, of those 50 centers that desensitized PLNF recipients, 37 (74%) used PP/IVIg.

*dNumbers represent the percent on the basis of those who answered the question about anti-CD20 antibody. For example, of those 49 centers reporting use of anti-CD20, 27 stated that they never used it in PLNF situations.

*eFor ABOi transplants, the number represents those who precondition with A2, B, or A1 donors. Of 30 centers that performed ABOi transplants, 24 (80%) precondition one of those blood type donors and 15 (50%, not shown in table) reported always preconditioning for ABOi transplants.

**50% reported always preconditioning these recipients; with regards to specific donor blood types, 60% reported preconditioning patients with A2 donors, 60% with B donors, and 63% with A1 donors, with 80% of centers reporting preconditioning at least one of these blood types. For ABOi transplants, of those preconditioning recipients, 83% reported using PP/IVIg, 29% using IVIg, and 29% using other modalities.

### Use of Pretransplant Anti-CD20 Antibody

More than half of all centers (55% for PLNF, 53% for PFNC, 59% for PCC, and 62% for ABOi) reported giving preoperative rituximab (Table 1). Of the centers that reported using rituximab, 45 provided more detail regarding their dosing regimen. Most of these centers reported using 375 mg/m², but doses ranged from 150 mg to 1 g.

### DSA Testing

We asked centers to further define their methods of antibody testing. Of the 46 centers that routinely desensitized PFNC patients and answered this question (four centers did not answer the question), 44 (96%) routinely tested for the presence of DSA. All 21 centers performing PCC who answered this question (one center did not answer the question) routinely confirmed the presence of DSA. Testing modalities of choice included Luminex testing, Labscreen, flow cytometric crossmatch, and other cell-based modalities. One center reported using the novel c1q assay created at Stanford University. Thresholds for a positive test varied from 300 to 3000 median fluorescent intensity for Luminex testing and from 10 to 60 mean channel shifts for flow cytometry. Similarly, strength of reactivity considered too high to initiate desensitization varied from a complement-dependent cytotoxicity (CDC) titer of 1:8 to 1:512. ABO testing modalities included tube-test anti-human globulin, saline drop tube method, isoagglutinins, Coombs, agglutination with two-tube dilution, and gel card direct tube test. Titers considered too high to initiate preconditioning for ABOi varied from 1:8 to 1:2048. We caution that although these responses provide a sense of the breadth of testing modalities used in IKT centers, these were free-response questions that do not lend themselves to quantifying the use of these various modalities.

### Discussion

In this national survey of kidney transplant centers, with responses representing 84% of the live-donor kidney transplant volume in the United States, wide dissemination of incompatible kidney transplant practices was found. Of respondents, 74% reported performing at least one type of IKT (indicating a national range of 50% to 83%), with 70% (46% to 80%) crossing PLNF, 51% (34% to 69%) crossing PFNC, 18% (12% to 46%) crossing PCC, and 24% (16% to 50%) crossing ABO barriers. Desensitization was used by most centers crossing any of these barriers, with most reporting the use of PP/IVIg and approximately one half of centers using anti-CD20 antibody. However, not all centers used desensitization for lower strength antibody, with only 58% using desensitization for PLNF and 76% for PFNC; variations in immunosuppression (such as use of antithymocyte globulin) were not queried. Donor-specific or ABO antibody testing varied widely.

This survey represents a first step in cataloging current practices in managing anti-HLA and ABO antibody at centers throughout the United States. Much more detailed analysis of phenotypes, protocols, and outcomes will be needed to obtain an accurate picture of this emerging field.
The survey attempts to address the problem of the wide variability in the DSA strength among patients undergoing desensitization by defining three categories of antibody reactivity and the existing practice patterns associated with each category. This includes characterizing center-specific assessment of the need for desensitization associated with varying degrees of antibody strength in addition to willingness to transplant these patients. Although cutoffs for these three categories vary somewhat, a correlation has been consistently shown among escalating antibody levels, antibody-mediated rejection (AMR), and graft loss among patients undergoing desensitization (18). Even low levels of DSA have been associated with the development of posttransplant AMR and poorer outcomes (19).

Although there appears to be widespread practice of IKT throughout the United States, the utility and efficacy of desensitization for DSA remains largely anecdotal and unproven (20). Only a few randomized trials have been published, showing a modest improvement in outcomes, PRA reduction, or transplant rate with high-dose IVIg (21,22). There are also numerous small single-center series showing good short-term outcomes after desensitization with high-dose IVIg or PT/IVIg, although rates of AMR and graft loss are higher than for transplants among unsensitized patients (5,6,8,23). Vo et al. used high-dose IVIg and anti-CD20 to desensitize 20 patients and achieved an 80% transplant rate and a 94% graft survival rate 12 months after treatment and transplant, respectively (8). These studies have many limitations, including variable antibody testing techniques, patient populations, phenotypes, and treatment protocols as well as inconsistencies related to the definitions of sensitization and response to therapy. There are very limited long-term outcome data on transplantation after desensitization. A report by Haririan et al. found that 14 patients desensitized for a positive flow crossmatch with 5 years of follow-up had a graft survival of 69.4% (24).

HLA sensitization affects 30% of the patients on the kidney deceased-donor waiting list. More than 8000 registrants are highly sensitized (PRA >80%). Annual transplant rates for highly sensitized patients are as low as 6.5% (8). For most highly sensitized patients there are two options: remain on dialysis or undergo desensitization. On average, patients who undergo compatible transplantation live twice as long as patients who remain on dialysis (4). For those patients who have willing but HLA-incompatible donors, KPd offers the possibility of finding a compatible live donor. Unfortunately, KPd opportunities for highly sensitized patients are quite limited (2). Given the current options, desensitization may provide the best outcome, quality of life, and health care savings for many sensitized patients (2). However, better long-term outcomes data and prospective studies are necessary to definitively demonstrate an advantage to this therapy.

On the other hand, the results of ABOi transplants appear to be better than those of HLA-incompatible transplants. Our group recently reported 1-, 3-, and 5-year ABOi graft survival rates of 98.3%, 92.9%, and 88.7%, respectively, which are comparable to United Network for Organ Sharing data for compatible live-donor kidney transplants (9). This can be achieved with only a brief escalation in immunosuppression and without long-term B cell suppression from splenectomy or anti-CD20. Groups from Japan and Sweden have published very similar results (25,26). In the survey presented here, fewer centers reported transplantation across ABO barriers than desensitization for HLA antibody, and it remains unclear whether these excellent results from very specialized centers will be maintained when the techniques become more widely disseminated.

It is likely that outcomes of IKT will be inferior to those of compatible transplants because of a combination of (1) the immunologic risk inherent to the incompatibility, (2) the risks of the actual desensitization procedure, and (3) latent factors (such as increased comorbidity) associated with the highly sensitized recipient population. Current regulatory and quality assurance paradigms do not account for the use of this modality among centers performing these specialized transplants. Regulatory agencies use SRTR multivariate regression models for risk adjustment, and expected survival is calculated by mathematical formula on the basis of the estimated effect of several donor and recipient factors on transplant outcomes. The “expected survival” calculated by these models is likely not an accurate estimate for the outlying IKT population. Centers offering desensitization to a large enough cohort of patients are likely to experience reduced patient and graft survival rates, which could trigger regulatory action. Regulatory pressures may inhibit the development of larger, better trials that are necessary to answer important questions and compare the effectiveness of different desensitization protocols. Similarly, costs and insurance reimbursement for these procedures may also represent disincentives.

We acknowledge that registry-based risk prediction for IKT will be imperfect and limited by misclassification. Indeed, we found that cutoffs for PLNF and PFNC vary between centers. However, it is likely that even a simple adjustment (for example, any patient who has undergone pretransplant desensitization) will capture a high proportion of the explanatory power associated with IKT. The remaining nuances will have to be determined later. However, we point out that this kind of misclassification and imperfection associated with registry-based risk prediction already exists in the current transplant outcomes models. For example, diabetes is treated as a binary variable in which the spectrum of diabetes as it pertains to risk (age of onset, duration of disease, glucose control, sequelae) is likely just as wide, or perhaps even wider, than the spectrum of IKT as it pertains to risk.

Several limitations of this survey merit discussion. First, our response rate was 67%; although this is a very high response rate for a survey study, and although our respondents represented 84% of the volume of live-donor kidney transplants in the United States, any response rate <100% makes prevalence estimates challenging. We have addressed this limitation by providing a range that is based on upper and lower bounds sensitivity analyses whenever prevalence estimates were provided. Because some centers do not even test using Luminex, and as such might unknowingly be transplanting patients with low levels of DSA, we might be underestimating the proportion of centers performing PLNF transplants. Our inferences are also

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Disclosures
None.

References
6. Zachary AA, Montgomery RA, Ratner LE, Samaniego-Picota M, Haas M, Kopchalska D, Leffel MS: Specific and durable limitation by the binary nature of our study questions: We asked providers to indicate if they did or did not perform a certain type of IKT, but not how many of these cases were performed. We made this choice purposefully, under the likely assumption that estimating the number of cases that a center performed without actually enumerating these cases would be highly unreliable, particularly in light of the wide variation in what centers actually defined to be IKT. We hope that a future study in which IKT recipients are actually enumerated and studied in multiple centers will better inform this research question. Finally, the nuances of each center’s IKT practice (e.g., details of rituximab dosing and details of DSA testing) were obtained only through open-ended questions, limiting our inferences at this level to qualitative ones.

In conclusion, we have shown that a higher proportion of transplant centers perform IKT than might be inferred from the literature. Future research should be focused on developing a national IKT registry and capturing data that are not currently being reported. From these data, appropriate risk adjustment models and novel approaches to quality assurance and outcome evaluation can be developed. Most importantly, there is a need for multicenter randomized trials to establish best practices and to assess the effectiveness of desensitization in offering a survival benefit to sensitized patients.


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