

ORIGINAL ARTICLE

Kidney recipients with allograft failure, transition of kidney care (KRAFT): A survey of contemporary practices of transplant providers

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Kidney allograft failure and return to dialysis carry a high risk of morbidity. A practice survey was developed by the AST Kidney Pancreas Community of Practice workgroup and distributed electronically to the AST members. There were 104 respondents who represented 92 kidney transplant centers. Most survey respondents were transplant nephrologists at academic centers. The most common approach to immunosuppression management was to withdraw the antimetabolite first (73%), while only 12% responded they would withdraw calcineurin inhibitor (CNI) first. More than 60% reported that the availability of a living donor is the most important factor in their decision to taper immunosuppression, followed by risk of infection, risk of sensitization, frailty, and side effects of medications. More than half of respondents reported that embolization was either not available or offered to less than 10% as an option for surgical intervention. Majority reported that ≤50% of failed allograft patients were re-listed before dialysis, and less than a quarter of transplant nephrologists performed frequent visits with their patients with failed kidney allograft after they return to dialysis. This survey demonstrates heterogeneity in the care of patients with a failing allograft and the need for more evidence to guide improvements in clinical practice related to transition of care.

KEYWORDS

clinical research/practice, dialysis, immunosuppression/immune modulation, kidney failure/injury, kidney transplantation/nephrology, transitional care

Abbreviations: AST-KPCOP, American Society of Transplantation Kidney Pancreas Community of Practice; CNI, calcineurin inhibitor; KDIGO, Kidney Disease Improving Global Outcomes; KRAFT, Kidney Recipients with Allograft Failure - Transition of Care; PRA, panel reactive antibodies; SRTR, Scientific Registry of Transplant Recipients.

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1 | INTRODUCTION

Despite improvement of long-term kidney allograft survival, allograft failure with return to dialysis is common. It is estimated that 12% of patients on the current kidney transplant waiting list have had a prior failed transplant.¹ Returning to dialysis remains a major challenge for patients and providers. Patients face a higher risk of morbidity and mortality in addition to depression and social challenges during the transition period when immunosuppression is not well monitored.² The estimated mortality rate in patients with failed allograft is 16% in the first year following allograft failure with persistently increased risk compared to those starting dialysis without a prior failed transplant.^{3,4}

Two major causes of mortality after returning to dialysis are infections and cardiovascular disease.⁴ Continuing immunosuppressive medications exacerbates the risk of infections. In a study by Gregoor et al, patients with failed allograft who continued on low-dose immunosuppression had an increased risk of infections and mortality compared to patients in whom immunosuppressive medications were discontinued.⁵ Conversely, weaning off immunosuppressive medications carries a higher risk of sensitization to HLA molecules which may reduce opportunities for second kidney transplant, increase dialysis time between transplants, and necessitate more complex immunosuppressive treatment in the future due to positive crossmatch or rejection.⁶

Additionally, a failed allograft can cause a chronic inflammatory state that can lead to erythropoietin-resistant anemia, hypertension, chronic pain, hematuria, and even allograft rupture.⁷⁻¹⁰ Options for medical management in symptomatic rejection of the failed allograft are limited, and the number of cycles of pulse steroids that should be attempted prior to proceeding with a surgical intervention is not well defined.

Timely referral of patients with failed allograft for retransplantation is crucial, as the median waiting time for sensitized patients with a failed allograft is increased. Clinics for patients with a failing allograft have been established by some transplant centers to facilitate renal replacement counseling, transition of care, dialysis access placement, and the management of immunosuppression medication after starting dialysis.¹¹

The purpose of this study was to survey transplant providers and understand the current practice related to reduction of immunosuppression, perceived risks associated with continuing immunosuppression, and management of patients with a failing allograft including the transition of care to general nephrologists.

2 | METHODS

2.1 | Survey design

In 2017, the American Society of Transplantation Kidney Pancreas Community of Practice (AST-KPCOP) established a workgroup to study Kidney Recipients with Allograft Failure – Transition of Care (KRAFT) to understand the current data and practice patterns related to the management of recipients with a failing allograft. The workgroup developed the questions collaboratively and the survey was piloted with the KPCOP workgroup members. Where needed, the wording of the questions was adjusted for clarity. The final survey consists of 25 questions; 4 questions related to the approach for tapering immunosuppression, 10 related to perceived risks associated with tapering immunosuppression, 6 questions related to monitoring a patient with a failing allograft, 3 related to the management of rejection in a patient with a failed allograft, and three related to program description which included provider role, practice type, and transplant hospital name or United Network for Organ Sharing (UNOS) Center ID. Responses were anonymous, but UNOS ID/hospital name was used for tracking and to identify one representative response per program.

2.2 | Survey administration and participants

The survey was approved by the Weill Cornell Medicine Institutional Review Board (submission number 1805019273) on May 18, 2018 and approved by the Education Committee of AST for distribution. The survey was built into the REDCap[®] Survey tool and distributed via electronic link on the KPCOP Hub in December 2018 followed by individual email distribution to the transplant program medical directors on February 2019, March, 2019 and April 2019. We received 53 responses by the end of February, 35 by the end of March, and the remaining 30 thereafter. The survey was open until August 9, 2019. Each workgroup member actively encouraged their colleagues to complete the survey. We registered a total of 118 responses and 10 of those responses were from individuals who had already completed the survey once and therefore were not allowed to proceed to complete the survey.

Of the 108 responses, two were excluded due to incomplete responses to the survey. Of the 106 remaining responses, 12 responses were from providers outside the United States. Of the 94 U.S. responses, 14 represented multiple responses from the same centers resulting in a total of 80 unique responses, 77 adults and three children.

We included the first complete response from each of the 80 U.S. programs and included the 12 additional responses from outside of the United States. Of these 12 non-US responses, 3 were from Canada, 3 from the Middle East, and 6 did not identify their country.

2.3 | Participating programs

To compare the characteristics of the transplant programs that provided a response compared to those who did not, we identified 77 unique U.S. adult transplant programs that perform more than 10 transplants per year. Based on the Scientific Registry of Transplant Recipients (SRTR) and UNOS ID, we identified 119 U.S. adult transplant programs that did not respond to the survey and performed at least 10 transplants per year. We extracted the following program characteristics from the SRTR data for transplants occurring between July 1, 2017 and June 30, 2018: adult kidney transplant volume, age, gender, race, previous transplants, panel reactive antibodies (PRA), and cause of end-stage renal disease.

2.4 | Statistical analysis

Each kidney transplant center was represented only once in the analysis. For programs with multiple respondents, we selected the first complete response to represent the center, consistent with previous surveys.¹²⁻¹⁴ Responses to each survey question were described with percentages or frequencies, as appropriate, using the number of respondents to a given item as the denominator.

To compare the characteristics of kidney transplant centers that responded and to those that did not respond, Chi-square tests were conducted to compare percentages for categorical variables and *t* tests were used to compare frequencies or means for continuous variables. All tests were two-sided. Statistical significance was determined by an alpha level of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute Inc.).

3 | RESULTS

3.1 | Survey participants

There were 92 unique responses used to perform the analysis and generate all the figures excluding Table 1, which was generated using SRTR data. Majority of the respondents, 84%, were transplant nephrologist, 12% were transplant surgeons, and 4% were other providers, and 87% of the participants had an academic affiliation.

3.2 | Participating program characteristics

Of the 196 adult kidney transplant programs with more than 10 transplants, we received a response from 41% (*n* = 77), representing

approximately 49% of all adult kidney transplant volume recorded between July 1, 2017 and June 30, 2018. Compared to adult transplant programs that did not respond, participating centers had higher volume of living and deceased donor kidney transplants and female transplant patients (Table 1). There was no statistically significant difference in patient age, race, percentages of repeat transplants, sensitized patients, or cause of end-stage kidney disease between responding centers and non-responding centers.

3.3 | Approach for immunosuppression reduction

Among the 92 participating kidney transplant centers, 61% reported that there was a need to standardize reduction of immunosuppression in patients with a failing kidney allografts. Centers were asked about which immunosuppressive medications should be stopped first. The majority, 73% of providers, stated that antimetabolite should be stopped first. Only 12% of providers reported that they stopped calcineurin inhibitors (CNIs) first and 2% of providers reported stopping steroids first. An additional 13% reported that there is no unified protocol for which medication would be stopped first (Figure 1A).

When asked about their approach to stop all immunosuppression if the expected waiting time for a second kidney was more than 3 years, 30% respondents said they tapered medications over 2-3 months, while 20% continued low doses of immunosuppression medications until the patient received the next kidney transplant. Other respondents tapered according to urine output: 21% tapering if the urine output was less than 0.5 L and 4% tapering if the urine output is less than 1 L. About one fifth (21%) of responders said they had no unified protocol.

Clinicians were also asked about their immunosuppression management if there was no living donor and the waiting time for the next kidney transplant was more than 3 years; 47% tapered all immunosuppression medications within 2-6 months, 21% kept prednisone and tapered the rest, 10% kept low-dose CNI and tapered the rest, 5% kept CNI and prednisone and tapered the antimetabolite, 3% kept low doses of all immunosuppression medications, and 2% kept a low dose of antimetabolite and tapered the rest.

When asked about the management of immunosuppression in patients with failing allograft who had a possible living donor, 38% of respondents said they continued CNI and prednisone and stopped antimetabolite; 32% kept low doses of all immunosuppression medications; 21% kept all immunosuppression medications without reduction; and 10% reported no unified protocol (Figure 1B).

3.4 | Factors in the decision to taper off immunosuppression medications

When asked if continuing immunosuppression after starting dialysis is considered a risk factor of adverse events and mortality, 71%

TABLE 1 Characteristics of the adult kidney transplant programs responding to the survey

Program characteristics	Responded ^a (n = 77)	Did not respond ^a (n = 119)	p value
Percentage of adult transplant performed	49.2%	50.8%	
Kidney transplant, median (Q1, Q3)	118 (67, 183)	64 (33, 104)	<.0001
Living donor transplants, median (Q1, Q3)	31 (13, 53)	17 (7, 30)	.008
Deceased donor transplants, median (Q1, Q3)	84 (46, 119)	50 (24, 78)	<.0001
Recipient's age 65 and older, median percentage (Q1, Q3)	19% (16, 23)	20% (15, 27)	.29
Female, median percentage (Q1, Q3)	40% (36, 44)	39% (33, 44)	.04
Race/ethnicity, median percentage (Q1, Q3)			
Caucasian	44% (28, 66)	48% (30, 65)	.56
African American	22% (11, 37)	21% (11, 33)	.62
Hispanic	9% (4, 27)	10% (5, 25)	.68
prior transplant, median percentage (Q1, Q3)	13% (10, 17)	12% (9, 16)	.15
Peak PRA >80, median percentage (Q1, Q3)	14% (11, 21)	14% (10, 19)	.42
Cause of ESKD, median percentage, (Q1, Q3)			
Glomerular disease	25% (20, 29)	25% (19, 30)	.52
Diabetes mellitus	24% (21, 30)	27% (20, 33)	.12
Hypertension	22% (15, 29)	21% (15, 29)	.99

Abbreviations: ESKD, end-stage kidney disease; PRA, panel reactive antibodies; Q, quartile.

Bold values used to reflect statistical significance.

^aAdult kidney transplant programs with less than 10 transplants during the July 1, 2017 and June 30, 2018 interval were not included in this table.

agreed that continuing immunosuppression was a risk factor of adverse events, 14% thought continuing immunosuppression was a risk factor while 15% were not sure. We examined the essential factors that would influence the providers' decision toward tapering off immunosuppression. Each factor was graded on a semiquantitative scale: very important, intermediate important, and not very important (Figure 2).

More than 60% reported that the availability of a living donor is the most important factor in their decision to taper off immunosuppression, followed by risk of infection, risk of sensitization, frailty, and side effects of medication. The least important factors were reported to be urine volume (33%), followed by age of the patient (26%) and other comorbidities (20%).

3.5 | Medical and surgical management of the side effects of failed allograft

When asked about the initial approach for managing signs and symptoms of a failing allograft (multiple choice question), 85% responded that they treated with high-dose steroids while 35% of the respondents referred patients for an allograft nephrectomy as the initial management. Less than 6% made other immunosuppression adjustments and/or interventions including increasing the dose of CNi, increasing the dose of antimetabolite, or referring for coil embolization.

To be more specific, we asked about the timing of referral for allograft nephrectomy (multiple choice question). We found that

79% referred patients for nephrectomy if there were persistent signs and symptoms of rejection, 55% referred patients when patients first started to have symptoms, 36% referred patients if patients had anemia with limited response to erythrocyte-stimulating agents, and 8% reported that there was no unified protocol.

If a patient was scheduled for a nephrectomy, 33% of respondents continued prednisone for some time after the procedure, 33% stopped all medications immediately after the surgery, 30% stopped all medications within a week or two after the surgery, and 2% stopped before the surgery.

Coil embolization was not commonly performed. The majority (60%) of the respondents reported that less than 10% of their patients underwent embolization for failed allograft and 32% reported that embolization was not available at their center.

3.6 | Preparing for the next kidney transplant

In terms of listing for the next kidney transplant, 32% of respondents reported that 25–50% of the patients were listed for transplant before starting dialysis, 28% reported less than a quarter were preemptively listed, 22% reported that majority, 50% to 80%, were preemptively listed, while only 6% reported that more than 80% were listed before dialysis initiation. Twelve percent were unsure (Figure 3A).

There was variation in how and when PRAs were checked in patients with failed allografts. A majority, 76% of centers, responded

(A) What is your initial approach toward reduction of immunosuppression in a failed allograft?

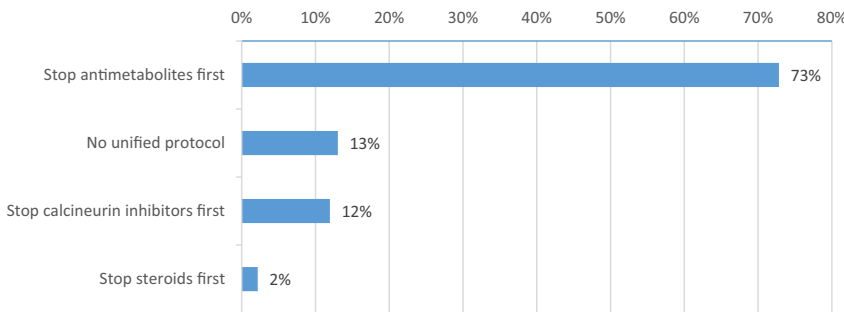
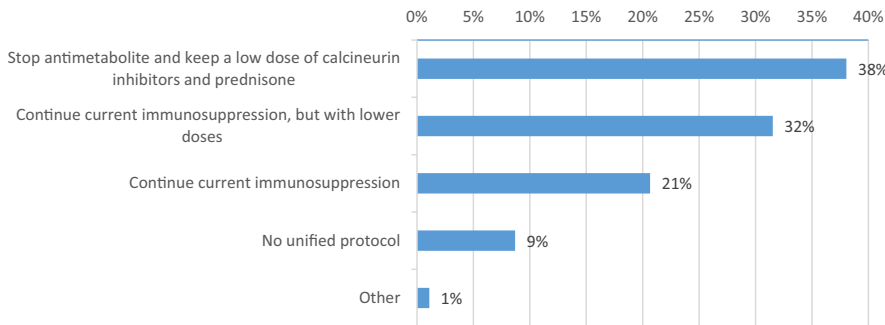


FIGURE 1 (A) Initial approach toward reduction of immunosuppression medications in patients with failed allografts. (B) Approach toward immunosuppression management in a failed allograft if living donor is available [Color figure can be viewed at wileyonlinelibrary.com]

(B) What is your approach toward immunosuppression management in a failed allograft if the patient has a possible living donor?



Perceptions of the essential components of factors in decision to taper off immunosuppression

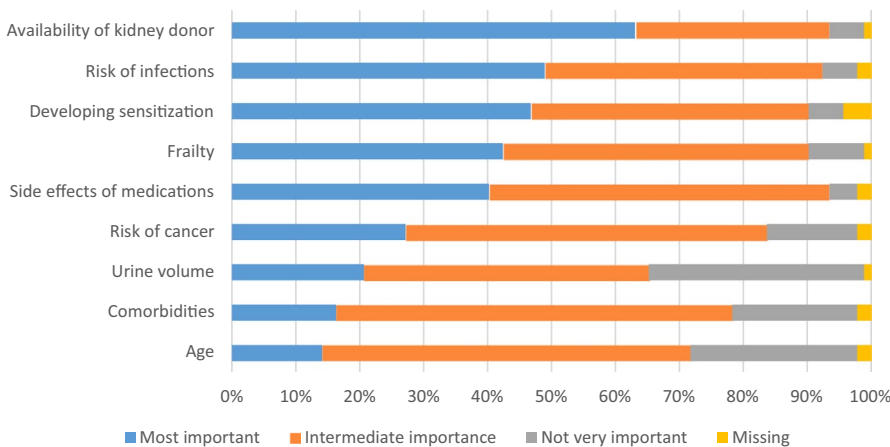


FIGURE 2 Perception of important factors in decision to taper immunosuppression [Color figure can be viewed at wileyonlinelibrary.com]

that they would check PRA only if the patient was listed for another kidney transplant, 15% would check PRA every 3 months, 2% every 6 months, and 2% every year. Four percent did not know how often PRAs were checked.

immunosuppression medications, 17% did only one visit, and 11% never saw their patients after they started dialysis (Figure 3B). As for communication with the general nephrologists to discuss transition of care, 49% reported always, 28% sometimes, 7% rarely, and 2% never, while 14% did not provide an answer (Figure 3C).

3.7 | Communications and transition of care

After starting dialysis, 36% of transplant nephrologists responded that they did not have a unified protocol for follow-up, 21% did follow-up visits every 3–6 months until patients were off

3.8 | Centers with multiple responses

There were 14 duplicates from 13 centers that were excluded from the analysis. Side by side comparison of the responses using one

response per center versus inclusion of all responses demonstrates that there was less than 5% difference for each of the responses.

4 | DISCUSSION

This contemporary survey of predominantly U.S. transplant practitioners characterizes current practice patterns for the management of immunosuppression and the care of the recipient with a failing kidney allograft. Our data come from transplant providers who care for 49% of adult transplant centers across the United States and demonstrates not only heterogeneity in the management of the failed kidney allograft recipients but also the need for more data to guide management. Our data demonstrate that (1) there is a need to standardize immunosuppressive management in a patient with a failed kidney allograft with the goal of improving patient outcomes, (2) the possibility of a living donor was the most important factor in the decision to wean or not wean off immunosuppressive therapies, (3) <30% of the programs relist majority of their patients with a failing kidney allograft prior to starting dialysis, and (4) <30% followed patients at regular intervals after kidney allograft failure.

Our survey responses suggest “a more consistent approach to” immunosuppression management and withdrawal in patients with a failed kidney allograft is needed. More than two thirds of the respondents reported that the first medication they stopped in a patient with a failed allograft was antimetabolite, whereas 12% stopped CNIs first. This represents a change from a 2012 survey, wherein 58% of respondents stopped antimetabolites first and 38% tapered CNI first.¹⁵ The current practice to maintain CNIs over antimetabolite therapy may have been influenced by recent studies suggesting that the need for transplant nephrectomy was decreased with continuation of CNI therapy. A retrospective single-center study published in 2014 examined the impact of weaning of immunosuppression and reported that 0 of 24 patients who were maintained on CNIs required transplant nephrectomy, compared to 41% of patients who were weaned off immunosuppression.⁶

At the present time, there is paucity of prospective data identifying the best approach for managing immunosuppression after a failed kidney transplant. Based on review of the literature, Pham and colleagues suggest continuing immunosuppression in those with a potential living donor or with some residual renal function and suggest discontinuing antimetabolite/mTOR inhibitors at start of dialysis and tapering the CNI over the next 4–6 weeks followed by slow tapering of prednisone.¹⁶ Similarly, the British Transplantation Society suggests (Grade 2C), despite low evidence, to taper immunosuppression after allograft failure but also suggests maintaining immunosuppression in those who may be re-transplanted within 1 year.¹⁷ Our survey demonstrates that stopping the antimetabolite first and then taper CNIs is common in contemporary practice. However, our survey also demonstrates that there is great heterogeneity in the approach with 46% of responding providers tapering off all immunosuppressive therapies over 2–6 months period if there is no opportunity of transplant in the near future. Consistent with

published general guidelines, the survey respondents felt having the possibility of a living donor for repeat transplant was the most important factor they considered when deciding to wean immunosuppression. However, despite this agreement, the approach to immunosuppression reduction varied significantly.

Patients with a failed allograft are at higher risk of mortality after starting dialysis compared to those who were never transplanted. Previous papers suggest that this increased mortality is primarily due to cardiac (36%) or infection complications (17%).^{3,18} Maintaining full immunosuppression has been associated with increased risk of hospitalization and infection within 6 months of starting dialysis.¹⁹ Risk of infection was the second most important factor in deciding to wean off immunosuppression in our survey, after availability of a living donor for repeat transplant. On the other hand, the presence of a failed allograft in ESKD patients who had complete withdrawal of immunosuppressive therapies is associated with higher CRP levels, lower albumin, and decreased muscle mass compared to those who were never transplanted,⁸ parameters associated with frailty. These data suggest that both ends of the spectrum, continuing immunosuppressive therapies and withdrawing all immunosuppressive therapies, are associated with negative consequences for ESKD patient with a failed allograft, highlighting the need for more robust data and strategies to improve the management of these patients.

Avoidance of sensitization may be possible through slower tapering of immunosuppression and is also an important consideration when deciding to continue immunosuppression.²⁰ This risk of sensitization is not fully appreciated in the early months post-graft failure. Augustine and colleagues demonstrated that 56% of individuals were highly sensitized at 6–24 months post-kidney graft failure.⁶ Among individuals whose immunosuppression was weaned, sensitization increased from 21% at time of graft failure to 68% at 6–24 months post-graft failure. In contrast, those who remained on immunosuppression had minimal risk of sensitization. Furthermore, transplant nephrectomy secondary to acute rejection was required in 41% of those who were weaned off immunosuppression, while 0% of those who were still on immunosuppression required graft nephrectomy.

Urine output, which is a useful gauge of residual renal function, was ranked as the least important factor by respondents in our survey when deciding about weaning immunosuppression. A previous study has suggested a survival benefit with continuing immunosuppression in patients returning to peritoneal dialysis with allograft loss, and some residual kidney function.²¹ In our survey, of the 25% who would use urine volume to guide weaning of immunosuppression, 21% of the respondents would taper immunosuppression if urine output was <0.5 L while only 4% would taper if urine output was <1 L. While there are little data to support tapering of immunosuppression based upon urine output, Jassel et al did find mortality benefit in patients who remained on immunosuppression. This survival benefit was higher at higher levels of preserved GFR.²¹

Timely referral for another kidney transplant is vitally important, as the time to re-transplantation may be increased due to sensitization status. Our survey showed that 60% of the respondents

(A)
What percentage of your patients with a failing allograft are re-listed for the next transplant before starting dialysis?

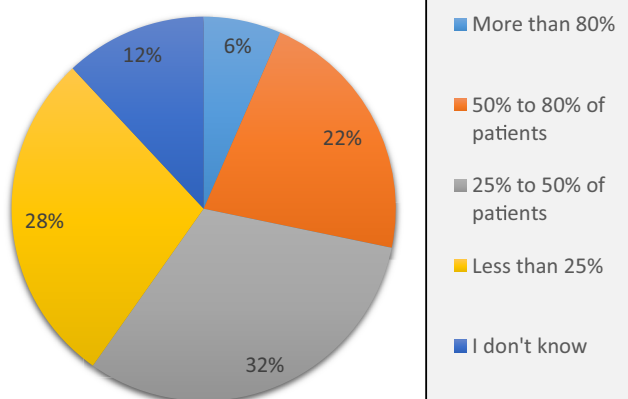
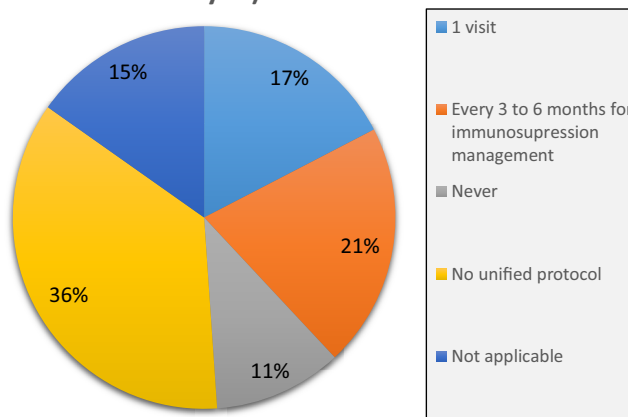
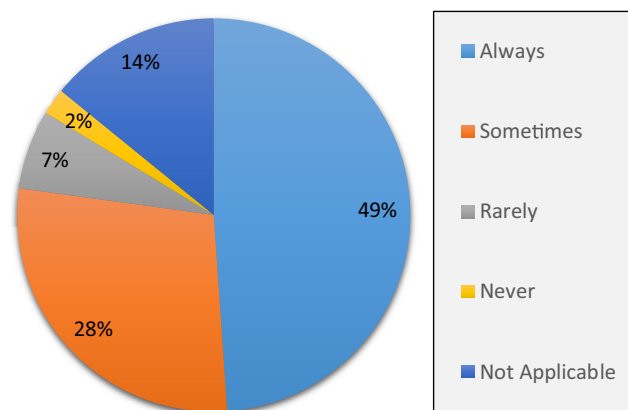


FIGURE 3 (A) Re-listing for the next kidney transplant before starting dialysis. (B) Frequency of follow-up with transplant nephrologists after starting dialysis. (C) Team discussion about transition of care for patients with a failed allograft [Color figure can be viewed at wileyonlinelibrary.com]

(B)
If you are a transplant nephrologist, how often do you see a patient with failed allograft (after starting dialysis)?



(C)
If you are a transplant nephrologist, how often do you or your team discuss the transition of care to general nephrology for patients with a failed allograft?



reported that less than half of their patients with a failed kidney allograft were listed preemptively for another kidney transplant. More efforts are needed to improve referral rates. Prompt referral for repeat transplant is consistent with a general recommendation of the 2020 Kidney Disease Improving Global Outcomes (KDIGO) transplant candidate guideline to refer potential kidney transplant candidates for evaluation at least 6–12 months before anticipated dialysis initiation to facilitate identification and evaluation of living donors and plan for possible preemptive transplantation.²²

Many general nephrologists may not be familiar with the management and goals of immunosuppression after allograft loss. Unfamiliarity with immunosuppression and lack of follow-up with transplant centers may lead to mismanagement and unfavorable outcomes. Our study showed that less than a quarter of transplant nephrologists perform frequent follow-up visits with their failed allograft patients who started dialysis. At the same time, around 75% of transplant nephrologists would communicate, always or sometimes with nephrologists in the community regarding care of their patients with allograft failure.

For medical and surgical management, the majority of the respondents (85%) use high-dose steroids for the management of initial symptoms, and 79% refer for nephrectomy if there are persistent signs or symptoms of rejection. As for the management of medications around the time of nephrectomy, there is a clear disagreement among respondents, and adequate data regarding the optimal approach are lacking. Despite previous publication suggestions that embolization carries less mortality and less complications than surgical allograft nephrectomy,^{23,24} 32% of respondents reported that embolization was not available, and 60% reported that embolization compromised <10% of surgical nephrectomies.

Our study has several limitations. First, respondents' answers to the survey questions might not be generalizable to the entire transplant community. We used the first response from each center and this may not reflect the overall practice patterns of a given transplant center. Second, not all transplant centers were represented in this survey; however, the centers in the United States that responded represent 49% of the total yearly kidney transplant volume in the United States. Furthermore, it should be noted that our study did not address the challenge associated with prescribing and monitoring maintenance immunosuppression following graft failure. Last, we did not examine the question of what percentage of patients would be eligible or be interested in a subsequent transplant.

In conclusion, this survey of kidney transplant centers highlights the heterogeneity in the practice of immunosuppression withdrawal in patients with failing allografts. Clear areas of opportunity exist for formal studies to address how best to adjust immunosuppression to mitigate high rates of morbidity and mortality during this transition time period. Additionally, we identified opportunities for improvement in referral rates for preemptive listing for repeat transplant and in communication regarding follow-up care of patients returning to dialysis. This study highlights the need for additional data to support our practices and to develop standardized protocols regarding the care of patients with failed allografts.

ACKNOWLEDGMENTS

This manuscript is a work product of the American Society of Transplantation's Kidney and Pancreas Community of Practice (KPCOP) Failing Allograft Workgroup. The authors thank survey respondents, including members of the AST Kidney-Pancreas COP. An abstract describing portions of this work was presented as an abstract at the 2019 American Society of Nephrology Kidney Week, Washington, DC.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

Data are available upon request and approval from authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Alhamad T, Lubetzky M, Lentine KL, et al. Kidney recipients with allograft failure, transition of kidney care (KRAFT): A survey of contemporary practices of transplant providers. *Am J Transplant*. 2021;21:3034–3042. <https://doi.org/10.1111/ajt.16523>