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Immunosuppression after renal allograft failure: a survey of US practices

Bayliss GP, Gohh RY, Morrissey PE, Rodrigue JR, Mandelbrot DA. Immunosuppression after renal allograft failure: a survey of US practices.

Abstract: Background: Little data exist to guide the management of immunosuppression after renal graft failure. More aggressive tapering of immunosuppressive medications may reduce the risk of infection, but may increase the risk of rejection and sensitization.

Methods: To document current practices in the US, we emailed a questionnaire to medical and surgical transplant directors as identified by the United Network for Organ Sharing (UNOS).

Results: Emails were sent to 221 programs, of which 93 (42.1%) responded. About 24.7% of respondents reported adjusting immunosuppression according to a standard protocol; 75.3% said practices are physician dependent. The majority said that 80 or 100% of patients are off all immunosuppression one yr after returning to dialysis. The most important factors cited in deciding whether to stop immunosuppression were plans to retransplant (40.2%) and signs and symptoms of rejection (37.0%). When asked which immunosuppressive medications are continued indefinitely, 21.5% responded prednisone and 71.0% said none. Respondents most commonly said they performed graft nephrectomy only if there are signs and symptoms of rejection (47.3%) or if signs and symptoms of rejection fail to respond to steroids (34.4%).

Conclusions: In the absence of good data to guide decisions on immunosuppression in patients with failed allografts, practices in the US vary greatly. More data are needed to determine which policies lead to the best outcomes.

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Key words: renal transplantation – immunosuppression – graft failure

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Decisions about how to taper immunosuppression in patients who have returned to dialysis after graft failure are complex. Continuing immunosuppression may increase the risk of infection and malignancy, as well as worsen metabolic parameters that increase cardiovascular risk. Stopping immunosuppression may increase the risk of sensitization, thus reducing the chance of retransplant or of rejection of a subsequent renal transplant. Drug cessation also may reduce urine output and increases the risk of acute rejection from a failed transplant, possibly necessitating allograft nephrectomy. Graft nephrectomy allows discontinuation of immunosuppression, but exposes the patient to further surgery and may increase the risk of sensitization.

Although there is little data on outcomes from different approaches to immunosuppression after

graft failure, these decisions have important implications for a large number of patients. The number of patients starting dialysis due to a failed kidney transplant was approximately 5600 in 2009, representing 4.6% of all patients starting and restarting dialysis (1). By 2010, 15.8% of patients on the waiting list for a kidney were waiting for a retransplant (2).

Transplant patients who return to dialysis have a poorer prognosis than patients with a functioning allograft: the unadjusted 10-yr survival in patients returning to dialysis after graft loss is below 40%, compared to more than 75% for patients with ongoing graft function (3). The majority of deaths after transplant failure are from cardiovascular causes or infection (4).

To our knowledge, none of the national databases, such as United Network for Organ Sharing

(UNOS) or United States Renal Data System (USRDS), have data on whether patients who were re-transplanted had a previous graft in place, or whether their immunosuppression had been continued or stopped.

Studies of nephrectomy after transplant have shown mixed results in terms of sensitization, subsequent allograft survival and patient survival over the years. Several showed an increase in panel reactive antibodies following allograft nephrectomy, but did not find an effect on subsequent re-transplantation (5–7). One retrospective study of USRDS data suggested that patients undergoing nephrectomy within 12 months of transplant have a higher risk of death, but lower risk of rejection of repeat transplant, compared with nephrectomy more than 12 months post-transplant (8). In a more recent large review of USRDS data, researchers found that receiving an allograft nephrectomy was associated with a 32% lower adjusted relative risk for death (9). Leaving the failed allograft in may lead to increased inflammation and resistance to erythropoietin (10). Still it is not clear whether this has an effect on subsequent retransplant (11).

The data on whether to continue immunosuppression are no more robust. One retrospective study of patients with graft failure who returned to dialysis found an increased risk of infection and mortality in the group who continued on low-dose immunosuppression compared with the group in which immunosuppression was discontinued. They further found that continuing immunosuppression did not lead to fewer rejections, but they did not measure antibody levels (12). In the absence of evidence from prospective controlled trials, clinicians have largely been guided by their own experience and expert opinion (13).

Here, we surveyed US transplant centers to document current practices regarding tapering of immunosuppression and nephrectomy after renal graft failure. This is an important first step to help programs develop their own protocols by allowing them to see how others address the same problem and provide them with ideas that they can consider adopting. It also provides information to guide future studies to address which practices lead to better outcomes.

Methods

A list of medical and surgical directors for 235 US kidney transplant centers was purchased from UNOS. Because UNOS did not provide email addresses, we searched the internet and called centers to obtain the current email addresses of the

medical and/or surgical director. We were unable to obtain email addresses for 14 programs. We designed an 18 question survey using the Research Electronic Data Capture (REDCap) survey manager. The survey was evaluated for content and clarity by colleagues with expertise in nephrology, transplant surgery and psychometric research. After receiving institutional review board approval from the Beth Israel Deaconess Medical Center, we sent emails describing the study purpose along with a secured hyperlink to complete the online survey. The email was sent three times between March 27, 2012 and May 2, 2012. None of the emails were returned as undeliverable. We asked respondents to provide their UNOS program code so we could track whether multiple responses were received from a particular program. For the one program that had two respondents, we used the medical director's responses in the statistical analyses.

Survey responses were coded and downloaded into Statistical Package for the Social Sciences for analysis. Data are expressed as means and standard deviations or the percentage of centers with specific responses. Survey responses were examined by program patient volume (larger vs. smaller programs, determined a priori to the median program size), respondent specialty (nephrologist vs. surgeon), and type of center (private vs. university). Analyses included *t*-tests for continuous variables, the Fisher exact test for variables with two categories or a two-tailed chi-square test for variables with three or more categories.

Results

Respondent characteristics

The survey was sent to 221 different transplant programs and 93 (42.1%) responded; some respondents did not answer all questions, and in those cases, the *n* is <93. Table 1 shows the characteristics of the respondents. The majority of transplant programs were either university or university-affiliated medical centers, performing adult or adult and pediatric transplants. Respondents came from all 11 UNOS regions of the country.

The mean number of transplants performed in 2011, including combined organ kidney transplants, was 94.3 (*n* = 85, range 4–317), with a median of 75. The mean number of nephrectomies performed by respondents in 2011 was 4.95 (*n* = 81, range 0–20), with a median of 3. The mean ratio of nephrectomies to transplants, a rough measure of frequency of nephrectomy, was 6.1% (*n* = 81, range 0–22%).

Table 1. Characteristics of programs and respondents

What is your position within the transplant program? n = 86	Program director nephrologist % 53.5	Program director surgeon % 44.2	Other % 2.3
What types of kidney transplants are performed in your program? n = 86	Adult only % 43.0	Pediatric only % 7.0	Both adult and pediatric % 50.0
Which of the following best characterizes your transplant center? n = 86	University % 58.1	Private, university affiliated % 22.1	Not university affiliated % 19.8

Approach to immunosuppression

Most respondents said the decision to stop or continue immunosuppressants was physician dependent as opposed to protocol driven (75.3 vs. 24.7%, n = 93) and reported that adjustments in immunosuppression were made by the transplant center as opposed to the nephrologist prescribing dialysis (78.5 vs. 21.5%, n = 93). Almost all respondents said they tapered immunosuppression after patients returned to dialysis with a failed transplant (98.9% tapered immunosuppression vs. 1.1% who left patients on full immunosuppression, n = 92).

More than 95% of respondents said that their standard immunosuppression regimen included mycophenolate mofetil (MMF) and tacrolimus (Tacro). About 74.2% said their standard regimen included prednisone. Only 15.1% of respondents said their regimen included sirolimus, 8.6% included azathioprine (AZA), and 17.2% included cyclosporine (CSA) (Table 2). In tapering immunosuppressants, 57.6% of respondents first stop antimetabolites (MMF or AZA) and then stop calcineurin inhibitors (Tacro or CSA). But 38% said they initiated the taper with calcineurin inhibitors and then removed antimetabolites. In response to which immunosuppressants are given indefinitely to patients after graft failure, 71% of programs said none, 21.5% said prednisone, and a small number of respondents leave patients on an antimetabolite or calcineurin inhibitor (Table 2). Three respondents reported leaving patients on both prednisone and an antimetabolite. In response to a separate but related question about

how many patients are off all immunosuppression one yr after returning to dialysis, 37.6% of respondents said all of their patients, and 31.2% of programs reported that 80% of their patients are off all immunosuppression one yr after returning to dialysis (Fig. 1). Only 5.4% of programs reported that none of their patients are off all immunosuppression. By adding all the products of percent respondents times percent patients off all immunosuppression ($0.2 \times 10.8 + 0.4 \times 9.7 + 0.6 \times 5.4 + 0.8 \times 31.2 + 1.00 \times 37.6$), we calculated that 71.8% of patients are reported as being entirely off immunosuppression at one yr after starting dialysis. This is almost identical to the 71% reporting “none” to the separate question about “which immunosuppressive medications are continued indefinitely after graft failure,” thus providing an internal control.

We also asked about factors programs considered important when deciding to continue vs. stop immunosuppression after graft failure. In order of most to least frequently cited, they included ongoing signs and symptoms of rejection, plans to

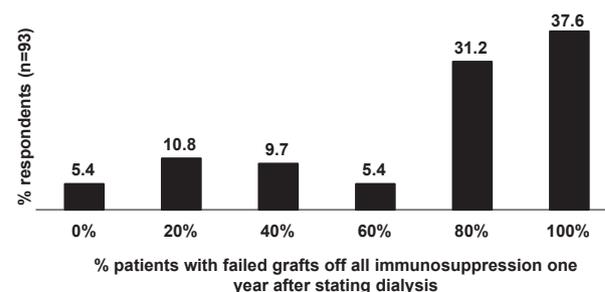


Fig. 1. Approximately what percentage of your centers' patients with failed grafts is off all immunosuppression one yr after starting on dialysis?

Table 2. Immunosuppression regimens

	MMF/AZA %	Tacro/CSA %	Sirolimus %	Prednisone %	None %
What drugs do you use in your standard immunosuppression regimen? n = 93	95.7/8.6	95.7/17.2	15.1	74.2	NA
If a patient's transplant fails, which drug do you wean off first? n = 92	57.6	38.0	0.0	4.3	0
Which drug do you usually wean next? n = 93	35.5	55.9	2.2	6.5	0
Which drugs do you leave patients on indefinitely after graft failure and return to dialysis? n = 93 ^a	5.4	5.4	0.0	21.5	71.0

AZA, azathioprine; CSA, cyclosporine; MMF, mycophenolate mofetil; Tacro, tacrolimus.

^aThree respondents said they leave patients on both prednisone and an antimetabolite, so the percentages add up to over 100%.

retransplant the patient, a history of infections in general or BK nephropathy in particular, residual urine output, a history of rejection, and the cost of medication (Table 3). Other factors, cited in respondent comments, included adrenal insufficiency from stopping prednisone, history of cancer, current degree of human leukocyte antigen sensitization, risk of developing donor specific antibodies, and surgical risk of nephrectomy. In response to a separate question about the single most important factor in deciding whether to continue or stop immunosuppression, programs most commonly cited plans to retransplant and ongoing signs and symptoms of rejection (Table 3).

Nephrectomies were most often performed for ongoing signs and symptoms of rejection, or for signs and symptoms of rejection that did not respond to steroids (Fig. 2). Few programs report performing nephrectomies on all failed grafts or on all grafts failing within a year of transplant. Other reasons, cited in the comments, for performing nephrectomies included infection related to the allograft, concern for post-transplant lymphoproliferative disorder, and ongoing inflammatory syndrome as manifested by weight loss or anemia.

Table 3. Factors considered in stopping vs. continuing immunosuppression

	% responding it is a factor (n = 93)	% responding it is the single most important factor (n = 92)
Ongoing signs and symptoms of rejection	76.3	37.0
Plans to retransplant	66.7	40.2
History of infections	46.2	5.4
History of BK nephropathy	46.2	2.2
Urine output	37.6	2.2
History of rejection	36.6	2.2
Cost of medication	34.4	2.2
Other	16.1	8.7

BK, virus.

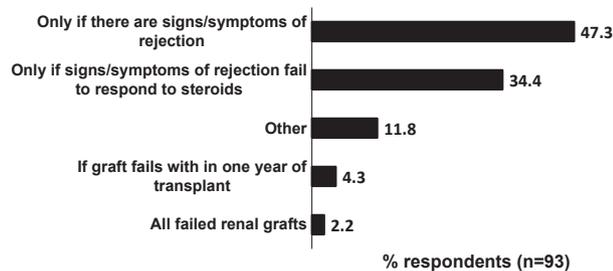


Fig. 2. When does your program perform a nephrectomy of a failed renal graft?

Predictors of responses

We sought associations between respondents' answers and their program characteristics, including number of transplants, number of nephrectomies, UNOS region, academic vs. private hospital, pediatric vs. adult transplant, and also whether the program director was a nephrologist or surgeon. Given the large number of possible associations examined, we required a $p < 0.01$ for statistical significance, and none of the associations reached this threshold.

Discussion

Physicians involved in the care of renal transplant recipients whose graft has failed often debate the question of how to adjust the immunosuppression. In this survey of US kidney transplant program directors, we find that many policies vary between programs. While decisions about tapering immunosuppression after graft failure are more commonly made by transplant center staff rather than nephrologists prescribing dialysis, most programs do not have standard protocols to guide the taper, so decisions are physician dependent (Table 1). However, we do find that over 70% of patients are off all immunosuppressants by one yr after graft failure. This large proportion of patients off immunosuppression was determined both from a question (Table 2) about which immunosuppressant are continued indefinitely after graft failure (answer = none), and a question about which proportion of patients are off all immunosuppression by one yr after graft failure (Fig. 1). Only 1% of programs report maintaining full immunosuppression after graft failure.

As is known from UNOS data, kidney transplant recipients most commonly receive triple immunosuppression, including a calcineurin inhibitor, an antimetabolite, and prednisone. We find that the most common approach to tapering is to first stop the antimetabolite, then the calcineurin inhibitor, and then prednisone, although various other approaches are sometimes used (Table 2). We are not aware of any data supporting any particular order of tapering over others, but suspect that this order has become common because of results of many trials performed over the past 20 yr in which just one of the three immunosuppressants was withdrawn (14). These trials generally found that rejection was most common with stopping steroids and least common with stopping antimetabolites (15).

A number of factors are considered by physicians in deciding whether or not to taper

immunosuppressive medications (Table 3), but two factors were by far the most commonly cited as the single most important factor. “Plans to re-transplant” is probably the most commonly cited because of concerns that stopping immunosuppression will lead to sensitization, thus increasing the chance of future positive cross-match and increasing the chance of rejection of subsequent transplants. “Signs and symptoms of rejection” would of course preclude discontinuation of immunosuppression at that time. “History of infections” was not commonly cited as the single most important factor in deciding whether to stop immunosuppression, but it was cited as a factor by 46.2% of respondents (Table 3). Presumably, the high number of programs that entirely stop immunosuppression is strongly weighing the potential risk of future infections, malignancies, and cardiovascular disease, as some of the respondents described in their comments; 37.6% of programs consider urine output in deciding whether to continue or stop a patient’s immunosuppression, presumably because continued urine output has been shown to provide a survival benefit in dialysis patients (16, 17). However, only 2.2% consider urine output as the single most important reason for continuing immunosuppression.

Graft nephrectomy is performed relatively rarely, with a reported mean of five nephrectomies per year. The most common reason to perform nephrectomy is “signs and symptoms of rejection,” while somewhat fewer programs cite “signs and symptoms of rejection that fail to respond to steroids” (Fig. 2). Patients undergoing nephrectomy would presumably be included among those off all immunosuppression, as immunosuppression is not required in the absence of a graft. It appears that most programs try to minimize or eliminate immunosuppression as much as possible, while keeping the rate of nephrectomies relatively low.

The validity of any questionnaire such as ours has several potential limitations. First, we have no way of confirming how accurately reported practices reflect actual events. However, we do not believe respondents would have any motivation to be deceptive about any of their practices regarding immunosuppression, especially as the answers were fully confidential. Second, the 42% of programs that responded may not accurately reflect all programs in the country. The mean program size of 94.3 kidney transplants in 2011 is slightly larger than the mean of 74.9 transplants performed, which might bias responses. However, the responses in our study did not differ significantly by program type or size, suggesting that program

characteristics do not significantly affect responses. In addition, the 74% of programs using prednisone is roughly similar to the proportion reported in the Scientific Registry of Transplant patients (63%) (2), data, suggesting that at least with respect to standard immunosuppression protocols, the respondents are similar to programs across the country.

Future studies will be required to define the risks and benefits of different approaches to immunosuppression. In particular, rates of infection and sensitization from stopping vs. continuing immunosuppression can be readily measured in a retrospective fashion. Ultimately, a randomized controlled trial will be required to determine outcomes from these different approaches.

Authors’ contributions

George P. Bayliss: Designed the questionnaire, analyzed data, wrote the manuscript. Reginald Y. Gohh and Paul E. Morrissey: Reviewed the questionnaire for clarity and relevance and reviewed the final manuscript. James R. Rodrigue: Reviewed the questionnaire, conducted statistical analysis, reviewed the manuscript. Didier A. Mandelbrot: Designed the questionnaire, designed the web survey instrument, analyzed data, and edited the manuscript.

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