Transplant Nephrectomy Improves Survival following a Failed Renal Allograft

Juan Carlos Ayus,* Steven G. Achinger,[†] Shuko Lee,[‡] Mohamed H. Sayegh,[§] and Alan S. Go[‖¶]

*Department of Clinical Research, Renal Consultants of Houston, Houston, Texas; [†]Physicians Clinical Research, San Antonio, Texas; [‡]Veterans Administration Hospital, San Antonio, Texas; [§]Transplantation Research Center, Renal Division, Brigham and Women's Hospital and Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts; [‖]Division of Research, Kaiser Permanente of Northern California, Oakland, California; and [¶]Departments of Epidemiology, Biostatistics, and Medicine, University of California at San Francisco, San Francisco, California

ABSTRACT

There is a growing number of patients returning to dialysis after a failed kidney transplant, and there is increasing evidence of higher mortality among this population. Whether removal of the failed renal allograft affects survival while receiving long-term dialysis is not well understood. We identified all adults who received a kidney transplant and returned to long-term dialysis after renal allograft failure between January 1994 and December 2004 from the US Renal Data System. Among 10,951 transplant recipients who returned to long-term dialysis, 3451 (31.5%) received an allograft nephrectomy during follow-up. Overall, 34.6% of these patients died during follow-up. Receiving an allograft nephrectomy associated with a 32% lower adjusted relative risk for all-cause death (adjusted hazard ratio 0.68; 95% confidence interval 0.63 to 0.74) after adjustment for sociodemographic characteristics, comorbidity burden, donor characteristics, interim clinical conditions associated with receiving allograft nephrectomy, and propensity to receive an allograft nephrectomy. In conclusion, within a large, nationally representative sample of high-risk patients returning to long-term dialysis after failed kidney transplant, receipt of allograft nephrectomy independently associated with improved survival.

The prevalence and incidence of ESRD are projected to increase substantially in the United States during the next several decades.[1] Although kidney transplantation improves survival in patients with ESRD,[2,3] risk for death after renal allograft failure is an underappreciated problem. Crude death rates of US dialysis patients after renal allograft loss exceed that of patients on the kidney transplantation waiting list,[4,5] and high mortality rates after allograft loss have also been observed in Canadian registries.[6] Repeat transplantation is associated with improved survival among patients with failed renal allografts,[4] but only approximately 15% of these patients undergo repeat transplantation.[4] Thus, optimal treatment of the large majority of these patients

who do not receive repeat kidney transplantation is a challenging problem. Given that approximately 2000 patients annually enter dialysis in

the United States after allograft failure, there is a growing population of long-term dialysis patients at increased risk for death.

The presence of a failed allograft at dialysis initiation is associated with anemia and hypoalbuminemia—predictors of poor outcomes among dialysis patients.[7,8] It has been postulated that these abnormalities may be explained by inadequate predialysis care,[8,9] but they may also reflect chronic inflammation, which is a major risk factor for death among dialysis patients.[10] A chronic inflammatory syndrome characterized by hypoalbuminemia, elevated C-reactive protein, anemia, and elevated serum ferritin in association with retained renal allografts among dialysis patients can occur even in patients without symptomatic allograft rejection, and this inflammation can be ameliorated after allograft nephrectomy[11]; however, few data exist about whether allograft nephrectomy leads to improved survival in these patients, because there have been no randomized clinical trials and only one previous published observational study, which had several methodologic limitations.[12]

To address these issues, we examined the impact of failed allograft removal on risk for death in a large, representative cohort of patients returning to dialysis after failed kidney transplant. We hypothesized that removal of failed renal allografts would be associated with improved survival, even after adjustment for potential confounders and treatment selection bias.[13]

RESULTS

Patient Characteristics

Assembly of the analytic cohort is summarized in Figure 1. Among 10,951 patients who returned to dialysis after failed kidney transplant, 3451 (31.5%) received nephrectomy of the transplanted kidney during follow-up. In patients receiving allograft nephrectomy, median time between return to dialysis and nephrectomy was 1.66 yr (interquartile range 0.73 to 3.02 yr).

Compared with patients who did not receive nephrectomy, those who received nephrectomy were on average 4.6 yr younger and more likely to be black (Supplementary Table 1). Patients receiving a nephrectomy were less likely to be Hispanic; be male; use tobacco; and have previous myocardial infarction or other known coronary heart disease, heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, insulin use, chronic obstructive pulmonary disease, cancer, and inability to ambulate or transfer. Patients who received nephrectomy were more likely to have higher serum creatinine concentration and higher serum albumin. Only minor absolute differences were noted between those who did and did not receive nephrectomy with regard to donor cause of death, cold ischemia time, peak panel reactivity, HLA antigen mismatches, and pretransplantation dialysis status. Overall use of OKT3/thymoglobulin and steroids after transplantation was slightly

more common among patients who received nephrectomy. During follow-up, patients who received nephrectomy were much more likely than those who did not receive nephrectomy to have a hospitalization with a discharge diagnosis of fever, anemia, sepsis, urinary tract infection, or complication of the transplanted kidney (Supplementary Table 1).

Receipt of Allograft Nephrectomy and Death from Any Cause

Overall, the mean follow-up was 2.93 ± 2.26 yr, and 3785 patients of the cohort were identified as having died by the end of follow-up (1106 in nephrectomy group, 2679 in non-nephrectomy group) in December 2004. Only 124 patients met criteria for being lost to follow-up during the study period. The unadjusted rate of death was significantly lower with receipt of nephrectomy compared with no nephrectomy (Figure 2). In multivariable extended Cox regression analyses, after adjustment for the propensity score to receive nephrectomy and other potential confounders, receipt of allograft nephrectomy was associated with a 32% reduction (95% confidence interval [CI] 26 to 37%) in the relative rate of death compared with not receiving nephrectomy (Table 1). We conducted six additional sensitivity analyses including or excluding specific patient subgroups that may have influenced estimates of treatment effectiveness for allograft nephrectomy, but there were no clinically relevant differences in the favorable point estimates associated with receipt of nephrectomy (Table 1).

Repeat Transplantation and Perioperative Mortality Rates

Those receiving transplant nephrectomy were more than twice as likely to receive a second transplant during the follow-up period than those who did not undergo nephrectomy of the initial failed allograft (10.0 *versus* 4.1%; $P < 0.001$; Figure 3). Among the 3451 patients undergoing transplant nephrectomy during the follow-up period, the rate of death within 30 d of the transplant nephrectomy was only 1.5% (53 deaths).

DISCUSSION

With larger numbers of patients entering long-term dialysis after failed kidney transplant in the United States and worldwide, optimal management of the failed allograft is an increasingly important question. Within a nationally representative sample of patients with ESRD, we observed a high absolute mortality rate overall and that receipt of renal allograft nephrectomy was associated with a lower rate of death from any cause compared with retaining the renal allograft, even after adjustment for potential confounders and selection bias. Our findings were also consistent in various sensitivity analyses (Figure 2, Table 1).

Lack of consensus exists about the optimal management of the failed renal allograft. In the United States, the traditional approach has been to perform allograft nephrectomy only for
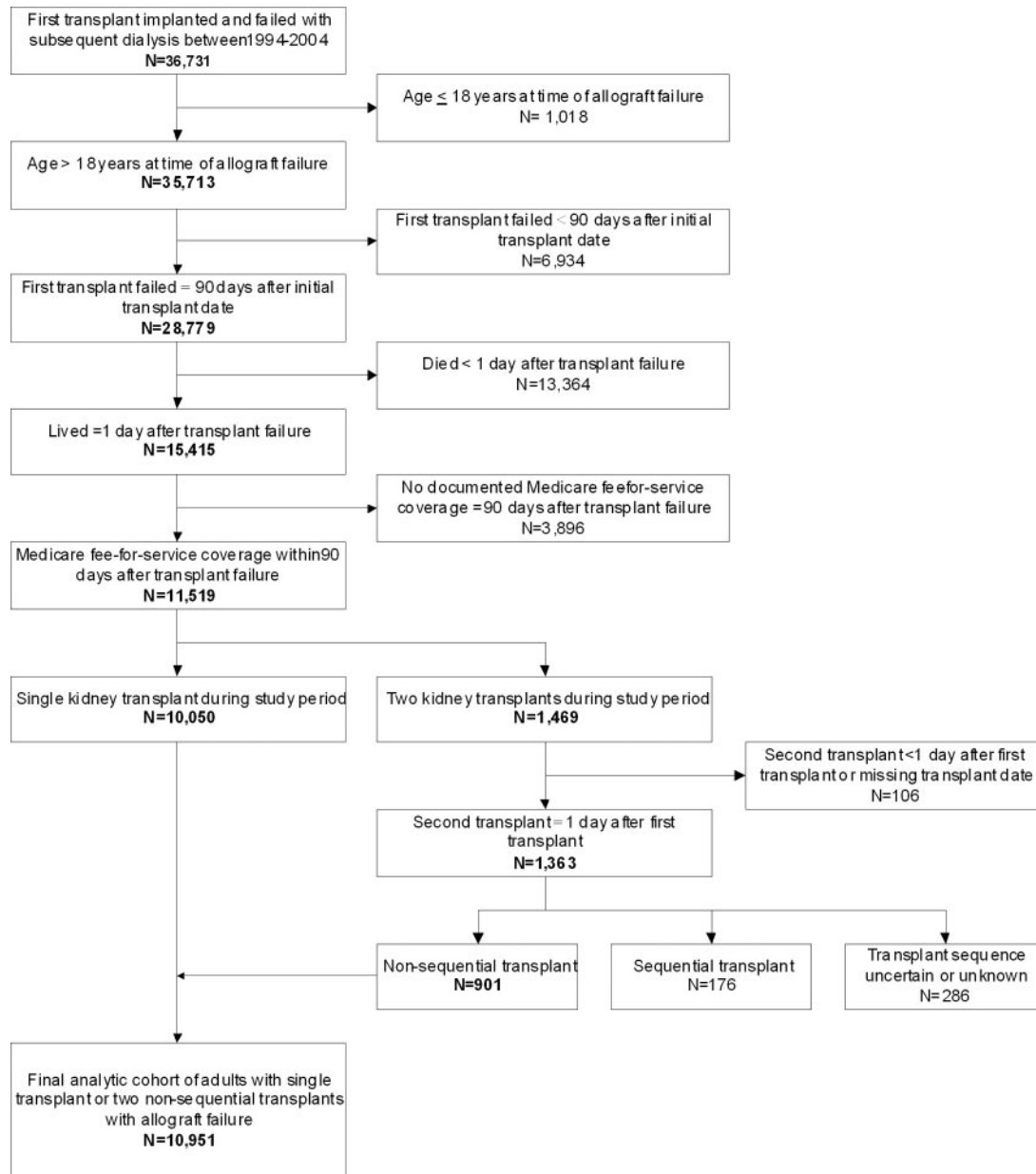
Figure 1. Assembly of analysis cohort of 10,951 patients who returned to maintenance dialysis after a failed kidney transplant between 1994 and 2004 in the USRDS is shown.

patients who have a clear clinical indication such as hyperacute allograft rejection, hematuria, serious infection, graft thrombosis, or graft intolerance syndrome.[14,15] The practice of retaining failed allografts *in situ* is also partially predicated on the historically high perioperative mortality rates that have been associated with allograft nephrectomy (reported range 6 to 37%)[13,16]; however, in this study, we report a large representative sample and report a much lower mortality rate (1.5%) in association with allograft nephrectomy. Previous authors have argued against allograft nephrectomy because of increased recipient immunoreactivity presumably as a result of increased exposure to foreign antigens during the nephrectomy operation.[17–19] We examined this outcome in our study cohort and

surprisingly found that rates of repeat transplantation were significantly higher in the nephrectomy group than in the non-nephrectomy group (Figure 3). The reason for this increased rate of repeat transplantation cannot be determined from our analysis, although it may reflect better health in the nephrectomy group through either lower comorbidity burden or improved health status after nephrectomy as a result of reduced chronic inflammation. Either way, this finding argues against withholding transplant nephrectomy because of a presumed reduced chance of repeat transplantation.

Our results of improved survival after allograft nephrectomy challenge the traditional practice of retaining renal allografts after transplant failure. Our study extends beyond a recent analysis us-
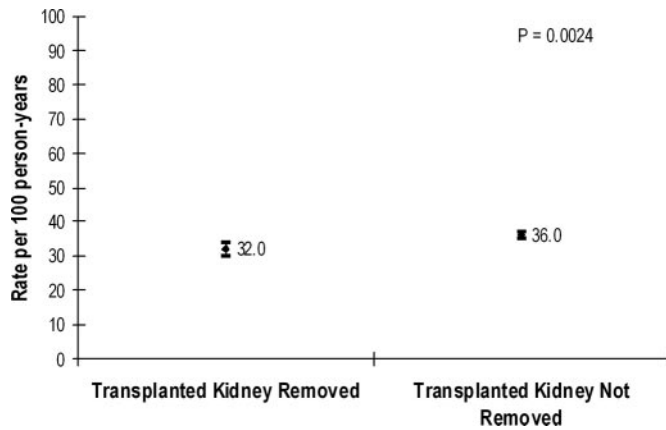
Figure 2. Unadjusted rate of death from any cause associated with or without receipt of renal allograft nephrectomy in 10,951 patients returning to maintenance dialysis after a failed kidney transplant between January 1, 1994, and December 31, 2004, is shown.

ing US Renal Data System (USRDS) data that focused on observed differential outcomes associated with allograft nephrectomy in patients with transplant failure categorized as early (<12 mo after transplantation) *versus* late (≥12 mo after transplantation)[12]; however, that study included a more limited set of potential confounders, did not account for clinical events during follow-up that could have affected the likelihood of receiving nephrectomy and associated outcomes, and had likely misclassification of a large number of deaths attributed to "transplant failures" (*i.e.*, occurring within <1 d after "transplant failure"). In contrast, our study observed a beneficial association of allograft nephrectomy on mortality regardless of the timing of transplant failure after addressing several of these issues.[12]

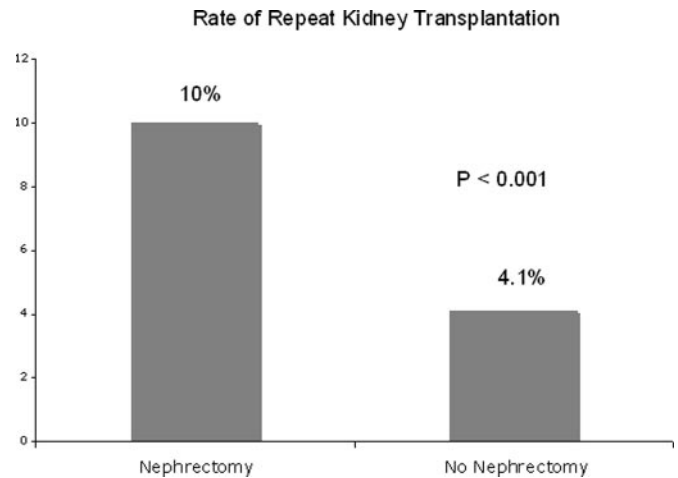The reasons for the high mortality rate seen in patients with

Figure 3. Unadjusted rate of repeat transplantation associated with or without receipt of previous renal allograft nephrectomy in 10,951 patients returning to maintenance dialysis after a failed kidney transplant between January 1, 1994, and December 31, 2004, is shown.

failed renal allografts are not known; however, we previously showed that the chronically rejected renal allograft is a nidus of immunoreactivity[11] that can perpetuate chronic inflammation—a major risk factor for cardiovascular mortality in patients receiving long-term dialysis. This situation is analogous to the presence of clotted arteriovenous grafts with subclinical infection in patients on hemodialysis, which can contribute to a chronic inflammatory state characterized by hypoalbuminemia, elevated C-reactive protein, and increased anemia[20,21]—all markers of poor outcomes in these patients.[10,22] Thus, we postulate that chronic inflammation may be playing a role in the excess mortality in patients with a failed kidney transplant. An additional po-

Table 1. Multivariable association of receipt of allograft nephrectomy with death from any cause in patients who had a failed kidney transplant and returned to dialysis

Analysis	Adjusted HR (95% CI) for Death for Nephrectomy *versus* Non-nephrectomy
Main	
original cohort (n = 10,951)	0.68 (0.63 to 0.74)
original cohort with adjustment for transplant center (n = 10,951)	0.68 (0.63 to 0.74)
Sensitivity	
original cohort + patients whose transplants failed <90 d after initial transplant date (n = 13,702)	0.67 (0.63 to 0.71)
subset of original cohort who survived ≥30 d after transplant failure (n = 10,886)	0.69 (0.66 to 0.74)
original cohort + patients without documented Medicare fee-for-service coverage within 90 d after transplant failure (n = 14,352)	0.67 (0.63 to 0.72)
original cohort + patients with two transplants in which the transplant sequence was uncertain or unknown (n = 11,237)	0.68 (0.63 to 0.73)
subset of original cohort whose duration of transplant before failure was <12 mo (n = 1545)	0.76 (0.65 to 0.90)
subset of original cohort whose duration of transplant before failure was ≥12 mo (n = 9318)	0.65 (0.60 to 0.71)

Results are given for the overall cohort and six sensitivity analyses examining the potential influence of inclusion or exclusion of specific patient subgroups. All models were adjusted for quartile of propensity score, age, gender, race, lack of medical insurance, coronary disease, previous myocardial infarction, previous cardiac arrest, congestive heart failure, cerebrovascular disease, diabetes, diagnosed hypertension, chronic obstructive pulmonary disease, cancer, inability to ambulate, inability to transfer, obesity, serum creatinine, serum albumin, hemoglobin, donor age, donor race, anoxia, donor cause of death, cold ischemia time, year of transplantation, and interim hospitalizations for any of the following: Complication of anemia, abdominal pain, urinary obstruction, sepsis, urinary tract infection, malnutrition, or complication of transplanted kidney. HR, hazard ratio.

tential deleterious effect of retention of a failed renal allograft may be continued routine use of low-dosage immunosuppressive therapies after return to maintenance dialysis, because immunosuppressive drugs may delay the need for ultimate nephrectomy and contribute to an increased risk for cardiovascular and infectious complications.[11,13]

Our study was strengthened by use of the nationally representative USRDS population across the past decade, with systematic follow-up for death and collection of standardized data elements for all patients at the time of initiating or returning to dialysis. Thus, our results are highly generalizable to our target population of interest. We attempted to control for potential biases using several approaches to examine mortality associated with receipt of nephrectomy in those with failed kidney transplant. Furthermore, in our primary cohort analyses, we selected strict inclusion criteria to exclude patients in whom the allograft did not survive at least 3 mo, because they may have had classical indications for nephrectomy, such as hyperacute rejection and graft thrombosis, and to enhance uniform availability of relevant covariates and follow-up. Next, we applied a propensity score method that considered as candidate variables both baseline characteristics and interim clinical events to address residual treatment selection bias from measured confounders. Finally, we performed several sensitivity analyses to demonstrate the robustness of our findings. Despite this, as an observational study of clinical practice, our analysis remains susceptible to the effects of residual confounding and treatment selection bias. We did not have information on longitudinal use of pharmacologic and other therapies or updated comorbidity data included on the USRDS medical evidence form. Of note, there were many differences in the baseline characteristics in many important comorbidities between the nephrectomy and non-nephrectomy groups, and this may have had an impact on patient survival and the decision to perform transplant nephrectomy. This factor may have biased the study outcome, despite the steps taken to mitigate bias in our analysis. In summary, our results should be viewed in light of these methodologic limitations inherent to registry studies.

In conclusion, patients who underwent allograft nephrectomy after renal allograft failure had improved survival after adjustment for potential confounders and likelihood of receiving nephrectomy. This was coupled with very low perioperative mortality rates and higher crude rates of retransplantation in association with allograft nephrectomy. Our results raise questions about the current clinical paradigm and suggest that routine allograft nephrectomy in stable dialysis patients with a failed renal allograft should be evaluated against current management strategies in a randomized trial as a possible strategy for improving outcomes among this growing population of high-risk patients with ESRD.

CONCISE METHODS

Study Sample

Using data from the USRDS,[23] we assembled a cohort of patients who returned to long-term hemodialysis or peritoneal dialysis after failed

kidney transplant. We identified from USRDS files all patients who were older than 18 yr, underwent a single kidney transplant or two nonsequential kidney transplants, and returned to long-term dialysis after renal allograft failure between January 1, 1994, and December 31, 2004. We excluded patients whose renal allograft failed within 90 d after transplantation ($n = 6934$), patients who died within <1 d after renal allograft failure ($n = 13,364$), those who did not have Medicare fee-for-service insurance after the first 90 d after the return to dialysis ($n = 3896$), and those without confirmed sequential transplants ($n = 568$; Figure 1).

The study was approved by the University of Texas Health Science Center at San Antonio institutional review board. Waiver of informed content was obtained because of the nature of the study.

Receipt of Renal Allograft Nephrectomy

Receipt of nephrectomy for the transplanted kidney during follow-up was ascertained from USRDS files for Medicare claims for any acute hospitalizations with Current Procedural Terminology codes for allograft nephrectomy.[24]

Mortality

The primary outcome was death from any cause through December 31, 2004, which was identified from USRDS files. Patients were considered lost to follow-up when there was no evidence of dialysis billing claims received by the USRDS for 12 consecutive months in the absence of an identified death date.[25]

Covariates

Information from the USRDS 2728 Medical Evidence Form[24] completed closest to the start of dialysis was used to identify the following variables: Age, gender, race/ethnicity, primary modality of dialysis, insurance status, tobacco use, known ischemic heart disease, previous acute myocardial infarction, previous cardiac arrest, congestive heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, use of insulin, diagnosed hypertension, chronic obstructive pulmonary disease, malignancy, documented inability to transfer or ambulate, body mass index, serum creatinine, blood urea nitrogen, serum albumin, and hemoglobin.

We also ascertained selected variables related to their transplant from the USRDS United Network for Organ Sharing transplant registration forms. These included donor age, donor race, living *versus* cadaveric donor, transplant center, cause of donor death, cold ischemia time of the transplanted kidney, occurrence of delayed graft function, peak panel-reactivity antibody level, HLA donor–recipient mismatch, year of transplantation, receipt of pretransplantation dialysis, and immunosuppressive therapies used.

During follow-up, we also identified from Medicare claims any acute hospitalizations that included primary or secondary discharge *International Classification of Diseases, Ninth Edition* codes for the following clinical conditions that may be associated with receiving allograft nephrectomy: Fever (780.6), anemia (285.2, 285.21, 285.29, 285.9), hematuria (599.7), abdominal pain (789.0, 789.0x), urinary obstruction (593.89, 599.6, 599.60, 599.69), sepsis (785.52, 790.7, 995.9, 995.90, 995.91, 995.92), urinary tract infection (590.1x, 590.2,

590.3, 590.8x, 590.9, 599.0), cachexia or malnutrition (783.2, 783.7, 799.4), and complications of the transplanted kidney (996.81).

Statistical Analysis

Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). Continuous variables were compared between groups using t test or Wilcoxon rank test, and categorical variables were compared using χ^2 or Fisher exact test.

We examined the association between removal of the renal allograft and risk for death using several approaches. First, unadjusted rates (per 100 person-years) of death from any cause with associated 95% CIs were calculated for periods with or without allograft nephrectomy. Next, to address possible treatment selection bias, we constructed a propensity score[26] for the likelihood of receiving allograft nephrectomy during follow-up using logistic regression (c statistic = 0.76) and included as covariates variables known to be associated with a clinical indication for nephrectomy and any other characteristics that differed between the two groups. We next performed multivariable extended Cox regression comparing the risk for death associated with receipt of allograft nephrectomy during follow-up that adjusted for quartile of propensity score, variables previously shown to be associated with mortality after failed transplant, and any differences in any other characteristics between those who did and did not die during follow-up. Finally, to test the robustness of our estimates, we adjusted for initial transplant center and conducted a series of separate sensitivity analyses that tested the impact of including the subgroup of patients whose initial transplants failed <90 d after transplantation, restricting to only patients who survived at least 30 d after initial transplant failure, including patients who did not have evidence of Medicare fee-for-service coverage after 90 d after allograft failure, including the subset of patients with two transplants in which the sequence was uncertain or unknown and in subgroups of patients with both early (<12 mo) and late (>12 mo) transplant failure.

DISCLOSURES
None.

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Table 1. Characteristics of patients who returned to dialysis after a failed kidney transplan between 1994 and 2004 and did or did not receive nephrectomy of the transplanted kidney during follow-up

Characteristic	Overall (n = 10,951)	Transplanted Kidney Removed (n = 3451)	Transplant Kidney not Removed (n = 7500)	P
Age (yr; mean ± SD)	45.7 ± 14.0	42.6 ± 13.3	47.2 ± 14.1	<0.001
Race/ethnicity (n [%])				<0.001
Hispanic	952 (8.7)	289 (8.4)	663 (8.8)	
non-Hispanic black	4405 (40.2)	1658 (48.0)	2747 (36.6)	
non-Hispanic white	5131 (46.9)	1364 (39.5)	3767 (50.2)	
other	463 (4.2)	140 (4.1)	323 (4.3)	
Male (n [%])	6567 (60.0)	2041 (59.1)	4526 (60.4)	0.23
Hemodialysis as primary dialysis modality (n [%])	7588 (88.1)	2143 (87.6)	5445 (88.4)	0.34
Lack of medical insurance (n [%])	675 (6.2)	232 (6.7)	443 (5.9)	0.10
Current tobacco use (n [%])	536 (4.9)	142 (4.1)	394 (5.3)	0.01
Comorbidities (n [%])				
known coronary heart disease	916 (8.4)	166 (4.8)	750 (10.0)	<0.001
previous myocardial infarction	311 (2.8)	49 (1.4)	262 (3.5)	<0.001
previous cardiac arrest	45 (0.4)	10 (0.3)	35 (0.5)	0.18
congestive heart failure	1355 (12.4)	279 (8.1)	1076 (14.4)	<0.001
cerebrovascular disease	320 (2.9)	75 (2.2)	245 (3.3)	0.002
peripheral vascular disease	639 (5.8)	111 (3.2)	528 (7.0)	<0.001
diabetes	2533 (23.1)	579 (16.8)	1954 (26.1)	<0.001
insulin requiring	1726 (15.8)	376 (10.9)	1350 (18.0)	<0.001
diagnosed hypertension	6919 (63.2)	1902 (55.1)	5017 (66.9)	<0.001
chronic obstructive pulmonary disease	199 (1.8)	30 (0.9)	169 (2.3)	<0.001
cancer	181 (1.7)	36 (1.0)	145 (1.9)	<0.001
inability to ambulate	125 (1.1)	16 (0.5)	109 (1.5)	<0.001
inability to transfer	36 (0.3)	2 (0.1)	34 (0.5)	<0.001
Body mass index (kg/m^2; mean ± SD)	26.4 ± 6.7	26.5 ± 6.8	26.4 ± 6.7	0.97
Serum creatinine (mg/dl; mean ± SD)[a]	9.0 ± 4.5	9.8 ± 4.7	8.7 ± 4.4	<0.001
Blood urea nitrogen (mg/dl; mean ± SD)[a]	88.5 ± 35.1	87.5 ± 34.8	88.9 ± 35.2	0.77
Serum albumin (g/dl; mean ± SD)[a]	3.3 ± 0.7	3.3 ± 0.7	3.2 ± 0.7	0.03
Hemoglobin (g/L; mean ± SD)[a]	9.6 ± 1.9	9.4 ± 1.9	9.6 ± 1.9	0.06

Characteristic	Overall (n = 10,951)	Transplanted Kidney Removed (n = 3451)	Transplant Kidney not Removed (n = 7500)	P
Transplant characteristics				
donor age (yr; n [%])				0.42
<25	2750 (25.1)	895 (25.9)	1855 (24.7)	
25 to 50	5206 (47.5)	1610 (46.7)	3596 (48.0)	
>50	2888 (26.4)	916 (26.5)	1972 (26.3)	
missing	107 (1.0)	30 (0.9)	77 (1.0)	
donor race (n [%])				0.10
white	8591 (78.5)	2666 (77.3)	5925 (79.0)	
black	1932 (17.6)	648 (18.8)	1284 (17.1)	
other/unknown	428 (3.9)	137 (4.0)	291 (3.9)	
donor cause of death/donor status (n [%])				<0.001
anoxia	748 (6.8)	237 (6.9)	511 (6.8)	
cerebrovascular/stroke	3729 (34.0)	1247 (36.1)	2482 (33.1)	
head trauma	3643 (33.3)	1239 (35.9)	2404 (32.0)	
CNS tumor	84 (0.8)	33 (1.0)	51 (0.7)	
other specify/unknown	293 (2.7)	86 (2.5)	207 (2.8)	
living donor	2454 (22.4)	609 (17.6)	1845 (24.6)	
cold ischemia time (h; n [%])				<0.001
0 to 12	3546 (32.4)	970 (28.1)	2576 (34.4)	
12 to 24	4420 (40.4)	1499 (43.4)	2921 (38.9)	
>24	2260 (20.6)	759 (22.0)	1501 (20.0)	
missing	725 (6.6)	223 (6.5)	502 (6.7)	
delayed graft function (n [%])[b]	2292 (22.8)	803 (25.3)	1489 (21.6)	<0.001
peak reactive antibody[c]	2 (0, 13)	3 (0, 22)	2 (0, 11)	<0.001
unknown (n [%])	485 (4.4)	164 (4.8)	321 (4.3)	
HLA antigen mismatches (median [range])	4 (3 to 5)	4 (3 to 5)	3 (2 to 5)	<0.001
unknown (n [%])	374 (3.4)	130 (3.8)	244 (3.3)	
year of transplantation (n [%])				0.50
1994	1845 (16.8)	578 (16.8)	1267 (16.9)	
1995	1716 (15.7)	549 (15.9)	1167 (15.6)	
1996	1611 (14.7)	533 (15.4)	1078 (14.4)	
1997	1380 (12.6)	439 (12.7)	941 (12.5)	

Characteristic	Overall (n = 10,951)	Transplanted Kidney Removed (n = 3451)	Transplant Kidney not Removed (n = 7500)	P
1998+	4399 (40.2)	1352 (39.2)	3047 (40.6)	
duration of transplant (yr; mean ± SD)	2.8 ± 2.4	2.6 ± 1.8	3.8 ± 2.4	<0.001
pretransplantation dialysis				<0.001
no dialysis	626 (5.9)	138 (4.1)	488 (6.7)	
hemodialysis	9868 (93.3)	3183 (95.4)	6685 (92.4)	
peritoneal dialysis	0 (0.0)	0 (0.0)	0 (0.0)	
unknown	79 (0.8)	17 (0.5)	62 (0.9)	
duration of dialysis (yr; mean ± SD)	2.8 ± 2.4	2.8 ± 2.4	2.5 ± 2.4	<0.001
immunosuppression used				
antirejection	1494 (13.9)	552 (16.3)	942 (12.8)	<0.001
cyclosporine	71 (0.7)	28 (0.8)	43 (0.6)	0.16
OKT3/thymoglobulin	575 (5.4)	217 (6.4)	358 (4.9)	0.001
ATG/ALG	117 (1.1)	44 (1.3)	73 (1.0)	0.16
steroids	998 (9.3)	381 (11.2)	617 (8.4)	<0.001
tacrolimus	67 (0.6)	26 (0.8)	41 (0.6)	0.20
rapamycin	7 (0.1)	5 (0.2)	2 (0.03)	0.04
azathioprine	37 (0.3)	13 (0.4)	24 (0.3)	0.64
mycophenolate mofetil	81 (0.8)	27 (0.8)	54 (0.7)	0.74
other	189 (1.80)	63 (1.90)	126 (1.70)	0.61
missing	213 (1.90)	56 (0.03)	157 (2.10)	
induction	9173 (85.4)	2935 (86.5)	6238 (85.0)	0.04
cyclosporine	2756 (25.7)	897 (26.4)	1859 (25.3)	0.22
OKT3/thymoglobulin	2706 (25.2)	920 (27.1)	1786 (24.3)	0.002
anti-lymphocyte globulin/anti-thymocyte globulin	839 (7.8)	265 (7.8)	574 (7.8)	0.98
steroids	8044 (74.9)	2607 (76.8)	5437 (74.0)	0.002
tacrolimus	772 (7.2)	235 (6.9)	537 (7.3)	0.47
rapamycin	226 (2.1)	84 (2.5)	142 (1.9)	0.07
azathioprine	2580 (24.0)	839 (24.7)	1741 (23.7)	0.26
mycophenolate mofetil	1922 (17.9)	636 (18.7)	1286 (17.5)	0.13
other	2740 (25.5)	905 (26.7)	1835 (25.0)	0.07
missing	213 (1.90)	56 (0.03)	157 (2.10)	
maintenance	10,559 (98.3)	3342 (98.4)	7217 (98.3)	0.56
cyclosporine	7464 (69.5)	2407 (70.9)	5057 (68.9)	0.03

Characteristic	Overall (*n* = 10,951)	Transplanted Kidney Removed (*n* = 3451)	Transplant Kidney not Removed (*n* = 7500)	*P*
OKT3/thymoglobulin	113 (1.1)	45 (1.3)	68 (0.9)	0.06
ATG/ALG	35 (0.3)	8 (0.2)	27 (0.4)	0.26
steroids	10,292 (95.9)	3261 (96.1)	7031 (95.8)	0.47
tacrolimus	3198 (29.8)	1041 (30.7)	2157 (29.4)	0.17
rapamycin	764 (7.1)	262 (7.7)	502 (6.8)	0.10
azathioprine	3551 (33.1)	1159 (34.1)	2392 (32.6)	0.11
mycophenolate mofetil	5925 (55.2)	1914 (56.4)	4011 (54.6)	0.09
other	351 (3.3)	104 (3.1)	247 (3.4)	0.42
missing	213 (1.90)	56 (0.03)	157 (2.10)	
Hospitalization during follow-up for or complicated by[d]				
fever	2131 (19.5)	1005 (29.1)	1126 (15.0)	<0.001
Anemia	7717 (70.5)	3003 (87.0)	4714 (62.9)	<0.001
Hematuria	0 (0.0)	0 (0.0)	0 (0.0)	1.00
abdominal pain	989 (9.0)	493 (14.3)	496 (6.6)	<0.001
urinary obstruction/obstructive nephropathy	538 (4.9)	242 (7.0)	296 (4.0)	<0.001
Sepsis	1511 (13.8)	588 (17.0)	923 (12.3)	<0.001
urinary tract infection	4435 (40.5)	1675 (48.5)	2760 (36.8)	<0.001
cachexia or malnutrition	302 (2.8)	125 (3.6)	177 (2.4)	<0.001
complication of transplanted kidney (transplant rejection)	8925 (81.5)	3448 (99.9)	5477 (73.0)	<0.001

CNS, central nervous system.

[a]To convert to SI units, multiply the value in conventional units by the following for serum creatinine (88.4, μmol/L), blood urea nitrogen (0.357, mmol/L), albumin (10, g/L), and hemoglobin (10.0, g/L; or 0.6206, mmol/L)

[b]Defined as need for dialysis before hospital discharge after transplantation.

[c]Expressed as % (95% CI).

[d]Coded during any hospitalization occurring after return to dialysis after failed kidney transplant.</.>

Allograft Nephrectomy after Transplant Failure: Should It Be Performed in All Patients Returning to Dialysis?

Heidi M. Schaefer and J. Harold Helderman

Department of Medicine, Division of Nephrology, Vanderbilt University School of Medicine, Nashville, Tennessee

Although considerable advances in the field of transplantation have improved short-term outcomes, little impact has been made on the long-term success of transplant allografts. As a result, a substantial proportion of patients will ultimately return to dialysis and the milieu of ESRD. Approximately 20% of all renal patients on the transplant waiting list in the United States have had a previously failed allograft.[1] This population has high mortality with 10-yr survival of <40% and with some suggesting that continued efforts to maintain the allograft through the use of low-dosage immunosuppression as contributing.[2] In this issue of *JASN*, Ayus *et al.*[3] report that patients who have failed allografts, return to dialysis, and undergo allograft nephrectomy have improved survival as compared with those in whom the allograft is retained. This is an interesting finding and one that will generate considerable discussion in the transplant community and further fuel the debate regarding the role of transplant nephrectomy in the treatment of this particular subset of patients.

We agree there may be beneficial effects of transplant nephrectomy, but one should not generalize the findings of Ayus *et al.* recommending removal of allografts to all patients without considering the limitations of their study. First and foremost, this is a retrospective interrogation of the US Renal Data System database with their results being subject to the methodologic limitations of database reviews. The population evaluated is limited to patients who had Medicare as the primary payer, and files for Medicare claims with CPT codes for allograft nephrectomy are used to determine who had their transplant removed. This may limit to some degree the applicability of their findings to other patient populations.

In examining the results of Ayus *et al.*, patients who underwent allograft nephrectomy were significantly younger, had fewer comorbid conditions, and were more likely to

receive treatment for rejection with antibody preparations and steroids. Comorbid conditions were determined from the US Renal Data System 2728 Medical Evidence Form completed closest to the start of dialysis. One could obviously argue that the reason for the decreased mortality in the group of patients undergoing nephrectomy was that they were a younger, healthier population as compared with those with retained transplants, who may have been considered too high risk to undergo a surgical procedure. To address this treatment selection bias, the authors performed regression analyses to adjust for characteristics that differed between the two groups and found that survival, when adjusted for all factors, associated independently with allograft nephrectomy. We agree with the authors as stated in their discussion, despite these statistical methods, their analysis remains susceptible to the effects of residual confounding and selection bias.

The authors hypothesize that excess mortality in the group with retained transplants may be due to an ongoing inflammatory state. In fact, in a previously published study, the authors showed prospectively that patients who had failed allografts and clinical symptoms and underwent nephrectomy had enhanced responsiveness to erythropoietin, resolution of hypoalbuminemia, and improvement in the biochemical markers of chronic inflammation.[4] Our group has shown similar findings.[5] In a retrospective review of 345 patients with failed kidney transplants, 79% of patients ultimately required nephrectomy primarily for clinical symptoms. Upon histologic examination of the resected transplant specimens, significant inflammation was noted in the vast majority.[5] One must realize that in both populations, patients who underwent nephrectomy had associated clinical symptoms, and, as such, the results may not be generalizable to asymptomatic patients with failed allografts.

Ayus *et al.*[3] also suggest that ongoing use of low-dosage immunosuppression contributes to excess mortality by increasing the risk for cardiovascular and infectious complications. Although hypothesis generating, no definitive conclusions can be made because the routine use of immunosuppression after transplant failure is not available in the United Network for Organ Sharing database. It would be interesting to examine the characteristics of patients who have ESRD and remain on long-term low-dosage immunosuppression as compared with those who are weaned completely off to determine whether those who are weaned off and remain asymptomatic have fewer comorbid complications and lower biomarkers of inflammation.

Ayus *et al.*[3] make a solid case for allograft nephrectomy after return to dialysis, but it is necessary to consider the reasons that this might not be appropriate for all patients. The obvious argument is that a surgical procedure with associated hazards may be too high risk for some patients. A study of 70 consecutive patients who underwent allograft nephrectomy showed that almost 50% required transfusion in the perioperative period and that 15% had major

surgical complications, with infection being the most frequent.[6]

Another argument is that removal of the graft leads to immunoreactivity and increased panel-reactive antibodies. In a similar retrospective review of the United Network for Organ Sharing database, Johnston et al.[7] noted significantly higher panel-reactive antibodies before repeat transplantation in patients who had undergone allograft nephrectomy. In patients with first graft survival ≥12 months, allograft nephrectomy was associated with an increased risk for repeat transplant failure, suggesting there may be some benefit for retransplantation by leaving the failed graft in place. Ayus et al.[3] note increased rates of repeat transplantation in patients who underwent allograft nephrectomy but do not comment on overall survival of those grafts.[5]

We agree that the finding noted by Ayus et al.[3] that allograft nephrectomy associates with improved survival is important and hypothesis generating. With a growing number of patients returning to dialysis after a failed transplant, it is vital to optimize their treatment and to consider the potential role of nephrectomy in this subset with high morbidity and mortality. Further studies should be carried out in an appropriately designed prospective manner.

DISCLOSURES

None.

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