Fever, Infection, and Rejection After Kidney Transplant Failure

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Background. Patients returning to dialysis therapy after renal transplant failure have high morbidity and retransplant rates. After observing frequent hospitalizations with fever after failure, it was hypothesized that maintaining immunosuppression for the failed allograft increases the risk of infection, while weaning immunosuppression can lead to symptomatic rejection mimicking infection.

Methods. One hundred eighty-six patients with failed kidney transplants were analyzed for rates of hospitalization with fever within 6 months of allograft failure. Patients were stratified by the presence of full immunosuppression versus minimal (low-dose prednisone) or no immunosuppression, before hospital admission. Subsequent rates of documented infection and nephrectomy, as well as patient survival, were ascertained.

Results. Hospitalization with fever within 6 months of allograft failure was common, occurring in 44% of patients overall. However, among febrile hospitalized patients who had been weaned off of immunosuppression before admission, only 38% had documented infection. In contrast, 88% of patients maintained on immunosuppression had documented infection ($P<0.001$). In both groups, dialysis catheter–related infections were the most common infection source. Allograft nephrectomy was performed in 81% of hospitalized patients with no infection, compared to 30% of patients with documented infection ($P<0.001$). Mortality risk was significantly higher in patients with concurrent pancreas transplants or who were hospitalized with documented infection.

Conclusions. Maintenance immunosuppression after kidney allograft failure was associated with a greater incidence of infection, while weaning of immunosuppression commonly resulted in symptomatic rejection with fever mimicking infection on presentation. Management of the failed allograft should include planning to avoid both infection and sensitizing events.

Keywords: Kidney transplantation, Immunosuppression, Transplant nephrectomy, Hospitalization, Failed allograft.

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While kidney transplantation has transformed the management of end-stage kidney disease, kidney allograft survival is limited, and there are growing numbers of patients with failed allografts returning to dialysis therapy (*1*). Unfortunately, mortality rates are higher in patients with failed allografts who are relisted for transplant, compared to patients with no transplant history (*2*). Hospitalization and sepsis after transplant failure occur frequently (*3*). Many patients are admitted to the hospital with fever, and it is unclear if such admissions occur resulting from infection on immunosuppression or, alternatively, inflammation related to the retained allograft. Febrile symptoms tend to resolve after transplant nephrectomy in patients with rejection, but late rejection and nephrectomy itself contribute to morbidity and cost (*4*). The authors of this study and others have previously shown that weaning of immunosuppression after failure led to higher rates of nephrectomy for cause and antibody sensitization (*5, 6*). In this study, the authors sought to explore the rates and outcomes related to hospitalizations with fever caused by infection or rejection early after allograft failure, stratified by the presence of full maintenance immunosuppression versus minimal (low-dose prednisone) or no immunosuppression. The first

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TABLE 1. Demographics and rates of hospitalization in patients who weaned vs. maintained immunosuppression

	Weaned (n=143)	Maintained (n=43)	*P* value
Age at failure	46±14	43±11	0.207
Female	66 (46%)	17 (40%)	0.447
African American	84 (59%)	9 (21%)	<0.001
Median graft survival (mo)	72 (range 1–306)	92 (range 1–276)	0.084
Living donor transplant	39 (27%)	6 (14%)	0.089
Pancreas transplant	7 (5%)	24 (56%)	<0.001
Hospitalization (6 mo)	93 (65%)	28 (65%)	0.992
Hospitalization with fever	65 (45%)	17 (40%)	0.496
Hospitalization with infection	25 (17%)	15 (35%)	0.015
Allograft nephrectomy	60 (42%)	11 (26)%	0.053

6 months following allograft failure was examined, as the patients still had significant contact with the transplant center during this time, allowing more accurate analysis, and future intervention based on our data could be directed by the transplant center more readily during this period.

RESULTS

Patient Demographics

Of 300 patients with failed kidney transplants, 186 were followed and managed locally after failure of the allograft. Demographic data for this subset are shown in Table 1, comparing patients who were weaned from immunosuppression early on versus those who were maintained on immunosuppression. Thirty-one patients also had a history of pancreas transplantation, and patients who maintained immunosuppression were more likely to have received a previous pancreas transplant (56% vs. 5%, *P*<0.001). There were no significant differences in patient age or gender, but more African American patients weaned immunosuppression. While there was a trend towards longer median survival in patients who were maintained on immunosuppression, this difference was not significant.

Hospitalization and Infection

Of the 186 patients, 121 (65%) were hospitalized within 6 months of allograft failure. Rates of hospitalization were identical between patients who were maintained on immunosuppression and patients who were weaned from immunosuppression before hospitalization (Table 1). Hospitalization with fever also occurred at a similar rate between patient groups (45% vs. 40%, *P*=ns). We examined the impact of maintaining or weaning immunosuppression on the rate of actual infection and found that an infectious source was identified much more commonly in patients maintained on immunosuppression. Of those hospitalized with fever, the rate of infection was just 38% in patients who had weaned compared to 88% in those maintained on immunosuppression before admission (*P*<0.001). Table 2 displays the characteristics of patients admitted with fever (n=82) stratified by the presence or absence of infection. Patients without infection were more likely to be African American and had a shorter median allograft survival time. There were fewer pancreas transplant recipients in this subgroup as well, and a large majority (95%) had weaned immunosuppression before admission.

A multivariable analysis of all 186 patients was conducted to examine the independent relationship of the above variables, along with patient age, with the risk of febrile hospitalization in the absence of infection. In this model, African American patients had an odds ratio of 2.23 (95% CI 0.99–5.03, *P*=0.053), while longer graft survival per month had an odds ratio of 0.99 (95% CI 0.98–0.99, *P*=0.014) for the event. In addition, weaning of immunosuppression conveyed a 6.97-fold risk (95% CI 1.41–34.33, *P*=0.017) for admission with fever in the absence of infection. Conversely, a similar analysis was conducted to determine associations for admission with actual infection. In this model, only the continuation of maintenance immunosuppression predicted the outcome, with an odds ratio of 3.26 (95% CI 1.19–8.89, *P*=0.021).

Sources of infection in patients who weaned versus maintained immunosuppression are shown in Tables 3A and 3B. Opportunistic infections with fungal and mycobacterial etiologies were documented in two patients from each group, but the most common source of infection in both groups was hemodialysis catheter–related line infection.

TABLE 2. Comparison of patients hospitalized with fever but no identified infection vs. those hospitalized with fever and documented infection

	No infection (n=42)	Infection (n=40)	*P* value
Age at failure	43±14	47±14	0.212
Female	20 (48%)	20 (50%)	0.832
African American	30 (71%)	20 (50%)	0.047
Median graft survival (mo)	53 (range 7–152)	94 (range 6–202)	0.006
Living donor transplant	8 (19%)	8 (20%)	0.915
Pancreas transplant	3 (7%)	9 (23%)	0.050
Weaned immunosuppression	40 (95%)	25 (63%)	<0.001
Allograft nephrectomy	34 (81%)	12 (30%)	<0.001

TABLE 3A. Infections in patients maintained on immunosuppression and hospitalized with fever

Infectious source	Cases
Venous catheter–related bloodstream infections (4 gram positive, 1 gram negative)	5
Urosepsis/pyelonephritis (2 gram negative, 1 candidal)	3
Pneumonia (1 suspected bacterial, 1 histoplasmosis)	2
Cellulitis (both suspected bacterial)	2
Clostridium difficile colitis	2
Peritonitis in a peritoneal dialysis patient (gram positive)	1

Forty-two patients admitted with fever had negative blood and urine cultures, with no source of infection detected (Table 2). Such patients were sometimes labeled as having a "fever of unknown origin" and most received antibiotics and underwent extensive evaluations for infection. The majority of these patients (95%) had weaned off immunosuppression, although almost half (20/42) remained on low-dose prednisone monotherapy (≤10 mg/day) at the time of admission. Nephrectomy was commonly performed and occurred within 1 year of allograft failure in 81% of these patients, compared to just 30% of patients hospitalized with infection ($P<0.001$). All patients without documented infection who underwent nephrectomy had resolution of fever following surgery, and 1-year post-allograft failure mortality rates were low overall, occurring in three patients (5%). In contrast, 1-year mortality was 25% for the 12 patients with documented infection who underwent nephrectomy, although this difference was not significant.

For the entire cohort, nephrectomy rates were 42% in patients who weaned from immunosuppression versus 23% in those who were maintained on immunosuppression ($P=0.026$). Pathologic reports from explanted kidneys were somewhat limited. In patients maintained on immunosuppression who subsequently underwent nephrectomy, acute rejection was described in explants from 4 of 11 patients (36%). Some of these patients had immunosuppression weaned after infection and subsequently required nephrectomy for symptomatic rejection. Alternatively, in patients who weaned immunosuppression after failure, acute rejection was described in explants from 40 of 60 (67%, $P=0.058$). Two of 11 (18%) explants from the immunosuppression maintenance group and 4 of 60 (7%) of the weaned group demonstrated histological signs of infection with pyelonephritis ($P=0.212$).

Variables associated with patient mortality within 1 year of failure are shown in Table 4. Patients who died within 1 year of failure were more likely to have had a pancreas transplant, hospitalization, hospitalization with fever, and hospitalization with documented infection. Patients weaned from full immunosuppression demonstrated better survival on Kaplan-Meier analysis (1-year survival of 85.7% for the full immunosuppression group and 92.1% for those weaned from immunosuppression), as did patients without concurrent pancreas transplants or documented infections (Fig. 1). On multivariate Cox analysis, survival differences were related to differences in infection (HR 2.64, 95% CI 1.44–4.82, $P=0.002$), concurrent pancreas transplant (HR 3.22, 95% CI 1.22–8.55, $P=0.018$), or age (HR 1.04, 95% CI 1.02–1.07, $P=0.001$). Weaning of immunosuppression (HR 0.91, 95% CI 0.38–2.15, $P=0.82$), failed living donor transplant (HR 1.91, 95% CI 0.85–4.30, $P=0.117$), and allograft nephrectomy (HR 1.43, 95% CI 0.71–2.91, $P=0.32$) were not independently predictive of mortality when added to the multivariable model, nor were other demographic factors.

DISCUSSION

Following recent studies describing high rates of sepsis and mortality in patients returning to dialysis (*2, 3*), this study sought to determine the etiology of hospitalization for fever after transplant failure. Overall hospitalization rates were similar between patients maintained on immunosuppression and those weaned from immunosuppression, but a high rate of infection was observed in patients on immunosuppression within the first 6 months of allograft failure. Our experience mirrored data from a recent registry analysis (*3*), which found that nearly one quarter of patients had hospitalization for sepsis at a median of just over 5 months post-failure. Risk factors for sepsis in that study included older age, obesity, diabetes, cardiovascular disease, and hemodialysis therapy. Mortality rates related to sepsis were significant, and death occurred in 21.3% of patients within 30 days of admission (*3*).

Data on immunosuppression usage was not available in the above registry study, and there is limited data on the risk of maintaining or weaning immunosuppression after transplant failure. One frequently cited study found a higher risk for infection in patients who maintained immunosuppression (*7*). One limitation of that analysis was that it compared patients at different time points after transplant failure. The group on immunosuppression was studied at a

TABLE 3B. Infection in patients weaned off immunosuppression and hospitalized with fever

Infectious source	Cases
Venous catheter–related bloodstream infections (6 gram positive[a], 4 gram negative[a], 1 fungal)	11
Urosepsis/pyelonephritis (all gram negative)	4
Peritonitis in peritoneal dialysis patients (1 gram positive, 2 gram negative, 1 mycobacterial)	4
Pneumonia (both suspected bacterial)	2
Clostridium difficile colitis	2
Cellulitis (suspected bacterial)	1
Groin abscess (polymicrobial)	1

[a] *One case each complicated by endocarditis.*

TABLE 4. Demographics and rates of hospitalization in patients who survived vs. died within 12 months of allograft failure

	Survived (n=170)	Died (n=16)	*P* value
Age at failure	46±14	46±14	0.823
Female	75 (44%)	8 (50%)	0.653
African American	86 (51%)	8 (50%)	0.964
Median graft survival (mo)	82 (range 1–306)	78 (range 27–133)	0.680
Living donor transplant	41 (24%)	4 (25%)	0.895
Pancreas transplant	23 (14%)	8 (50%)	<0.001
Weaned immunosuppression	132 (78%)	11 (69%)	0.422
Hospitalization (6 mo)	106 (62%)	15 (94%)	0.012
Hospitalization with fever	70 (41%)	12 (75%)	0.009
Hospitalization with infection	30 (18%)	10 (63%)	<0.001
Allograft nephrectomy	65 (38%)	6 (38%)	0.954

median of 147 days from transplant failure, compared to 590 days after failure in the group off immunosuppression. The risk of morbidity and mortality is higher in the early period after transplant failure (*8, 9*), and it is not surprising that there were more infections in the cohort on immunosuppression (*7*). Dialysis catheters likely contribute to the risk of infection early after allograft failure, and may explain the independent association with sepsis and hemodialysis in registry data (*3*). In the experience herein, opportunistic infections were seen in a subset of patients, but catheter-related line sepsis was the most common etiology of infection for all patients, regardless of immunosuppressive status. Lack of timely placement of permanent hemodialysis access may reflect the challenges and shortfalls observed in preparing transplant patients for ESRD (*10*).

It was alternatively observed that there is a high rate of hospitalization for fever in the absence of infection in patients who were weaned from immunosuppression, as the majority of such patients had no identified source of infection during the hospital stay. Many of these patients were treated with antibiotics, and some had extensive evaluations for occult infection. Ultimately, the majority of these patients underwent transplant nephrectomy, either because of symptoms attributable to the allograft or because no other source of fever could be identified, and nephrectomy led to resolution of fever in all patients. A recent study examined associations with transplant nephrectomy after allograft failure (*11*). In that study, patients with nephrectomy were younger with fewer comorbid conditions, yet had higher rates of hospitalization for fever and sepsis. Collectively, these data suggest that some patients admitted to the hospital with fever after allograft failure may be erroneously labeled with infection or sepsis, while actually exhibiting symptoms of allograft rejection. Lack of early recognition of such rejection may lead to prolonged and costly hospital admissions with associated patient morbidity.

The risk of infection on immunosuppression therefore appears to be offset somewhat by the risk of symptomatic rejection and sensitization after weaning immunosuppression. In a similar cohort of patients, weaning of immunosuppression was previously identified as an independent risk factor for late sensitization, after controlling for living donor retransplantation, allograft nephrectomy, and other factors (*6*), suggesting that both maintaining and weaning immunosuppression have significant risks. The optimal strategy for immunosuppression management after allograft failure remains to be elucidated—especially for the patient who might desire repeat transplantation and do not have a clinical reason to maintain immunosuppression (i.e., a functioning pancreas transplant). One strategy yet to be studied is the undertaking of early allograft nephrectomy in the presence of immunosuppression. Such a strategy may reduce the risk of infection related to immunosuppression maintenance and the risk of sensitization related to immunosuppression withdrawal. There has been a historical association of transplant nephrectomy with possible sensitization (*12*), but almost all studies examining this issue have been performed on patients who underwent transplant nephrectomy for cause—after a potential sensitizing event. Sensitization is probably less likely if symptoms have not developed.

This analysis has limitations. It has a smaller number of patients relative to recent registry analyses, although it provides details on weaning of immunosuppression unavailable in registry data. Secondly, a fairly strict standard was utilized for the definition of infection in efforts to minimize subjectivity and, as objective in-patient diagnosis of viral syndromes is difficult and often a diagnosis of exclusion, some of these patients could certainly have missed nonbacterial infections. In addition, the analysis is retrospective and has the limitations inherent with such a study, including lack of standardized data points, limited data on rational for post-allograft failure immunosuppression management, and other such issues that may confound analysis. Prospective monitoring of patients with allograft failure would strengthen these data. Registries of patients with failed allografts, as well as trials that randomize patients to weaning or maintaining immunosuppression or to elective early nephrectomy, would add greatly to the understanding of optimal patient management after allograft failure.

In conclusion, it was found that maintaining patients on immunosuppression other than low-dose prednisone after failure of the kidney allograft led to a greater rate of hospitalization with infection, which was associated with a higher early mortality rate. In contrast, weaning patients from immunosuppression led to a high rate of febrile hospitalization unrelated to documented infection, and to a high rate of nephrectomy for cause—suggesting a risk of sensitization. The lower rate of nephrectomy in patients on

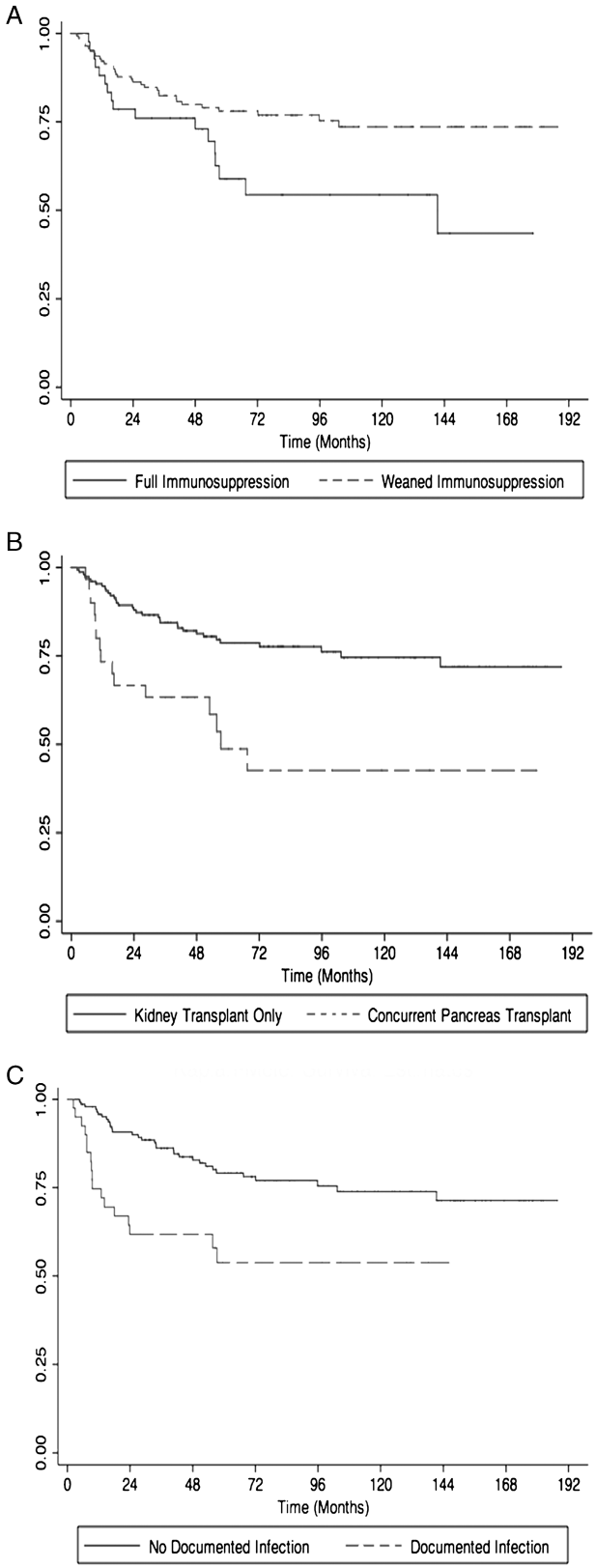

FIGURE 1. Kaplan-Meier survival curves by immunosuppression status in the entire cohort (A) (P=0.021), concurrent pancreas transplant in the entire cohort (P=0.0004) (B), and hospitalization with documented infection in the entire cohort (P=0.001) (C).

maintenance immunosuppression suggests that the symptoms prompting nephrectomy in most patients resulted from weaning immunosuppression, leading to symptomatic rejection as well as alloantibody sensitization (*6*). As both maintaining and weaning immunosuppression in the presence of the failed allograft can result in major complications, alternative approaches to management of the failed allograft should be considered. These data argue that transplant centers should take a more active role in the management of the failed allograft, with recognition of the high risk of both infectious and noninfectious etiologies leading to hospitalization with fever after failure.

MATERIALS AND METHODS

Patients and Data

This study was reviewed and approved by the Institutional Review Board at University Hospitals Case Medical Center (UHCMC). A retrospective analysis was conducted on the outcomes of patients at UHCMC with kidney transplant failure occurring between January 1998 and January 2011. Patients who died within 30 days of kidney transplant failure were excluded from analysis. Demographic data were collected including age at the time of allograft failure, gender, race, previous donor status (living vs. deceased), pancreas transplantation, and duration of previous allograft survival. Data were obtained for all patients out to 1 year.

Records of first hospitalization in the 6 months after kidney allograft failure were reviewed for patients with active local follow-up at UHCMC after transplant failure. Hospitalizations occurring at the time of allograft failure were excluded. In addition, patients who were retransplanted within 6 months of failure were excluded from the analysis of hospitalization. Patients hospitalized with fever (≥37.8°C) on presentation or within 24 hr of admission were identified, and medical records including laboratory and diagnostic tests were reviewed. Based on these records, febrile illnesses were categorized as being associated with or without documented infection (culture positivity, pneumonia on chest radiograph or bronchoscopy, or hard signs on admitting physical examination such as cellulitis or abscess). Cultures drawn before antibiotics were given at outside dialysis units before hospital admission were routinely captured by the admitted services and were included in the analysis.

Data on weaning of immunosuppression in the first 6 months after kidney failure also was recorded. All patients who weaned immunosuppression had done so by 120 days after failure. Typically, calcineurin inhibitors and antimetabolites were stopped abruptly and steroids were tapered. Because we noticed a number of late rejection episodes in patients on low-dose prednisone monotherapy, we defined weaning as the elimination of all immunosuppressive therapy with the exception of prednisone at a dose ≤10 mg/day. Thus, patients on any combination of calcineurin inhibitor therapy, mTOR inhibitor therapy, mycophenolate, or azathioprine were considered to have maintained immunosuppression. Transplant nephrectomy within 12 months of transplant failure was recorded as well. At the time, there was not an established institutional protocol for nephrectomy after allograft failure, and nephrectomy was typically undertaken only in the face of symptomatic rejection, infection of the allograft, or symptomatic cause. An exception to this practice was the occasional nephrectomy performed at the time of retransplantation to provide adequate space for a new kidney allograft. Such nephrectomies performed at the time of retransplantation were not included in the nephrectomy analysis. Finally, patient survival up to 12 months from the time of allograft failure was recorded.

Statistical Analyses

Values are shown as mean±SD, median, or percentage. Baseline demographic data between patient groups were analyzed using t test for continuous variables and Pearson chi-square test for dichotomous variables. Analyses of hospitalization for fever and infection were performed in a

similar manner. Nonparametric testing was performed in the analysis of allograft survival (Mann-Whitney *U* test). Logistic regression analyses were utilized to determine variables independently associated with febrile hospitalization with or without infection, and variables associated with patient mortality. Cox proportional hazard modeling was performed, and survival analysis utilized Kaplan-Meier survival function and log-rank testing. A two-sided *P* value of <0.05 was considered to indicate statistical significance. All analyses were performed using SPSS version 18 (SPSS, Chicago, IL) or Stata 12.1 (StataCorp, College Station, TX).

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