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Timing of Return to Dialysis in Patients with Failing Kidney Transplants

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ABSTRACT

In the last decade, the number of patients starting dialysis after a failed kidney transplant has increased substantially. These patients appear to be different from their transplant-naïve counterparts, and so may be the timing of dialysis therapy initiation. An increasing number of studies suggest that in transplant-naïve patients, later dialysis initiation is associated with better outcomes. Very few data are available on timing of dialysis reinitiation in failed transplant recipients, and they suggest that an earlier return to dialysis therapy tended to be associated with worse survival, especially among healthier and younger patients and women. Failed transplant patients may also have unique issues such as continuation of immunosuppression versus withdrawal or the need for remnant allograft nephrectomy with regard to dialysis reinitiation. These patients may have a different predialysis preparation work-up, worse blood pressure control, higher or lower serum phosphorus levels, lower serum bicarbonate concentration, and worse anemia management. The choice of dialysis modality may also represent an important question for these patients, even though there appears to be no difference in mortality between patients starting peritoneal versus hemodialysis. Finally, failed transplant patients returning to dialysis appear to have a higher mortality rate compared with transplant-naïve incident dialysis patients, especially in the first several months of dialysis therapy. In this review, we will summarize the available data related to the timing of dialysis initiation and outcomes in failed kidney transplant patients after returning to dialysis.

In the last decade, the number of patients starting dialysis after a failed kidney transplant has increased substantially. These patients provide a set of challenges to general nephrologists that differ from transplant-naïve patients, and which often require involvement of transplant nephrologists. In this review, we will summarize the available data related to the timing of dialysis initiation and outcomes in failed kidney transplant patients.

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Incidence of Failed Kidney Transplant Patients in Maintenance Dialysis

In recent decades, kidney graft loss has emerged as an important cause of end stage kidney disease requiring dialysis initiation in the United States (1,2). Figure 1 shows the proportion of failed kidney transplant patients among all incident dialysis patients in the past 22 years in the United States (1). Whereas the proportion of failed kidney transplant patients was stable in the last two decades (4–5% of all patients), the absolute number reinitiating dialysis treatment increased from 2463 in 1988 to 5588 in 2010 (1). In Canada and in Australia, 2–3% of all incident dialysis patients were failed kidney transplant patients (3,4). A similar trend may also exist in Europe, but the European Renal Association – European Dialysis and Transplant Association registry did not collect data on the number of

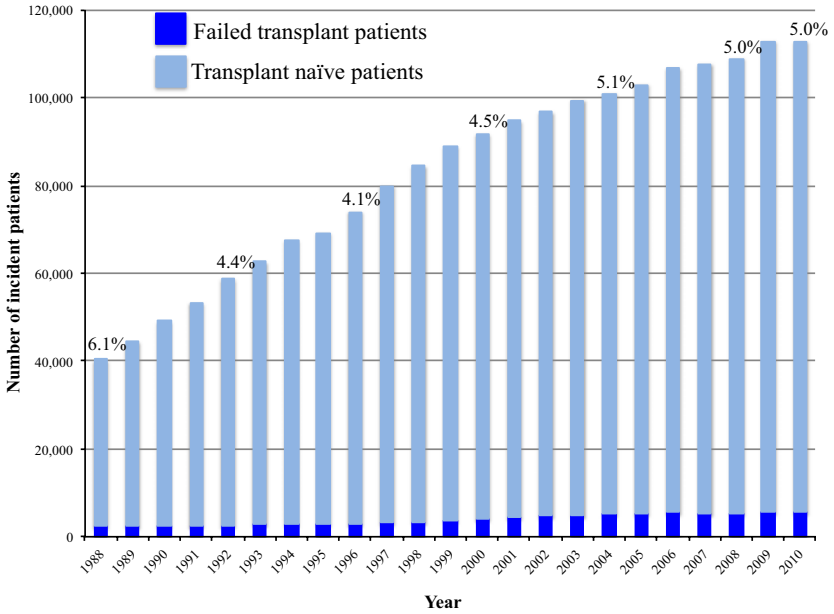

FIG 1. Proportion of failed kidney transplant patients in all incident dialysis patients in the last 22 years in United States (source USRDS).

patients who return to dialysis following a failed kidney transplant.

Studies Comparing Dialysis Reinitiation at High Versus Low eGFR in Patients with Failed Kidney Transplants

The authors recently published a more detailed review on the topic of initiation of dialysis in transplant-naïve and transplant failure patients (2). To the best of our knowledge, only a few studies from 15 to 20 years ago support dialysis initiation with high estimated glomerular filtration rate (eGFR) (5–11). Most of these early studies showed that initiation with a higher eGFR was associated with lower mortality, but these studies were small and did not adjust for potential confounders. Nevertheless, based on these results, the general practice in the 1980s, 1990s, and 2000s was initiation of dialysis at higher eGFR regardless of the patients' comorbidities. More recently, several observational studies have questioned the benefits of early dialysis initiation (12–17). A major limitation of these studies is that the characteristics of patients who initiated dialysis with high versus low eGFR differ significantly (2).

Data from randomized controlled trials examining the optimal timing for the initiation of dialysis were lacking until 2010, when the results of the *Initiating Dialysis Early and Late* (IDEAL) study were published (18,19). Patients were eligible for the IDEAL study if they had progressive chronic kidney disease (CKD) (including a failing kidney transplant) and a creatinine clearance (CCr) between 10 and 15 ml/min/1.73 m^2. The CCr was estimated via the Cockcroft–Gault equation and corrected for body surface area (20). Patients were randomly assigned to either commence dialysis with a CCr of 10.0–14.0 ml/min/1.73 m^2 (early-start group) or to continue to receive routine medical care and commence dialysis with a CCr of 5.0–7.0 ml/min/1.73 m^2 (late-start group) (19). During a median follow-up of 3.6 years, 37.6% (152 of 404 patients) of early starters and 36.6% (155 of 424 patients) of late starters died, resulting in a hazard ratio for early versus late dialysis initiation of 1.04 (95% CI: 0.83–1.30; $p = 0.75$) (18). The authors concluded that, with careful clinical management, dialysis could be safely delayed for some patients until CCr drops below 7 ml/min/1.73 m^2 or until more traditional clinical indicators emerge (18).

In contrast to the many studies in transplant-naïve CKD patients, to the best of our knowledge, there are only two studies that assessed the association between eGFR at reinitiation of dialysis and mortality in failed kidney transplant patients (21,22).

Gill et al. examined 4741 failed kidney transplant patients for more than a year after reinitiation of dialysis in the United States, including 1016 (21%) who died during the follow-up period, mostly due to cardiac (36%) and infectious (17%) causes (21). The patients were followed up for 15 ± 11 months after initiation of dialysis after transplant failure. The eGFR was significantly higher in nonsurvivors than in survivors (9.7 ± 4.8 versus 8.0 ± 3.7 ml/min/1.73 m^2). Each 1 ml/min/1.73 m^2 higher eGFR at dialysis reinitiation was associated with a 4% higher risk of death after reinitiating dialysis (21). Of note, this study has several limitations similar to those in observational studies of transplant-naïve patients including confounding by indication, i.e., the sickest patients tend to require dialysis initiation

at higher levels of residual renal function (21). This could have been at least partially addressed by using propensity scores, as Beddhu et al. did in transplant-naïve CKD patients (15), or by an instrumental variable approach (23).

The second study was published by Molnar et al. (22). In this analysis, we linked the 5-year data in a large dialysis organization with the Scientific Registry of Transplant Recipients to identify 747 failed kidney transplant patients with CKD stage 5 who had restarted dialysis therapy with eGFR <15 ml/min (22). Patients were 44 ± 14 years old and included 42% women. A propensity score for early (eGFR >10.5 ml/min/1.73 m^2) versus late reinitiation of dialysis was fit by logistic regression. Male gender, diabetes mellitus, and peripheral vascular disease were associated with higher odds of early dialysis reinitiation (22). In an unadjusted model, each 1 ml/min/1.73 m^2 higher eGFR at dialysis reinitiation was associated with a 6% higher risk of death (22). In the fully adjusted model, eGFR at the start of dialysis was not associated with the risk of death (HR: 1.02, 95% CI: 0.96–1.07). However, there was a trend of lower eGFR associated with lower mortality risk (22). In addition, each 1 ml/min/1.73 m^2 higher eGFR was associated with a higher death risk in fully adjusted models in some subgroups, including women and younger patients. The mortality hazard ratio (HR) was estimated across tertiles of the fitted score (22). The HR for death associated with higher eGFR across the lowest to highest tertiles of propensity scores of early dialysis initiation (corresponding to the healthiest to sickest patients) were 1.10 (0.98–1.24), 1.00 (0.91–1.10) and 0.99 (0.92–1.07), respectively, indicating a trend toward higher mortality risk with earlier dialysis initiation in the healthiest patients (22). Similar results were found when we reanalyzed our data using 854 failed kidney transplant patients with CKD stage 5, who had restarted dialysis therapy with eGFR <20 ml/min. Figures 2A and 2B show the cubic spline models for the unadjusted and adjusted associations of eGFR at the start of dialysis and mortality, respectively.

We concluded that an earlier return to dialysis therapy tended to be associated with worse survival, especially among healthier and younger patients and women. Whether earlier dialysis reinitiation in failed renal transplant patients is harmful or not warrants additional studies.

At the time of this review there are no additional observational studies or randomized controlled trials to answer the important question about early or late reinitiation of dialysis and the associated outcomes of patients with failed kidney transplants.

Methodological Pitfalls of Studies Comparing Dialysis Reinitiation at High versus Low eGFR

Almost all studies on the initiation of dialysis in failed transplant and transplant-naïve patients were observational and therefore have some important limitations. The apparent survival gain of early dialysis initiation in these studies is likely owing to lead-time bias (rather than actual improvements in the course of disease) (12). Another major source of bias in these studies is confounding by indication, whereby the severity of a patient's symptoms might determine the timing of dialysis initiation. Although a randomized controlled trial would avoid this issue, the magnitude of confounding by indication could be somewhat mitigated by using novel statistical techniques such as propensity scores (15,22), or instrumental variables in observational studies.

Another major pitfall of these studies is the use of eGFR. All eGFR equations are based on serum creatinine. Serum creatinine-based estimates may not accurately reflect true GFR, especially if using different equations in diverse populations across studies. It is well known (24) that under steady state conditions, creatinine is produced at a relatively

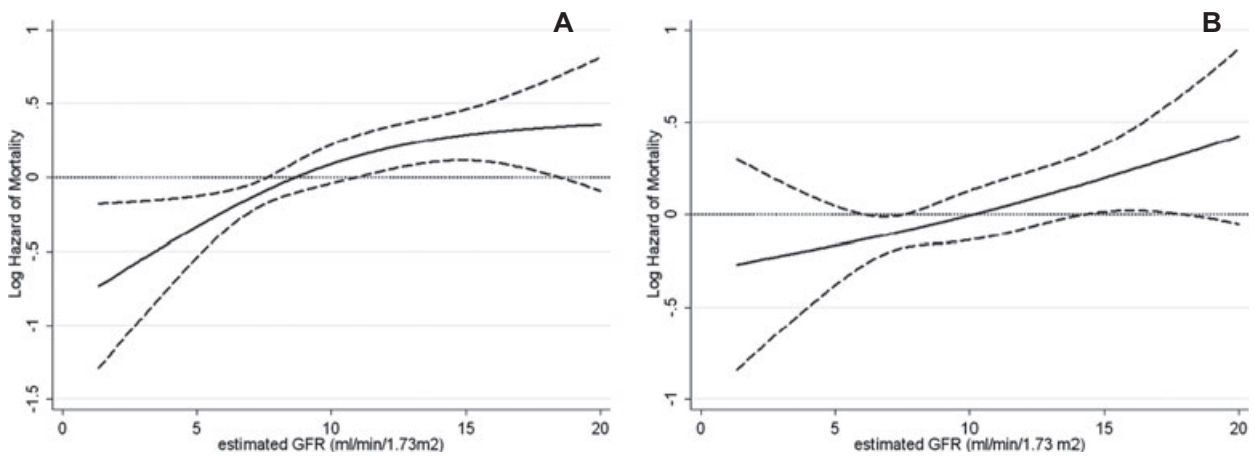

FIG 2. Hazard ratio (95% CIs) of death across the entire range (0–20 ml/min) of the eGFR level using unadjusted (A) and fully adjusted* (B) Cox regression analyses in 854 long-term failed transplant patients who restarted HD therapy*adjusted for: age, gender, diabetes, serum albumin, body mass index, and presence atherosclerotic heart disease.

constant rate depending on the absolute amount of muscle mass (25), filtered by the glomeruli and secreted by the proximal tubules. As there is little to no tubular reabsorption of creatinine, its renal clearance is often used to estimate GFR. With stable kidney function, the concentration of serum creatinine can also reflect skeletal muscle mass, if its nonmuscle mass-dependent variations (such as that due to renal filtration or meat intake) can be accurately accounted for (24) and the 24-hour urinary creatinine excretion is constant (25). It is thus possible that studies showing higher mortality associated with higher eGFR (i.e., lower serum creatinine, when adjusted for age, gender and race) are confounded by the potentially lower muscle mass. Cystatin C, a new marker of kidney function, has recently been shown to provide a more accurate measure of GFR. Most of the cystatin C-based equations have been shown to provide improved accuracy in GFR measurements when compared with creatinine-based Modification of Diet in Renal Disease (MDRD) equations (26). Thus, cystatin C-based equations may offer an advantage over the MDRD equation in kidney transplant patients (26).

Finally, all of these aforementioned studies are not able to take into account the patterns of dialysis reinitiation in kidney transplant patients. Under ideal circumstances, when patients have a slow decline in GFR, dialysis reinitiation is planned and there is sufficient time for preparation and management of CKD-related complications (establishment of a vascular access or peritoneal dialysis catheter insertion, psychological preparation, anemia treatment, etc.). Unfortunately, a significant number of kidney transplant patients require urgent reinitiation of dialysis upon the development of acute kidney injury (AKI) from sepsis, cardiac event, acute rejection, or other unpredictable events. Emergency or urgent dialysis starts are well-known risk factors for death (27).

Impact of CKD Management in Renal Transplant Patients

Early referral to nephrology services and initiation of dialysis under optimal circumstances have both been associated with improved outcomes (27–29). Although nephrologists follow most kidney transplant patients, evidence exists that their management is not as optimal as one would expect. In a prevalent cohort of UK kidney transplant patients ($n = 9542$), 15.7% and 3.1% were found to have CKD stage 4 and 5, respectively. When compared with patients already on dialysis, they were found to have worse blood pressure control, higher serum phosphorus, lower bicarbonate and lower hemoglobin (30). Similarly, a cross-sectional study of 72 Canadian kidney transplant patients with CKD stage 4 and 5 found that hypertension was less well controlled and anemia was less likely to be treated than in a similar patient population with native CKD (31). In an analysis of data pooled from Dialysis Outcomes and Practice Patterns Study (DOPPS) Phases 1–3, Perl et al. found that clinical practice targets were less likely to be met in patients with failed transplants returning to dialysis than in transplant-naïve dialysis patients (32). These patients were also less likely to commence dialysis with a functioning fistula or graft (32).

The reasons for this apparently suboptimal care are not clear. Acute graft loss may result in unanticipated return to dialysis, but in general, the rate of decline of GFR is slower in transplant CKD than in native CKD (33,34). It is possible that efforts are concentrated on interventions attempting to salvage transplant function rather than optimizing predialysis care. Concerns regarding the applicability of treatment guidelines to CKD in transplant patients may also be a factor.

A recently published study examined the effects of changing from a physician-led approach to CKD care in kidney transplant patients to an advanced nurse practitioner-led collaborative approach based on models of care in other chronic illnesses (35). A total of 68% of patients managed by the intervention strategy reached at least 7 of 9 clinical targets versus 10% of patients followed in the traditional model. More patients had discussions on planned renal replacement treatment modality (88% versus 13%). There was a reduction in emergency department visits and hospital admissions (35). Whether these improvements positively impact patient outcomes after the reinitiation of dialysis remains to be determined.

Modality Choice for the Patient with a Failing Kidney Transplant

It is known that more than 5500 patients start their dialysis treatment after graft loss in the United States in 2010 (1). Whether retransplantation, peritoneal dialysis, conventional hemodialysis, or home hemodialysis have the best outcome after a failed kidney transplant has not been well studied. Table 1 shows studies comparing outcomes of different dialysis modalities in failed kidney transplant patients.

It is well known that the higher the number of retransplants, the lower the expected long-term graft survival (36). However, patient survival has been shown to be comparable between first and subsequent transplants (36). In addition, a survival benefit has been detected in retransplanted patients compared with those remaining on dialysis (37). However, this survival benefit was not present if expanded criteria donor kidneys were used for retransplantation (38). Perl et al. analyzed data from more than 2000 failed kidney transplant patients in the Canadian Organ Replacement Register and showed a significant 45% lower mortality

TABLE 1. Studies comparing outcome of different modalities in failed kidney transplant patients

Authors/year	Cohort size	Groups	Follow-up time	Main results
Davies/2001 (43)	45	PD compared to HD	Up to 125 months	PD and HD groups had similar outcome
Sasal et al./2001 (39)	85 (42 failed kidney Tx patients)	Kidney failed PD compared to Tx naïve PD	Up to 100 months	Failed kidney transplant patients reported higher mortality and complication risk
Duman et al./2004 (40)	116 (34 failed kidney Tx patients)	Kidney failed PD compared to Tx naïve PD	Up to 5 years	Similar patients and technique survival
Rao et al./2005 (41)	25,362 (675 failed kidney Tx patients)	Compared transplant-naïve dialysis, deceased/living kidney transplant, failed kidney transplant dialysis and retransplant	Up to 8 years	The transplant-naïve and failed kidney transplant dialysis patients have equivalent mortality risk and that mortality is significantly reduced upon retransplantation
De Jonge et al./2006 (44)	60	PD compared to HD	Up to 60 months	PD and HD groups had similar outcome
Mujais and Story/2006 (77)	1464 (494 failed kidney Tx patients)	Failed kidney transplant patients on PD compared to new dialysis initiation or transfer from HD	Up to 4 years	Similar outcome between the groups; however, the retransplant rate was lower in failed kidney transplant group
Perl et al./2011 (3)	2110	HD compared to PD and preemptive transplant	Median of 2.9 years	Patients had preemptive transplant had better outcome; however, the PD and HD outcome was similar

HD, hemodialysis; PD, peritoneal dialysis; Tx, transplant.

for retransplantation compared with conventional hemodialysis therapy (3).

The first studies examining patients with failed kidney transplants aimed to assess whether these patients had higher mortality on dialysis than their transplant-naïve counterparts (39–41). Rao et al. examined more than 25,000 patients from the Canadian Organ Replacement Register and found that the transplant-naïve and transplant failure patients on dialysis have equivalent mortality risk and that mortality is significantly reduced upon retransplantation (42). Other early studies showed similar survival with conventional hemodialysis and peritoneal dialysis for failed kidney transplant patients (43,44), and similar results were found in the largest published analysis by Perl et al. (3). Survival was not influenced by initial dialysis modality choice, with similar effects of dialysis modality on both early and late survival (3). Perl et al. also concluded that factors such as the era in which the allograft failed, duration of allograft function, and pretransplant history were associated with the likelihood of survival of patients returning to dialysis after graft loss (3). In addition, individuals who initially underwent preemptive transplantation were found to have the greatest survival of all patients with failed kidney transplants (3).

Previous studies showed that nocturnal home hemodialysis was associated with better survival in maintenance hemodialysis patients (45,46). However, to the best of our knowledge, there has been no study comparing the outcomes of failed kidney transplant patients (re)initiated on home hemodialysis versus conventional hemodialysis or peritoneal dialysis.

Immunosuppression Withdrawal and Transplant Nephrectomy

The best approach to withdrawing immunosuppression following transplant failure has been poorly studied to date. Canadian authors suggested that patients returning to peritoneal dialysis may benefit from continuing some immunosuppression, to maintain residual renal function in the graft (47). There is also an argument that weaning of immunosuppression may lead to sensitization to HLA antigens (48). In an attempt to balance the risks of continued therapy versus acute or symptomatic rejection of the failed graft, most units opt for a stepwise cessation of antimetabolites and calcineurin inhibitors followed by a tapering of corticosteroids. In a study of 197 patients with failed kidney transplants between 1972 and 1996, Smak Gregoor et al. showed an increase in mortality due to both infection and cardiovascular causes in those who continued on immunosuppression (49). However, all those in whom immunosuppression was stopped underwent transplant nephrectomy (49).

Transplant nephrectomy is performed for indications such as early/immediate graft loss, overt rejection of the failed transplant and symptoms of "graft intolerance". At this time, it remains controversial whether routine nephrectomy should be recommended after returning to dialysis for patients with late graft loss. Previously, routine allograft nephrectomy has not been recommended, based on largely historical concerns regarding excessive complication rates (50–52) and the increased risk of sensitization adversely impacting access to and outcome of a subsequent kidney transplant (53–55). Donor-specific antibodies have been shown to be more common after allograft nephrectomy (56,57). Other studies have failed to demonstrate a negative impact on second transplant outcomes despite rising PRA (58,59). In addition, one recent study suggested that allograft nephrectomy following early graft loss may protect against sensitization (60). It should be kept in mind that these studies used antibody detection techniques that are much less sensitive than those currently available, and may underestimate

the degree of sensitization both before and after graft loss.

The timing of allograft nephrectomy may have an impact on patient prognosis. Johnston et al. examined United States Renal Data System (USRDS) data on 19,107 transplant failure patients returning to dialysis between 1995 and 2003, and compared those with early graft failure (<12 months, $n = 3707$) with those with graft survival of greater than 1 year (61). The early failure group was more likely to undergo nephrectomy (56% versus 27%). Adjusting for relevant variables, those who had nephrectomy following early graft failure (versus those who did not) had a higher risk of death, but a lower risk of repeat transplant failure. The opposite was true in those who had nephrectomy following later graft failure (HR for death 0.89 and HR for subsequent transplant failure 1.20) (61). It is important to note the limitations of this study. It included deaths within 1 day of graft failure, and no data on the indication for allograft nephrectomy were available. It is possible that confounding by indication may explain the mortality difference observed between the early and late groups (61).

Another USRDS study by Ayus et al. looked at 10,951 transplant patients returning to dialysis between 1994 and 2004, having excluded those whose graft failed within 90 days, and those who died within 1 day of graft failure. They found an allograft nephrectomy rate of 31.5%. Patients undergoing nephrectomy were typically younger and had fewer comorbidities (62). Adjusting for socioeconomic variables, comorbidities, donor characteristics, and a propensity score reflecting the probability of undergoing nephrectomy, the authors concluded that allograft nephrectomy was independently associated with a reduction in mortality (adjusted HR for mortality 0.68, 95% CI: 0.63–0.74) (62). This association persisted after numerous sensitivity analyses. Rates of retransplantation were higher in the nephrectomy group (10.0% versus 4.1%) probably reflecting a selection bias (62). Thirty-day mortality following allograft nephrectomy was 1.5% (62).

The technique of nephrectomy also needs to be further examined. A number of small studies have demonstrated good results from transplant embolization rather than surgical nephrectomy, with reduced procedure-related morbidity and mortality (63,64).

There are other potential consequences of retaining a failed kidney allograft. A failed allograft is increasingly being recognized as a risk factor for a more pronounced chronic inflammatory state compared with ESRD alone, contributing to erythropoiesis stimulating agent resistance (65), endothelial dysfunction (66), and features consistent with protein energy wasting/malnutrition inflammation complex syndrome (67,68), which have in turn been associated with a greater risk of cardiovascular and infection-related mortality in CKD (69), dialysis (70), and kidney transplant patients (71).

Mortality and Quality of Life After Kidney Transplant Failure

Mortality and quality of life are the two most relevant outcomes for patients with a failed kidney transplant. In the analysis of approximately 19,000 first kidney transplant patients returning to dialysis using USRDS data, Ojo et al. identified a significant mortality risk, with 34.5% of patients dying during the follow-up period, and 5-year survival rates as low as 36% in certain groups (72). In addition, studies of both US and Canadian registry data demonstrate a three-fold higher annual adjusted death rate in patients with graft failure compared with those with continued function, with cardiovascular and infectious causes of death most prominent (73,74). The Canadian study demonstrated that the relative risk of death was greatest in the first 6 months after transplant failure (73). Nevertheless, it was not known whether failed kidney transplant patients have worse survival than their transplant-naïve counterparts. Rao et al. used Canadian Organ Replacement Register data on over 25,000 patients starting renal replacement therapy between 1990 and 1998 to compare outcomes among transplant-naïve individuals and those with failed allografts. No difference was observed between these groups (41).

However, when the same investigators compared *wait-listed* dialysis patients with those returning to dialysis using the Scientific Registry of Transplant Recipients database, they found an increased risk of death in the latter (42). When comparison was limited to those relisted for kidney transplantation, the difference was less pronounced (42). The relative risk of death was highest in the first week and remained elevated at 30 days, lending credence to the theory of an early vulnerable period following return to dialysis (42). This phenomenon was also reported by Gill et al. in their description of the continuum of ESRD treatment, with death rates peaking at 3 months after kidney transplant failure (75). Rates of septicemia have also been shown to be high in this period (76).

In addition to these studies, Perl et al. recently examined data from the DOPPS studies to compare outcomes between transplant-naïve wait-listed dialysis patients and those with graft failure (32). When adjusted for laboratory parameters, demographic covariates, and 13 comorbid conditions, all-cause mortality, cardiovascular deaths, and infection-related deaths were more likely in the retransplant group. Quality of life was also reduced in those with graft failure (32).

Common themes emerge from these observational studies, and others which examine the causes of death after graft loss (21). Cardiovascular disease and infections are the leading causes of death in this population. Moreover, nonimmunologic factors appeared to be significant contributors to the observed excess mortality (21).

Conclusions

Over the last several decades an increasing number of patients have returned to chronic dialysis after failure of their kidney transplants. These patients are different from transplant-naïve patients, in that they have a higher mortality rate, may not receive adequate preparation before the initiation of dialysis, and may also have specific issues such as immunosuppression withdrawal or the need for allograft nephrectomy. Currently, there is insufficient evidence to make strong recommendations about what the standard practice should be in these patients. We feel that starting dialysis early based solely on an eGFR criterion is not justified and could in fact be harmful in some cases. Depending on this single metric for such a crucial decision is likely flawed; thus, alternative and more reliable measures are required. Observational studies and randomized controlled trials are needed to examine this important area of clinical practice for both kidney transplant and dialysis physicians.

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