Overcoming Barriers to Long-Term Graft Survival

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• **Although short-term kidney graft survival has improved in recent years, the focus has shifted to the challenge of improving long-term graft survival. Acute rejection, chronic allograft nephropathy, and cardiovascular disease are associated with graft loss and patient death. Reducing the potential for such posttransplantation complications may improve long-term graft survival. In addition, gaining a better understanding of the role that various immunosuppressive therapies have in decreasing the risk for graft injury will help clinicians make better-informed decisions about appropriate treatment regimens for individual kidney transplant recipients.** ***Am J Kidney Dis*** **47(S2):S52-S64.**

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THE INCIDENCE OF acute rejection has decreased progressively during the last decade with the advent of more efficacious immunosuppressive therapies. One might expect that decreased episodes of acute rejection ultimately would lead to better graft survival. However, in the same period, there has been little improvement in long-term graft survival.[1] Therefore, the current focus is on reducing late graft dysfunction while also minimizing immunosuppressive adverse events.

Understanding and defining the process of long-term injury to the transplanted kidney is essential for improving graft and patient survival. It is hoped that this better understanding will lead to a positive impact on graft and patient survival over time. In addition, new immunosuppression regimens are being investigated. As transplant physicians and nephrologists progressively gain a better understanding of the many differences between current treatment protocols, it is hoped that posttransplantation renal function and long-term graft survival will improve.

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TRENDS IN LONG-TERM GRAFT SURVIVAL

The frequency of late graft loss is approximately 7% per year in Canada and the United States.[2] In a single-center study of 429 patients who underwent transplantation between 1990 and 2000, results indicated that the stability of renal function may be increasing, which is believed to correlate with an overall decrease in acute rejection episodes and treatment with new immunosuppressive agents.[2] However, a more recent study[1] found that renal function and graft survival have not improved despite advances in kidney transplantation.

In a recent pooled analysis, rates of acute rejection and early graft failure improved considerably during the past 2 decades; however, the rate of late graft failure remained relatively constant.[3] Likewise, analysis[4] of actual (versus projected) half-lives for patients who underwent kidney transplantation between 1988 and 1995 showed no significant improvement in long-term graft survival (Table 1). The 2-year increase in overall half-lives during the 7-year time frame primarily was caused by improvements in retransplantation. However, improving long-term graft survival has been more difficult in recent years given that the age of donors and recipients has increased, waiting time to transplantation has increased, more transplantations are being performed on high-risk patients, and more extended-criteria donor kidneys are being used. Therefore, the small improvement in graft half-lives still shows progress.

Meier-Kriesche et al[1] also analyzed data from more than 62,000 adult first-transplant recipients

Table 1. Death-Censored Graft Survival by Year of Transplantation

Transplantation Year	Half-Life Graft Survival (y)
1988	6.0
1989	6.8
1990	7.0
1991	7.5
1992	7.4
1993	7.6
1994	7.8
1995*	8.0

NOTE. Analysis by means of Kaplan-Meier method.
*Kaplan-Meier half-life based on time to 51% survival.
Data from Meier-Kriesche et al.[4]

and found that, from 1995 to 2000, acute rejection rates decreased from 35.7% to 14.6% in the 0- to 6-month posttransplantation period, from 21.4% to 6.0% in the 6- to 12-month posttransplantation period, and from 22.5% to 2.9% in the 12- to 24-month posttransplantation period. Overall, 6-year graft survival rates were similar for patients without acute rejection versus those who experienced acute rejection with near-complete recovery of baseline renal function (74.4% versus 72.7%, respectively). However, in patients who experienced acute rejection and less than complete recovery of baseline renal function, graft survival rates were associated with lower graft survival, and they declined in proportion to the degree of impairment in renal function (Table 2).

Because the overall rate of graft loss remains unacceptably high, reducing the risk for late graft loss has become a current challenge in kidney transplantation.

RISK FACTORS FOR KIDNEY GRAFT DYSFUNCTION AND LOSS

The duration of graft survival after transplantation is dependent on the quality of the donor kidney, as well as severity and frequency of various insults. Such insults can occur early after transplantation or they may occur either discretely at later times or reflect cumulative low-grade injury, which may lead to a decline in renal function and, ultimately, graft failure.

Histological and clinical associative factors related to graft failure include early acute rejection, late rejection, nonadherence, and chronic allograft nephropathy (CAN).[5] The development of proteinuria after kidney transplantation also is associated with increased renal failure.[6] Patient survival also was lower in patients with proteinuria, and relative risk for death increased with increased severity.[6] It was concluded that proteinuria is an independent predictor of both graft failure and patient death.

Opelz et al[7] analyzed data from 29,751 deceased-donor kidney transplantations and found a significant association between elevated systolic blood values posttransplantation and poorer kidney graft survival ($P < 0.0001$). Elevated diastolic blood pressure also was a significant predictor of subsequent graft failure. Elevated blood pressure was associated with poorer long-term outcomes even when rejection was not present. In addition, increased systolic blood pressure resulted in decreased graft survival regardless of diastolic blood pressure.

Reports suggested a relationship between the length of time a patient is on dialysis therapy before transplantation and graft survival after transplantation. In a retrospective cohort study[8] of 81,130 kidney transplant recipients from the US Renal Data System (USRDS) registry, patients who were on dialysis therapy for 181 days or longer had a significantly greater rate of graft failure after transplantation, whereas patients who had a shorter duration of dialysis therapy (<6 months) experienced no detrimental effect on graft or patient survival after transplantation.

Delayed graft function also was associated with significantly lower 3-year graft survival rates compared with those who did not experience DGF (84% versus 68%, respectively; $P < 0.001$) according to the United Network for Organ Sharing Renal Transplant Registry, including 165,151

Table 2. Overall 6-Year Graft Survival Rates by Acute Rejection and Recovery of Baseline Renal Function

Acute Rejection During Posttransplantation Months 6-12	Baseline Renal Function Recovered at 1 Year Posttransplantation (%)	6-Year Allograft Survival (%)
No acute rejection	—	74.4
Acute rejection	95-100	72.7
Acute rejection	85-95	67.0
Acute rejection	75-85	50.2
Acute rejection	<75	38.0

NOTE. Cockcroft-Gault formula was used to estimate GFR.
Data from Meier-Kriesche et al.[1]