Kidney Transplantation in the Context of Renal Replacement Therapy

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Kidney transplantation has dramatically evolved from a life-saving yet unproven therapy for patients with renal failure to a mature field that is the preferred treatment for those suffering from ESRD. Patients who receive a transplant experience a 68% lower risk of death compared with those waiting on dialysis for a transplant. This benefit is afforded to all patient subgroups including the elderly (≥70 yr), and diabetics, who can gain 11 yr of extra life with transplantation. Prolonged transplant wait times result in a higher risk of death but this can be ameliorated with preemptive transplantation. Future challenges will focus on appropriate organ allocation and addressing long-term renal function and comorbid conditions so patients can enjoy the full benefits of transplantation.

For those individuals who have been fortunate enough to work with, or even better, be mentored by John Curtis, determining where kidney transplantation fits into the overall hierarchy of renal replacement therapy would not even be a question. Long before studies showed that transplantation is the preferred treatment modality for the vast majority of patients with renal disease, he taught many of us the importance of actively caring for each kidney transplant, and by extension, each patient. Even before individual centers had wait lists measured in the thousands, he understood the value of a transplant and the dedication, by both transplant professionals and patients, it took for each patient to fully realize this gift. Eventually science would catch up to Dr. Curtis’s intuition, intellect, and teachings, and he would applaud the rigors and scrutiny of the scientific method that would prove the preeminent role that transplantation has for patients experiencing renal disease. For many of us that had benefitted by working with John Curtis, that concept had been taught and practiced for years.

For many, it is difficult to envision any discussion of renal disease without considering the impact of transplantation. For children with congenital abnormalities, delaying the inevitable progression to ESRD until a successful preemptive transplant can be preformed is now standard therapy. For those individuals with immunologic diseases that have failed therapy, transplantation is still an option, but the concern over recurrence of their native disease must be considered. For the elderly or those patients with diabetes, extending their lives, improving their quality of life, and the resultant reduction of overall medical costs with transplantation have significant public health benefits. However, these current widely held concepts were not universally accepted in the recent past. Concern about the cost of renal transplantation and long-term outcomes relegated it as a therapy that was still without a clear place in the continuum of care for chronic renal disease (1–3).

Kidney Transplantation in the Infancy of ESRD Therapy

The first successful kidney transplant was performed in 1954 between two identical twins by Dr Joseph Murray. Over the next decade, remarkable advancements occurred that allowed transplantation to be offered to a broader range of patients, with organs emanating from distantly related live donors to deceased donors. By 1965, amazing short-term graft survival had been achieved, reaching nearly 80% from living donor sources and approaching 65% for deceased donor recipients (4). As the life-saving nature of dialysis and transplantation became more apparent and the availability of each modality became more widespread, it was appreciated that the enormous costs of these therapies could quickly eclipse the ability of most Americans to afford these treatments. In 1972, Medicare coverage was extended to patients with ESRD, and therefore, access to dialysis and transplantation would be more equitable if cost restraints were removed.

Remarkable parallels exist in our nation’s current efforts to offer universal health insurance to all Americans compared with the situation in the 1970s. At that time, many hoped that the adoption of Medicare coverage for ESRD would be the first step in the development of a national catastrophic health insurance program (3). Even at a time where fewer patients qualified for ESRD, soaring costs were a significant concern. It was estimated that by 1972, annual costs associated with ESRD were
$600 million but were expected to increase to $1.9 billion by 1987 (3). In fact, ESRD expenditures account for more than $32 billion today and nearly 6.4% of the overall Medicare budget according to 2008 data from the U.S. Renal Data System.

Because of the concern about the initial cost of renal transplantation and its still unproven long-term advantage, many physicians still viewed dialysis as the preferred treatment method for chronic renal failure. This view was summarized nicely in an editorial by Rennie in 1978, when he discussed the societal impact of dialysis and transplantation. He stated “A successful transplant means less expense during the period in which the graft is functioning, but the risk to life is greater...So even although it offers a much better quality of life while it works, a transplant in most cases can be considered only a temporary respite from the basic form of treatment, which is dialysis” (2).

Kidney Transplantation and Patient Survival Advantage

This prevailing opinion was finally changed by the landmark article by Wolfe et al. (5) in 1999. To address the valid concerns of many that it was solely caused by selection bias that transplant patients had superior outcomes to those on dialysis, they performed a series of analyses of only eligible transplant candidates. Using data from the U.S. Renal Data System of >250,000 patients receiving dialysis and 46,000 patients wait listed for a renal transplant, outcomes were analyzed for those patients who received a deceased donor transplant versus those who remained on the waiting list. Among some of their findings, they were able to quantify the magnitude of benefit of transplantation compared with remaining on dialysis even in high-risk groups such as the elderly and those with diabetes. Patients wait listed for a transplant had a 49% lower risk of death compared with the entire group on dialysis when adjusted for age, diabetes, and other factors. For patients receiving a deceased donor renal transplant, their risk of death was even more impressive, with a 69% reduction in risk. When comparing only those patients on the wait list versus those who received a transplant, the benefits were early and marked. Even after taking into account the risk of surgery, early complications, infections, and cardiac events, the relative risk death after transplantation equaled that of remaining on dialysis after only 106 d. Long term, there was a 68% lower risk of mortality, shown in Figure 1. Notably, benefit was seen in all groups but especially in diabetics, with an increase of 11 yr in their projected lifespan.

As a result of the surging dialysis population and armed with the knowledge that renal transplantation was in fact life-saving, as opposed to a life enhancing therapy, the number of patients on the transplant wait list increased dramatically. Between 1998 and 2007, the total number of candidates wait-listed for a renal transplant at year-end rose by 86% to nearly 72,000 patients (6). Along with swollen wait lists and resultant prolonged waiting times came another important finding. Cosio et al., (7) using data from Ohio State University, were the first to show that there was a significant negative effect on post-transplant mortality with increasingly long dialysis times before transplantation. They showed that after 7 yr of follow-up, those patients who were never dialyzed before receiving their transplant had only a 7% mortality compared with 23% for those who dialyzed for <3 yr and 44% for those dialyzing for >3 yr. This remarkable effect on mortality seemed to be caused by two major causes: a higher infection rate on dialysis and worsened cardiac risk factors, namely a higher prevalence of left ventricular hypertrophy and cardiomegaly with increasingly long dialysis times. These finding were subsequently confirmed and extended in a larger population by Meier-Krieshe et al. (8) using the U.S. Renal Data System registry. His group quantitated the risk on mortality of increasing dialysis times and compared it with other commonly considered risk factors for patient survival. They also showed that mortality increased in a linear manner with increasing dialysis times. For patients on dialysis for >4 yr, the relative risk of death was higher than receiving a deceased donor transplant (compared with a living donor transplant) and receiving azathioprine (compared with mycophenolate mofetil). Only diabetes conferred a higher risk of death compared with prolonged dialysis, but that excess risk was not as great as might be thought, 1.99 versus 1.72 relative risk of death, respectively.

The accumulation of cardiac risks with an increasingly long dialysis duration may have a multitude of causes including cardiomyopathy related to hypertension (9), hyperlipidemia with resultant atherosclerotic cardiac disease (10), or coronary calcification related to disordered calcium metabolism and calcium-based phosphorus binders (11). Regardless of the cause, it has been difficult to show that aggressive treatment of these conditions will improve survival of dialysis patients. Even among a widely accepted and proven therapy in the general population, statins have failed to show a benefit in the dialysis population. Two large-scale, well-designed, prospective trials failed to show an impact on survival in patients with ESRD who received highly potent statin agents, atorvastatin or rosu-

![Figure 1. Adjusted relative risk of death among 23,275 recipients of a first cadaveric transplant. The reference group was the 46,164 patients on dialysis who were on the waiting list (relative risk, 1.0). Values were adjusted for age, gender, race, cause of ESRD, year of placement on the waiting list, geographic region, and time from first treatment for ESRD to placement on the waiting list. The points at which the risk of death and the likelihood of survival were equal in the two groups are indicated. A log scale was used. Used by permission from Wolfe (5).](image)
vastatin, even in a high-risk group including diabetics (12,13). In distinction to dialysis patients, however, a large prospective, placebo-controlled study, the ALERT trial, was able to show a 35% risk reduction in the secondary endpoint of combined cardiac death or nonfatal myocardial infarction even with the use of the relative low-potency statin fluvastatin (14). Therefore, dialysis may result in an accumulating burden of risk factors that are difficult to correct until transplantation occurs. However, some of these factors may be improved with intensive nocturnal hemodialysis. A small case-control study has suggested that a selected group of patients receiving nocturnal hemodialysis may have comparable outcomes to those who received a deceased donor renal transplant (15).

Numerous studies have shown the marked impact of ESRD on patient survival compared with transplantation and the general population (7,8,16,17) (Figure 2). This impact is most dramatic in younger patients where annual mortality rates are >100 times greater in the patients with ESRD compared with the general population. Even in older patients where mortality rates would be expected to high, transplantation has a dramatic impact on survival (18,19). Rao et al. (19) has shown that, even in patients older than age 70, transplantation offers a 41% lower risk of death compared with those that remain wait listed. Older patients (>49 yr of age) now account for nearly 60% of the active waiting list compared with just 45% 10 yr earlier, and for patients 65 yr and older, there has been a 78% increase (6).

Kidney Transplantation, Transplant Trends, and Allocation Issues

Even as the data clearly show that nearly all patient groups benefit from transplantation, there is widespread recognition that the organ shortage will continue into the foreseeable future, thereby limiting this life-saving therapy. In an attempt to make organ allocation more equitable, several proposals have been discussed. Most notably, the concept of net benefit or “life years following transplant” (LYFT) was considered as an important component of any new kidney allocation system (20). This has met substantial resistance from both patient and physician groups because of a concern over the shifting of kidneys away from the ever-enlarging group of older patients on the wait list (21,22). The more recent concept of matching the projected longevity of the allograft with the projected longevity of the recipient may solve some of the ethical and practical dilemmas of organ allocation (23).

With the knowledge that transplantation can be life-saving but given the realities of an ever-enlarging wait list for a deceased donor kidney, live donor organ transplantation has surged by 37% from 1998 to 2007 to fill the void. The largest increase in living donors in recent years has come from unrelated live donors, both spousal and other emotional connected donors (e.g., friends, coworkers) (6,24). However, this steady expansion of living donation peaked in 2004 and has continued to fall up to the present time. Several factors may account for this reduction in live donation but concerns about long-term safety, especially in African-American, older, or hypertensive donors may cause transplant centers to pause their pursuit of these donor groups (25-27).

Preemptive Kidney Transplantation

Patients, and the nephrologists caring for them, have increasingly become more proactive, and in ever increasing numbers, these patients are presenting for evaluation for transplantation. This is especially true for a particularly high-risk group: diabetics who are age 50 and older. Between 1998 and 2006, the number of older diabetics who were preemptively wait listed increased by 245%. Although the total number of older diabetic patients who actually received a preemptive living donor transplant remained relatively small, 55 patients in 2006, it still represented nearly a three-fold increase from 1998 (6). Preemptive transplantation confers a significant benefit in terms of both patient and allograft survival as shown by Kasiske et al. (28). They examined nearly 40,000 patients who underwent renal transplantation between 1995 and 1998. Surprisingly, they discovered that 39% of patients received a preemptive deceased donor transplant. Irrespective of the donor source, recipients who received either a live donor or deceased donor benefited nearly equally. For those receiving a preemptive living donor transplant, there was a 27% reduction in allograft failure and a 31% reduction in patient death. Although the exact cause of the survival benefit remains unclear, Meier-Kriesche et al. (29) has suggested that preemptive renal transplantation may halt the progression of cardiovascular disease. In their study, they showed a substantial reduction in cardiovascular deaths at 3 yr in those who received a preemptive transplant compared with increasing lengths of time on dialysis. Even in patients with a very brief dialysis duration (0 to 6 mo), there was a 34% relative reduction in cardiovascular mortality for those patients who received a preemptive transplant.

Figure 2. Cardiovascular mortality rate in the general population and in kidney failure treated by kidney transplantation or dialysis. Cardiovascular mortality defined by death caused by arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema in the general population (GP; National Center for Health Statistics) compared with kidney failure treated with dialysis or kidney transplant (U.S. Renal Data System). Used by permission from Sarnak (16).
Enhancing Long-Term Patient and Graft Outcomes

As immunosuppressive advancements have allowed acute rejection rates to plummet, the focus for many caring for transplant patients has shifted from the sacred 1-yr allograft survival, which reached 95% in recipients of living donor organs (30), to long-term patient and graft outcomes. Although it is beyond the scope or intent of this paper to adequately address this crucial topic, several notable topics merit attention. Immunosuppressive regimens using sirolimus or belatacept designed to reduce calcineurin toxicity have had impressive short-term outcomes, although the long-term results of these protocols is still unclear (31,32). For physicians focusing on cardiovascular risk factor reduction, we have suggested that transplant physicians may be especially vigilant in addressing these risks, whether it be the simple addition of cardioprotective use of aspirin to tighter glucose control, lipid management, or achieving BP goals (33). What is becoming more appreciated is that maintaining allograft function and improving patient well being is essential. For those patients who return to dialysis, the vast majority are never transplanted again, with most series showing a retransplantation rate of only 13 to 37% (34).

Conclusion

Kidney transplantation has made enormous advancements in a brief time. Placing transplantation in the context of renal replacement therapy has completed a full circle, going from a true life-saving procedure, to a luxury that enhanced the quality of life, and ultimately returning to be recognized as life saving once again. As more patients experience this miraculous gift, we must give credit to John Curtis for propelling the knowledge of this field and allowing us to become better physicians to care for these patients as we follow in his footsteps.

Disclosures

None.

References

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