

Preemptive transplantation and the transplant first initiative

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Purpose of review

Preemptive kidney transplant (PKT) is the focus of a new initiative, 'Transplant First'. This initiative focuses on increasing patient transition to transplantation prior to the need for dialysis. This review will evaluate the benefits of PKT and means to accomplish this goal.

Recent findings

Outcomes data show PKT significantly improves long-term survival for the recipient and the allograft. In addition quality of life is improved. This also holds true for children and particularly for adolescents. In 2008, 5.7% of incident patients with end-stage renal disease were placed on the waiting list before beginning dialysis and 0.8% underwent preemptive living donor transplant before wait listing. If patients are evaluated before starting dialysis and are acceptable candidates, up to 40% will receive a preemptive transplant. Recent articles stress that patients want information from their physician; important impediments to PKT remain provider and patient education, insurance coverage and patient reluctance to ask for living donation.

Summary

Preemptive transplant saves lives. Increased education focused on providers, patients and entire communities is key, as is an increase in living donation. Furthermore, to maximize the impact of transplant first, increased living donor protections and immunosuppression coverage for the life of the allograft are essential.

Keywords

kidney transplant, living donor, preemptive

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Introduction

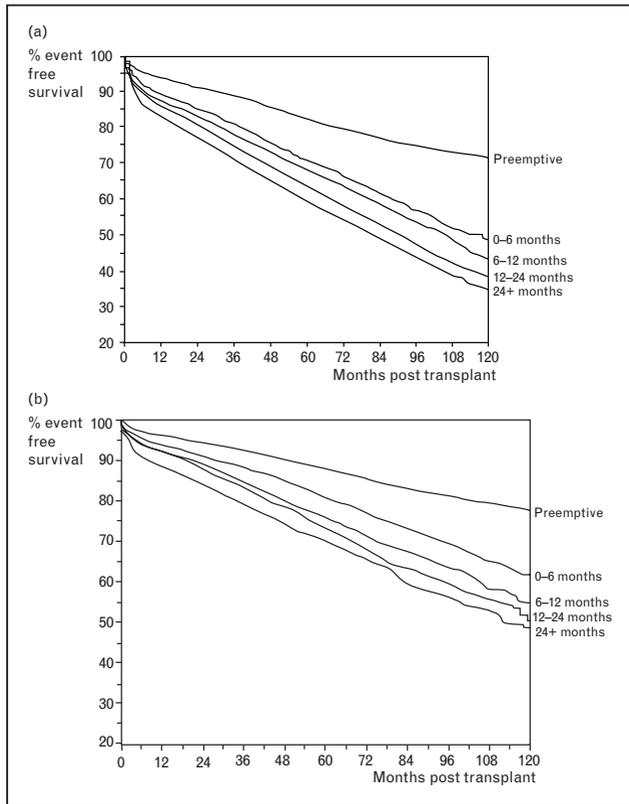
Kidney transplant provides better long-term survival than staying on dialysis. The best survival is seen in those transplanted prior to starting dialysis, otherwise known as preemptive transplant. In order to help improve the potential to offer preemptive transplantation for patients with chronic kidney disease it is important to review the current state of knowledge of outcomes of preemptive transplant, the impediments to patients reaching transplant centers early enough to be able to receive a preemptive transplant and the impact of living donation.

Impact of preemptive transplantation

'Transplant First' is a new initiative in end-stage renal disease (ESRD) care initiated in 2008 as part of the US National Kidney Foundation's 'End the Wait Campaign' (www.kidney.org/news/end_the_wait/recommendations.cfm). The article started the 'Transplant First' initiative. Thought leaders from all disciplines of medicine convened to determine what the bottlenecks to preemptive kidney transplantation (PKT) were and what should be done to improve access to PKT [1]. The key directive is

to transplant patients prior to needing dialysis, otherwise known as PKT. The importance of this issue is embedded in the increasing numbers on the transplant waiting list and the improved outcomes demonstrated by recipients of PKT. Preemptive kidney transplantation has been shown by analysis of the Organ Procurement and Transplant Network (OPTN) and United States Renal Data System (USRDS) data as well as data globally, to be associated with decreased rejection rates, improved allograft and patient survival and maintained recipient employment [2–13] (Fig. 1). Improved survival has held true after excluding six antigen matched kidneys and adjustments for HLA matches, panel reactive antibody (PRA) level, recipient age, immunosuppression, delayed graft function and recipient race [5]. Donor variability was removed as a confounder in one study by comparing recipients of kidneys from the same donor [5]. Improved graft and patient survival continues to be seen in all age groups including adolescents [3,4,10], Fig. 2. Additional advantages of preemptive transplant over other treatments in the young are improved growth and quality of life [14]. Patients with diabetes also gain a survival advantage with PKT [9,15]. Other benefits include cost savings through dialysis avoidance, lack of the need for a

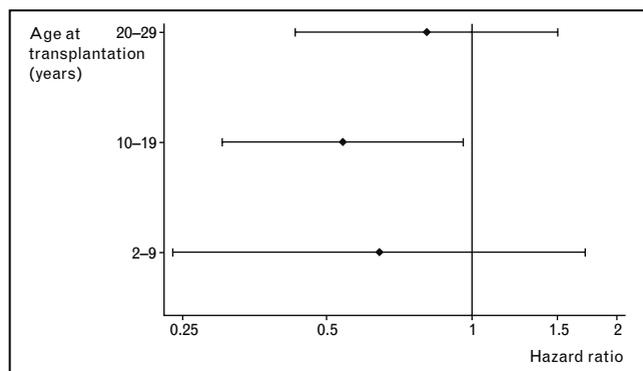
Figure 1 Unadjusted graft survival by dialysis time



Unadjusted graft survival after receiving a deceased donor (a) or living donor (b) kidney transplant preemptively or after 6 to over 24 months on dialysis reprinted with permission from [6].

dialysis access, fewer sensitization events, fewer dialysis catheter-related infections, less hepatitis, less cardiac systolic dysfunction, less hypertension, less delayed graft function and decreased overall hospitalizations [6,16–18].

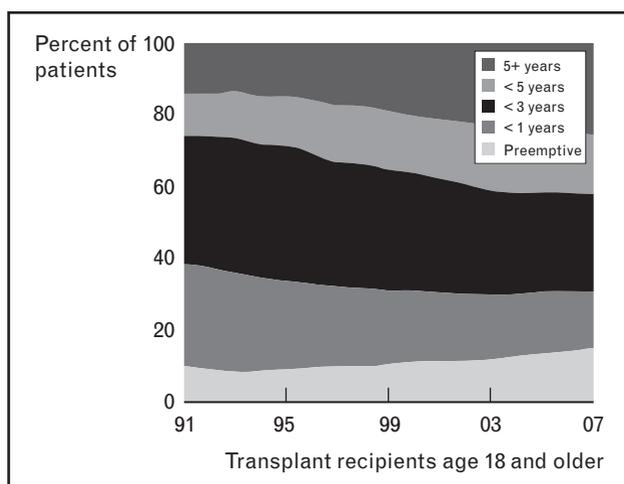
Figure 2 The impact (hazard ratio) of recipient age on graft failure according to timing of the transplant, preemptive compared to six to 24 months after starting dialysis



Data were adjusted for gender, donor age, HLA mismatches, country of transplantation, peak panel reactive antibody level and vintage reprinted with permission from [5].

Possible limitations of the data supporting PKT include the impact of lead time bias for PKT recipients as well as the unattainable goal of considering all recipient characteristics, surgical factors and practice patterns that may impact outcome [13]. For instance, there is the potential that recipient selection bias contributes to these findings with healthier recipients being more expeditiously evaluated and listed for transplantation. These patients may have not only less exposure to severe chronic kidney disease (CKD) but also other associated characteristics that impact outcome. The optimum study is impossible to perform as that would require randomizing patients preemptively waitlisted to transplant or remaining on the wait list. A less optimum approach is to analyze those waitlisted preemptively and followed through their ESRD care (wait listing, dialysis, transplant). The closest study to this approach compared outcomes by duration of ESRD with fine granularity (dialysis duration of 0–14 days, 15–60 days, 61–180 days, 181–365 days, etc). Survival using these dialysis time frames was equivalent in all of the groups of patients transplanted at less than 180 days of dialysis. Worse survival was seen starting in those on dialysis over 181 days [19]. This study of course does not highlight the other advantages of avoiding dialysis such as employment, cost and quality of life. Additionally, the negative impact of dialysis is highlighted by the fact that the benefit of living donor transplantation (the best possible option) compared with deceased donor declines with more recipient time on dialysis [5].

Residual native kidney function could also confound the conclusion that PKT contributes to better overall outcomes by providing kidney function above and beyond the kidney transplant. However, Kasiske *et al.* [2] showed that the pretransplant serum creatinine was no different between the preemptive (7.0 mg/dl) and nonpreemptive (7.3 mg/dl) recipients [2,20,21]. MDRD glomerular filtration rate (GFR) less than 10, 10–14.9 and greater than 15 at the time of preemptive transplant did not determine graft survival. Early preemptive transplantation with higher eGFR is not needed to improve allograft function [21]. Ishani *et al.* [20] showed that residual renal function at transplant (MDRD eGFR <15 cm³/min, mean 8.6 ± 2.7 versus ≥15 cm³/min, mean 21.1 ± 8.4) did not impact 6-month posttransplant function, patient or allograft survival [20]. Although there are instances when centers offer PKT to recipients with eGFRs by MDRD of at least 20 cm³/min/1.73 m², the concern over early exposure to immunosuppressive medications and complications appears to be minimal as most if not all patients who undergo PKT meet the criteria for ESRD [3,22]. Even so, continual review of risks and benefits of the timing of transplant is needed [22].

Figure 3 The percentage of kidney transplants by dialysis status at transplant by year from a USRDS report

Access to preemptive transplantation

Preemptive listing for kidney transplantation occurs in 16.6–21.3% of listed patients [23]. Scientific Registry of Transplant Recipients (SRTR) data was reviewed for characteristics leading to preemptive waitlisting. Medicare coverage was an impediment for those aged 64 years and under but not those over 65 years [23]. Preemptive listing occurs in 19.1–21.3% of adult patients aged 30 and older. Patients with polycystic kidney disease (41.9%) and glomerulonephritis (24.6%) are more often preemptively listed compared with those with hypertension (12.2%) and diabetes (14.4%). Education level also impacts preemptive listing with fewer listed for PKT if they have a high school education (17.1%) compared with post-college graduate school (33.5%). Larger transplant program size appears to correlate slightly with preemptive listing.

Preemptive transplantation occurred in 25% of adult recipients of living donor transplants and about 10% of deceased donor recipients in the late 1990s and early 2000s [2]. Pediatric recipients enjoyed slightly higher rates of PKT, 34% for living donor and 14% deceased donor [3]. The current overall preemptive transplant rate from the 2009 USRDS report is 15% of all transplants, up from 9–10% in the early 1990 (Fig. 3; www.usrds.org/2009/view/v2_00b_precis.asp). Recipients of preemptive transplants are more frequently younger, white, working, nondiabetic, covered by private insurance and have higher levels of education [2,23]. Medicare coverage appears to be an impediment to PKT for those waitlisted at less than 64 years of age [23]. Looking at the entire cohort of individuals developing ESRD, only about 5.7% of incident patients with ESRD were placed on the waiting list before beginning dialysis and 0.8% under-

went preemptive living donor transplant without being placed on the waiting list [1]. Of the roughly 7% of incident ESRD patients who were evaluated before dialysis and found to be acceptable transplant candidates, 39% received PKT [1]. In summary, 2.5% of incident patients with ESRD undergo PKT. In the nonwhite populations, 1% of patients receive PKT.

Other issues including access to care influence access to PKT. From the 2009 USRDS annual report for 2007 data, one in three patients beginning ESRD therapy in 2007 had seen a nephrologist for a year or less, and 24% for a longer period; 43% had not received nephrology care. Longer time in nephrology care has been associated with increased preemptive transplant evaluation [24]. This poor referral rate to nephrology and to PKT occurs in the setting of a huge financial outlay for ESRD care. Medicare spending for ESRD in 2007 was \$23.9 billion, and non-Medicare spending \$11.4 billion (www.usrds.org/2009/view/v2_00b_precis.asp). Medicare costs per person per year in 2007 were nearly \$62 000 overall, ranging from \$24 572 per transplant patient to \$73 008 for those receiving hemodialysis. In alignment with USRDS data, nephrologists report that impediments to early transplantation include late referral to their practice and too much delay between a patient's referral and the time the patient is seen at the transplant center [25]. Individual patient characteristics also impact nephrology referral for transplantation. Nephrologists more often decide not to discuss PKT if the patient has poor health status, is nonadherent, has multiple medical problems, is 'too old', has no prescription drug coverage and has inadequate health insurance to cover the costs of transplant [25]. Likely some of these concerns have come directly or indirectly from the transplant centers themselves. Finally, variability in transplant center selection criteria and candidate pools confuse nephrologists and other providers, thus impairing referral [26]. Variable criteria come from different financial risks some centers are willing to take in order to provide transplantation to higher risk patients, the differences between transplant center acceptance of the range in payer ability to correctly assess candidate comorbidity risk so that the center accepting such patients is not disadvantaged and the willingness of some centers to be innovative when it comes to learning how to improve transplantation for high-risk individuals.

Barriers to preemptive transplantation

Patients report that barriers to PKT include the beliefs that dialysis must precede transplant, transplant is the last resort treatment and discomfort in asking for a living-donor transplant [27••] (www.kidney.org). These same investigators also learned that 27% of study individuals' first discussion about transplantation was after dialysis

started, 10% had not discussed transplant with a health-care provider and 33% relayed that the option of a living donor had been first mentioned only after dialysis was begun, especially for minority patients. Patients also stated that they were open to receiving education from many sources although the most frequently preferred option was a one-on-one with a physician (44%). Early awareness of living donor transplantation seemed to be associated with an overall likelihood of undergoing the procedure. In summary, the major patient barriers to PKT are access to early CKD treatment by nephrology, CKD treatment education including transplantation as an option and information about transplant finances [27**].

Even before transplant specific education comes the reality that everyone perceives their need for care differently; some patients are just not open to becoming educated about the different treatment options for ESRD, as they have not come to terms with their illness [28]. They wish to remain 'normal'. This article outlines the unique psychosocial issues affecting patients with CKD and how an educational program about preemptive living donor transplant should be designed and administered to increase PKT. The program is focused on minimizing the disruption of starting two treatment techniques and maximizing early transplant health, graft survival employability and retention of insurance coverage [28]. Additionally, as living donor transplantation is often a prerequisite for PKT, the discomfort individuals have in asking someone to donate must be recognized [28]. A 'Discussion Guide' to assist patients asking for a living donor kidney is shown in the following list.

- (1) Provide information about
 - (a) Living donor evaluation process and surgery
 - (b) Medical and psychosocial risks associated with being a living donor
 - (c) Role of a living donor advocate in supporting living donor
- (2) Identify benefits of openly asking family members to consider living donation
 - (a) Offers family members the opportunity to learn about transplant and to ask questions
 - (b) Provides opportunity for family to brainstorm solutions to any barriers
 - (c) Allows interested family member to volunteer and others to decline officially
 - (d) Provides interested family members with transplant center contact information and transplant education
- (3) Provide opportunity for patient to role-play and rehearse living donation discussion
 - (a) Create a list of people to include in discussion
 - (b) Brainstorm how the communication should happen: in writing, in person, through a family meeting

- (c) Clarify roles: the recipient, potential donor and transplant center must all agree to proceed in order for a living donor transplant to occur
 - (d) Practice phrasing the request, 'My medical team says living donor transplant is best for me. I want to tell you about that, hope you will consider learning more, but also don't want to pressure you.'
- (4) Prepare for a delayed response, or a 'no,' from loved ones and a way to close the conversation without harming the relationship with the potential donor.

Other techniques are story telling to friends about the need for transplant on Internet sites (Facebook, The Flood Sisters Blog (<http://floodsisters.org/blog/>), participation in webinars such as those sponsored by LivingKidney-DonorNetwork (www.lkdn.org/) or other communication pathways (Tweeter/Twitter).

Increasing preemptive transplantation

When all is said and done, PKT is the goal for ESRD care, with better outcomes, less cost and more retained quality of life. What we now know is that access to transplant evaluations is hindered by late referrals to nephrology and transplant centers, lack of nephrologists prioritizing transplant at the beginning of CKD care and lack of transplant focused education at the beginning of CKD training, especially the option for living donation. Additionally, lack of clarity as to transplant candidacy requirements and the different financial imperatives for different centers make it difficult for a nephrology office or the dialysis units to make sure that they can correctly refer a patient. Dialysis units also must share the burden as it is not in their best financial interest to refer 'healthy patients' for transplant; these units must be vigilant in developing processes that encourage transplant referral, particularly if they are participating in predialysis CKD education. An additional impediment to PKT is lack of health insurance. Forty per cent of patients rely on Medicare as the primary source of insurance for their evaluation for kidney transplantation; if a patient is younger than 65 years there is a 3-month wait on dialysis before becoming Medicare eligible. However, a patient is Medicare eligible once transplanted if not eligible by age criteria or being on dialysis at the time of evaluation. Once transplanted no matter the age, patients' evaluation and transplant are retrospectively covered. However, a new process is needed. Even if transplant centers can regain the evaluation costs after the patient becomes Medicare eligible after receiving a kidney transplant, the months of outlay without reimbursement are difficult for some centers to tolerate and the entire process is not comprehensible for most patients. And medication coverage stops after 36 months; why should a living donor donate if the organ will be lost after 3 years because the

recipient will not have access to immunosuppressive medications? Initiating Medicare coverage earlier in CKD care prior to starting dialysis would increase access to PKT. Prolonging immunosuppressive coverage for the lifetime of the allograft would increase transplant survival and decrease return to dialysis. Leaders of the 'Transplant First' initiative are in the process of encouraging modification of Medicare CKD coverage to begin with stage 4 CKD and increasing immunosuppressive medication coverage to the lifetime of the allograft (www.kidney.org/news/end_the_wait/recommendations.cfm) [7,16].

Other educational needs include a focus on primary care and nephrology education about the benefits of and process for obtaining PKT. Elementary and high school health classes need to discuss kidney disease as an aspect of healthcare people must prioritize. Community and cultural centers should be in the educational loop to get the word out about kidney disease and its treatment (e.g. www.nkdep.nih.gov/). Dialysis centers must partner with transplant centers to help educate about and facilitate transplantation for ESRD patients (www.kidney.org/news/end_the_wait/recommendations.cfm). Patient education also needs to focus on means to identify a living donor. Continual public education is needed to encourage donation from those who are healthy as well as to inform them about the possibility of living donor exchange. Ultimately, living donation helps us all. In this spirit, if people do step forward to be living donors, personal roadblocks such as lost wages, costs of travel and lodging should be incorporated into the evaluation costs of living donation. Also, life and health insurance should not be denied on the basis of prior living donor status and health insurance for all complications of donation should be provided for all living donors for their lifetime. Preventive care should also be covered by donation related healthcare policies.

Living donation is the future of transplantation and cost savings. As such, research focused on maintaining allograft function should be a priority for funding agencies. There is an increased need for financial support for research on organ preservation, transplant immunology and comparative trials of treatments that are truly unique, not only those containing older immunosuppressive medications. Preemptive kidney transplantation saves lives, improves quality of life and is the goal of ESRD care. Comprehensive healthcare reform and research should support this goal.

Conclusion

The optimal therapy for patients with ESRD is preemptive kidney transplant. This is owing to the function of the allograft and not residual kidney function. Improve-

ments in patient access to nephrology and transplant care are needed. This will require improved education of healthcare providers including dialysis units. Community education about living donation as well as policy surrounding living donor health coverage will also need to be addressed.

Acknowledgement

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 609).

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