

# Chapter 24: Renal Transplantation in the Older Adult

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## BACKGROUND

Many patients once thought too high risk for renal transplantation, including those with advancing age, are now routinely transplanted. Although the number of patients younger than 50 yr of age added to the waiting list for kidney transplantation has remained relatively static during the last decade, in the age group over 65 yr, both the number of patients newly placed on the waiting list and the number of patients transplanted have tripled in the same time frame.<sup>1</sup> Accordingly, persons over age 65 made up approximately 16% of both the waiting list and of kidney transplant recipients in 2006 compared with only 8% in 1997. Despite tremendous growth, this only represents a small fraction of kidney transplants in an age distribution that makes up one half of incident dialysis patients.

## PATIENT AND GRAFT SURVIVAL WITH RENAL TRANSPLANTATION

Kidney transplantation is the treatment modality of choice for people with ESRD. Several single-center studies have shown that kidney transplantation is safe and successful in older recipients. In suitable older candidates, renal transplantation improves patient survival over remaining on dialysis. Although renal transplantation more than doubles the expected lifetime of an older person with ESRD (Table 1), the remaining life years only reach about one half of that expected in people of the same age. Kidney allograft survival in older transplant recipients is often comparable to that of younger patients when the survival analysis is censored for death (*i.e.*, a patient who dies with a functioning graft is not viewed as a graft failure).

Longitudinal registry studies of mortality have examined the survival benefit of transplantation by comparing long-term dialysis patients who remained on the transplant waiting list with those

who received a transplant from a deceased donor. Wolfe *et al.*<sup>2</sup> evaluated >46,000 patients listed between 1991 and 1997, comparing survival by age groups, but the older age group was limited to patients who were 60 to 70 yr of age because transplantation was infrequent in people over age 70 during the study period. Older transplant recipients were shown to have an improved cumulative survival rate after the first posttransplant year. Their projected life span increased by 4 yr, and the long-term risk of death decreased by 61%.

Although waiting times and comorbidity have increased since the study of Wolfe *et al.*, it seems that renal transplantation in older adults still has acceptable results. In a more recent study using national registry data, Rao *et al.*<sup>3</sup> showed that even patients over the age of 70 derive a survival benefit with transplantation. In the long term (18 mo after transplant), the relative risk (RR) of death was 56% lower for transplant patients *versus* waiting list patients ( $P < 0.0001$ ). The survival benefit was impressive in those with diabetes or hypertension as a cause of their kidney failure; in these patients, the RR of death with a transplant dropped by 47 and 44% ( $P < 0.0001$ ).

## MORTALITY IN OLDER RENAL TRANSPLANT CANDIDATES/RECIPIENTS

The continued growth in the overall number of people registered on the renal transplant waiting list has led to a parallel increase in waiting times for older patients, increasing the odds that older patients will die before receiving a transplant. Older

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**Table 1.** Life expectancy by age group

Age Group (yr)	General US Population	Dialysis	Transplant
60–64	21	4.6	12.7
65–69	17.2	3.9	10.6
70–74	13.8	3.3	8.9
75–79	10.8	2.8	7.4

Source: USRDS 2007 Annual Data Report.

candidates who wait years for a deceased donor are at a marked disadvantage compared with younger patients because of their poorer baseline health at onset of ESRD, rapid changes in health on dialysis, and higher mortality on the waiting list. Patient age and duration of dialysis affect a transplant candidate's risk of death. A patient over age 64 who is expected to wait 5 yr for a deceased donor organ has about a 50% chance of dying before being transplanted. Furthermore, older patients have higher rates of postoperative mortality; therefore, the time to which patient survival exceeds remaining on dialysis for older transplant recipients is significantly longer than for younger recipients.

### COMORBIDITY IN OLDER RENAL TRANSPLANT CANDIDATES

Along with the aging of the dialysis population has come a higher degree of medical complexity in renal transplant candidates. Not surprisingly, a higher burden of comorbidity measured by the Charlson Comorbidity Index has been associated with increased perioperative and long-term mortality in older renal transplant recipients in the United States and Canada. A US registry study<sup>4</sup> of nearly 40,000 kidney transplant recipients (approximately 9000  $\geq$ 60 yr of age) examined the impact of increased age and comorbidities on 1-yr patient survival by including the type of donor organ (younger *versus* older deceased donors) and early organ function (immediate *versus* delayed function) in the analysis. The overall 1-yr mortality rate was 10.5%, which substantially increased in recipients of an older donor kidney with comorbidities, from 16% in diabetics to 42.3% labeled as having chronic obstructive pulmonary disease. Despite an increased burden of comorbidities, it seems that the overall survival of older transplant recipients has improved from 1990 to 1999. Regardless of multiple studies evaluating the impact of comorbidities on outcomes, no

**Table 2.** Special issues to consider in older transplant candidates and recipients

Cardiovascular disease
Infection/malignancy risk
Psychosocial factors
Immune function
Physical function
Cognition
Patient expectations/quality of life

concrete predictors exist to inform clinicians which patients will not benefit from transplant.

### PATIENT SELECTION FOR TRANSPLANTATION

Interested older ESRD patients who lack medical or surgical contraindications should be referred for a renal transplantation evaluation. Each transplant program develops its own written criteria for determining a patient's suitability for placement on the waiting list or transplantation. Therefore, one should become familiar with centers that have greater expertise or comfort in transplanting older people.

Developing more selective criteria for candidate listing among older candidates has been advocated by some in the transplant community to reduce the number of patients on the list with marginal potential gain from transplant. Unfortunately, there currently are no valid screening criteria that accurately predict which patients will have minimal gain from renal transplantation.

The most recent US clinical practice guidelines<sup>5</sup> do not set an absolute age limit for evaluating potential renal transplant candidates. As more high-risk patients are placed on the waiting list, the process of evaluating and maintaining candidacy consumes increasing resources. The standard pretransplant evaluation is heavily weighted on cardiovascular risk assessment and malignancy screening. The current approach acknowledges that social support and patient expectations must be addressed<sup>6</sup>; however, guidelines are not concrete. Physicians are encouraged to use their best judgment when deciding candidacy for older candidates and to assess potential candidates on an individual basis.

The Canadian consensus guidelines on eligibility for kidney transplantation<sup>7</sup> recommend that careful consideration of the current waiting time for a deceased donor kidney and the older patient's expected survival beyond that period should be considered when deciding whether or not to proceed with wait listing or transplantation in older patients. Although there are little data to support the assessment of physical function or nutrition in the decision-making process, the Canadian guidelines extrapolate data from other disease states that suggest that poor functional capacity or malnutrition might be associated with an increased risk of death on the waiting list or after transplantation. Additionally, cognitive function should be evaluated because it affects the ability to adhere to a complex post-transplant regimen. The trajectory of cognition in older adults after transplantation is unclear. Although many of the assessments mentioned are not routine, there are some data supporting incorporating such assessments in the future.

### WAITING LIST STATUS

It is important to recognize that, although the total number of candidates on the kidney transplant waiting list continues to

grow, the number of active patients on the kidney transplant waiting list has stabilized, and the number of inactive patients on the waiting list has rapidly expanded.<sup>1</sup> The number of patients over age 65 yr on inactive status (registered on the waiting list but will not be called in for transplant) quadrupled from 2002 to 2006, representing 17% of the inactive waiting list at the end of 2006. This finding coincides with an Organ Procurement and Transplantation Network (OPTN) policy implemented in November 2003 that allows inactive candidates to accrue points for waiting time for the entire duration of time they are listed. Although this policy acknowledges that a person's health is a dynamic process, it underscores the need for the primary nephrologist to be aware of a patient's status on the waiting list so that they may communicate with the transplant center when an individual's health status changes because older patients may have a limited window for successful transplantation. Likewise, timely communication with the transplant center may help prevent unsuitable candidates from being transplanted. Both the US and Canadian guidelines emphasize that the medical fitness of older waitlisted patients be reviewed on a regular basis.

## DONOR OPTIONS

The median waiting time for a standard deceased donor kidney for a recipient over age 65 is nearly 4 yr, which is compounded by the reality that an older person's medical suitability may decline faster on the waiting list than younger patients. Better donor organs are associated with lower death rates after renal transplantation. The majority of patients over age 65 yr receive standard donor kidneys, followed by live donors, and last, expanded donors. In an effort to expand the donor pool, two trends have emerged: the increased utilization of both older deceased and older living donors for older recipients.

## EXPANDED CRITERIA DONORS

The 2002 Expanded Criteria Donor (ECD) policy was a formal attempt by the transplant community to maximize the use of deceased donor kidneys that had been recovered for transplantation, in part by decreasing the discard rate of older donor kidneys. An expanded criteria donor is any deceased donor over age 60 or a deceased donor over age 50 with two of the three following criteria: serum creatinine >1.5 mg/dl at the time of procurement, death from cerebrovascular accident, or history of hypertension. Despite a 70% increased risk of graft failure compared with a reference group of younger ideal donor kidneys, recipients of ECD kidneys are still expected to have a survival benefit over remaining on dialysis. The ECD policy has increased access to transplantation, primarily for patients over age 50 yr, who receive the majority of ECD organs. Although the ECD policy is viewed as successful, it must be recognized that some believe that such policies unfairly direct less desirable kidneys to older people. An ongoing

challenge is to establish which patients will benefit the most from these kidneys; however, benefit analyses suggest that older patients have the most to gain when receiving an ECD reduces the waiting time to transplant. The time spent waiting for a standard deceased donor kidney varies widely by region of the country.

## OLDER LIVING DONORS

Because many older recipients will not live long enough to receive a deceased donor kidney transplant, another donor option that deserves special mention is the use of older living kidney donors. Living donation in the elderly has grown to the point that people over age 60 now receive over one third of live donor transplants. Recipients of older living donor kidneys have lower graft survival than younger living donor recipients but have superior patient and graft survival compared with all deceased donor options.

## DECISION ABOUT DONOR TYPE

Kidneys from younger and healthier donors are associated with lower death rates but require longer waiting times. Schold and Meier-Kriesche<sup>8</sup> examined whether certain patient groups would benefit from being transplanted sooner with an ECD *versus* delaying transplant in favor of possibly receiving a better donor kidney. In separate analyses, the authors estimated the expected survival for transplanted patients with short (<2 yr) *versus* longer durations (2 to 4 yr) of pretransplant dialysis. For patients over 65 yr old, the life expectancy for ECD recipients with <2 yr on dialysis was 5.6 yr, which was comparable to both Standard Criteria Donor (SCD) (5.3 yr) and living donor recipients (5.5 yr) after 4 yr of pretransplant dialysis. This is yet another study emphasizing the need for timely transplantation in older transplant candidates because the survival benefit of a standard or live donor kidney transplant seems to be negated by longer waiting times on dialysis before receiving a kidney transplant. Shifting of ECD kidneys to older patients shortly after they are placed on the waiting list and SCD kidneys to younger patients may therefore be the most efficient resource utilization, meeting the goal of expanding life expectancies for both age groups.

## POSTTRANSPLANT MANAGEMENT

### Pattern of Acute Rejection, Infections, and Malignancy

A unique aspect of transplanting older patients includes the aging of the immune system, which is clinically manifested as a lower risk of acute rejection (supported by most studies) and an increased risk of infections and death from infectious causes compared with younger transplant recipients. The risk for infections is linear in older waitlisted patients compared with an exponential slope in older transplant recipients, which suggests a magnification caused by transplant immunosuppres-

sion. The slope for posttransplant malignancies is linear in older transplant patients; however, it is steeper than that seen in similar dialysis patients on the waiting list.

Although older patients have lower rates of acute rejection, the impact of acute rejection may be more significant in this patient population. Because older patients more often receive older donor kidneys, it is believed that these grafts may not be able to recover from the insult of acute rejection, especially considering the aging milieu of the recipient that may be associated with poorer repair processes. Additionally, older patients have less reserve and may not tolerate aggressive acute rejection therapies because of the heightened risk for infection.

### Immunosuppression

The observations that older transplant recipients have lower rates of acute rejection, higher rates of infections, and an exaggerated malignancy risk have led many transplant physicians to use less aggressive immunosuppressive strategies in older transplant recipients. Options include lower drug doses or concentrations, rapid steroid withdrawal or minimization, non-lymphocyte depleting antibody induction regimens, or avoidance of induction agents altogether. Often, lower concentrations of calcineurin inhibitors (cyclosporine or tacrolimus) are targeted in recipients of expanded criteria donor kidneys to minimize the vasoconstrictive effect because many of these donor kidneys already have a certain degree of vascular disease at the time of implantation. At this time, there are insufficient data in the transplant literature to provide the clinician with the optimal immunosuppressive regimen for the older transplant recipient.

### Chronic Allograft Failure

Older recipient age is a significant risk factor for the development of interstitial fibrosis and tubular atrophy (aka, chronic allograft nephropathy). Older donor age is synergistic with older recipient age in terms of the risk for chronic graft failure, especially beyond 36 mo after transplant.

### CONCLUSIONS

The aging of the ESRD population is leading to an increased demand for renal transplantation by older adults. In carefully selected recipients, patient and graft survival are acceptable. Older transplant recipients benefit the most when transplanted sooner. Older donor kidneys (from both deceased and living donors) are increasingly used for transplantation in this population. Older recipients have lower rates of acute rejection but are at higher risk for the complications of overimmunosuppression, such as infections and malignancies. Older transplant recipients are also more likely to die with a functioning graft or lose their allograft to chronic allograft fibrosis and tubular atrophy compared with younger recipients. The optimal immunosuppressive approach is unclear, but most transplant physicians use less immunosuppression overall in the older transplant recipient.

### TAKE HOME POINTS

- There is a large and growing representation of older candidates on the kidney transplant waiting list, both active and inactive status
- The proportion of newly transplanted patients over age 65 has doubled over the past decade and is expected to continue growing
- There are no concrete predictors to aid clinicians with the selection of older people for transplantation; however, a higher burden of comorbidity has been associated with increased perioperative and long-term mortality in older renal transplant recipients
- Time spent on dialysis before renal transplantation is an important modifiable risk factor for both patient and graft survival
- Older donor kidneys (both deceased “expanded criteria” and older living donors) are increasingly being used to help meet the demand for kidney transplantation by older people with renal failure
- Expanded criteria donor (ECD) organs may decrease the waiting time to transplantation; older adults who are transplanted with ECD soon after being placed on the waiting list have similar outcomes to older recipients of younger donor kidneys.
- Older transplant recipients are at higher risk of developing infectious complications and malignancies, however, their risk of acute rejection appears lower
- In the long term, the risk for chronic allograft nephropathy is higher
- The optimal immunosuppressive regimen in older renal transplant recipients is unknown; however, clinical studies support using less immunosuppression overall

### DISCLOSURES

None.

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## REVIEW QUESTIONS: RENAL TRANSPLANTATION IN THE OLDER ADULT

1. A 71-yr-old male has been dialysis-dependent for 3 yr. He seeks your advice about his candidacy for renal transplantation and potential donor options. He previously thought he was “too old” for a transplant. He has a 60 yr old friend who is a potential donor. You determine that he is medically fit for transplant. Which of the following is a reasonable assessment of his risk?
  - a. He is at higher risk of acute and chronic rejection because of his age
  - b. He is more likely to die on dialysis than receive a young deceased donor transplant; he should consent to receiving an older live or expanded criteria donor organ
  - c. He is not a suitable candidate for transplantation because of his advanced age and prolonged time on dialysis
2. A 68-yr-old male with polycystic kidney disease wants a renal transplant so he can live longer. Which of the following statements is true?
  - a. Renal transplantation improves patient survival over remaining on dialysis
  - b. Better donor organs are associated with lower death rates
  - c. ECDs are most beneficial when they reduce the waiting time to transplant for older recipients
  - d. All of the above
3. Which of the following transplant immunosuppressive strategies is preferable in older renal transplant candidates?
  - a. No induction immunosuppression
  - b. Reduced mycophenolate mofetil (Cellcept) dose
  - c. The optimal regimen is unknown
  - d. Steroid avoidance