

Kidney Transplantation Among the Elderly: Challenges and Opportunities to Improve Outcomes



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Elderly patients (>65 years old) represent the fastest growing population among the ESRD patients and those awaiting kidney transplantation. There is ample evidence to suggest that kidney transplant in the elderly population offers the best chance of survival and improves health-related quality of life compared to remaining on dialysis. Although all these emerging facts are encouraging, this population brings with them complex medical problems including frailty, cognitive impairment, and multiple comorbidities. These issues can be barriers to transplantation and threaten the well-being of the patients after transplantation. Furthermore, aging results in changes to the immune system and affects the pharmacokinetics of immunosuppressants. All these changes can increase risk of complications such as infections and malignancy. Because death with a functioning graft is a common cause of graft loss, the new kidney allocation system has been implemented in an attempt to maximize allograft utilization and minimize unrealized graft years. This may result in longer wait-times for the elderly. In this review, we will highlight the barriers to kidney transplant, characterize transplant-related issues in the elderly, and propose alternative strategies under the new allocation system.

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The definition of an “elderly” person is somewhat arbitrary and usually refers to the age when one receives pension. Due to this lack of consensus in the age cutoff, present studies involving elderly patients suffer from a lack of uniformity and generalizability. In general, however, most studies define elderly patients as patients aged above 60 or 65 years. According to the most recent US Renal Data System annual report, the number of incident ESRD cases aged more than 65 years has increased dramatically over the past decade. Currently, elderly patients make up almost half the incident dialysis patients in the United States.¹ It is, therefore, not surprising that patients aged older than 65 years represent the fastest growing group on the wait-list with the numbers increasing from 6991 (12.9%) in 2003 to 20,115 (20.8%) in 2013.² This trend, although encouraging, fails to highlight the fact that the percentage of elderly patients wait-listed or transplanted within the first year of dialysis (9.9%) is still lower compared with the overall rate of 15.8% and is much lower compared to their younger counterparts, perhaps reflecting the reluctance and hindrance to refer elderly patients for transplantation (Fig. 1).¹ Advanced age per se is not a contraindication for transplantation, in fact, mounting evidence suggests that transplantation improves survival and quality of life in this group of patients.

The immunologic and metabolic changes that occur with aging put elderly transplant recipients at a heightened risk for infections and malignancies after transplantation. Managing the immunosuppression in this group of patients is a fine line between adequate and over immunosuppression.³ This review will highlight barriers to kidney transplantation in elderly patients with advanced CKD and characterize transplant-related issue for the elderly. We will also review the outcomes of kidney transplantation among the elderly and the influence of the new allocation policy on kidney transplant in the elderly.

BARRIERS TO KIDNEY TRANSPLANTATION IN ELDERLY TRANSPLANT CANDIDATE

With the mounting evidence that kidney transplantation offers improved survival and quality of life in ESRD patients, more elderly patients are currently being referred for transplant evaluation. This population of patients brings with them a unique set of problems, including frailty, cognitive impairment, and comorbidities less commonly seen in the other age groups.^{4,5} All these factors have been associated with morbidity and mortality after transplant.⁶ Geriatric assessment tools may provide useful information in evaluating the physical and cognitive function in these patients, as the standard workup does not always test for such things as frailty and cognitive function. Geriatric assessment tools that can be used as part of the workup include the Charlson Comorbidity Index, which assigns a score for each comorbid condition, and the sum of the scores from the different comorbid conditions is then used to predict mortality, the Lawton scale for instrumental activities of daily living, testing hand grip strength, evaluating gait speed, and administering either the mini-mental status examination or the Montreal Cognitive Assessment.⁷ The development of a model using the aforementioned assessment tools may help physicians counsel their elderly patients about

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challenges they may face after transplantation and whether kidney transplantation is the best choice for them.

Frailty and Transplantation

There have been a number of instruments developed to assess frailty. Frailty as a measure of physiological reserve was first described and validated by Fried and colleagues⁸ in the geriatric population. The concept of a frailty phenotype created by Fried and colleagues consists of 5 domains including shrinking (weight loss), weakness (decrease grip), exhaustion (effort and motivation), low physical activity, and slowed walking speed (15 feet). Each domain yields a score of 1 when present, and the higher the score, the higher the degree of frailty.^{8,9} In a systematic review of all the different tools used to assess frailty, de Vries and colleagues¹⁰ found that the frailty index was one of the better instruments developed to assess frailty as it covers all the frailty factors. The frailty index is a quantitative measure defined as the proportion of deficits (symptoms, signs, functional impairments, and laboratory abnormalities) present in an individual, which can be used to estimate survival probability.¹¹

Frailty has been shown by Makary and colleagues to be a risk factor for postoperative complications (odds ratio [OR] 2.54; 95% confidence interval [CI] = 1.12-5.77), prolonged hospital stay (OR 1.69; 95% CI = 1.28-2.23) and discharge to a skilled nursing facility (OR 20.48; 95% CI = 5.54-75.68). In the renal population, McAdams-Demarco and colleagues¹² showed that frailty is 5× higher in hemodialysis patients than in the community-dwelling older adults. The same author went on to show that in kidney transplant recipients, the presence of frailty was associated with early hospital readmission within 30 days of kidney transplant discharge (45.8% vs 28%, $p = .005$)¹³ and with mortality, whereby frail recipients had a 2.17-fold increased mortality compared to non-frail recipients (95% CI = 1.01-4.65).¹⁴ Interestingly, this association was not due to age alone as younger, frail patients also had higher mortality compared to their non-frail counterparts. Although these data do not address the question of whether frail patients should remain on dialysis or be transplanted, it does highlight the need to risk stratify and possibly optimize the functional status of transplant candidate especially elderly ESRD patients before transplantation. Studies are needed to address whether improvement in frailty improves transplant outcomes.

Cognitive Impairment and Transplantation

The association between cognitive impairment and CKD is increasingly being recognized.^{15,16} The underlying mechanism is unclear, but possible mechanisms

proposed include silent ischemia and neural toxicity due to uremic toxins.¹⁶ The proportion of patients with cognitive impairment increases with increasing age; hence, with more elderly ESRD patients being referred for transplantation, transplant physicians will need to decide whether these patients are suitable candidates for transplantation. There is a scarcity of literature regarding the transplantation of patients with any degree of cognitive impairment. Available data suggest that patients with mental impairment have comparable outcomes compared to normal controls with minimal allograft loss due to noncompliance.^{17,18} However, the transplantation of patients with cognitive impairment will require significantly more resources and strong social support to ensure that the patients are compliant with their medications after transplant.

Comorbidity and Transplantation

Comorbidities such as diabetes and hypertension are commonly seen in patients with ESRD. With increasing age, the prevalence of comorbidities increases as well.

Not surprisingly, patients with more comorbidities have a higher risk of mortality after transplantation as shown in 2 separate studies by Grosso and colleagues and Karim and colleagues, respectively. The authors retrospectively studied 223 first time deceased donor kidney transplant recipients between 2000 and 2007 and found that increasing Charlson Comorbidity Index was associated with increased risk of death after transplantation. (hazard ratio [HR] 3.87; 95% CI = 1.06-14.06)^{19,20} Similarly, Karim and colleagues reviewed

CLINICAL SUMMARY

- Kidney transplant in the elderly offers the best survival and improves health-related quality of life compared to remaining on dialysis.
- Elderly patients have complex problems such as frailty, cognitive impairment, and multiple comorbidities, all of which, threaten patient and allograft survival after transplant.
- Aging results in changes to the immune system and affects the pharmacokinetics of drugs, which may increase the risk of complications such as infections and malignancies after transplantation.
- The new allocation system, which emphasizes longevity matching, may result in longer wait-times for the elderly patients; hence, alternative strategies should be pursued.

19,103 patients transplanted in England from April 2001 through March 2012 and found that patients over 70 had an increased risk of death with a deceased donor transplant as time from transplantation progressed. At a median follow-up of 4.4 years, the risk of death was higher with certain comorbid conditions such as congestive heart failure, 60%, and peripheral vascular disease, 57.1%, compared with diabetes, 38%. The overall risk of death was attenuated if these elderly patients received a living donor vs a deceased donor transplant (20.7% vs 34.9%, $p = .002$).²¹ The current allocation system takes into account age, duration on dialysis, diagnosis of diabetes, and history of prior solid organ transplant. It does not take into account other comorbidities prevalent in the elderly population; thus, the onus of deciding whether the patient is a suitable candidate for transplant and whether this scarce resource is best used in elderly patients with limited life expectancy is on the evaluating physician. Wu and colleagues examined 266 patients aged more than

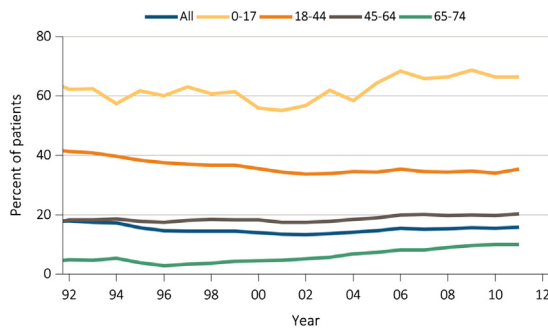


Figure 1. Percent of incident patients being wait-listed or receiving a kidney transplant within 1 year of ESRD initiation, by age. The trend of patients aged older than 65 years being wait-listed or transplanted is increasing although the percentage is still lower compared to the younger age groups. Data source: U.S. Renal Data System, USRDS 2014 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.

60 years for donor and recipient characteristics that predict patient and graft survival. The authors found that comorbidity significantly have an impact on patient survival (HR 1.17, 95% CI = 1.03-1.34) in deceased donor but not in living donor kidney transplant recipients (HR 1.01, 95% CI = 0.8-1.3) suggesting that elderly patients with multiple comorbidities may benefit from living donor transplant.²²

TRANSPLANT ISSUES IN THE ELDERLY

Aging and the Immune System

As shown in Figure 2, aging is related to changes in both drug metabolism and immune system function. Alteration

in the immune function with normal aging can lead to less effective vaccination, enhanced risk for infection, and malignancy in the elderly population.^{3,23} In the setting of transplantation, this may also translate into less allograft rejection and better allograft survival as shown in some studies.^{3,24,25} However, there has also been reports of higher rates of acute rejection especially if the donor was aged older than 65 years.^{26,27}

As the volume and morphology of the lymphoid organs undergo changes with age (increasing fatty infiltrate, fibrosis, and reduction in germinal center), there is a corresponding change in the repertoire of lymphocytes with a decrease in the number of naïve T cells (CD45RA⁺) and a shift toward more memory T cells (CD45RO⁺).^{28,29} The reduction in naïve T cell populations has been thought to be the reason for the lower rates of acute rejection seen in the elderly population, although clinically, this has not translated into successful immunosuppression minimization in this population.³⁰ Furthermore, elderly transplant patients are also noted to have a higher rate of allograft loss. Pascher and colleagues³¹ showed in their animal study that older rats receiving kidney allografts have an accelerated rate of allograft loss possibly due to the presence of more memory T cells. These findings have not been replicated in humans but do throw caution to immunosuppression minimization in the elderly transplant population. The co-stimulatory pathway including the B7-CD28-CTLA4 and CD40-CD154 pathways has been shown to be dysfunctional with aging.³² This may have implications as co-stimulation blockers such as belatacept are used in the prevention of acute rejection in kidney transplantation.

Although total lymphocyte number may be decreased in elderly individuals, production of antibody especially non-organ specific antibody (anti-dsDNA, anti histone antibody, rheumatoid factor) is increased. This has led to

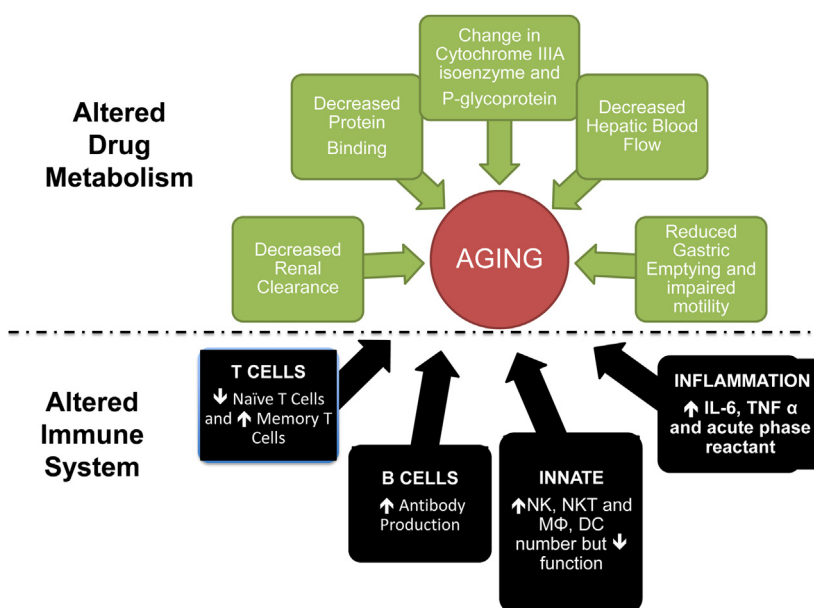


Figure 2. Age associated changes in drug metabolism and immune function.

increased autoimmunity seen in the elderly population.²⁹ There is no study, to date, looking specifically at the effect of aging on antibody-mediated rejection.³³

Aging has also been reported to affect the innate immune system, compromise signal transduction pathways including toll-like receptors, and impair cytokine release.^{32,34} In addition, aging is associated with a pro-inflammatory state.³⁴ The significance of all these changes in the transplant of an elderly candidate is still unclear, and more studies are required to determine how immunosuppression should be tailored in an elderly transplant patient in the setting of all these changes.

Aging and Immunosuppression

In addition to the immunosenescence hypothesis leading to lower acute rejection rates in the elderly, there is evidence to suggest that aging can affect drug metabolism, which may also account for the lower acute rejection rates and higher risk for infections.

Potential pharmacokinetic changes that may affect drug levels in the elderly include impaired kidney clearance, decreased protein binding resulting in increased free drug levels, and decreased hepatic blood flow, which results in a reduction in hepatic drug clearance through the cytochrome IIIA isoenzyme and the P-glycoprotein counter transport.³⁵ Jacobson and colleagues showed in the Deterioration of Kidney Allograft Function study that older recipients have a higher normalized tacrolimus trough level despite receiving a lower dose of tacrolimus compared to middle-aged or young adult recipients. A similar finding was seen in patients who received cyclosporine.³⁶ The exact cause for this finding could not be elucidated in the studies but does alert clinicians to be more vigilant when monitoring drug levels in the elderly recipients.

With the mounting evidence that elderly transplant recipients have lower acute rejection rates and increased vulnerability to infections and malignancies,³⁷ immunosuppression minimization seems like an intuitive step. However, the increasing use of expanded criteria donors (ECD) kidneys and the preferential allocation of these kidneys to elderly recipients have added another level of complexity to the immunosuppression management in this population. In a study looking at the use of induction agents in elderly transplant recipients in the United States, Gill and colleagues found that high-risk recipients (Panel Reactive Antibody > 20%, African Americans, prior kidney transplantation), or low-risk recipients who received high-risk kidneys (ECD, donation after cardiac death, or cold ischemic time > 24 hours) had a higher risk of rejection and functional graft loss with the use of IL2 receptor antagonist compared to rabbit anti-thymocyte globulin (rATG).³⁸ In this study, low-risk recipients who received low-risk kidneys had similar long-term outcomes whether they received IL2 receptor antagonist or rATG. Palanisamy and colleagues,³⁹ similarly, found that elderly patients treated with rATG had lower acute rejection rates and better quality of life although the difference did not reach statistical significance for the former outcome.

This seemingly conflicting data with elderly patients having lower acute rejection risk yet do better with stronger induction agents could be explained by: (1) The enhanced immunogenicity of kidneys from older donors, which may increase the risk of acute rejection⁴⁰; (2) Elderly kidney recipients who have experienced acute rejection have worse outcomes compared with their younger counterparts due to lower kidney reserve and higher risk of infectious complications when they are treated for rejection.^{41,42}

There have been no studies looking at the different maintenance immunosuppression regimens on transplant outcomes in elderly transplant recipients. The dearth of data to guide the management of immunosuppression in elderly transplant patients suggest that prospective studies are needed to better understand which induction and maintenance regimens are better suited for improving transplant outcomes in the elderly. With advancements in the field of immunology and molecular biology, there is ample literature looking at the effect of immunosuppressant on the various cell population and gene expressions after transplantation.⁴³⁻⁴⁵ Perhaps, the best strategy for the elderly patients would be to individualize their immunosuppressive regimen based on their immune reserve rather than relying on the current "one size fits all" approach. To date, however, there have been no studies that use the immunophenotype of patient to tailor immunosuppressants after transplant.

OUTCOMES OF KIDNEY TRANSPLANT IN THE ELDERLY

Patient and Allograft Survival

A number of studies have shown improvement in overall life expectancy for those who have received a kidney transplant compared with those who remain on dialysis and on the wait-list. In a landmark study, Wolfe and colleagues examined mortality rates in 22,889 dialysis patients on the wait-list and compared them with those of 23,275 patients who received a cadaveric kidney transplant between the years of 1991 and 1997. Elderly patients between ages of 60 to 74 had a 61% reduction in the long-term risk of death after transplant compared with wait-listed patients. There was also a projected increase in life span of 4 years in patients between the ages of 60 and 74 years.⁴⁶ Rao and colleagues, examined mortality rates in 5667 patients aged older than 70 years who were either wait-listed on dialysis or had received a kidney transplant. The mortality risk was 56% lower for transplant recipients (relative risk = 0.44; 95% CI = 0.39-0.50). Patients with diabetes as the cause of ESRD had a 47% lower mortality risk compared with wait-listed patients, and those with hypertension had a 44% lower risk.⁴⁷ A Norwegian study also found a survival advantage favoring transplantation for patients aged 70 years and older. Five-year survival was 31% among wait-listed patients and 49% in transplant recipients.⁴⁸ The study population was analyzed according to year in which dialysis was started as well. They found that there was no apparent benefit of transplantation in the group who started dialysis between 1990 and 1999 ($n = 173$; HR 1.01; CI = 0.58-1.75), whereas there was a significant

benefit of transplantation among those starting dialysis between 2000 and 2005 ($n = 113$; HR 0.40; CI = 0.19-0.83).⁴⁸ The European Renal Association-European Transplant Association's annual report includes data from national and regional kidney registries from 30 countries in Europe. Per the 2011 annual report, the probability of patient survival after deceased donor transplant was higher in those patients aged 65 years and older at 5 years in the adjusted model, adjusted for gender, and primary kidney disease, compared with those patients on dialysis (71.7% vs 28.1%). Patients who received a living donor transplant had an even higher probability of survival at 84.8% at 5 years.⁴⁹ Finally, in an analysis looking at the Organ Procurement and Transplantation Network (OPTN)/United Network of Organ Sharing database, Huang and colleagues showed that kidney transplant recipients aged older than 80 years have a higher perioperative mortality and a lower 2-year patient survival compared with recipients aged between 60 and 69 years old. However, death-censored graft survival was comparable. In addition, comparable survival was observed between recipients of standard criteria donor and ECD kidneys.⁵⁰

Health-Related Quality of Life

Among older adults with kidney failure, improvements in health-related quality of life (HRQoL) related to kidney transplant may be a key consideration. Transplantation has been widely held to improve HRQoL. A meta-analysis of 14,500 transplant patients demonstrated significant improvements in physical, mental, and social well-being.⁵¹ In this meta-analysis, there was no examination of whether the elderly had a different benefit from kidney transplant compared with younger recipients. More recently, Fujisawa and colleagues studied the differences in scoring between transplant patients and those on hemodialysis. In the areas of physical functioning, bodily pain, general health, and social functioning, kidney transplant patients had significantly higher scores compared with dialysis patients. There was, however, no significant difference between scaled scores of patients who had received a cadaveric vs living donor transplant or between men and women.⁵² Rebollo and colleagues examined HRQoL in transplant patients, chronic dialysis patients, and the general population using the Spanish version of the Short-Form-36. Transplant patients were shown to have similar HRQoL compared with that of the general population, with differences being very small in the group of patients aged older than 65 years. Transplant patients aged older than 65 years had significantly higher scores compared with chronic hemodialysis patients in the categories of physical functioning, general health perception, and mental health.⁵³ A Canadian study that focused on utility of transplantation, measured cost-utility in both patients aged younger than 60 years and those aged older than 60 years. In patients aged more than 60 years, the cost of pretransplant care was 65,720 annually, by 2 years after transplant, the cost of care was 21,160 annually. Costs were mostly decreased secondary to decreased health-care contact time, decrease in child care-associated costs, and decrease in transportation costs.⁵⁴

IMPACT OF THE NEW ALLOCATION POLICY ON KIDNEY TRANSPLANTATION IN THE ELDERLY

As the gap between kidney supply and demand continues to widen, there is an increasing need for a better allocation system—one that promotes maximum utilization of the current available kidney allografts, minimizes unrealized graft years, and lowers allograft discard rates. In 2003, OPTN Board of Directors instructed the Kidney Allocation Review Subcommittee to review the existing allocation policy. Several policy changes later, an allocation policy based on the Kidney Donor Profile Index with longevity matching was approved by OPTN and officially implemented in January 2015.⁵⁵ With the new policy, the top 20% of candidates with the highest estimated post-transplant survival will receive priority for kidneys with a Kidney Donor Profile Index of $\leq 20\%$. Under this new age-matched allocation system, it remains to be seen whether elderly patient will have to wait longer for a kidney. In the meantime, encouraging elderly transplant candidates to consider alternatives including accepting an ECD kidney or exploring living donor transplant should be reinforced to minimize time on dialysis.

The impact of wait-time on outcomes was shown in the study conducted by Gill and colleagues. The authors showed that survival benefit decreases with increase in wait-time, and the effect was particularly significant in elderly patients with more comorbidities.⁵⁶ Elderly transplant candidates are also at high risk of dying while on the waiting list as demonstrated in the article by Schold and colleagues⁵⁷ whereby 46% of transplant candidates aged older than 60 years are projected to die before receiving a deceased donor kidney transplant. For this reason, to minimize time on dialysis, elderly transplant candidates may consider accepting an ECD kidney. Schold and Meier-Kriesche⁵⁸ showed that elderly patients who accept an ECD kidney after 2 years on dialysis have comparable survival rates (5.6 years) to elderly patients who receive a standard criteria donor kidney (5.3 years) or living donor kidney (5.5 years) after 4 years of dialysis. Based on the aforementioned findings, older transplant candidates with high comorbid burden should consider receiving a lower quality kidney to minimize wait-time and lower the risk of dying while awaiting kidney transplant.

Elderly patients may also benefit from receiving a kidney from a living donor. Wu and colleagues examined the effects of baseline comorbidities on kidney transplant outcomes in transplant recipients aged older than 60 years. The elderly patient with greater baseline comorbidity had significantly worse patient and graft survival compared with those patients aged younger than 60 years, but this effect was attenuated in older patients who received a kidney from a living donor. Baseline comorbidity was not different between recipients of kidneys from living vs deceased donors.²²

CONCLUSION

Kidney transplant confers a survival advantage in elderly ESRD patients and also has a positive impact on HRQoL. Although it is encouraging that the referral rates for kidney transplant have improved in this population, there are still many barriers to transplantation for these patients.

There is also a paucity of kidney transplant studies that include elderly patients; hence, data to help guide the management of immunosuppressant in this population are severely lacking. A clear need exist for more studies to be conducted in this population to better elucidate the best strategies for pretransplant evaluation to optimize patients for transplant and for post-transplant care in this population.

Geriatric syndromes including frailty, cognitive impairment, and falls are commonly seen in the elderly ESRD patients and may stand in the way of a successful transplant. Increasing efforts to address these problems before transplantation will be prudent to the improvement of transplant referral rates and the transplant outcomes in these patients. Furthermore, the increasing awareness of these problems in this population is needed to allocate more resources to help these patients with their daily activities and enhance compliance after transplantation. The increasing understanding of changes in the immune system and drug metabolism with age has led the transplant community to realize that management of these elderly transplant recipients may be different compared with their younger counterparts. Yet, there are very few studies to guide the care of these patients. More studies targeting this population are needed to help us better understand the issues that affect the elderly transplant patients and how we can tailor their immunosuppression to optimize outcomes. Finally, with the new allocation policy in place, it remains to be seen the impact of the system on the elderly transplant candidates. In the meantime, transplant centers should continue to encourage living donor or ECD kidney transplant to minimize wait-time on dialysis. With these efforts to understand and improve care in these patients, kidney physicians will be more prepared to face the increasing demand from elderly dialysis population who will eventually be referred for transplantation.

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