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REVIEW

An old virtue to improve senior programs

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Summary

Over the past decades, there have been significant demographic changes in patients awaiting deceased donor kidney transplants, with the largest increases in the ≥65 year-age group. Because most allograft failures in older recipients are the result of death with a functioning graft, the transplant community has adopted the position that older donor kidneys, with reduced half-lives, often can provide suitable, lifelong function for an elderly recipient. Since 1999, the Eurotransplant Senior Program (ESP) allocates kidneys from donors ≥65 years, without prospective matching for HLA antigens, to local transplant candidates ≥65 years. The rationale behind this policy was to expedite the change of the elderly to receive a transplant and to reduce cold ischemia time to prevent ischemic injury and hereby delayed graft function and the increased risk of rejection. Two issues have been identified with the use of old donor kidneys. First, there is an increased incidence of acute interstitial rejection, compared with kidneys from younger donors and secondly, once a rejection episode occurs, the ability to mount a tissue repair process seems impaired. Especially in the elderly, avoiding acute rejection must be balanced against the greater risk of excessive immunosuppression, putting these recipients at higher risk of infection and malignancy. Combined matching for age as well as HLA-DR antigens may further improve the results of Senior Programs.

Introduction

In the Western world, there is a progressive increase in the number of patients with end stage renal failure, which is mainly because of an increase in patients aged 65–75 years and, in more recent years, over the age of 75 year. As successful renal transplantation improves both longevity and quality of life compared with long-term dialysis treatment [1], more elderly patients are placed on the transplant waiting list. Within Eurotransplant, between 1991 and 2007, there has been a significant increase in kidney transplant recipients over 65 years from 3.6% to 19.7%, while the proportions of patients aged 46–64 year remained the same and those aged <46 year decreased (Fig. 1). In the meantime, also the demand for kidneys has increased progressively and the pressure to expand criteria of donor acceptability has intensified continuously. Whereas donor age over 40 years was once a major reason cited for discarding kidneys from deceased donors, between 1988 and 1995, UNOS registered a 172% increase in the number of deceased donors of over 50 years of age, which resulted in an increase in older donors from 12% to 25% [2]. In Eurotransplant, between 1991 and 2007, the proportion of older kidney donors increased significantly from 12.5% to 38.5% (>55 years) and from 2.3% to 18.1% (>64 years) (Fig. 1). Improved patient survival is a well-established benefit of renal transplantation, but the magnitude of improved patient survival is not uniform across patient subgroups [1]. Older recipients are more likely to die with a functioning graft than younger recipients, whereas death-censored graft failure, defined as a need for re-transplantation or maintenance dialysis, is less common [3,4]. In the elderly, infectious causes are among the leading primary causes of death. Patients over 60 years, who receive kidney from older deceased donors

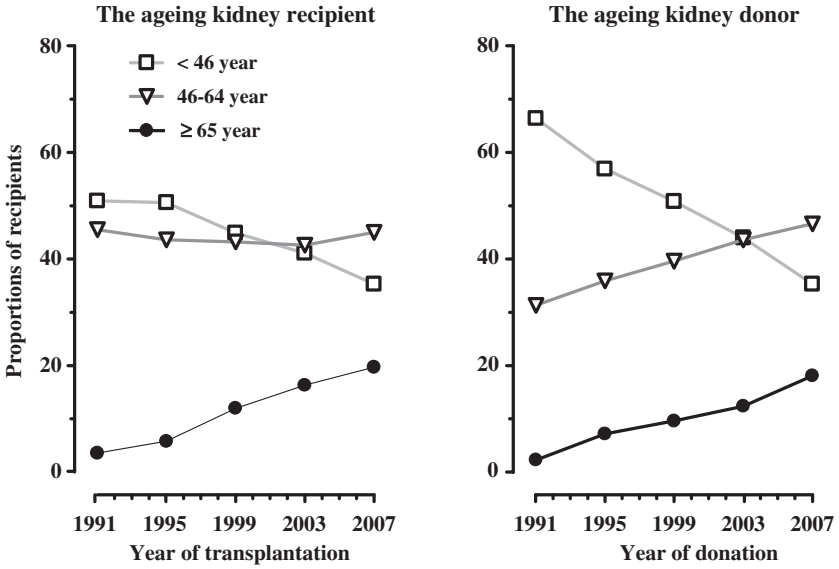

Figure 1 Proportions of Recipients and deceased kidney Donors according to Age.

are also more likely to experience an acute rejection episode [5] and have an increased risk of chronic allograft loss [6]. Part of the increased risk of chronic allograft nephropathy may be explained by an increased susceptibility to calcineurin inhibitor (cyclosporine or tacrolimus) related nephrotoxicity [7]. Calcineurin inhibitor minimization would seem especially attractive to recipients of older donor kidneys [8], but it is important to note that if they experience a single acute rejection episode, this is more likely to shorten graft and patient survival significantly [9].

Patient survival in the elderly

There are no randomized trials comparing the clinical outcomes of transplantation with dialysis in the elderly. The study by Wolfe *et al.* on mortality in dialysis and transplant patients showed that death rates were lower in transplanted patients compared with those who remained on the waiting list. This benefit extended to all causes of end-stage renal disease (e.g. glomerulonephritis, congenital renal disease, diabetes mellitus, and hypertension) and all categories of patients. This landmark study compared 228.552 patients on dialysis, of whom 46.164 had been placed on the waiting list for a first deceased donor renal transplant, with 23.275 transplant recipients. Overall mortality in transplant recipients of all ages was consistently less than that for age-matched patients who remained on the waiting list. For patients over 60 years, annual death rates (per 100 patient years) were 23.2 while on dialysis, 10.0 on the waiting list, and 7.4 after transplantation. The relative benefit of transplantation has since been confirmed and extended to patients over the age of 70 years [10] and even over the age of 75 years [11]. After the first year, excluding excess initial mortality associated with the transplant procedure, the projected increase in life span of patients aged 60–74 was about 4 years with a 29% decrease in the long-term risk of death 5 years after transplantation. Also, recipients over 65 years of age who received expanded criteria kidneys lived on average 3.8 years longer than their wait-listed counterparts, despite lower graft outcomes [12]. The important perspective remains that successful transplantation with either a regular or even a marginal donor kidney is associated with a substantial improvement in longevity and in quality of life.

Nearly 50% of graft loss in older patients occurred because of death versus only 15% in younger patients [13]. In itself it is not surprising that mortality rates after transplantation are greater in the elderly [14]. Several studies have documented an increased incidence of infections, including opportunistic infections, with increasing age of the transplant recipient. Of note, in patients ≥65 years the annual adjusted infectious disease death rate approaches that of patients on dialysis (16.7 and 20.0 per 1000 patients), while infectious death rates were 6.1 and 15.4 for transplant recipients and wait-listed patients aged 40–49 years, respectively [15]. The risk of infectious death increased with increasing age, being 5-fold greater for recipients over the age of 65 years compared with recipients aged 30–39 years [5]. In a case control study, comparing the incidence of infection in transplant recipients older and younger than 65 years, the increased incidence of fungal and viral infections were not significantly different, but bacterial infections occurred in 70% of the elderly compared to 28% of the younger patients [16]. Death caused by infection only occurred in the older patients.

Graft survival in the elderly

Excluding patient death, chronic allograft nephropathy is the major cause of late graft loss after renal transplantation [17,18]. An independently increased risk of chronic renal allograft loss has been reported in the elderly [6]. When graft survival is censored for patient death, there appears to be an inconsistency in different studies with respect to outcome in older and younger transplant recipients. In a study including 1100 patients transplanted in Scotland between 1989 and 1999, 8-year patient survival was 82%, 49% and 33% for those aged 18–49 years, 60–65 years and ≥65 years, respectively [19]. When graft survival was censored for patient death, 8-year graft survival was approximately 70% in all age groups. Using USRDS data collected between 1988 and 1997, uncensored graft survival fell from approximately 60% at 8 years for recipients aged 18–49 years to approximately 30% for those ≥65 years [6]. In this study, an effect of age was also observed when graft survival was censored for patient death. Death-censored graft loss was approximately 70% in patients aged 19–49 years, but approximately 50% in those ≥65 years. Using the Eurotransplant data of all consecutive transplants performed between January 1 2000 and January 1 2005, graft survival at 1 year after transplantation was significantly ($P < 0.0001$) worse in recipients ≥65 years than in all other recipient age groups (Fig. 2).

The time to failure of a renal allograft is determined by the initial function achieved after transplantation, the number and severity of insults, and a number of tissue characteristics. The insults a graft usually encounters include ischemia/reperfusion injury, acute rejection episodes, drug-related nephrotoxicity, hypertension and hyperlipidemia. Tissue susceptibility to injury and its ability to repair damage are important tissue characteristics. Pharmacokinetic parameters are generally little influenced by age, but the degree to which the drug suppresses the immune system or the greater susceptibility of kidneys from older donors to the nephrotoxic effect of certain drugs is unpredictable. Longitudinal studies of elderly individuals have shown with aging a diminution in renal reserve, along with functional constraints on the kidney's ability to respond appropriately to challenges of either excesses or deficits [20]. There appears to be a more delicate balance between adequate immunosuppression and excess non-immune toxicity. This is supported by the fact that at the present outcome parameters in the elderly are dominated by increased death from cardiovascular causes and infectious diseases.

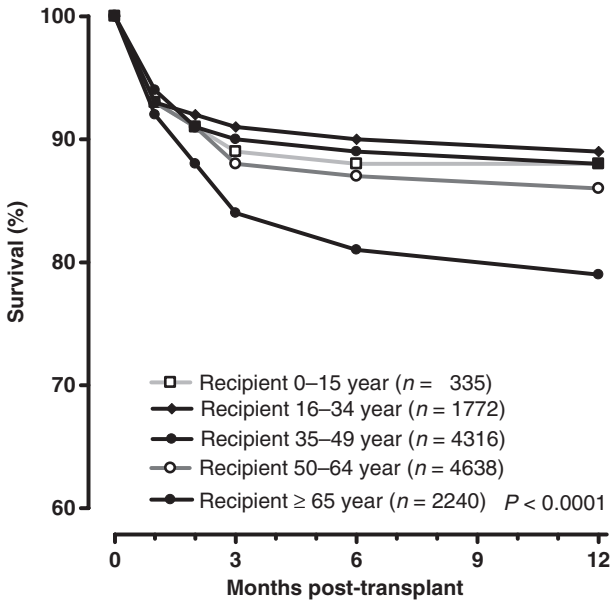

Figure 2 Graft Survival stratified by Recipi ent Age Consecutive first deceased donor kidney transplants. Eurotransplant Jan 1, 2000–Dec 31, 2004.

Acute rejections with intimal arteriitis have a negative impact on graft prognosis, whereas acute interstitial rejection episodes had no discernible impact [21]. As older kidneys experience an increase in *interstitial type* acute rejection episodes that are associated with increased graft loss later on, this suggests an age-related limited ability of the tissue to repair after injury [9]. Consistent with this view is a study from Spain in which an increased graft loss was observed of kidneys from old donors if such kidneys had experienced acute rejection episodes or delayed graft function [22]. In a time-dependent analysis of risk factors for graft loss, delayed graft function and acute rejection were identified as risk factors for graft loss in the first 5 years but thereafter donor age seemed to be the most important factor [23]. Prophylactic treatment with anti-lymphocyte antibodies was administered to a substantial fraction of these patients [22,23] or only rejections requiring antibody therapy were considered [23].

The explanation for the increased loss of grafts from old donors that have experienced acute rejection episodes is that such kidneys have fewer nephrons that function adequately and that the summation of damage results in an earlier demise of the graft compared with younger donor kidneys. Previous studies have reported that old donor age or the presence of one or more acute rejection episodes are associated with decreased death-censored graft survival [24]. Although there is increasing evidence that subclinical acute rejection is associated with the subsequent development of chronic allograft nephropathy [25–28], a causal link between asymptomatic infiltrates and chronic allograft nephropathy has not been formally proven. It has been proposed that graft parenchymal cells undergo premature senescence or aging as a result of multiple injuries and repair [29,30]. If progressive loss of renal mass or

senescence is the mechanism of increased graft loss, then it is expected that grafts from older donors show a progressive decrease with time and that the rate of decline of function correlates with donor age. However, Kasiske *et al.* found no effect of donor age on the rate of decline in graft function between 1 year and last follow-up [31]. Current data best fit the hypothesis that increased graft loss of older donor kidneys is related to summation of injury, including an increased incidence of acute rejection episodes, in the early post-transplantation months together with an impaired ability to repair the tissue (Fig. 3).

Quality of the transplanted tissue appears to be a key factor to explain the striking difference between renal allografts from living and deceased donors, both in the incidence of acute rejection and chronic allograft nephropathy [32–34]. A long held belief is that the adverse effect of donor age on graft survival is only evident in deceased donor transplants, but not in selected living donor transplants [24]. A recent study from Norway however challenged this view, reporting an increased incidence of acute rejection episodes when the live donor was over 65 years of age [35]. In their multivariate analysis, donor age over 65 years and steroid-resistant acute rejection were independent risk factors for graft loss between 3 months and 5 years post-transplant.

Age-matching for the elderly

The disparities of organ availability, disproportionate numbers of patients placed on the waiting list, and the aging population with end-stage renal disease have resulted in the development of old-for-old transplantation programs. As most allograft failures in older recipients were the result of death with a functioning graft, the transplant community has adopted the position that older donor kidneys, with reduced half-lives, often can provide suitable, lifelong function for an elderly recipient.

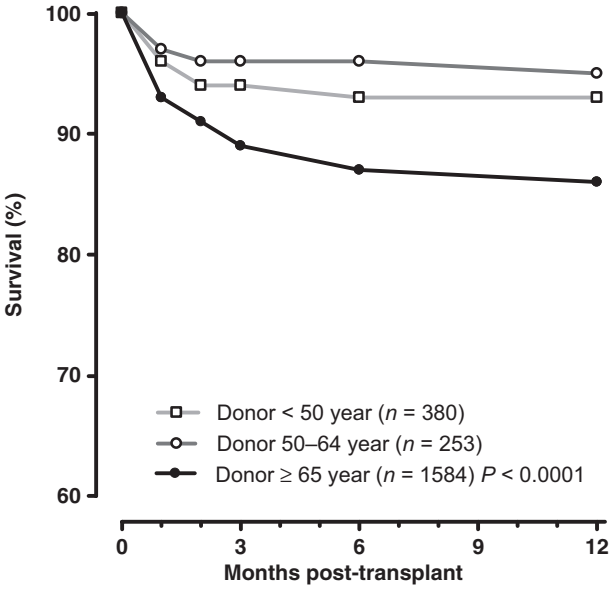

Figure 3 Death-censored Graft survival Recipients >65 years stratified by donor age Consecutive first deceased donor kidney transplants. Eurotransplant Jan 1, 2000–Dec 31, 2004.

The survival of older kidneys according to recipient age has been examined in more than 74 000 UNOS patients [3]. Giving older kidneys to older recipients did not appear to have a major effect on graft survival independent of the effects of recipient and donor age *per se* as there did not appear to be any consistent interactions of specific recipient donor combinations. There was no consistent pattern across all of the possible recipient-donor age combinations that would suggest that giving younger or older kidneys to younger or older recipients altered the risk of graft failure [3]. In a multivariate Cox proportional hazard analysis, kidneys from donors of 55 years of age or older, the risk of graft failure was not higher or lower for recipients of different ages. This is in accordance with the data from two single-center studies that failed to find an independent effect of donor and recipient age differences on graft survival [4,36]. As was the case for graft survival, giving older kidneys to older recipients did not appear to have any major effects on patient survival, or death-censored graft survival, independent of the effects of recipient and donor age *per se*.

An analysis of the same UNOS database has also shown that between 1988 and 1998, recipients over 54 years 46.2% more often received a kidney from a deceased donor over 54 years than expected if differences in recipient and donor age had not been a factor in deciding to accept an offered kidney for transplantation or not. These recipients less often (33.5%) received kidneys from donors 18 to 29 years old than expected [3]. Thus, in the past decades, there was indeed a selection bias in clinical practice to allocate kidneys from old donors to older recipients and it has even been suggested that the outcome of transplantation of older kidneys can be optimized when these kidneys are transplanted into older recipients [37,38]. The most important argument to be reluctant with allocating kidneys from older deceased donors to younger (especially under 50 years) recipients is the significantly increased risk of transplant failure [39]. At 5 years, there is already a 25% difference in graft survival rate between transplants from young and old donors, and the projected graft half-life decreased from 10.2 years if the donor was between 16 and 20 years of age to 5 years for grafts that came from donors who were 60 years of age [40]. In a retrospective analysis of more than 1200 transplant recipients, the combination of a young recipient and a donor older than 55 years yielded

the worst outcome at 8 years with a graft survival of only 24% [41]. Interestingly, the best outcome was observed if an older donor kidney was allocated to an elderly recipient. It was noted, however, that regardless of recipient age, graft loss because of rejection was higher with kidneys from older donors [41]. The poorer graft survival of older kidneys has been attributed in part to a greater susceptibility to ischemia-reperfusion injury and delayed graft function, which in turn may make the allograft more susceptible to acute rejection and graft failure [22].

Since 1999, the current Eurotransplant Senior Program (ESP) allocates kidneys from older (≥65 years old) donors, without prospective matching for HLA antigens, to older (≥65 years old) local transplant candidates [42]. Allocation without the effort to achieve matching for HLA antigens constituted a significant deviation from European allocation standards. Recently, the program also accepted re-transplants or immunized recipients, provided unacceptable antigens were identified and excluded by the transplanting center. The rationale behind this policy was to expedite the change of the elderly to receive a transplant and to reduce the incidence of delayed graft function. Such an allocation system encouraged the use of older donor organs that otherwise might have been discarded and also placed older recipients on the transplant waiting list.

The impact of increasing age on death-censored graft outcome appears to be amplified if the age of the kidney donor is also taken into account. Patients aged ≥65 years who received a kidney from a donor aged ≥55 years had a relative risk of graft loss that was 3.6-fold greater than patients aged 18–34 years receiving a kidney from donor aged 16 to 24 years [43]. The additional effect of increasing donor age on death-censored graft survival is also apparent within recipients aged ≥65 years transplanted in the Eurotransplant countries between January 1, 2000 and December 31, 2004 (Fig. 3). A significant ($P < 0.0001$) difference in death-censored graft loss, occurring within the first 3 months, was found in recipients ≥65 years who received a kidney from a donor ≥65 years of age. This observation has a great clinical significance, as even without specific old-for-old allocation there is already a powerful trend in clinical practice to offer older kidneys to older recipients [44]. Both recipient and donor age have important effects on graft survival, but the effects of donor age are much stronger than those of recipient age.

The aging kidney and the challenges of transplantation

According to a large multivariate analysis, 30% in variability in long-term graft outcome could be explained by donor age [45]. One explanation may be the observed selection bias over the past decades to allocate kidneys from old donors to older recipients [3]. In addition, two other issues have been identified with the use of old donor kidneys. First, there is an increased incidence of acute interstitial rejection, compared with kidneys from younger donors and second, once a rejection episode occurs, the ability to mount a tissue repair process seems impaired. This view is supported by the fact that the adverse effect of donor age on graft survival was found in deceased donor transplants over the age of 50 years [9], as well as in living donor transplants 65 years or older [24].

Aging is a normal biological process characterized by atrophy and the gradual loss of functioning cells with a genetically determined susceptibility [46,47]. On the other hand, the finding that approximately a third of patients in their eighties, in particular those without cardiovascular risk factors, did not show any change in the glomerular filtration rate [48] and that some inbred rat strains do not develop age-related renal damage [49], suggest that the renal dysfunction in the majority of the elderly is because of accumulation of injuries induced by minimal and/or clinically undetected renal disease on top of the aging process itself.

Tissue injury, irrespective of the cause, elicits a stereotypic response, which increases the immunogenicity [50]. Several studies have documented that recipients of kidneys from older donors are more likely to experience acute rejection episodes [9,41,51–53]. These studies have recently been confirmed by the 5-year analyses of the Eurotransplant Senior Program [54]. The increased immunogenicity may be explained by the presence of pro-inflammatory cytokines, increased expression of major histocompatibility complex antigens in epithelial and endothelial cells or the recruitment and activation of antigen-presenting cells [55–58]. In a study of 304 living donor transplant recipients with stable graft function, those with borderline changes or asymptomatic infiltrates in protocol biopsy specimens at day 14 after transplantation were found to have a higher incidence of acute rejection than those with normal biopsies [59]. Untreated borderline infiltrates in clinical biopsies performed 2–3 months after deceased donor transplantation tended to persist, but the majority (72%) did not progress to clinical acute rejection within the next 40 days [60]. Newer drug regimen significantly reduced the incidence of both early and late clinical acute rejection, but disappointingly, the prevalence of subclinical rejection remained essentially unchanged [61]. A relative shift from subclinical rejection towards clinically apparent rejection in these more to injury susceptible older kidneys could explain why recipients of kidneys from older donors are more likely to experience acute rejection episodes [9,41,51–53].

How to improve outcome in the elderly

Several studies have shown that outcome after deceased donor transplantation is influenced by independent parameters as cold ischemia, donor and recipient age and gender, sensitization (percent panel reactive antibody), and HLA compatibility [62–65]. Also in the current era of very effective immunosuppressive therapy, the advantage of HLA compatibility is still evident from the superior graft survival of fully HLA-matched kidney grafts [66]. The excellent results achieved with living unrelated kidney donation have indicated that factors, such as HLA-matching and donor age, may be less important than the benefit of receiving a (selected) kidney with normal renal function without the summation of insults associated with brain death and cold storage [32]. As the lowest graft survival rates have been observed in six HLA mismatched transplants, the decision to use kidneys from older deceased donors without prospective matching is less straightforward.

The presumption that elderly patients are less prone to acute rejection is an oversimplification of clinical practice. In general, it can be stated that the immune response is naturally depressed in the elderly, a condition sometimes referred to as immune senescence. With aging, the T-cell-dependent antibody response after vaccination, interleukin-2 synthesis, IL-2 receptor density on T lymphocytes, activator protein-1 and T cell nuclear factor have all been reported to decrease [67–69]. Many of these data, however, were obtained comparing individuals at the extremes of age and not in the for-renal-transplantation-most-relevant-age categories. Therefore, although it is conceivable that the alterations in immune responsiveness with aging have an effect on the risk of infection in the elderly, the magnitude of this effect for the prevention of acute rejection episodes appears to be rather small. In our experience, even with a dual immunosuppressive regimen consisting of steroids and ciclosporine, the difference in the incidence of acute rejection episodes in patients over 50 years of age was modest and only found with kidneys from young donors [9]. No difference in acute rejection was noticed following transplantation of an older donor kidney either in patients over 50 or 60 years of age at the time of transplantation [9,70]. In addition, recent data also indicate an independently increased risk of chronic renal allograft loss in the elderly [6].

In theory, one could improve the outcome of old donor kidneys by the prevention of delayed graft function as well as acute rejection episodes. It is conceivable that early and potent immunosuppressive therapy attenuates the interaction between renal aging changes, ischemia-reperfusion injury and the immune response. Thus, there are suggestions that prophylactic treatment with anti-lymphocyte antibodies may decrease the increased incidence acute rejection of older donor kidneys. Such an approach may be acceptable for younger recipients, but given the excess rates of infectious complications, it should be seriously questioned in the elderly. Avoiding acute rejection by antibody therapy must be balanced against the greater risk of over immunosuppression in the elderly, putting these recipients at higher risk of infections and malignancies [71,72].

HLA-DR matching was shown to be important in the first period of transplantation, followed by HLA-B, and finally HLA-A [73,74]. Both acute rejection and subclinical rejection are associated with the degree of incompatibility for HLA-DR antigens [59,75–77]. Asymptomatic infiltrates in early biopsies after living donor transplantation most likely represent a donor-specific immune response as it correlated with HLA-DR mismatching, underscoring the fact that clinical immunosuppression is imperfect [59,78]. A more sophisticated way to improve the balance in the elderly is to combine age-matching with the old virtue of prospective matching for HLA-DR antigens [74]. Foreign tissue antigens tend to be ignored unless the tissue is injured in which case it is more likely that they provoke and activate an immune response [79]. Grafts from older deceased donors already have more age related injury and inflammation at the time of procurement and transplantation [80–83], which in turn may increase immune recognition. After deceased donor transplantation, older donor age and the presence of chronic lesions, defined by interstitial fibrosis and tubular atrophy, at the time of implantation were found to be associated with subclinical inflammation in protocol biopsies obtained 3 months after transplantation [75]. Although data from the UNOS registry have suggested that the poor 5-year graft survival rate of kidneys from donors over age 60 is not improved with better matching for HLA antigens [40], the effect of matching for HLA-class II antigens on the incidence of acute rejection in the elderly remains to be determined [74]. Since the past decade only 7% of all kidneys have been allocated with 2 HLA-DR mismatches, the experience with 2 HLA-DR mismatched transplants within the Eurotransplant community is still very limited..

The net benefit of preventing delayed graft function over matching for HLA antigens is however still unresolved. Including DR-compatibility in old-for-old allocation is a feasible option, as the polymorphism of HLA-DR is far lower than that for HLA-A and HLA-B. Matching for the seroequivalent of HLA-DR antigens implies in case of the ''broad'' antigens only 10 specificities. A small simulation study performed by analyzing 541 consecutive organ donors procured in 46 centers (six countries, with small, medium, and large centers) in

Eurotransplant revealed that only 24/541 (4.4%) could not be allocated with full HLA-DR compatibility locally, but in all cases nationally (unpublished observation). Even with (limited) prospective matching, the ESP data suggest that there are several additional options to reduce cold ischemia times. As the large majority of kidneys can be allocated locally or regionally, inclusion of full HLA-DR compatibility as the primary allocation criterion is not expected to result in increased cold ischemia times, but may reduce acute rejection rates and transportation costs. The main gain, however, is expected on the side of the patients, because all patients irrespective of their HLA phenotype will have a similar chance to receive a well-matched organ which is associated with a decreased incidence of acute rejection during the fist post-transplantation year, resulting in better renal allograft function and survival.

Conclusion

Over the past decades, there have been significant demographic changes in patients awaiting deceased donor kidney transplants. In particular, the waiting list for renal transplantation has grown significantly older, with the largest increases in the ≥65 years age group. At present, outcome parameters in the elderly are dominated by increased death from infectious disease causes. The impact of increasing age on death-censored graft outcome appears to be amplified if also the age of the kidney donor is taken into account. The therapeutic index for clinical immune suppression appears to be even narrower in the elderly than in younger renal transplant recipients [6,84]. Although difficult to prove, a causative relationship between treatment of acute rejections and increased morbidity and mortality caused by infections in the elderly is highly likely. There is no doubt that extra boluses of steroids or treatment with poly- or monoclonal antibodies add significantly to post-transplant morbidity. Recently, a new deceased donor kidney allocation system, including a strategy to rank candidates in part by the estimated incremental years of life that are expected to be achieved with a transplant from a specific available deceased donor, has been proposed [85]. This concept, termed life years from transplant or LYFT, may prove to be a valuable tool to redesign allocation systems and may in the future become available for a wider range of recipients and potential donor kidneys, including extended-criteria donors and living donors.

The Eurotransplant Senior DR-compatible Program (ESDP) is a new initiative to introduce full HLA-DR compatibility (defined as 0 HLA-DR mismatches), while maintaining the ESP principle of local or regional allocation and reduced cold ischemia times. Especially in the elderly, allocation of older deceased donor kidney based on DR-compatibility, reducing the need for rejection treatments and the additional risk of infectious complications, may prove to be the preferred future approach. The validity of this approach, allocation via ESDP versus ESP, will be prospectively evaluated in the setting of paired kidneys and a standardized immunosuppressive regimen in the participating centers. The important perspective remains that a successful transplantation with a marginal donor kidney by adopting the old virtue of matching for HLA antigens may further improve the already substantial improvement in life expectancy as well as quality of life in the elderly.

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References

1. Wolfe RA, Ashby VB, Milford EL, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant [see comments]. *N Engl J Med* 1999; **341**: 1725.
2. Cecka JM. The UNOS Scientific Renal Transplant Registry – ten years of kidney transplants. *Clin Transpl* 1997; **12**: 1.
3. Kasiske BL, Snyder J. Matching older kidneys with older patients does not improve allograft survival. *J Am Soc Nephrol* 2002; **13**: 1067.
4. Roodnat JI, Zietse R, Mulder PG, *et al.* The vanishing importance of age in renal transplantation. *Transplantation* 1999; **67**: 576.
5. Meier-Kriesche HU, Ojo A, Hanson J, *et al.* Increased immunosuppressive vulnerability in elderly renal transplant recipients. *Transplantation* 2000; **69**: 885.
6. Meier-Kriesche HU, Ojo AO, Cibrik DM, *et al.* Relationship of recipient age and development of chronic allograft failure. *Transplantation* 2000; **70**: 306.
7. Feutren G, Mihatsch MJ. Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases. International Kidney Biopsy Registry of Cyclosporine in Autoimmune Diseases. *N Engl J Med* 1992; **326**: 1654.
8. Ekberg H, Tedesco-Silva H, Demirbas A, *et al.* Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; **357**: 2562.
9. de Fijter JW, Mallat MJ, Doxiadis II, *et al.* Increased immunogenicity and cause of graft loss of old donor kidneys. *J Am Soc Nephrol* 2001; **12**: 1538.
10. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older

than 70 years of age: results from the Scientific Registry of Transplant Recipients. *Transplantation* 2007; **83**: 1069.
11. Buchler M, Halimi JM, Najjar AA, *et al.* Living with a functioning kidney transplant at 74 yr or older: a national epidemiological study. *Clin Transplant* 2004; **18**: 681.
12. Ojo AO, Hanson JA, Meier-Kriesche H, *et al.* Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 2001; **12**: 589.
13. Takemoto S, Terasaki PI. Donor age and recipient age. *Clin Transpl* 1988; **3**: 345.
14. Doyle SE, Matas AJ, Gillingham K, Rosenberg ME. Predicting clinical outcome in the elderly renal transplant recipient. *Kidney Int* 2000; **57**: 2144.
15. Meier-Kriesche HU, Ojo AO, Hanson JA, Kaplan B. Exponentially increased risk of infectious death in older renal transplant recipients. *Kidney Int* 2001; **59**: 1539.
16. Trouillhet I, Benito N, Cervera C, *et al.* Influence of age in renal transplant infections: cases and controls study. *Transplantation* 2005; **80**: 989.
17. Paul LC. Chronic allograft nephropathy: An update. *Kidney Int* 1999; **56**: 783.
18. Chapman JR, O'Connell PJ, Nankivell BJ. Chronic renal allograft dysfunction. *J Am Soc Nephrol* 2005; **16**: 3015.
19. Oniscu GC, Brown H, Forsythe JL. How great is the survival advantage of transplantation over dialysis in elderly patients? *Nephrol Dial Transplant* 2004; **19**: 945.
20. Epstein M. Aging and the kidney. *J Am Soc Nephrol* 1996; **7**: 1106.
21. van Saase JL, van der Woude FJ, Thorogood J, *et al.* The relation between acute vascular and interstitial renal allograft rejection and subsequent chronic rejection. *Transplantation* 1995; **59**: 1280.
22. Moreso F, Seron D, Gil-Vernet S, *et al.* Donor age and delayed graft function as predictors of renal allograft survival in rejection-free patients. *Nephrol Dial Transplant* 1999; **14**: 930.
23. Prommool S, Jhangri GS, Cockfield SM, Halloran PF. Time dependency of factors affecting renal allograft survival. *J Am Soc Nephrol* 2000; **11**: 565.
24. Kerr SR, Gillingham KJ, Johnson EM, Matas AJ. Living donors >55 years: to use or not to use? *Transplantation* 1999; **67**: 999.
25. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. Natural history, risk factors, and impact of subclinical rejection in kidney transplantation. *Transplantation* 2004; **78**: 242.
26. Veronese FV, Noronha IL, Manfro RC, Edelweiss MI, Goldberg J, Goncalves LF. Prevalence and immunohistochemical findings of subclinical kidney allograft rejection and its association with graft outcome. *Clin Transplant* 2004; **18**: 357.
27. Legendre C, Thervet E, Skhiri H, *et al.* Histologic features of chronic allograft nephropathy revealed by protocol biopsies in kidney transplant recipients. *Transplantation* 1998; **65**: 1506.
28. Mengel M, Chapman JR, Cosio FG, *et al.* Protocol biopsies in renal transplantation: insights into patient management and pathogenesis. *Am J Transplant* 2007; **7**: 512.
29. Halloran PF, Melk A, Barth C. Rethinking chronic allograft nephropathy: the concept of accelerated senescence. *J Am Soc Nephrol* 1999; **10**: 167.
30. Melk A, Halloran PF. Cell senescence and its implications for nephrology. *J Am Soc Nephrol* 2001; **12**: 385.
31. Kasiske BL. The influence of donor age on renal function in transplant recipients. *Am J Kidney Dis* 1988; **11**: 248.
32. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors [see comments]. *N Engl J Med* 1995; **333**: 333.
33. Cecka JM. Living donor transplants. *Clin Transpl* 1995; **10**: 363.
34. Terasaki PI, Cecka JM, Gjertson DW, Cho YW. Spousal and other living renal donor transplants. *Clin Transpl* 1997; **12**: 269.
35. Oien CM, Reisaeter AV, Leivestad T, Dekker FW, Line PD, Os I. Living donor kidney transplantation: the effects of donor age and gender on short- and long-term outcomes. *Transplantation* 2007; **83**: 600.
36. Newstead CG, Dyer PA. The influence of increased age and age matching on graft survival after first cadaveric renal transplantation. *Transplantation* 1992; **54**: 441.
37. Cecka JM, Terasaki PI. Optimal use for older donor kidneys: older recipients. *Transplant Proc* 1995; **27**: 801.
38. Gjertson DW, Terasaki PI, Cecka JM, Takemoto S, Cho YW. Senior citizens pool for aged kidneys. *Transplant Proc* 1997; **29**: 129.
39. Fabrizii V, Winkelmayer WC, Klauser R, *et al.* Patient and graft survival in older kidney transplant recipients: does age matter? *J Am Soc Nephrol* 2004; **15**: 1052.
40. Terasaki PI, Gjertson DW, Cecka JM, Takemoto S, Cho YW. Significance of the donor age effect on kidney transplants. *Clin Transplant* 1997; **11**: 366.
41. Waiser J, Schreiber M, Budde K, *et al.* Age-matching in renal transplantation. *Nephrol Dial Transplant* 2000; **15**: 696.
42. Smits JM, Persijn GG, van Houwelingen HC, Claas FH, Frei U. Evaluation of the Eurotransplant Senior Program. The results of the first year. *Am J Transplant* 2002; **2**: 664.
43. Meier-Kriesche HU, Cibrik DM, Ojo AO, *et al.* Interaction between donor and recipient age in determining the risk of chronic renal allograft failure. *J Am Geriatr Soc* 2002; **50**: 14.
44. Schold JD, Kaplan B, Chumbler NR, *et al.* Access to quality: evaluation of the allocation of deceased donor kidneys for transplantation. *J Am Soc Nephrol* 2005; **16**: 3121.
45. Gjertson DW. A multi-factor analysis of kidney graft outcomes at one and five years posttransplantation: 1996 UNOS Update. *Clin Transpl* 1996; **11**: 343.

46. Baylis C, Corman B. The aging kidney: insights from experimental studies. *J Am Soc Nephrol* 1998; **9**: 699.
47. Kang DH, Anderson S, Kim YG, *et al.* Impaired angiogenesis in the aging kidney: vascular endothelial growth factor and thrombospondin-1 in renal disease. *Am J Kidney Dis* 2001; **37**: 601.
48. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985; **33**: 278.
49. Dodane V, Chevalier J, Bariety J, Pratz J, Corman B. Longitudinal study of solute excretion and glomerular ultrastructure in an experimental model of aging rats free of kidney disease. *Lab Invest* 1991; **64**: 377.
50. Halloran PF, Homik J, Goes N, *et al.* The ''injury response'': a concept linking nonspecific injury, acute rejection, and long-term transplant outcomes. *Transplant Proc* 1997; **29**: 79.
51. Cho YW. Expanded criteria donors. *Clin Transpl* 1998; **13**: 421.
52. Knight RJ, Burrows L, Bodian C. The influence of acute rejection on long-term renal allograft survival: a comparison of living and cadaveric donor transplantation. *Transplantation* 2001; **72**: 69.
53. Basar H, Soran A, Shapiro R, *et al.* Renal transplantation in recipients over the age of 60: the impact of donor age. *Transplantation* 1999; **67**: 1191.
54. Frei U, Noeldeke J, Machold-Fabrizii V, *et al.* Prospective age-matching in elderly kidney transplant recipients – A 5-year analysis of the Eurotransplant Senior Program. *Am J Transplant* 2008; **8**: 50.
55. Khoruts A, Mondino A, Pape KA, Reiner SL, Jenkins MK. A natural immunological adjuvant enhances T cell clonal expansion through a CD28-dependent, interleukin (IL)-2-independent mechanism. *J Exp Med* 1998; **187**: 225.
56. Shoskes DA, Parfrey NA, Halloran PF. Increased major histocompatibility complex antigen expression in unilateral ischemic acute tubular necrosis in the mouse. *Transplantation* 1990; **49**: 201.
57. Penfield JG, Wang Y, Li S, *et al.* Transplant surgery injury recruits recipient MHC class II-positive leukocytes into the kidney. *Kidney Int* 1999; **56**: 1759.
58. Lu CY, Penfield JG, Kielar ML, Vazquez MA, Jeyarajah DR. Hypothesis: is renal allograft rejection initiated by the response to injury sustained during the transplant process? *Kidney Int* 1999; **55**: 2157.
59. Choi BS, Shin MJ, Shin SJ, *et al.* Clinical significance of an early protocol biopsy in living-donor renal transplantation: ten-year experience at a single center. *Am J Transplant* 2005; **5**: 1354.
60. Meehan SM, Siegel CT, Aronson AJ, *et al.* The relationship of untreated borderline infiltrates by the Banff criteria to acute rejection in renal allograft biopsies. *J Am Soc Nephrol* 1999; **10**: 1806.
61. Nickerson P, Jeffery J, Gough J, *et al.* Effect of increasing baseline immunosuppression on the prevalence of clinical and subclinical rejection: a pilot study. *J Am Soc Nephrol* 1999; **10**: 1801.
62. Morris PJ, Johnson RJ, Fuggle SV, Belger MA, Briggs JD. Analysis of factors that affect outcome of primary cadaveric renal transplantation in the UK. HLA Task Force of the Kidney Advisory Group of the United Kingdom Transplant Support Service Authority (UKTSSA). *Lancet* 1999; **354**: 1147.
63. Nyberg SL, Matas AJ, Kremers WK, *et al.* Improved scoring system to assess adult donors for cadaver renal transplantation. *Am J Transplant* 2003; **3**: 715.
64. Held PJ, Kahan BD, Hunsicker LG, *et al.* The impact of HLA mismatches on the survival of first cadaveric kidney transplants. *N Engl J Med* 1994; **331**: 765.
65. Thorogood J, Persijn GG, Schreuder GM, *et al.* The effect of HLA matching on kidney graft survival in separate posttransplantation intervals. *Transplantation* 1990; **50**: 146.
66. Doxiadis II, Smits JM, Persijn GG, Frei U, Claas FH. It takes six to boogie: allocating cadaver kidneys in Eurotransplant. *Transplantation* 2004; **77**: 615.
67. Fagiolo U, Amadori A, Biselli R, *et al.* Quantitative and qualitative analysis of anti-tetanus toxoid antibody response in the elderly. Humoral immune response enhancement by thymostimulin. *Vaccine* 1993; **11**: 1336.
68. Gillis S, Kozak R, Durante M, Weksler ME. Immunological studies of aging. Decreased production of and response to T cell growth factor by lymphocytes from aged humans. *J Clin Invest* 1981; **67**: 937.
69. Whisler RL, Liu B, Wu LC, Chen M. Reduced activation of transcriptional factor AP-1 among peripheral blood T cells from elderly humans after PHA stimulation: restorative effect of phorbol diesters. *Cell Immunol* 1993; **152**: 96.
70. Palomar R, Ruiz JC, Zubimendi JA, *et al.* Acute rejection in the elderly recipient: influence of age in the outcome of kidney transplantation. *Int Urol Nephrol* 2002; **33**: 145.
71. Meier-Kriesche HU, Friedman G, Jacobs M, Mulgaonkar S, Vaghela M, Kaplan B. Infectious complications in geriatric renal transplant patients: comparison of two immunosuppressive protocols. *Transplantation* 1999; **68**: 1496.
72. Johnson DW, Nicol DL, Purdie DM, *et al.* Is mycophenolate mofetil less safe than azathioprine in elderly renal transplant recipients? *Transplantation* 2002; **73**: 1158.
73. Opelz G, Wujciak T, Dohler B, Scherer S, Mytilineos J. HLA compatibility and organ transplant survival. Collaborative Transplant Study. *Rev Immunogenet* 1999; **1**: 334.
74. Doxiadis II, de Fijter JW, Mallat MJ, *et al.* Simpler and equitable allocation of kidneys from postmortem donors primarily based on full HLA-DR compatibility. *Transplantation* 2007; **83**: 1207.
75. Naesens M, Lerut E, Damme BV, Vanrenterghem Y, Kuypers DR. Tacrolimus exposure and evolution of renal allograft histology in the first year after transplantation. *Am J Transplant* 2007; **7**: 2114.

76. Rush DN, Jeffrey J, Gough J, Nickerson P. Predicting rejection: is early diagnosis achievable and important? *Graft* 1999; **2**: 31.
77. Nankivell BJ, Fenton-Lee CA, Kuypers DR, *et al.* Effect of histological damage on long-term kidney transplant outcome. *Transplantation* 2001; **71**: 515.
78. Shapiro R, Randhawa P, Jordan ML, *et al.* An analysis of early renal transplant protocol biopsies – the high incidence of subclinical tubulitis. *Am J Transplant* 2001; **1**: 47.
79. Zinkernagel RM, Hengartner H. Antiviral immunity. *Immunol Today* 1997; **18**: 258.
80. Nyengaard JR, Bendtsen TF. Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec* 1992; **232**: 194.
81. Curschellas E, Landmann J, Durig M, *et al.* Morphologic findings in ''zero-hour'' biopsies of renal transplants. *Clin Nephrol* 1991; **36**: 215.
82. Kappel B, Olsen S. Cortical interstitial tissue and sclerosed glomeruli in the normal human kidney, related to age and sex. A quantitative study. *Virchows Arch [Pathol Anat]* 1980; **387**: 271.
83. Seron D, Carrera M, Grino JM, *et al.* Relationship between donor renal interstitial surface and post- transplant function. *Nephrol Dial Transplant* 1993; **8**: 539.
84. Oniscu GC, Brown H, Forsythe JL. How old is old for transplantation? *Am J Transplant* 2004; **4**: 2067.
85. Wolfe RA, McCullough KP, Schaubel DE, *et al.* Calculating life years from transplant (LYFT): methods for kidney and kidney-pancreas candidates. *Am J Transplant* 2008; **8**: 997.

