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# Trends in Kidney Transplantation over the Past Decade

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## Abstract

Kidney transplantation offers patients with end-stage renal disease the greatest potential for increased longevity and enhanced quality of life; however, the demand for kidneys far exceeds the available supply. This has led to an increase in the number of people on waiting lists and an increase in waiting time. In the US, the overall median wait time was 2.85 years in 2004. The projected median waiting time for adult patients awaiting a deceased donor kidney in 2006 is 4.58 years. The renal transplant community has pursued multiple avenues in an attempt to increase the donor pool, but this remains a major challenge. In the last decade, the number of live donor kidney transplants performed in the US and Canada has doubled and represents just over 40% of all donor kidneys. Among deceased donor kidneys, the largest percentage increases were seen in expanded criteria donor and donation after cardiac death kidneys. In the last decade, the age distribution among donors, and among patients on waiting lists or receiving a renal transplant, has shifted towards older age groups. There have been dramatic shifts in baseline immunosuppression with increased usage of induction agents and the nearly universal replacement of azathioprine by mycophenolate. Additionally, tacrolimus use has increased from 13% to 79% at discharge, while ciclosporin (cyclosporine) use has fallen from 76% to 15%. Although 1-year graft survival rates are excellent, only modest improvements have been observed in long-term graft survival rates in the last decade. Thus, efforts have shifted from improving early graft outcomes to altering the natural course of late graft failure. Death of transplant recipients from cardiovascular disease, infection and cancer remains an important limitation in kidney transplantation. Continued success in kidney transplantation will require increased numbers of donors, both living and deceased, as well as reduction in the primary causes of late transplant loss, namely premature patient death with a functioning graft and chronic allograft nephropathy.

Worldwide, almost 1.8 million people were treated for end-stage renal disease (ESRD) in 2004, up 6% from 2003 and up 20% from 2001.[1] Approximately 77% of these global ESRD patients were on dialysis treatment and 23% were living with a functioning kidney transplant.[1] Approximately 74% of kidney transplant recipients reside in North America and Europe.[1] Patients with ESRD who receive a kidney transplant have a greater survival than patients who remain on the waiting list.[2] The 5-year

survival rate for patients who received a kidney transplant between 1995 and 1999 was 74%, compared with 34% for wait-listed patients who initiated dialysis therapy.[3]

Although kidney transplantation offers the greatest potential for increased survival, enhanced quality of life and lower healthcare costs,[4] the demand for kidneys worldwide far exceeds the available supply. This has led to an increase in the number of people on waiting lists and an increase in waiting time.[3] This article provides an overview of kidney transplantation in Canada and the US in the last decade.

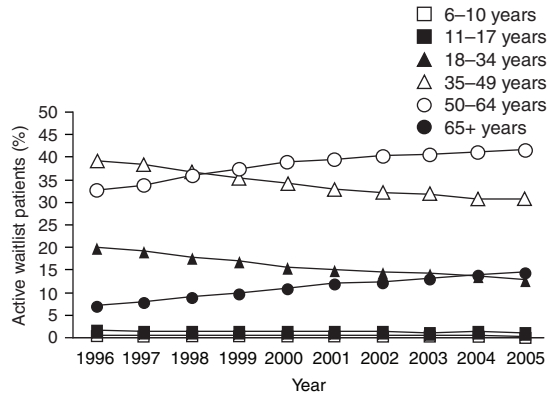


**Fig. 1.** Changes in proportions of active waitlist patients on the kidney transplant waiting list by age group, 1996–2005.[6]

## 1. Kidney Transplant Waiting Lists

The rate per million population (PMP) of patients waiting for a kidney transplant in 2005 was 233.3 in the US and 85.4 in Canada, far exceeding corresponding kidney transplant rates of 51.4 and 31.8 PMP.[5] The total number of patients waiting for a kidney transplant in the US has been continuously rising and has more than doubled in the past decade. In 1996 there were 32 262[6] patients on the renal wait list, and by 14 September 2007 there were 73 181 candidates in the US waiting for a kidney transplant.[7] Nearly 30 000 patients are added to the renal wait list each year, up 59% since 1996, when 18 330 patients were added.[6] The greatest number of new registrants was in the 50- to 64-year age group.[6]

Over the past decade, the age distribution of active waiting list registrants has continued to shift toward older age groups (figure 1): the percentage of adults over the age of 50 on the waiting list has increased steadily from 39% in 1996 to 56% in 2005, whereas the percentages of young adults and children have declined over the same period (from 59% to 43% for adults aged 18–49, and from 2% to 1% for children).[6] Factors contributing to the increased representation of older patients on the waiting list include an increased incidence of ESRD with aging, aging of the general population, and advances in transplantation that have allowed it to be considered as a viable option for patients with advanced age and comorbidities.[6] The percentage of Hispanic candidates on the deceased donor kidney waiting list has increased in the past 10 years from a low of 11% in 1996 to a high of 17% in 2005, while the percentage of African Americans has remained stable at 35%. In comparison, the percentage of white candidates has slowly declined from 46% in 1996 to 38% in 2005.[6]

Only approximately 25% of wait-listed candidates in the US receive a donor kidney in a given year.[6] The percentage of patients in the US who remain on the waiting list for over 3 years has continued to increase. In 1996, it was 15.7% and in 2005, 21% of patients waited over 3 years.[6] In 2002, the median time to transplant for new waiting-list registrants was 1136 days, compared with 1036 days in 1996.[6] Although more recent data cannot be calculated because waiting times have increased so much, the projected median waiting time for adult patients in the US listed in 2006 is 4.58 years.[3] Median waiting time in the 35- to 49-year age group approximates the overall median, while waiting times are shorter in the younger age groups and longer in the older age groups.[6] As would be expected, the death rate for adults on the waiting list rises with increasing age and is about 4-fold greater in patients aged 65–69 years than for those aged 20–29 years (139 per 1000 compared with 35 per 1000 patient-years at risk).[3] Approximately 6% of patients on the waiting list die each year.[3]

According to the Canadian Organ Replacement Register,[5] the number of patients on the waiting list

for a kidney transplant in Canada has increased by 15% since 1996 (2394) and has remained relatively constant in the last 5 years. In 2005, there were 2758 patients waiting for a kidney transplant in Canada. From 2000 to 2004, the median wait time to first kidney transplant among adult recipients awaiting a deceased donor kidney increased from 849 to 1293 days. In 2005, 38% of Canadian wait-listed patients received a kidney transplant and 2.4% died while waiting.[5]

## 2. Donor Characteristics

Multiple avenues have been pursued by the transplant community in an attempt to increase the pool of donor kidneys available for transplantation. In the past decade, the number of live donor kidney transplants performed in the US and Canada has almost doubled. In the US the number of living donor kidney transplants increased from 3668 in 1996 to 6563 in 2005,[6] while in Canada living donor kidney transplants increased from 265 in 1996 to 443 in 2005.[5] The rate of living donor kidney transplants is higher in the US than in Canada (2005 rate 20.3 vs 13.7 PMP).[5] The development of laparoscopic nephrectomy has partly contributed to the increase in live kidney donations, as have changes in the donor-recipient relationship. From 1996 to 2005, the percentage of unrelated donors increased from 16% to 34% in the US and from 17% to 22% in Canada. In addition, the use of anonymous donors, paired exchange and list exchange, as well as ABO incompatible and desensitization programmes have increased access to live donor kidney transplants.

There has been a 20% rise in deceased kidney donors in the US in the last 10 years. The annual growth in deceased kidney donation was 4% between 1995 and 2003, and increased to 8% between 2003 and 2004[8] following the introduction of the Organ Donor Breakthrough Collaborative in April 2003. However, the number of deceased donors in Canada has declined by 13%, from 678 in 1996 to 587 in 2005.[5] The rate of deceased donor kidney transplants is higher in the US than in Canada (2005 rate 31.1 vs 18.1 PMP).[5]

In the US, 59% (9509) of 16 072 kidney transplants performed in 2005 were from a deceased donor.[6] Approximately 76% of the deceased donor kidney transplants were standard criteria donor (SCD) kidneys, 16% were expanded criteria donor (ECD) kidneys, 7% were donation after cardiac death (DCD) kidneys, and <1% were ECD-DCD kidneys.[6] Between 1996 and 2005, increasing numbers of transplants were observed in all deceased donor categories: SCD increased by 15%; ECD 50%; DCD 726%; and ECD-DCD 469%.[6] Thus, while modest increases were observed in SCD donors, there were dramatic increases in ECD and DCD kidney transplants. Although national data on the use of ECD kidneys are not available for Canada, according to the Trillium Gift of Life Network, the province of Ontario has seen a rise in the use of ECD kidneys from just 8% of all deceased donors in 2001 to 22.5% in 2005, where ECD is defined as donor age older than 60 years, or any donor aged 50–59 years with at least two of the following: brain death from cerebrovascular accident, hypertension, creatinine at procurement >133 μmol/L.

## 3. Recipient Characteristics

While glomerular disease remains the most common primary diagnosis in kidney transplant recipients, its proportional distribution has decreased in the last decade (from 32% to 27%), while proportions of diabetes mellitus and hypertensive nephrosclerosis have increased from 20% to 22% and from 13% to 17%, respectively.[8]

In the past decade, the age distribution among kidney transplant recipients has shifted towards older recipients. As of 2005, 41% of recipients were in the 50- to 64-year age group, compared with 33% in 1996.[6] Conversely, 28% of recipients in 2005 were in the 35- to 39-year age group, compared with 36% in 1996. The percentage of recipients older than 65 years has increased from 6% in 1996 to 11% in 2005.[6] The percentage of White deceased donor recipients decreased from 59% in 1996 to 48% in 2005.[6] In contrast, the percentages of African American and Hispanic recipients increased from 26% to 30% and 10% to 15%, respectively. African

American and Hispanic patients continue to be underrepresented in the population of living donor recipients, accounting for 15% and 12% of this population respectively.[6] White recipients accounted for 66% of all living donor recipients in 2005.[6] This may be related to the racial disparities in living kidney donation, with low rates seen in several races, particularly among African Americans.[9] A higher incidence of disease along with a shortage of organs suitable for African Americans has caused the disparity in kidney transplantation to persist.[9]

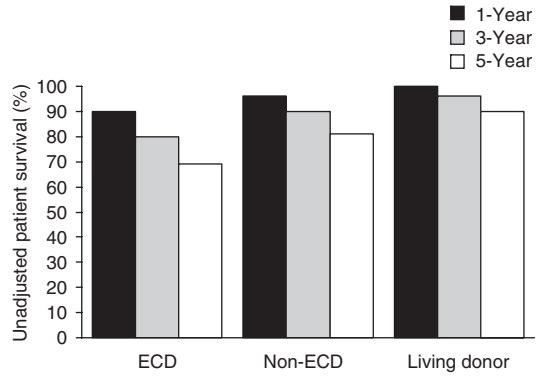


**Fig. 2.** Adjusted 5-year kidney patient survival for kidney recipients, by age and donor type, for transplants received 1999–2004.[6] **ECD** = expanded criteria donor.

## 4. Kidney Transplant Graft and Patient Survival

In the last 10 years, there has been continued improvement in short-term kidney transplant survival. The unadjusted 1-year allograft survival rate for SCD deceased transplants has increased from 87% in 1995 to 91% in 2004.[6] Similarly, the unadjusted 1-year allograft survival rate for living donor transplants has increased from 93% to 95% in the same period.[6] Unfortunately, the same success has not been seen in long-term allograft survival. For deceased donors, allograft half-life (conditional on 1-year graft survival) was 11.4 years in 1995 and actually fell to 10.5 in 2002.[3] For living donors, the half-life in 1995 was 18.4 years and 19.1 in 2002.[3] Given the improvements in early transplant outcome, efforts to improve overall results will need to focus on reducing premature patient death and late allograft losses.

The unadjusted 1-year patient survival rate following living donor kidney transplantation was 98%, while the unadjusted 1-year patient survival rates in SCD and ECD kidney recipients were 96% and 90%, respectively (figure 2).[6] At 5 years post-transplant, patient survival in recipients of ECD kidneys was 69%, 21% lower than patient survival in live donor recipients and 14% lower than survival in SCD recipients.[6] As expected, long-term patient survival decreased with increasing recipient age, regardless of donor category.[6]

Both donor and recipient age are important determinants of graft survival in the current era.[10] Kidneys from older donors have substantially lower graft survival than kidneys from younger donors, as recognized in the definition of ECD kidneys.[11] Regardless of donor age, older recipients gain fewer life-years from transplantation than younger recipients, mainly owing to increased mortality. Annual rates of death with a functioning graft in older recipients are more than twice as high as in younger recipients (6.6% in the 65- to 69-year age group compared with 2.9% in the 40- to 49-year age group).[10] Moreover, because a graft from a young donor is likely to survive for longer than the older recipient (>60 years) who receives it, there is a potential loss in graft-years. Based on 10-year survival curves, the average number of graft-years for young grafts (15–50 years) transplanted into young recipients (<60 years) was 7.4 years. This exceeds the survival expectancy of young grafts (15–50 years) in older recipients (>60 years) of 6.7 years.[10] Similarly, the projected lifetime patient survival in older (>60 years) recipients receiving an ideal young graft was calculated at 15.5 years, compared with 21.9 years in younger recipients (<60 years).[10]

The degree of human leukocyte antigen (HLA) matching has also seen changes over the past decade. In 1996, 14.4% of kidney transplant recipients had a zero-HLA mismatch kidney compared with 16.2% in 2005.[6] However, during the same period there was an increase in those who received kidneys with five or six HLA antigen mismatches from 24.0% to 41.4%.[6] The extremes of HLA antigen

mismatch continue to influence graft survival. For those who received a zero-HLA mismatch kidney, the 5-year allograft survival was 74.6% compared with only 65.8% for those who received a six-antigen mismatch kidney.[6] For patients with an intermediate degree of HLA matching (from one to four antigens mismatched) the effect on 5-year graft survival was less dramatic and ranged from 71.2% to 69.0%.[6] Although HLA matching remains an important predictor of long-term transplant survival, the growing wait list and lengthening wait times force us to consider issues other than just matching when allocating deceased donor kidneys for transplantation.

## 5. Immunosuppression Regimens

Significant progress has been obtained in the prevention of acute rejection in the first year after transplantation.[8] In 2004, only 12% of kidney transplant recipients were treated for acute rejection within 1 year, compared with 51% in 1996.[6] In the US, post-transplantation immunosuppression in the kidney recipient has changed considerably over the past decade. The use of induction agents has increased from being used in 39% of recipients in 1996 to 74% of recipients in 2005. The most commonly used induction agent was rabbit antithymocyte globulin (39%), followed by the two interleukin-2-receptor antagonists daclizumab and basiliximab (28% combined).[6] The use of steroid-free maintenance regimens has increased in the last 6 years. In 1999, only 3% of recipients were not receiving corticosteroids at discharge compared with 23% in 2004.[6] At 1 year post-transplantation, 20% of these patients were still not taking steroids. Mycophenolate mofetil has replaced azathioprine as baseline immunosuppression. By 2005, 87% of recipients were on mycophenolate mofetil or mycophenolate sodium at the time of discharge. The use of azathioprine has declined every year since 1996 and it is now prescribed to only 0.6% of kidney transplant recipients (figure 3).

Calcineurin inhibitors remain the most commonly used immunosuppressive agents, with tacrolimus largely replacing ciclosporin (cyclosporine) during the past 10 years. In 2005, 79% of recipients received tacrolimus at time of discharge and 15% received ciclosporin, a dramatic change from 1996, when 76% of patients received ciclosporin and 13% received tacrolimus.[6] Of all patients with grafts functioning at 1 year, only 1% were not on a calcineurin inhibitor.[6]

Sirolimus use for maintenance immunosuppression rose from 1.5% in 1996 to 17% in 2001, following US FDA approval in 1999. Its use, however, fell to 9% in 2005 and has decreased further in recent years.[1,6] A recent meta-analysis of randomized trials evaluated mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus in various immunosuppressive combinations.[12] When mTOR inhibitors were used to replace calcineurin inhibitors, the authors found no difference in acute rejection but there was a significant improvement in renal function.[12] In contrast, a recent database analysis found that the combination of sirolimus and mycophenolate mofetil had higher rates of acute rejection and graft loss compared with regimens using a calcineurin inhibitor.[13] Although retrospective analyses are of limited value in formulating conclusions because of selection bias issues, this concerning trend in long-term outcome warrants further evaluation.

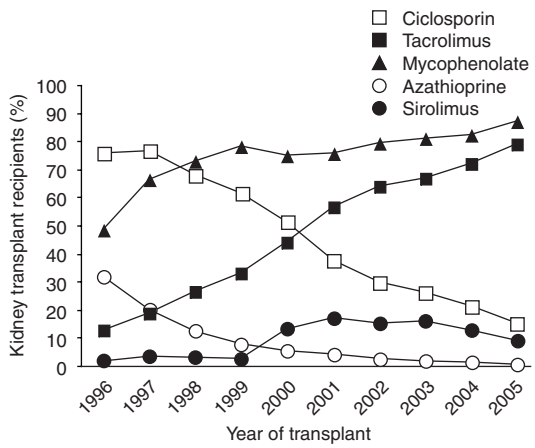


**Fig. 3.** Immunosuppression agents used for maintenance therapy in kidney transplant recipients, 1996–2005.[6]

## 6. Death in Kidney Transplant Patients

Although kidney transplant recipients have a survival advantage over those on dialysis, there remains a huge gap in life expectancy between a transplant patient and a member of the general population.[3] For example, a typical 40-year-old White female in the US has an expected remaining lifetime of 39.7 years compared with 24.1 years for a similar person with a kidney transplant, and only 7.2 years for a similar person on dialysis.[3] The leading causes of death in deceased donor kidney transplant recipients are cardiovascular disease (22%), infection (16%), malignancy (6.8%) and cerebrovascular/haemorrhage (6.3%) [figure 4].[14] Efforts at reducing cardiovascular risk among transplant recipients include aggressive treatment of hypertension as well as treatment of hyperlipidaemia.[14-16] In kidney transplant recipients treated with the cholesterol-lowering drug fluvastatin, there was a 38% reduction in the risk of cardiac death (relative risk [RR] 0.62; 95% CI 0.40, 0.96) and a 32% reduction in nonfatal myocardial infarction (RR 0.68; 95% CI 0.47, 1.00), compared with patients receiving placebo. Although these secondary cardiac outcomes are consistent with the beneficial effects of statins in other populations, this trial did not find a significant difference between treatment groups for the primary endpoint (occurrence of cardiac death, nonfatal myocardial infarction or coronary intervention procedure) or for all-cause mortality until the study was extended for 2 more years.[17]

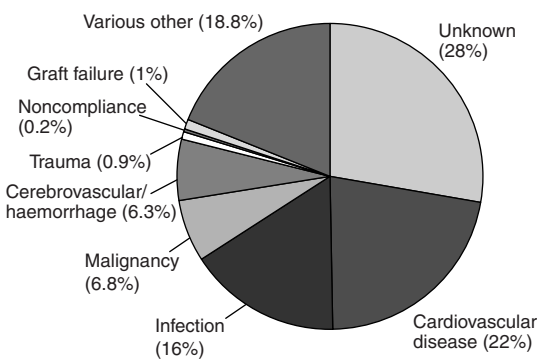


**Fig. 4.** Causes of death in deceased donor kidney transplant recipients, from 1993 to 2004 (reprinted from Adams,[14] with permission).

Since several immunosuppressive agents have a negative effect on cardiovascular risk factors, the use of immunosuppressive protocols that minimize exposure to these agents (e.g. reducing corticosteroid use and minimizing calcineurin inhibitor exposure) is a strategy being used to reduce cardiovascular morbidity and mortality.[14,16]

Population-based studies in the US and Australia have shown that the incidence of several cancers (e.g. skin, kidney and lymphoma) is higher in kidney transplant recipients than in the general or wait-listed population.[15,18] The incidence of malignancy has been estimated at 20% after 10 years of long-term immunosuppression, and malignancy is expected to surpass cardiovascular complications as the leading cause of death in kidney transplant recipients in the next 20 years.[19] The multifactorial aetiology of post-transplant malignancy involves impaired immunosurveillance of neoplastic cells and depressed antiviral immune activity, as well as direct oncogenic effects of immunosuppressive agents.[19,20] In reducing the disparity in survival between transplant recipients and the general population, prevention of malignancy must rely on a delicate balance in the management of immunosuppression, between rejection and malignancy risk.[19]

While calcineurin inhibitors and azathioprine have been associated with post-transplant malignancies, sirolimus has been linked with a lower incidence of tumours.[19] Moreover, experimental studies have demonstrated an antiproliferative as well as an antiangiogenic effect of sirolimus.[21,22] Conversion from ciclosporin to sirolimus has resulted in complete regression of Kaposi's carcinoma lesions[23,24] and regression of post-transplant lymphoproliferative disease.[25,26] Retrospective analyses and clinical studies have shown a reduction in the incidence of various cancers in kidney transplant recipients receiving mTOR inhibitors alone or in combination with calcineurin inhibitors.[27-30] Clinical trials in cancer research have shown that temsirolimus, a derivative of sirolimus, is an effective agent against certain tumour types, including renal cell carcinoma.[31]

## 7. Conclusion

Kidney transplantation has continued to improve over the past decade with dramatic reductions in acute rejection and improvements in short-term graft survival. This has allowed thousands of patients around the world a substantial improvement in health-related quality of life while reducing healthcare costs related to the treatment of ESRD. Unfortunately, we have not observed such dramatic improvements in long-term graft survival, which may be due to the changing demographics of both donors and recipients. Kidney transplant recipients are still plagued by excess cardiovascular disease and malignancy compared with those without kidney failure. In the next decade, it is hoped that we can overcome some of these problems and continue to see improvements in kidney transplantation, particularly with respect to long-term outcomes. For this to occur, the transplant community needs to focus on reducing premature death with a functioning graft and losses due to chronic allograft nephropathy. However, the greatest challenge of all, facing not only the transplant community but society as a whole, is the seemingly unattainable quest for sufficient organ donors. Efforts focused on improving both living and deceased organ donation will no doubt have the greatest impact for patients with ESRD by allowing more patients access to the benefits of kidney transplantation.

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