

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Long-Term Survival after Kidney Transplantation

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THE SURVIVAL ADVANTAGES OF TRANSPLANTATION OVER LONG-TERM DIALYSIS are generally well described, provided a given patient with end-stage kidney disease is deemed a candidate for a transplant.^{1,2} As of December 2018, in the United States, 554,038 patients with end-stage kidney disease were on long-term dialysis therapy and 229,887 had a functioning kidney transplant.³ As of February 2021, approximately 91,000 patients were awaiting kidney transplantation.⁴

Ultimately, usually after many years, some kidney transplants fail; improvement of long-term survival is a major goal for researchers, clinicians, and patients. Figure 1 is a schematic representation of modifiable kidney donor, recipient, and graft variables and post-transplantation events that could improve long-term survival. Increased survival would reduce the number of patients returning to dialysis, reduce the need for repeat transplantation, increase the number of kidneys available to those awaiting transplantation, shorten the overall wait time for transplantation, improve the quality and length of life, and reduce the financial burden on patients and the health care system.

The various aspects of survival after kidney transplantation affect a broad range of health care providers, including primary care physicians and specialists. This review summarizes the evolution of survival rates, demographic characteristics, and risk variables since the mid-1990s. We address post-transplantation events that impede long-term survival, factors relevant to racial or ethnic minority recipients, and improved health care coverage for immunosuppressive agents.

SHORT- AND LONG-TERM SURVIVAL RATES

The numbers of recipients of kidney transplants from deceased donors (Table 1) and living donors (Table 2) increased from 1996 to 2019 in the United States. The proportions of Black kidney donors (deceased donors, 13.5%; living donors, 12.0%) are similar to the proportion of Blacks in the overall U.S. population (13.4%). From 1996 to 2019, the number of kidneys from deceased donors grew steadily, a phenomenon due in part to organs that became available as a result of the opioid epidemic,⁵ but this increase has not kept up with the demand for transplants.

Graft and patient survival have improved over time (Figs. 2 and 3). For kidneys from deceased donors, the 10-year overall graft survival rate was 42.3% from 1996 to 1999 and increased to 53.6% from 2008 to 2011. The 10-year patient survival rate increased from 60.5% during the 1996–1999 period to 66.9% during the 2008–2011 period (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). This improvement has occurred despite increases in the recipients' age, body-mass index (BMI), frequency of diabetes, and length

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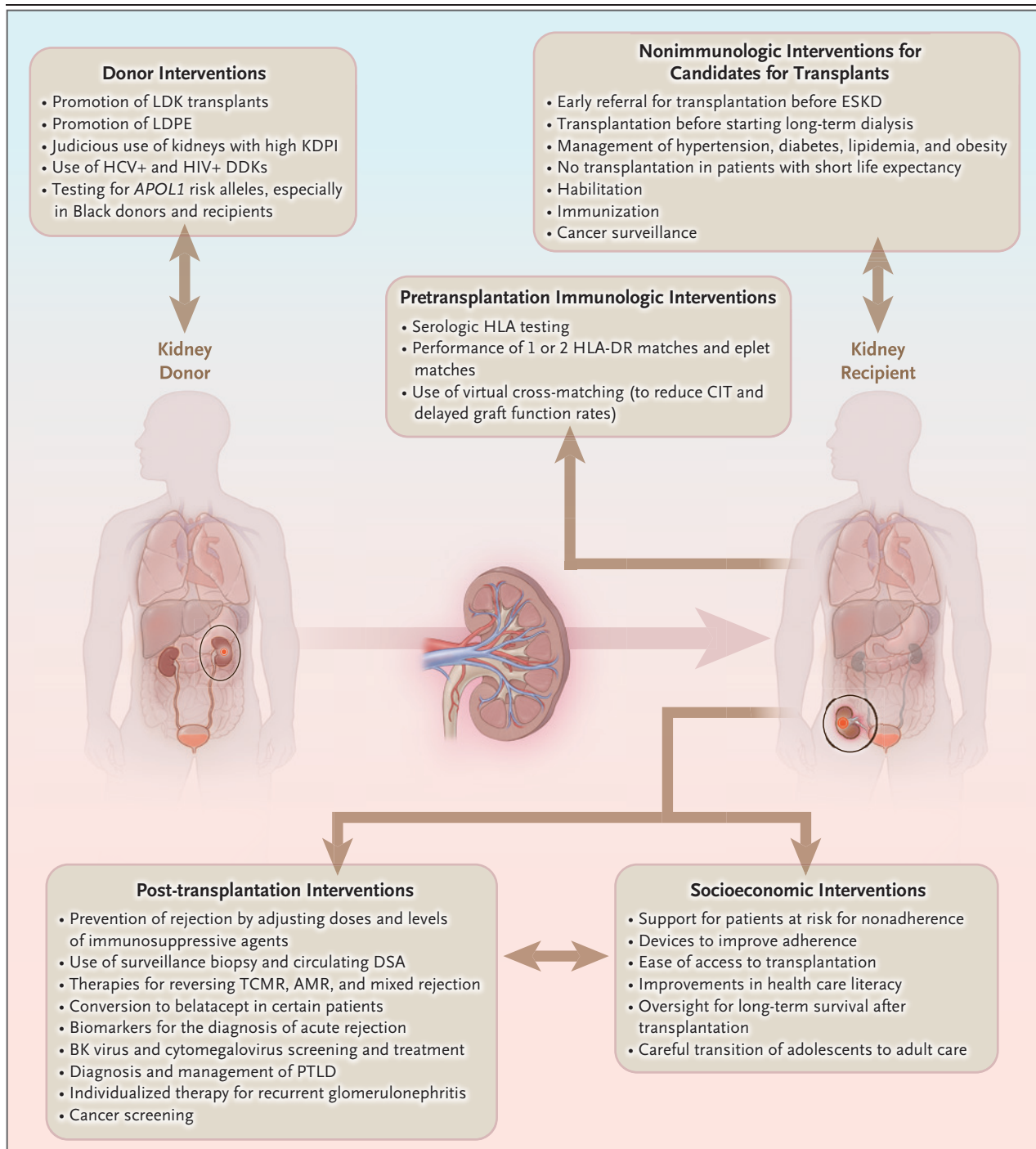


Figure 1. Interventions for Kidney Donors, Candidates, and Recipients That Affect Long-Term Survival.

AMR denotes antibody-mediated rejection, *APOL1* apolipoprotein 1, CIT cold ischemia time, DDK deceased donor kidney, DSA donor-specific antibody, ESKD end-stage kidney disease, HCV hepatitis C virus, HIV human immunodeficiency virus, KDPI Kidney Donor Profile Index, LDK living donor kidney, LDPE living donor paired exchange, PTLN post-transplantation lymphoproliferative disorder, and TCMR T-cell-mediated rejection.

of time undergoing dialysis, as well as a higher proportion of recipients with a previous kidney transplant. The improvement has also occurred despite increases in the age of donors, in the percentage of donations after circulatory death, and in the degree of HLA presensitization, expressed as calculated panel-reactive antibody levels (Table 1).

The survival of grafts from living donors has also improved, despite increases in donor age, calculated panel-reactive antibody levels, and HLA mismatches, and despite prior transplantation in the recipient (Table 2). In addition, a survival advantage of transplantation has been noted even when kidney transplants have higher scores on the Kidney Donor Profile Index, a measure of organ quality⁶ (Fig. 1), and has been observed among older and frailer recipients^{7,8} as well as those with diabetes and obesity.⁹

Long-term survival rates reported in the United States are lower than those reported by non-U.S. registries. For example, 5-year graft survival rates in the United States for primary kidney transplants from deceased donors and living donors were 72% and 85%, respectively, as compared with 81% and 90% in Australia and New Zealand, 79% and 87% in Europe, and 81 and 91% in Canada.¹⁰ A comparison between European and U.S. patients who received transplants from deceased donors during the period from 2005 through 2008 showed higher 5-year and 10-year graft survival rates among European recipients (77% and 56%, respectively) than among U.S. recipients (White, 71% and 46%; Hispanic, 73% and 48%; and Black, 62% and 34%).¹¹ A tricontinental analysis of 379,257 recipients of first kidney transplants revealed a higher graft failure rate among recipients in the United States than among those in the United Kingdom, Australia, and New Zealand.¹² Among U.S. recipients, a decline in survival starting 3 years after transplantation¹¹ has been attributed to and coincides with discontinuation of insurance coverage for long-term immunosuppressive medications.¹³ The long-awaited Immunosuppressive Drug Coverage for Kidney Transplant Patients Act (Immuno Bill, H.R. 5534), which stipulates lifelong coverage for immunosuppressive drugs for kidney transplant recipients, was approved by the U.S. Congress and became law in December 2020.

The observed improvement in long-term out-

comes has been ascribed to a decline in rates of clinical acute rejection, better pretransplantation cross-matching techniques, prudent use of paired-exchange transplants for candidates with incompatible living donors, surveillance for viral infections, and effective antiviral prophylaxis. Another contributing factor is improved medical management of acute rejection, viral infections, hypertension, lipidemia, cardiovascular disease, and post-transplantation cancer (Fig. 1; see the Supplementary Appendix for further information).

The leading causes of transplant failure, excluding death, are alloimmune injury and recurrent glomerulonephritis¹⁴ (Table S4). The Australian data registry reports rates of annual graft loss and death with functioning grafts of 2.6 and 2.2 events per 100 graft-years, respectively, and a combined rate of 4.7 events per 100 graft-years.¹⁵ During the first year after transplantation, most graft losses were due to technical issues and vascular complications (41% of graft losses), followed by acute rejection (17%) and glomerulonephritis (3%).¹⁵ Beyond 1 year, most graft losses were due to chronic rejection (63%) and glomerulonephritis (6%).

The primary causes of death with a functioning graft during the first year after transplantation were cardiovascular disease (31% of deaths), infection (31%), and cancer (7%).¹⁵ After the first year, the primary causes of death were cancer (29%), cardiovascular disease (23%), and infection (12%).

It is often difficult to ascertain a single cause of graft loss. Post-transplantation events such as acute rejection, viral infection, and cancer may be precipitated by nonmodifiable pretransplantation and perioperative factors related to the quality of the organ, cold ischemia time, and delayed graft function. Efforts to improve graft survival rates will need to focus on organ quality and the prevention and treatment of acute rejection, cardiovascular disease, infection, and cancer (Fig. 1).

IMMUNOSUPPRESSION AFTER KIDNEY TRANSPLANTATION

A combination of immunosuppressive medications targeting T cells is required to prevent kidney rejection and graft loss. Rabbit antithymocyte

Table 1. Trends in Demographic Characteristics of Adult Kidney Recipients and Deceased Donors According to Transplantation Period.*

| Characteristic | 1996–1999 | 2000–2003 | 2004–2007 | 2008–2011 | 2012–2015 | 2016–2019 | Total |
|---|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Total no. of transplants from living and deceased donors | 45,008 | 53,997 | 61,226 | 62,135 | 62,918 | 76,885 | 362,169 |
| No. of transplants from deceased donors | 29,823 | 31,472 | 36,971 | 38,962 | 41,458 | 53,139 | 231,825 |
| Recipients | | | | | | | |
| Median age (IQR) — yr | 48 (38–57) | 50 (40–59) | 53 (42–61) | 54 (44–63) | 55 (44–63) | 55 (44–64) | 53 (42–62) |
| Sex — % | | | | | | | |
| Male | 60.4 | 60.3 | 60.9 | 60.1 | 60.3 | 59.6 | 60.2 |
| Female | 39.6 | 39.7 | 39.1 | 39.9 | 39.7 | 40.4 | 39.8 |
| Race or ethnic group — %† | | | | | | | |
| White | 56.4 | 51.8 | 47.7 | 44.4 | 40.5 | 36.5 | 44.9 |
| Black | 27.5 | 30.0 | 31.1 | 33.2 | 33.6 | 34.1 | 32.0 |
| Hispanic | 10.2 | 12.0 | 13.6 | 14.5 | 16.8 | 19.5 | 15.0 |
| Other | 5.9 | 6.3 | 7.6 | 8.0 | 9.1 | 10.0 | 8.0 |
| Median BMI (IQR) | 25.5 (22.5–29.3) | 26.3 (23.0–30.2) | 27.0 (23.5–31.0) | 27.7 (24.1–31.9) | 27.9 (24.2–32.0) | 28.0 (24.2–32.1) | 27.3 (23.7–31.4) |
| Median dialysis duration (IQR) — mo | 32.2 (16.7–56.6) | 40.2 (21.3–67.4) | 43.7 (23.2–73.9) | 46.4 (24.9–78.3) | 54.9 (29.3–92.6) | 57.8 (29.6–92.6) | 46.7 (23.7–79.9) |
| Diabetes — % | 23.7 | 27.9 | 31.9 | 35.2 | 35.9 | 36.3 | 32.6 |
| Prior receipt of kidney transplant — % | 13.0 | 13.4 | 13.1 | 12.6 | 14.0 | 12.8 | 13.1 |
| Prior receipt of other organ transplants — % | 1.37 | 1.77 | 2.22 | 2.12 | 1.91 | 2.19 | 1.97 |
| Donors | | | | | | | |
| No. of deceased donors | 18,167 | 19,088 | 22,411 | 23,462 | 24,942 | 31,666 | 139,736 |
| Median age (IQR) — yr | 36 (20–49) | 38 (21–50) | 40 (23–51) | 40 (24–52) | 38 (24–51) | 38 (26–51) | 38 (23–51) |
| Sex — % | | | | | | | |
| Male | 58.8 | 59.2 | 59.8 | 59.9 | 60.7 | 61.0 | 60.1 |
| Female | 41.2 | 40.8 | 40.2 | 40.1 | 39.3 | 39.0 | 39.9 |

| Race or ethnic group — %† | | | | | | | | | |
|--|---------------|---------------|---------------|---------------|---------------|---------------|---------------|--|--|
| White | 76.9 | 73.9 | 69.5 | 68.3 | 67.8 | 67.7 | 70.1 | | |
| Black | 11.0 | 11.5 | 13.2 | 14.7 | 15.1 | 14.2 | 13.5 | | |
| Hispanic | 9.5 | 11.7 | 14.2 | 13.9 | 13.6 | 14.3 | 13.1 | | |
| Other | 2.5 | 2.9 | 3.1 | 3.2 | 3.5 | 3.9 | 3.3 | | |
| Median KDRI score (IQR)‡ | 1.1 (0.9–1.5) | 1.1 (0.9–1.4) | 1.2 (0.9–1.5) | 1.2 (0.9–1.5) | 1.2 (0.9–1.5) | 1.2 (1.0–1.5) | 1.2 (0.9–1.5) | | |
| Kidney donated after circulatory death — % | 1.4 | 3.1 | 8.3 | 13.3 | 17.0 | 22.0 | 12.2 | | |
| Transplants | | | | | | | | | |
| Median cold ischemia time (IQR) — hr | 20 (15–26) | 18 (13–24) | 18 (12–24) | 16 (11–23) | 16 (11–22) | 17 (12–23) | 18 (12–24) | | |
| Calculated panel-reactive antibody — % | | | | | | | | | |
| Mean | 17.8 | 18.6 | 20.7 | 19.6 | 24.8 | 26.2 | 21.8 | | |
| Median (IQR) | 4 (0–19) | 3 (0–20) | 2 (0–27) | 0 (0–28) | 0 (0–49) | 0 (0–54) | 0 (0–33) | | |
| No. of HLA-A, -B, and -DR mismatches | | | | | | | | | |
| Mean | 3.4 | 3.5 | 3.8 | 4.0 | 4.1 | 4.1 | 3.9 | | |
| Median (IQR) | 4 (2–5) | 4 (3–5) | 4 (3–5) | 4 (3–5) | 4 (3–5) | 4 (3–5) | 4 (3–5) | | |
| Delayed graft function — % | 25.5 | 24.6 | 25.0 | 25.2 | 27.1 | 29.3 | 26.4 | | |

* The age and body-mass index (BMI), the weight in kilograms divided by the square of the height in meters) of transplant recipients; proportion of recipients with diabetes, duration on dialysis before transplantation, calculated panel-reactive antibody, number of HLA mismatches, proportion of recipients who received kidneys from deceased donors after circulatory death, and delayed graft function have all increased over time for recipients of transplants from deceased donors. IQR denotes interquartile range.

† Race and ethnic group were assigned according to data recorded in the Scientific Registry of Transplant Recipients or the Organ Procurement and Transplantation Network database.

‡ The Kidney Donor Risk Index (KDRI) score usually ranges from 0.3 to 3.5, with higher values indicating lower graft survival.

Table 2. Trends in Demographic Characteristics of Adult Kidney Recipients and Living Donors According to Transplantation Period.*

| Characteristic | 1996–1999 | 2000–2003 | 2004–2007 | 2008–2011 | 2012–2015 | 2016–2019 | Total |
|---|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Total no. of transplants from living and deceased donors | 45,008 | 53,997 | 61,226 | 62,135 | 62,918 | 76,885 | 362,169 |
| No. of transplants from living donors | 15,185 | 22,525 | 24,255 | 23,173 | 21,460 | 23,746 | 130,344 |
| Recipients | | | | | | | |
| Median age (IQR) — yr | 42 (32–52) | 46 (35–55) | 48 (36–57) | 49 (38–59) | 50 (38–60) | 52 (40–61) | 48 (36–58) |
| Sex — % | | | | | | | |
| Male | 57.8 | 58.1 | 60.2 | 61.6 | 62.4 | 62.6 | 60.6 |
| Female | 42.2 | 41.9 | 39.8 | 38.4 | 37.6 | 37.4 | 39.4 |
| Race or ethnic group — %† | | | | | | | |
| White | 69.7 | 68.4 | 67.4 | 66.3 | 66.2 | 64.9 | 67.0 |
| Black | 14.7 | 14.9 | 15.0 | 14.1 | 12.8 | 12.6 | 14.0 |
| Hispanic | 11.3 | 11.8 | 12.5 | 14.0 | 14.5 | 15.3 | 13.3 |
| Other | 4.3 | 5.0 | 5.1 | 5.6 | 6.5 | 7.3 | 5.7 |
| Median BMI (IQR) | 25.0 (22.0–28.7) | 25.8 (22.6–29.9) | 26.4 (23.0–30.5) | 27.1 (23.6–31.3) | 27.3 (23.6–31.5) | 27.5 (23.8–31.5) | 26.7 (23.2–30.9) |
| Median dialysis duration (IQR) — mo | 9.7 (2.2–22.6) | 11.0 (2.0–27.4) | 10.6 (0.0–28.6) | 10.7 (0.0–30.4) | 10.3 (0.0–31.2) | 11.2 (0.0–31.5) | 10.6 (0.0–28.8) |
| Diabetes — % | 24.6 | 26.8 | 28.1 | 28.0 | 28.7 | 28.8 | 27.7 |
| Prior receipt of kidney transplant — % | 8.1 | 10.1 | 10.7 | 10.6 | 10.6 | 9.7 | 10.1 |
| Prior receipt of other organ transplants — % | 1.6 | 2.6 | 2.8 | 2.5 | 2.5 | 2.5 | 2.5 |
| Donors | | | | | | | |
| Median age (IQR) — yr | 39 (31–47) | 40 (32–48) | 41 (32–49) | 42 (33–51) | 43 (33–52) | 44 (34–54) | 41 (32–50) |
| Sex — % | | | | | | | |
| Male | 41.8 | 41.4 | 41.1 | 38.6 | 37.4 | 36.2 | 39.3 |
| Female | 58.2 | 58.6 | 58.9 | 61.4 | 62.6 | 63.8 | 60.7 |
| Race or ethnic group — %† | | | | | | | |
| White | 70.6 | 70.2 | 69.6 | 69.4 | 69.9 | 70.3 | 70.0 |
| Black | 13.8 | 13.7 | 13.3 | 12.1 | 10.7 | 9.1 | 12.0 |
| Hispanic | 11.4 | 11.6 | 12.6 | 13.8 | 13.9 | 14.5 | 13.1 |
| Other | 4.2 | 4.5 | 4.5 | 4.7 | 5.5 | 6.0 | 4.9 |
| Transplants | | | | | | | |
| LDPE transplants — % | 0.0 | 0.1 | 1.0 | 6.4 | 9.8 | 14.1 | 5.6 |
| Calculated panel-reactive antibody — % | | | | | | | |
| Mean | 8.1 | 8.6 | 11.8 | 9.5 | 11.3 | 11.2 | 10.2 |
| Median (IQR) | 0 (0–5) | 0 (0–5) | 0 (0–8) | 0 (0–0) | 0 (0–2) | 0 (0–4) | 0 (0–4) |
| No. of HLA-A, -B, and -DR mismatches | | | | | | | |
| Mean | 2.7 | 3.0 | 3.2 | 3.4 | 3.5 | 3.7 | 3.3 |
| Median (IQR) | 3 (2–4) | 3 (2–4) | 3 (2–5) | 3 (2–5) | 4 (2–5) | 4 (3–5) | 3 (2–5) |
| Delayed graft function — % | 5.2 | 4.9 | 4.1 | 3.6 | 3.0 | 2.9 | 3.9 |

* The mean age and BMI of recipients, the number of HLA mismatches, and the proportion of transplants from living donor paired exchange (LDPE) have increased over time for transplants from living donors.

† Race and ethnic group were assigned according to data recorded in the Scientific Registry of Transplant Recipients or the Organ Procurement and Transplantation Network database.

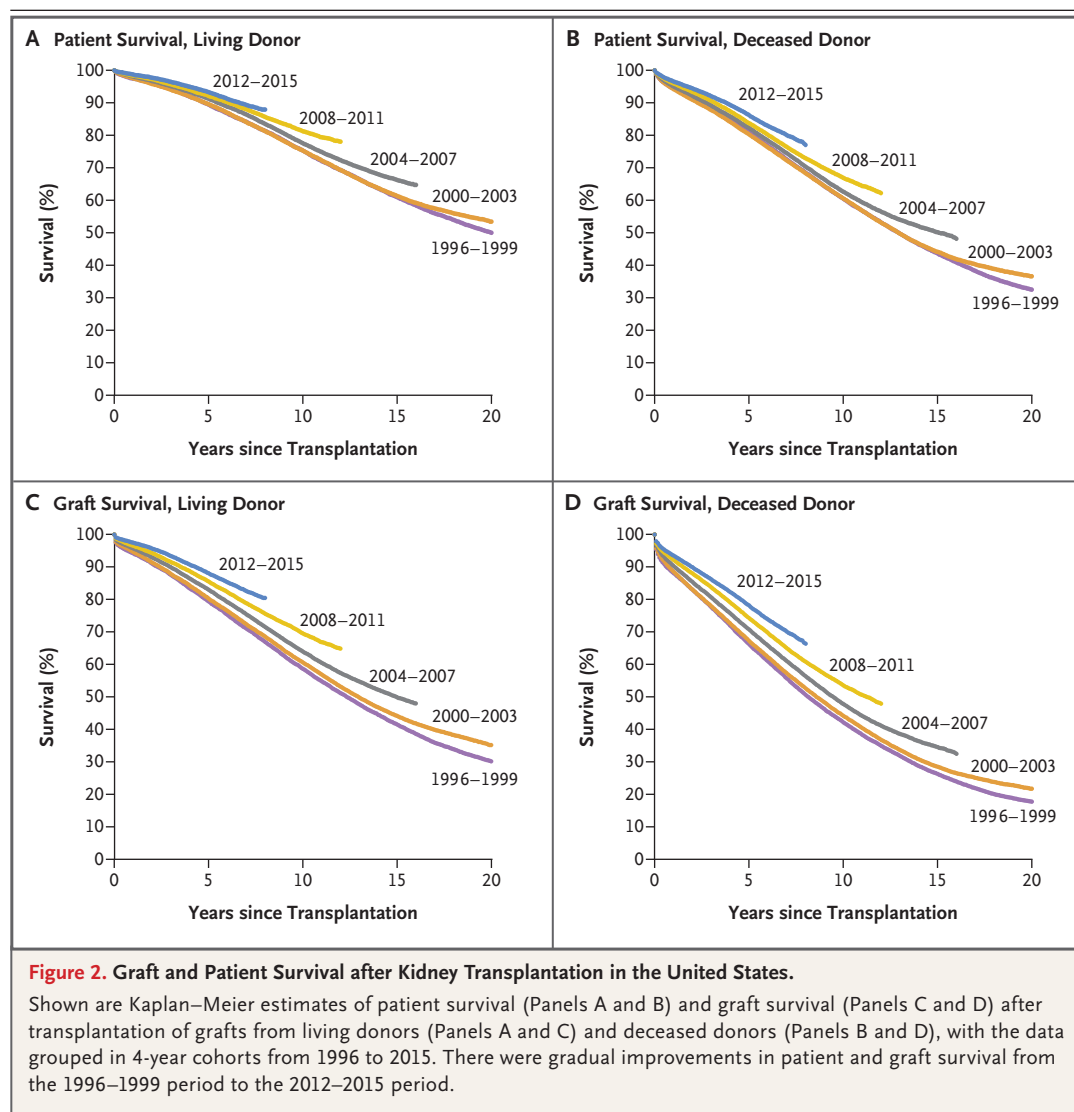


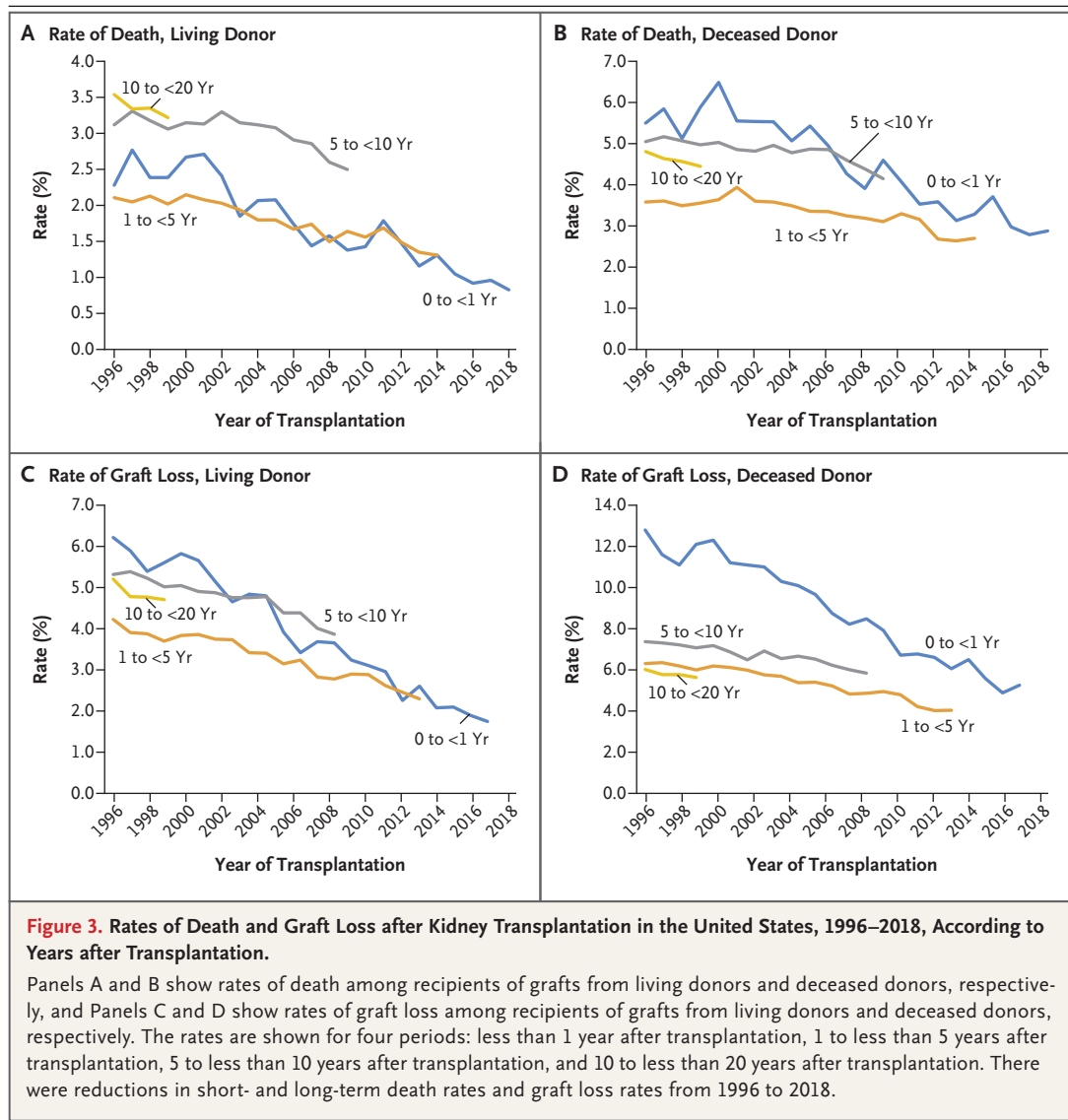
Figure 2. Graft and Patient Survival after Kidney Transplantation in the United States.

Shown are Kaplan-Meier estimates of patient survival (Panels A and B) and graft survival (Panels C and D) after transplantation of grafts from living donors (Panels A and C) and deceased donors (Panels B and D), with the data grouped in 4-year cohorts from 1996 to 2015. There were gradual improvements in patient and graft survival from the 1996–1999 period to the 2012–2015 period.

globulin (Thymoglobulin, Genzyme) and the humanized anti-CD25 monoclonal antibody basiliximab (Simulect, Novartis) are the most commonly used induction agents in the United States. Most patients receive a calcineurin inhibitor (cyclosporine or tacrolimus), typically in combination with an antimetabolite (azathioprine, mycophenolate mofetil, or mycophenolic acid) and a glucocorticoid. Mycophenolate mofetil has largely replaced azathioprine; however, azathioprine can be substituted during pregnancy, when mycophenolate mofetil is contraindicated, or if gastrointestinal intolerance of mycophenolate mofetil develops. The use of the mechanistic target of rapamycin (mTOR) inhibitors (sirolimus and everolimus)

and the costimulatory blocker belatacept has remained limited.

Calcineurin inhibitors are highly effective in preventing acute rejection but are inherently nephrotoxic,^{16–18} yet immunosuppressive regimens that are free of calcineurin inhibitors (i.e., mycophenolate mofetil and mTOR inhibitors) have been associated with high rates of acute rejection.¹⁸ Long-term use of mTOR inhibitors, with or without a calcineurin inhibitor, has been associated with an increased incidence of acute rejection, worsening renal function, and increased long-term mortality.^{19,20} Use of a combination of mycophenolate mofetil and belatacept has been limited because of high rates of acute rejection,



high cost, concerns about post-transplantation lymphoma, and the logistics of the required monthly belatacept infusions.^{21,22} However, in patients who do not have early acute rejection but do have side effects from calcineurin inhibitors, a switch to belatacept is an option.²³ Rapid glucocorticoid withdrawal has been associated with a slightly increased incidence of acute rejection²⁴ and has not been universally adopted. The combination of mycophenolate mofetil, tacrolimus, and low-dose prednisone remains the most common immunosuppressive regimen for kidney transplant recipients worldwide.

POST-TRANSPLANTATION EVENTS THAT AFFECT LONG-TERM SURVIVAL

DELAYED GRAFT FUNCTION

Some degree of renal perfusion injury is inevitable after kidney transplantation, but severe forms result in delayed graft function, defined as a requirement for dialysis in the first week after transplantation. Graft function is delayed in more than 25% of recipients of transplants from deceased donors (Table 1). Delayed graft function augments graft inflammation and fibrosis and may accelerate graft dysfunction and

lead to premature failure.²⁵ To date, pharmacologic agents have not proved helpful in reducing the incidence or severity of delayed graft function. Use of mild hypothermia in brain-dead donors has been reported to reduce rates of delayed graft function²⁶ but has not been adopted in clinical practice. The use of hypothermic pulsatile machine perfusion of kidneys from deceased donors, as compared with cold storage, has shown some benefit.^{27,28} Kidneys from deceased donors with high scores on the Kidney Donor Profile Index have been associated with an increased incidence of delayed graft function, which may affect long-term survival.²⁹ However, such organs remain a valuable source for patients with anticipated shorter life spans. Long-term graft survival of kidneys from deceased donors can be improved by reducing the severity of perfusion injury with a shorter cold ischemia time, especially for kidneys with high scores on the Kidney Donor Profile Index (Fig. 1).

ACUTE REJECTION

Episodes of acute rejection, typically confirmed by kidney biopsy, are common after kidney transplantation. Rejection episodes may be T-cell-mediated, antibody-mediated, or both and are graded on the basis of the widely accepted Banff classification (a classification that involves an integration of histologic features of the transplanted kidney with serologic and molecular diagnostic techniques; it also provides a consensus-based reporting system that offers precise composite scores and accurate diagnosis of allograft dysfunction and rejection; see Table S2).³⁰ Histologic diagnosis of acute rejection is descriptive and is graded according to the extent of lymphocytic infiltrates, an approach that is limited by sample size and variations in interpretation.³¹ Acute rejection, when discovered because of renal dysfunction, is referred to as clinical acute rejection, and subclinical rejection is diagnosed on the basis of surveillance biopsy. The incidence of clinical acute rejection and subclinical rejection during the first year after transplantation ranges from 10 to 15% and from 5 to 15%, respectively. Up to 40% of transplant recipients may have subclinical inflammation (borderline changes suggestive of rejection) during the first year after transplantation, which falls below the threshold for the diagnosis of rejection (T-cell-

mediated rejection, grade IA) in the Banff classification.³² Acute rejection negatively affects long-term survival, in accordance with the severity, persistence, and histologic type of rejection, and acute rejection that occurs more than 3 months after transplantation has a worse prognosis than acute rejection occurring earlier.^{33,34} Subclinical inflammation also has a deleterious effect on the outcome of transplantation.³⁵

Acute rejection in the first year after transplantation is primarily T-cell-mediated rejection, with fewer cases of antibody-mediated rejection, whereas after the first year, acute rejection is often a combination of antibody-mediated and T-cell-mediated rejection.³⁶ Confirmation of antibody-mediated rejection is provided by histologic evidence of capillaritis, defined as an accumulation of inflammatory cells in graft capillaries, the presence of complement fraction C4d in peritubular capillaries, and circulating donor-specific antibody against donor HLA antigens. Antibody-mediated rejection in the absence of donor-specific antibodies reflects either an inability to detect HLA antibodies with current platforms or mediation by non-HLA antibodies.³⁷ Acute rejection is the result of suboptimal immunosuppressive therapy, particularly in transplant recipients at high immunologic risk; non-adherence to immunosuppressive therapy³⁸; or a reduction in immunosuppressive medications because of infections or cancers.^{39,40}

Noninvasive Screening for Acute Rejection

The search for reliable biomarkers to diagnose acute rejection noninvasively is ongoing. Donor-specific antibodies against donor HLA antigens may be detected concurrently with histologic diagnosis of antibody-mediated rejection or may follow T-cell-mediated rejection.^{33,41} Donor-specific antibodies appearing early after transplantation represent a preformed or “memory” response causing antibody-mediated rejection. De novo donor-specific antibodies that develop late usually occur with mixed rejection. Patients with donor-specific antibodies that are persistent, preformed,⁴² or complement-fixing (C1q+)³⁴ and class II, with T-cell-mediated rejection,³³ have poorer outcomes.

The diagnosis of acute rejection has been correlated with urinary FOXP3 messenger RNA (mRNA)⁴³; a urinary signature of CD3ε mRNA,

interferon-inducible protein 10 mRNA, and 18S ribosomal RNA⁴⁴; transcriptomic signatures in blood⁴⁵; transitional B-cell cytokines in blood;⁴⁶ and a urinary exosome mRNA signature.⁴⁷ Transcriptional analysis of biopsy specimens at 1 year after transplantation revealed that a set of 13 genes predicted graft scarring and poor survival.⁴⁸ A gene microarray from graft biopsies has been analyzed in an attempt to develop a “molecular microscope” that can aid in the diagnosis of acute rejection, risk stratification, and prediction of graft loss.⁴⁹

The measurement of circulating cell-free DNA (cfDNA) and multigene expressions is approved by the Food and Drug Administration for the diagnosis of acute rejection.⁵⁰⁻⁵² However, the sensitivity of cfDNA for the diagnosis is only 59%.⁵⁰ Circulating cfDNA can be used to identify antibody-mediated rejection but not to differentiate Banff grade 1A rejection from borderline rejection.⁵³ The place of cfDNA measurement in clinical practice has yet to be established by randomized clinical trials. A multicenter trial identified a circulating 57-gene biomarker profile that correlates with acute rejection, including subclinical inflammation, as determined by surveillance biopsies. The sensitivity for acute rejection was 48%, and the specificity was about 80%.⁵²

The available biomarkers are inflammatory, injury, and genetic markers; none are specific for alloimmune injury. Moreover, these biomarkers do not differentiate among grades of T-cell-mediated rejection; they also do not differentiate between acute and chronic T-cell-mediated rejection. Instead of providing the basis for a specific diagnosis of acute rejection, noninvasive biomarkers may serve to determine graft quiescence (the absence of graft rejection) and permit more precise immunosuppression, with the goal of preventing infections, tumors, and acute rejection (Fig. 1). At present, immunosuppressive therapy should not be modified on the basis of biomarker tests alone.⁵⁴

Treatment of Acute Rejection

Prevention of acute rejection remains the key to achieving long-term graft survival (Fig. 1). Adequate tacrolimus exposure (trough levels of 7 to 12 ng per milliliter during the first year after transplantation and >5 ng per milliliter after the first year), with low-dose glucocorticoids and an antimetabolite, is central to the prevention of

early acute rejection and the development of de novo donor-specific antibodies.^{55,56} Strategies such as performing transplantation in recipients with two HLA-DR matches, matching at the amino acid level (eplet matching) as opposed to the whole-molecule level, and improving immunosuppression for those with a high eplet mismatch have been shown to decrease the risk of de novo donor-specific antibody formation and acute rejection and to improve long-term survival (Fig. 1).⁵⁷⁻⁵⁹

Patients with lower grades of T-cell-mediated rejection are treated with glucocorticoids, whereas those with higher grades receive antithymocyte globulin. Costimulatory blockers such as belatacept can control the alloimmune response and prevent the formation of donor-specific antibodies³⁶; however, costimulatory blockers do not reduce the incidence of donor-specific antibodies, as compared with tacrolimus.⁶⁰ Early antibody-mediated rejection is treated with glucocorticoids, plasmapheresis, and intravenous immune globulin. Other therapies (anti-CD20 antibodies,⁶¹ proteasome inhibitors,⁶² and anticomplement therapy⁶²⁻⁶⁵) are being investigated. Late antibody-mediated rejection may be treated by augmenting maintenance immunosuppressive therapy, but the benefit of plasmapheresis with intravenous immune globulin, proteasome inhibitors, and anti-CD20 antibodies remains questionable.⁶⁶ Therapies to block interleukin-6 (tocilizumab and clazakizumab) are under investigation.⁶⁷ The combination of a proteasome inhibitor and costimulatory blocker has the theoretical advantage of blocking donor-specific antibody formation at multiple levels and may be valuable for treating antibody-mediated rejection.⁶⁸ Trials of immune-cell therapies involving donor regulatory T cells and studies of donor-derived regulatory dendritic cells for the prevention and treatment of acute rejection are under way.⁶⁹⁻⁷¹ Although immune-cell therapies appear to have few side effects, prevention of acute rejection remains the best approach.

INFECTIONS

Vaccination status must be assessed and vaccinations administered before transplantation. Only inactivated vaccines should be given after transplantation. Detailed information about common post-transplantation viral infections is provided in Table S3.

Cytomegalovirus (CMV) infection is the most common opportunistic infection after transplantation. CMV-seronegative patients are at increased risk for CMV infection if they receive a kidney from a seropositive donor.⁷²⁻⁷⁴ In addition, CMV infection is a risk factor for acute rejection and graft failure.^{72,74} Prevention, early recognition, and treatment of CMV infection are essential. Fortunately, effective antiviral treatment is available in the form of valganciclovir.⁷⁴ Resistant CMV infections are usually characterized by *UL97* (kinase) and *UL54* (DNA polymerase) mutations. Patients with *UL97* mutations can be treated with foscarnet, and those with *UL54* mutations can be given cidofovir. Potential alternatives to valganciclovir (letermovir, maribavir, and neutralizing monoclonal antibodies) are under investigation.⁷⁵

Infection with BK virus is common in immunosuppressed kidney transplant recipients.³⁹ BK virus infection starts as viremia, progresses to viremia, and if unchecked, leads to nephropathy and transplant failure. BK virus nephropathy is characterized histologically by a plasma-cell and lymphocytic-rich interstitial nephritis that may be difficult to distinguish from acute rejection unless viral inclusions are recognized. Such differentiation is critical, because successful treatment of BK virus infection requires early recognition and reduction of immunosuppressive therapy. Switching of immunosuppressive agents and the addition of leflunomide, cidofovir, fluoroquinolones, and intravenous immune globulin have not proved effective as treatment. In the absence of an effective antiviral agent, the key to prevention of BK virus nephropathy is aggressive screening for viremia, with early reduction of immunosuppressive therapy.³⁹

Post-transplantation lymphoproliferative disease (PTLD) is predominantly a B-cell disorder, is frequently extranodal, and is associated with Epstein-Barr virus infection.⁴⁰ The development of PTLD is generally a consequence of effective immunosuppression and may reflect unrecognized overimmunosuppression. CD20+ PTLD can be effectively treated with anti-CD20 agents and cytotoxic chemotherapy when necessary, combined with minimization of immunosuppression. Adoptive T-cell therapy is being explored for the treatment of resistant CMV infection, Epstein-Barr virus-associated PTLD, and BK virus infection.⁷⁶

Influenza infections are common among kidney transplant recipients. Currently, however, the coronavirus disease 2019 (Covid-19) pandemic represents a serious threat to patients who have undergone kidney transplantation. Immunosuppression, advanced age, hypertension, diabetes, obesity, and chronic kidney disease put many transplant recipients at grave risk. A Covid-19 mortality rate of 13 to 32% has been reported among transplant recipients.⁷⁷⁻⁷⁹ Strict adherence to the Centers for Disease Control and Prevention guidelines for Covid-19 prevention is mandatory for this patient population, and reduction of immunosuppressive therapy, typically by discontinuing mycophenolate mofetil, is recommended in patients who have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).⁷⁷ The Pfizer-BioNTech, Moderna, and Johnson & Johnson/Janssen vaccines have been approved for emergency use and are awaiting full approval.^{80,81} A preliminary report shows that administration of two doses of Covid-19 vaccine in immunosuppressed transplant recipients reduces the rate and severity of infection with SARS-CoV-2.⁸² However, the antibody response after two doses may be insufficient, especially among transplant recipients who are receiving antimetabolite treatment,⁸³ and can be augmented by a third dose.⁸⁴ Covid-19 infection may still occur after vaccination in immunosuppressed kidney transplant recipients, which underscores the importance of following preventive guidelines recommended by the Centers for Disease Control and Prevention.

OTHER FACTORS THAT AFFECT SURVIVAL

SENSITIZATION

Patients with increased levels of antibodies to multiple HLA antigens have difficulty finding an immunologically matched, compatible kidney donor and may remain on the transplant waiting list for a prolonged period. Patients accrue time on the deceased donor waiting list and are assigned priority points on the basis of their degree of sensitization. Desensitization may be an option for transplantation candidates considered to be close to receiving an offer of a kidney from a deceased donor. Desensitization protocols involve the use of intravenous immune globulin, anti-CD20 antibody, and plasmapheresis, with

the goal of achieving a negative cross-match. Desensitized patients, however, remain at risk for the development of de novo donor-specific antibodies, antibody-mediated rejection, and graft loss. One study showed that patients who underwent desensitization and received a kidney from an HLA-incompatible donor had improved graft survival, as compared with patients who remained on the waiting list.⁸⁵ Administration of imlifidase, an enzyme that cleaves IgG, reduces the degree of sensitization, permitting a negative cross-match, yet antibody-mediated rejection develops in roughly 40% of patients who have undergone desensitization with imlifidase.⁸⁶ Since the introduction of the national kidney allocation system in 2014, highly sensitized patients have had improved access to the national pool of kidneys from deceased donors.

PAIRED EXCHANGE OF TRANSPLANTS FROM LIVING DONORS

Living donor paired transplant exchange, pioneered in South Korea and the Netherlands,^{87,88} is increasingly used for transplantation candidates with living donors who are incompatible on the basis of blood type or HLA matching (Fig. 1). The simplest living donor paired exchange transforms two incompatible donor-recipient pairs into two compatible donor-recipient pairs. The number of exchanges has been increasing (Table 2) since exchanges were legalized in the United States by the 2007 Charlie W. Norwood Living Organ Donation Act. An altruistic living donor can trigger a chain of living donor transplant exchanges.⁸⁹ Some living donor exchanges are governed by rules that provide equity for all participating candidates, even those with early graft loss.⁹⁰ Paired exchanges are also being performed with living donors who are biologically compatible but have relative degrees of incompatibility by virtue of age or size differences. Living donor paired exchange remains superior to desensitization for patients with incompatible living donors but is not ideal for highly sensitized patients.

APOL1, KIDNEY DISEASE, AND TRANSPLANTATION

Polymorphisms in the genes that encode apolipoprotein L1 (APOL1) are found much more often in persons of African ancestry than in other groups.⁹¹ Homozygosity for APOL1 kidney risk variants, which occur in up to a third of Blacks,

confers increased risks of nondiabetic chronic kidney disease, hypertensive nephrosclerosis, and focal segmental glomerulosclerosis (a phenomenon that is probably responsible for the increased incidence of end-stage kidney disease among Blacks)⁹² and an increased risk of end-stage kidney disease among Black living donors.⁹³ Furthermore, graft survival may be reduced for kidney transplants from deceased donors who were homozygous for APOL1.⁹⁴ APOL1 homozygosity may also account for the reduced long-term graft survival among Black recipients of kidney transplants. Some transplantation programs routinely test young, Black potential donors for APOL1 and advise those who are homozygous not to donate a kidney.⁹⁵

HIV INFECTION AND HEPATITIS C

Recipients with treated human immunodeficiency virus (HIV) infection can undergo kidney transplantation successfully, though the incidence of acute rejection may be increased.^{96,97} Organs from HIV-positive donors are typically discarded. The passage of the HIV Organ Policy Equity (HOPE) Act in 2013 has allowed organs from HIV-positive donors to be successfully allocated to HIV-positive recipients^{98,99} and may provide for expedited transplantation in HIV-positive patients. The availability of highly effective treatments for hepatitis C allows kidneys from donors with hepatitis C infection to be allocated to both hepatitis C-positive and hepatitis C-negative recipients^{100,101} (Fig. 1).

TRANSITION OF ADOLESCENTS FROM PEDIATRIC TO ADULT CARE

Transplant recipients between the ages of 14 and 23 years have an increased risk of graft failure and are particularly likely to have problems with adherence to immunosuppressive regimens.¹⁰² Nonadherence has a profoundly negative effect on the lives of young people, including quality of life, ability to return to work and school, sensitization, opportunities for repeat transplantation, and life expectancy.¹⁰³ Young patients may get lost in the process of transition from pediatric to adult health care delivery systems and may lose health insurance. Improved outcomes may be achieved with structured and personalized care, maintenance of insurance coverage, and a focus on patient education during the transition period.¹⁰⁴

CONCLUSIONS

Improvement in long-term survival after kidney transplantation has been gratifying, despite unfavorable changes in donor and recipient risk factors. Continuation of this trend will require a multipronged approach that addresses coexisting conditions before transplantation, health literacy, access to caregivers, and, especially among racial or ethnic minority and young transplant recipients, adherence to therapy. Innovative non-invasive biomarkers to diagnose and prevent acute rejection, adoptive T-cell therapy for post-transplantation viral infections, and newer therapies for T-cell-mediated rejection, antibody-mediated rejection, and desensitization are under investigation.

Nephrologists and primary care physicians must be adequately trained to care for kidney transplant recipients. A silver lining of the Covid-19 pandemic may be the incorporation of telemedicine into routine care to facilitate access to transplantation and post-transplantation care,

particularly for older patients and those in underserved and geographically remote communities. The discontinuation of insurance coverage for long-term immunosuppressive medications for kidney transplant recipients in the United States was an unnecessary impediment to long-term survival, for which patients and society paid a heavy price; the 2020 approval of lifelong health care coverage of these medications for transplant recipients in the United States is a victory that will pave the way toward further improvements in long-term survival.

The data reported here for all kidney transplants from living and deceased donors, as well as the survival analyses, have been supplied by the Hennepin Healthcare Research Institute as contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data and the opinions expressed in this article are those of the authors and do not necessarily represent interpretation by, an official policy of, or the opinions of the SRTR or the U.S. government.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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