Transplantation

When our two souls stand up erect and strong,
Face to face, silent, drawing nigh and nigher,
Until the lengthening wings break into fire
At either curved point, – what bitter wrong
Can the earth do to us, that we should not long
Be here contented?

Elizabeth Barrett Browning
Sonnets from the Portuguese, XXII
functioning kidney—is now approaching 90 percent. This improvement in short-term allograft survival has shifted attention to the two major remaining challenges in kidney transplantation: the shortage of organs and the lack of improvement in the rate of allograft failure after the first post-transplant year.

Many of the moral and ethical dilemmas facing kidney transplantation today are a direct result of the organ shortage. This shortage has given rise to lengthening waiting times for deceased donor kidneys. It has also created ethnic and geographic disparities in waiting times that continue to fuel a national debate on the best method for allocating deceased donor kidneys. In addition, it has created increasing pressure to use deceased donor kidneys that may function sub-optimally after transplantation. The Extended Criteria Donor (ECD) kidney allocation program of the Organ Procurement and Transplantation Network (OPTN) is one example of efforts to use deceased donor kidneys that would formerly have been discarded.

Similarly, the deceased donor kidney shortage has created enormous pressure for patients and their physicians to find living donors. Use of these donors is increasing, despite medical risks that would have precluded donation at most transplant centers just a few years ago. Increasing numbers of patients are also traveling abroad to purchase living donor kidneys. “Transplant tourism” and “organ trafficking” exploit the poor and disadvantaged for the purpose of obtaining kidneys for those with the means to do so, and these practices all result from the organ shortage.

In this chapter we chronicle the growth in the wait list and the increase in wait times in the U.S. We show trends in the use of ECD kidneys under the OPTN’s ECD program, as well as outcomes for patients on the deceased donor waiting list. We look as well at trends in transplantation rates by patient characteristics and geographic location, and show rates of donation from deceased and living donors, expressed both per million population and per 100 deaths.

The second major problem plaguing transplantation is the failure to improve patient and graft survival rates late after transplantation, e.g., after the first post-transplant year. We report here on the most recent trends in overall outcomes. Newer and better immunosuppressive medications have helped reduce early acute rejection and improve short term survival rates, and, indeed, one-year graft survival has improved. But conditional half lives have changed.

Since the early 1970s, when only one-half of kidney transplant recipients survived one year with a functioning kidney, there has been a remarkable improvement in outcomes. The norm for one-year allograft survival—i.e., patients surviving at least one year with a
very little, being slightly more than ten years for deceased donors and approximately 20 years for living donors. Why is this?

Immunosuppressive medications that reduce rejection have adverse effects that may contribute to graft dysfunction, as well as patient morbidity and mortality late after transplantation. Calcineurin inhibitors, for example, which have become the mainstay of immunosuppressive drug regimens, may cause acute and chronic nephotoxicity. Indeed, it is possible that much of the chronic allograft injury that accompanies progressive graft dysfunction is caused by calcineurin inhibitors. Too much immunosuppression can also result in higher rates of infection and malignancy. Similarly, several of the most commonly used immunosuppressive medications adversely affect a number of cardiovascular disease risk factors, including blood pressure, dyslipidemia, and glucose intolerance. This chapter illustrates trends in rates of hospitalization in the first year after discharge from the initial hospitalization for transplantation, overall and by reason for the hospitalization.

One way to prevent at least some of the complications of transplantation and immunosuppressive medications is to screen for disease and risk factors, and to use preventive measures for some of the most common post-transplant complications. We look here at the percentage of patients undergoing cardiac procedures in the year before and the years after wait listing and transplantation. We also show the cumulative incidence of cardiovascular disease events, new onset diabetes, and post-transplant malignancies, trends in the use of different immunosuppressive agents, and the use of common screening measures in the transplant population.

**Figure 7.48** "CHF is the most common reason for a cardiovascular hospitalization in patients with a kidney transplant, and urinary tract infections the most common cause of infectious hospitalizations." More than 60 percent of high-risk Medicare recipients have a cardiac stress test in the year before being placed on the wait list for deceased donor kidney transplantation.
Extended criteria donor (ECD) kidneys

7.11 Listings willing to accept an ECD kidney

7.12 Listings willing to accept an ECD kidney, by age, gender, & race, 2004–2005

7.13 Listings willing to accept an ECD kidney (percent), by state, 2004–2005

7.14 Listings willing to accept an ECD kidney, by OPTN region, 2004–2005

7.15 Likelihood of receiving a transplant within one year of listing, 1995–2004

7.16 Likelihood of dying while awaiting transplant, 1995–2004

7.17 Likelihood of being alive one year after listing, 1995–2004

7.18 Outcomes for first-time wait-listed patients five years after listing, 2000

More on transplant counts & rates: p.a. p.6–7, Chapter Four.
Outcomes: deceased donor transplants
first-time, kidney-only transplants

Outcomes: living donor transplants
first-time, kidney-only transplants

Figure 7.33 all transplants, 1995–2005. Figure 7.34 patients with functioning grafts upon discharge. Figure 7.35 preemptive retransplantations are counted as a return to dialysis. For total patients starting or restarting dialysis, refer to Figure p.2 in the Précis. Figures 7.36–7.37 first-time, kidney-only transplants. Cumulative incidences are estimated using the Kaplan-Meier method. Half-life estimates are conditional on first-year graft survival. Figure 7.38 transplants 1995–2005; most recent creatinine as reported to OPTN. Figure 7.39 includes preemptive retransplants, & excludes failures due to death. Figure 7.40 includes return to dialysis & preemptive retransplants, & excludes failures due to death. Figure 7.41 includes death with functioning transplant. Figure 7.42 adjusted for age, gender, & race. Preemptive retransplantations are counted as a return to dialysis. Figures 7.43 first-time, kidney-only transplants, 1999–2004. One-year cumulative incidence of acute rejection for transplants in the given year, as identified from OPTN follow-up data. Does not include acute rejection episodes at the time of transplant or acute rejections listed as the cause of graft failure. Kaplan-Meier methodology. Figure 7.44 recipients of first-time, kidney-only transplants, 2000–2002, with Medicare as primary payer. Biopsies identified from Medicare claims; see Appendix A for further details. Figure 7.45 first-time, kidney-only transplants, 1995–2004. Significantly below & above average adjusted graft failure ratios assessed at the 0.05 level of significance.

Most recent serum creatinine, 1995–2005 transplants
Hospitalization rates in the first year post-transplant, by cause, age, race, & donor type first-time, kidney-only transplants

In the past decade, rates of hospitalization (calculated per 100 transplant patient years) among Medicare recipients have declined in the first year after transplantation, but increased in the second and third years (Figures 7.46–47). Infections and cardiovascular disease are common causes of hospitalization. Congestive heart failure is the most common cardiovascular cause of hospitalization, while urinary tract infection is the most common cause of infectious hospitalizations. Interestingly, overall rates of hospitalization are similar, but the causes are quite different among different age groups. Hospitalizations for cardiovascular disease, for example, are much more common in older than in younger transplant recipients.

Figure 7.46 patients with first-time, kidney-only transplants, transplanted in the given year & followed for one year after discharge, & with Medicare as primary payor. Figure 7.47 patients with first-time, kidney-only transplants, transplanted in the given year & followed in years two & three after discharge, & with Medicare as primary payor. Figure 7.48 patients receiving a kidney transplant, 2001–2003, with Medicare as primary payor; cause-specific hospitalizations up to three years post-transplant. CHF: congestive heart failure; CVA: cerebrovascular accident; TIA: transient ischemic attack; AMI: acute myocardial infarction; UTI: urinary tract infection; CMV: cytomegalovirus infection.
Hospitalization rates in the second through third years post-transplant, by cause, age, race, & donor type for first-time, kidney-only transplants

Primary diagnosis of cardiac & infectious hospitalizations for patients receiving a kidney transplant, 2001–2003

More on hospitalization: Chapter Six, Chapter Eight (pediatric patients).
Cardiovascular disease testing of Medicare recipients is much more common among high-risk patients (Figures 7.49–53). Testing is more likely to occur in the year before being placed on the deceased donor wait list and in the year prior to transplantation, implying that many patients are undergoing screening. Unfortunately, whether testing is performed for screening or treatment cannot be discerned from these data. More than 60 percent of high-risk Medicare recipients receive a cardiac stress test during the year before being placed on the wait list for deceased donor kidney transplantation. Similarly, more than 70 percent of high-risk living donor kidney recipients have cardiac stress testing in the year before transplantation. Presumably, many of these patients are asymptomatic, and testing is done for screening purposes. Patients at high risk for cardiovascular disease—those older than 50, with diabetes, or with known cardiovascular disease—are much more likely to undergo a cardiac stress test than are low-risk patients.

For coronary angiography and/or stress testing, more than 80 percent and virtually 100 percent of high-risk Medicare patients are tested before wait-listing or transplantation, respectively. Coronary artery revascularization, however, occurs in fewer than 9 percent of these high-risk patients in the year prior to wait-listing or transplantation. Hence, the majority (more than 90 percent) of cardiac tests do not lead to an intervention with revascularization.

These figures are similar to what has been reported in single-center studies. Interestingly, the most common cardiovascular disease event after transplantation is hospitalization for congestive heart failure (CHF; Figure 7.54). By 36 months post-transplant, more than 20 percent of patients have been hospitalized for CHF. Strokes and transient ischemic attacks are the second most common post-transplant cardiovascular disease event.

![Graph showing cumulative incidence of cardiovascular events](image)

**Cumulative incidence of cardiovascular events**

*First-time transplant patients, 2000–2004*

- **AMI**: Acute myocardial infarction
- **CHF (hospitalization)**: Congestive heart failure
- **Cardiac arrest**: Cardiopulmonary arrest
- **CVA/TIA**: Cerebrovascular accident

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Cumulative Incidence (%)</th>
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<tbody>
<tr>
<td>AMI</td>
<td>Living donor: 40%</td>
</tr>
<tr>
<td>CHF (hospitalization)</td>
<td>Deceased donor: 30%</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td></td>
</tr>
<tr>
<td>CVA/TIA</td>
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**Months after transplant**

- **Coronary revascularization**: Cumulative incidence of coronary revascularization events among high-risk Medicare patients
- **Peripheral arterial disease**: Cumulative incidence of peripheral arterial disease events among high-risk Medicare patients
- **Cardiovascular/CVA death**: Cumulative incidence of cardiovascular/CVA death events among high-risk Medicare patients
- **Any cardiovascular/CVA event**: Cumulative incidence of any cardiovascular/CVA event among high-risk Medicare patients

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The incidence of new-onset diabetes is high after kidney transplantation, but varies according to the definition used. In Figure 7.55 we look at diabetes as defined using a previously validated (by survey) method that relies on Medicare claims. More than one-third of adults develop new-onset diabetes in the first three years after transplant—half of these in the first few months. Even more worrisome is the fact that 10 percent of children develop new onset diabetes in the three years following kidney transplantation.

Data from many studies have suggested that the incidence of cancer after kidney transplantation is higher than that found in the general population. However, the incidence varies substantially by cancer type and site (Figure 7.56). Particularly common are malignancies that have a putative viral cause. Skin cancers, for example, are most common. Lymphomas also occur frequently after kidney transplantation.

In the past decade, there have been dramatic changes in the immunosuppressive agents used at the time of discharge from the initial hospitalization after kidney transplantation (Figures 7.57–61). The use of cyclosporine A (CsA, standard formulation) in the initial immunosuppressive medication regimen declined dramatically, from 80 percent in 1995 to less than 10 percent two years later. The older CsA formulation was largely replaced by microemulsion CsA, used in almost 70 percent of transplant recipients in 1997. Between 1995 and 2005, however, CsA was gradually replaced by tacrolimus.

Similarly, the use of azathioprine as part of the initial immunosuppressive medication regimen fell dramatically between 1995 and 1997, being replaced by mycophenolate mofetil (MMF). By
The initial use of a biological agent for “antibody induction” after kidney transplantation has increased from about 25 percent to about 63 percent in the past decade. Roughly equal numbers of kidney transplant recipients receive an interleukin 2 receptor antagonist compared to some other antibody agent as part of the initial, prophylactic immunosuppressive medication regimen. For patients receiving a kidney transplant in 2003–2005, by far the most common initial immunosuppressive medication regimen included MMF and tacrolimus (Figure 7.62). A drug regimen that included CsA microemulsion and MMF was the second most commonly used combination.

In 2001, nearly 17 percent of patients were using the mammalian target of rapamycin (mTOR) inhibitor sirolimus as part of their initial immunosuppressive medication regimen. But use has since declined, likely due to the discovery of complications associated with the use of sirolimus early after kidney transplantation, including prolonged delayed graft function and impaired wound healing. This caused many centers to delay the use of sirolimus. (Patients who are switched to sirolimus after the initial hospital discharge are not included in the baseline percentages.)

The use of corticosteroids at the time of discharge from the hospitalization for an initial kidney transplant has gradually declined. However, in 2005, two-thirds of transplant recipients were still receiving corticosteroids as part of their early maintenance immunosuppressive medication regimen.

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### Figure 7.63
Period prevalent transplant patients transplanted in 1995 or later (7.63) or 2000 or later (7.64). Kaplan-Meier method. Location of follow-up care as identified to OPTN. *figure 7.65* Kidney transplant patients age younger than 62, 1998–2002. *figure 7.66* All kidney transplant patients. Medicare coverage determined at time of transplant. *figures 7.67 & 7.68* transplant: diabetic Medicare transplant recipients, 1995–2004, whose grafts function for at least one, two, & three years, respectively. General Medicare: prevalent beneficiaries (from 5 percent sample) who survive the two-year interval. Diabetic status determined from claims during first year; HbA1c & test strip use determined in second year. *figure 7.68* transplant population: Medicare transplant recipients, 1995–2004, whose grafts function for at least one, two, & three years, respectively. Lipid tests occur at least 30 days apart. General Medicare: prevalent beneficiaries (from 5 percent sample) who survive the entire year. Lipid tests occur at least 30 days apart. *figure 7.70* prevalent patients initiating therapy 90 days prior to January 1 of the year before the measurement year, alive & age 18–75 on December 31 of the measurement year, with Medicare as primary payor during the two-year period, & with diabetes in the measurement year. For patients with diabetes as the primary cause of ESRD, claims for eye exams are searched during the measurement year; for other diabetics, claims are searched during the measurement year & previous year. *figure 7.71* prevalent patients initiating therapy 90 days prior to September 1 of the year before the measurement year, alive & age 18–75 on December 31 of the measurement year, with Medicare as primary payor from September to December. *figure 7.72*

### Figure 7.71
Influenza vaccinations in transplant patients, by age, gender, & race

### Figure 7.72
Pap smears, by population (transplant & general Medicare), & by age & race/ethnicity (transplant only)

### Figure 7.73
Mammograms, by population (transplant & general Medicare), & by age & race/ethnicity (transplant only)

### Figure 7.74
Prostate screening, by population (transplant & general Medicare), & by age & race/ethnicity (transplant only)

### Figure 7.75
Colonoscopies, by population (transplant & general Medicare), & by gender, age, & race/ethnicity (transplant only)

transplant wait list
figure 7.5 The number of patients on the wait list for deceased donor kidney transplantation continues to grow, reaching 62,581 in 2005. figures 7.11–12 Over one-third of new listings are for Extended Criteria Donor kidneys, but the proportion varies by the age of the recipient, from less than 10 percent for ages 0–17 to more than half for those 65 years old.

transplantation & donation
figure 7.19 With the growth in ESRD, the rate of kidney transplantations per 100 ESRD patient years declined steadily between 1988 and 2002. It remained unchanged, however, between 2002 and 2005, keeping pace with the continued, albeit slower, increased incidence of ESRD.

graft survival
figures 7.36–37 One-year graft survival is now approaching 90 percent for recipients of deceased donor kidneys, and is even better for recipients of living donor kidney transplantations. Unfortunately, graft survival half-lives (conditional on one-year graft survival) have increased only gradually. Graft survival half-lives in recipients of living donor transplantations are almost two-fold higher than those in patients receiving a transplant from a deceased donor.

complications: hospitalizations
figures 7.46–47 Rates of hospitalization in the first year after the initial hospitalization for transplant have been relatively constant, but those in the second and third years have increased slightly. figure 7.48 Congestive heart failure is the most common reason for a cardiovascular hospitalization in patients receiving a kidney transplant, and urinary tract infections the most common cause of infectious hospitalizations.

complications: cardiovascular screening & events
figure 7.49 More than 60 percent of high-risk Medicare recipients have a cardiac stress test in the year before being placed on the waiting list for deceased donor kidney transplantation. Similarly, more than 70 percent of living donor kidney recipients receive cardiac stress testing in the year before transplantation. Most of these patients are asymptomatic, and presumably testing is done for screening purposes.

complications: diabetes & cancer
figure 7.55 In the Medicare population, new-onset diabetes is very common. More than one-third of adults develop diabetes in the three years following a kidney transplant—half of these in the first few months. figure 7.56 The incidence of cancer after kidney transplantation varies by cancer type and site. Particularly common are malignancies that have a putative viral cause.

immunosuppression
figures 7.57–61 In the past decade there have been dramatic changes in the immunosuppressive agents used at the time of discharge from the initial hospitalization after kidney transplantation.

patient follow-up & preventive care
figures 7.67–69 Monitoring of common complications, such as diabetes and dyslipidemias, is generally better among Medicare kidney transplant recipients than in the general Medicare population.

maps
National means & patient populations for maps can be found in the Excel file for this chapter—on our website at www.usrds.org, & also on the CD-ROM included at the back of this book.