For with my life was born some touch of dread,
And therewithal I heard her voice that said,
"Come down and learn to love and be alive,
For thee, a well-prized gift, today I give."

WILLIAM MORRIS
"THE EARTHLY PARADISE"
The major challenges of transplantation in the United States today include: 1) the donor shortage, 2) the inequities in access to transplantation, and 3) the relative lack of improvement in graft survival after the first post-transplant year.

The number of kidney transplants performed has steadily increased over the past 15 years. Most of the growth in transplantation has come from the use of living donors, especially living unrelated and distantly related donors. Unfortunately, the number of patients with ESRD has grown more rapidly than the number of transplants, and the rate of transplantation per 100 dialysis patient years has declined. All the while, the number of patients on the Organ Procurement and Transplantation Network (OPTN) waiting list, and the waiting time for deceased donor kidneys, have continued to increase.

The shortage of donors has created inequities in access to kidney transplantation. Patients in California and the Southwest wait longer for kidney transplantation than patients in the North Central states. People of color wait longer than whites. Women wait longer than men.

Donation rates for deceased donors have changed little, and remain lower for women and blacks compared to men and whites. More women are living donors than men, but the rate of living donation is similar for blacks and whites. Geographically, there are large differences in the rates of living and deceased kidney donations across the United States.

One-year graft survival has improved over the past eight years, due to declines in deaths with a functioning graft and patients returning to dialysis (or needing another transplant). There has been little improvement, however, in the rate of graft failure after the first post-transplant year, as measured by the one-year conditional graft survival half-life.

Slightly fewer graft failures are due to death with function than to return to dialysis or retransplantation. The rates per 100 patient years of patients dying with function have been constant, while the rates of patients returning to dialysis or needing retransplantation have declined. Losing a kidney transplant is often a harbinger of death, and more patients with failed kidney transplants die on dialysis than are retransplanted.

The most common cause of death after kidney transplantation is cardiovascular disease, followed by infections and malignancies. Risk factors for death with a functioning allograft include recipient male sex, donor female sex, use of an expanded criteria donor (by OPTN definition), the number of major histocompatibility mismatches, donor/recipient cytomegalovirus antibody status, and hepatitis B and C antibody status.
Screening tests that may reduce morbidity and mortality are obtained in many but not all appropriate transplant recipients. Hemoglobin A1C levels, for example, have been obtained more often in recent years. Among Medicare patients who were transplanted in 2002 and had grafts that functioned at least one year, approximately 80 patients had at least one A1C level in the first year. An even higher proportion of transplant patients have lipid monitoring, much higher than in the general Medicare population. Approximately 60 percent of women age 18–61 have Pap tests, and a similar proportion of women age 50–67 have mammograms. On the other hand, fewer male transplant recipients age 50 and older have screening for prostate cancer, possibly reflecting uncertainties over the utility of prostate cancer screening methods. The frequency of cancer screening tests is similar in different racial/ethnic groups, except for the notably low incidence of screening among American Indians.

The type of immunosuppressive medications used have changed dramatically over the past eight years, but it remains to be seen whether these changes will reduce long-term morbidity and mortality.

Finally, CMS—the Centers for Medicare and Medicaid Services—is setting minimal outcome standards for kidney transplant centers. Given expected statistical variability, the proposed CMS criteria will result in a disproportionate number of small centers being identified as having poorer outcomes, and therefore targeted for review by CMS. A Bayesian approach would offer an alternative, whereby fewer centers over time would fall below the proposed criteria, and the number of small centers that would require review by CMS would be substantially reduced.

**CHAPTER HIGHLIGHTS**

*Figure 7.2* The increase in the number of kidney transplantations has not kept pace with the growth in end-stage kidney disease. *Figure 7.4* Men are transplanted more frequently than women, and whites are transplanted relatively more often than people of color in the U.S. *Figures 7.14–15* There has been little improvement in late kidney allograft survival, as measured by one-year conditional half lives. *Figure 7.24* Cardiovascular disease is the most common cause of death after kidney transplantation. *Figure 7.59* Proposed CMS criteria for review will result in a disproportionate number of small centers being identified as having poorer outcomes.
Deceased donors/kidneys: a donation is counted twice if both kidneys are transplanted into different recipients. Deceased donors/donors: a donation is counted only once, whether or not both kidneys are eventually transplanted.

Deceased donors: kidneys

<table>
<thead>
<tr>
<th>Gender</th>
<th>Race</th>
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<tbody>
<tr>
<td>Male</td>
<td>White</td>
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<tr>
<td>Female</td>
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<tr>
<td></td>
<td>Native American</td>
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<td>Asian</td>
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Living donors

<table>
<thead>
<tr>
<th></th>
<th>0-19</th>
<th>45-59</th>
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<tbody>
<tr>
<td></td>
<td>16.1</td>
<td>&lt;18.5</td>
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<td></td>
<td>25.8</td>
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<td></td>
<td>18.5</td>
<td>&lt;21.2</td>
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</table>

Donor kidney shortage, however, has created inequities in the rates of transplantation. Men are transplanted relatively more frequently than women, and whites more often than people of color (Figure 7.4). There are also marked geographic variations in the transplant rate (Figures 7.3 and 7.6). The rate of deceased donor kidney transplantations has fallen dramatically, while the rate of living donor transplantations has grown slightly, due to an increase in the use of unrelated or distantly related donors (Figure 7.5).

Median waiting times for those who receive a kidney transplant have increased (Figure 7.8). Since waiting times are growing, the waiting time for patients still on the waiting list may be substantially longer than those for patients who have been transplanted. Fortunately, median waiting times are much shorter for children and adolescents. They are similar for men and women, but less so for whites compared to people of color. The number of people on the deceased donor waiting list continues to grow (Figure 7.9). Donation rates for deceased donor kidneys have declined slightly over the past decade, while those for living donor kidneys have risen (Figure 7.11).
One-year patient and graft survival rates have improved in the past eight years, for both deceased donor (Figure 7.14) and living donor transplants (Figure 7.15).

In contrast, there has been little improvement in late kidney allograft survival, as measured by one-year conditional half lives (Figures 7.14–15). The conditional half-life is the time when one half of the kidney grafts (that have already survived at least one year) have subsequently failed, either by death, return to dialysis, or retransplantation.

The number of patients returning to dialysis or being retransplanted has increased (Figure 7.17). Currently, about 5 percent of patients starting dialysis do so because they have had a kidney transplant that has failed. However, it is encouraging that, among grafts that have failed, the median duration of graft survival has gradually increased (Figures 7.18–19).

The rate of graft failure due to death with a functioning graft has remained relatively constant, at 3.4 per 100 patient years (Figure 7.20). The rate of graft failure due to patients returning to dialysis or receiving another kidney transplant has declined, and is now only slightly greater (about four per 100 patient years) than the rate of graft failure due to death with function. Altogether, the rate of graft failure is 7.4 per 100 patient years.

The rates of return to dialysis or preemptive transplantation are different in different patient populations (Figure 7.21). Rates are...
highest for children and adolescents and for patients age 18–34, and lowest for patients age 65 years and older, because proportionately more older patients die with a functioning kidney. Rates are similar for men and women, and approximately two-fold greater for blacks compared to whites and Asians.

The proportion of patients with graft failure who receive another kidney transplant before dying or returning to dialysis has increased slightly, and is now almost 10 percent (Figure 7.22). About half of the patients who return to dialysis after a kidney transplant eventually receive another kidney transplant, while half die on dialysis; (Figure 7.23) these rates were not different in 1996–1999 compared to 2000–2003.
ost commonly, death after kidney transplantation is attributed to cardiovascular disease (7.24). These cardiovascular disease deaths included cerebrovascular accidents, myocardial infarctions, arrhythmias, and other cardiovascular causes. The next most common cause of death is infection, followed by malignancy. Unfortunately, the cause of death is unknown in 30 percent of patients.

Mortality rates per 100 dialysis patient years are highest in the first four months after kidney transplantation (Figure 7.25). Thereafter, death rates due to cardiovascular disease, infections, and malignancies are relatively constant throughout the post-transplant period. It is worth noting that the number of deaths due to unknown causes increases dramatically with the duration of followup.

In five separate Cox proportional hazards models, we examine the adjusted relative risks of different risk factors for graft failure, death with a functioning graft, death due to infection, malignancy, and cardiovascular disease. Each of the models is fully adjusted for the other multiple recipient, donor, and transplantation characteristics.

In general, donor factors one would expect to be associated with reduced kidney function after transplantation are associated not only with lower graft survival, but also with higher mortality from all causes. The use of deceased donor kidneys, for example, is associated with lower graft survival and higher mortality (data not shown). Kidneys from female donors are associated with lower graft failure and higher mortality (Figure 7.26). Expanded Criteria Donor kidneys (as defined by the Organ Procurement and Transplantation Network for deceased donor kidney allocation) are associated with reduced graft and patient survival. (Figure 7.27)

While recipient gender is not associated with graft failure, men have a higher risk than women of dying with a functioning kidney (Figure 7.28). The increased mortality among men is due to a higher risk for death due to malignancies and cardiovascular disease.

Not surprisingly, the number of human leukocyte antigen (HLA) mismatches between the donor and the recipient is associated with the rate of graft failure (Figure 7.29). There is also a tendency, however, for the number of mismatches to be associated with death with a functioning graft, deaths due to infections, and
The risk for post-transplant cytomegalovirus (CMV) infection is determined by donor and recipient CMV antigen status. The lowest risk is associated with both the donor and the recipient being antibody negative (Figure 7.30). The highest risk is associated with the donor being antibody positive while the recipient being CMV antibody negative (Figure 7.30). The intermediate risk is associated with both the donor and the recipient being antibody positive. It is interesting that the risk for CMV infection, based on pretransplant donor and recipient CMV antibody status, parallels the risk for graft failure.

Although the prevalence of hepatitis B virus infection has declined over the past 25 years, having hepatitis B surface antigen (HBsAg) at the time of transplantation is still associated with worse outcomes (Figure 7.31). Most of this is attributable to a higher risk for death due to infections.

Hepatitis C virus infection is more common than hepatitis B infection. Infection with hepatitis C, usually indicated by the presence of an antibody to hepatitis C, is associated with poorer graft survival (Figure 7.32). Much of the reduced graft survival associated with hepatitis C is explained by an increased risk of death from infections.

Transplanting kidneys from donors with an antibody to hepatitis C is associated with an increased risk of graft failure, mostly due to death from infections (Figure 7.33). Interestingly, about 40 percent of kidneys from donors who are hepatitis C antibody positive are transplanted in individuals who are hepatitis C negative or have unknown hepatitis C status, according to data from the Organ Procurement and Transplantation Network forms.

Figures 7.24–33: Cox proportional hazards models, adjusted for year, age, gender, race, ethnicity, primary diagnosis, donor race, donor gender, cold ischemia time, prior dialysis time, donor/recipient CMV, hepatitis B & C serologies, education level, HLA mismatches, & body mass index. Figure 2.27: recipients of a deceased donor transplant only. GF: graft failure; DWF: death with functioning graft; CVD: cardio-/cerebrovascular disease.
Post-transplant complications & care

**Patients with OPTN followup, by years post-transplant**

- 0-2 years post-tx
- 3-4 years post-tx
- 5+ years post-tx

**Location of followup care**

- Transplant center
- Non-tx center/specialty MD
- Primary care MD
- Other

**Cumulative incidence of acute rejections**

- Deceased donor
- Living donor

**Transplants with delayed graft function**

- Deceased donor
- Living donor

**Post-transplant hospitalization rates**

- All-cause
- Infection
- Cardiovascular
- Other cause

**HbA1c testing in transplant patients**

- Transplant: 1 year post-tx
- General Medicare

**HbA1c testing in prevalent transplant patients, by donor type, age, & race/ethnicity: first year post-transplant**

(Figures 7.34–35) period prevalent transplant patients transplanted in 1988 or later. Kaplan-Meier method. Location of followup care as identified to OPTN.

(Figure 7.36) One-year cumulative incidence of acute rejections as identified from OPTN followup data. Recipients of first kidney-only transplants, 1998-2002 (N=58,825). Does not include acute rejection episodes at the time of transplant or acute rejections listed as the cause of graft failure. (Figure 7.37) includes only patients with functioning grafts upon discharge. (Figure 7.38) adjusted for age, gender, & race. (Figure 7.39) transplants 1995–2003; most recent creatinine as reported to OPTN. (Figures 7.40 & 7.41) diabet Marketing transplant recipients, 1999–2003. Kaplan-Meier


7.42 Lipid monitoring in transplant & general Medicare patients

7.43 Lipid monitoring in prevalent transplant patients, by donor type, age, & race/ethnicity: first year post-transplant

7.44 Prescribed (per day) diabetic test strips in transplant & general Medicare patients

7.45 Diabetic testing supplies in prevalent transplant patients, by donor type, age, & race/ethnicity: first year post-transplant

7.46 Pap smears, by population, donor type, age, & race/ethnicity

7.47 Mammograms, by population, donor type, age, & race/ethnicity

7.48 Prostate screening, by population, donor type, age, & race/ethnicity

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Method. (Figure 7.42) transplant: Medicare transplant recipients, 1995-2003, whose grafts function for at least one, two, & three years, respectively. General Medicare: prevalent beneficiaries (from 5 percent sample) who survive the entire year. (Figure 7.43) Medicare transplant recipients, 1999-2003. Kaplan-Meier method. (Figure 7.44) transplant: female Medicare beneficiaries, age 18-65 at time of transplant, transplanted 1999-2003. Percent screened within first three years post-transplant; Kaplan-Meier method. General Medicare: period prevalent female beneficiaries (from 5 percent sample), 2001-2003, who survive through 2003 & are 21-64 years old at the end of 2003. (Figure 7.45) transplant: female Medicare beneficiaries, age 50-67 at time of transplant, transplanted 1999-2003. Percent screened within first two years post-transplant; Kaplan-Meier method. General Medicare: period prevalent female beneficiaries (from 5 percent sample), 2002-2003, who survive through 2003 & are 52-69 years old at the end of 2003. (Figure 7.46) transplant: male Medicare beneficiaries, age 50 & older at time of transplant, transplanted 1999-2003. Percent screened within the first three years post-transplant; Kaplan-Meier method. General Medicare: period prevalent male beneficiaries (from 5 percent sample), 2001-2003, who survive through 2003 & are 53 & older at the end of 2003.
Over the past decade there have been dramatic changes in the immunosuppressive medications used immediately after kidney transplantation (Figures 7.49–55). In patients transplanted between 1995 and 1999, the most common regimen was based on microemulsion cyclosporine (Neoral) and mycophenolate mofetil, with steroids also used in most cases. For patients transplanted during 2000–2003, however, the most common regimen was tacrolimus and mycophenolate mofetil, also with steroids in most cases. It is tempting to examine correlations between different medications and outcomes, and the results of such analyses can be found in the literature. But there are many potential biases in the choice of medications for individual patients, and only randomized trials can determine the true effects on outcomes.

In 2005, CMS proposed setting minimal outcome standards for kidney transplant centers. The Hospital Conditions of Participation: Requirements for Approval and Reapproval of Transplant Centers to Perform Organ Transplants (CMS-3835-P) calls for centers with at least nine transplantations to undergo CMS review if the observed patient or graft survival rates are lower than expected (based on standardized mortality and graft survival ratios), and three criteria are met: one-sided p-value is <0.05, the number of observed events (deaths or graft failures) minus the number of expected events is greater than three, and the number of expected events is greater than 1.5.

We found that a large proportion of centers would fail one or more of these criteria (Figures 7.56–57). Indeed, during 1998–2003, more than 15 percent would have met the proposed CMS review criteria. In contrast to the proposed CMS methodologies, a Bayesian analytical method that stabilizes estimation across all transplant center sizes would require fewer centers to be reviewed (Figure 7.58). This is because smaller centers (<100 transplants during the 30-month test period), with results that are more likely than those of larger centers to fluctuate year-to-year due to chance, would be reviewed less often than with the CMS methodology. Large centers, on the other hand, would be reviewed in similar numbers. This Bayesian approach reduces the 95 percent confidence intervals for graft failure, especially for small centers (Figure 5.59).

Given expected statistical variability, the proposed CMS criteria will result in a disproportionate number of small centers being identified as having poorer outcomes, and therefore targeted for review. A Bayesian approach offers an alternative whereby substantially fewer centers over time would fall below a minimal standard.

(Figures 7.49–53) first, kidney-only transplants, 1995–2003. Immunosuppression identified to UNOS.

(Figures 7.54–55) first-time, kidney-only transplants, 1995–2003. Maintenance immunosuppression identified to OPTN. 
[Figures 7.56–61] small centers: those with fewer than 100 transplants during the 30-month test period; refer to Appendix A for further details. 

Figure 7.59: random sample of 120 transplant centers.
7.56 Percent of transplant centers failing each proposed criterion for graft failure

- p-value < 0.05 (for a test of ratio = 1)
  - Small centers
  - Large centers
  - Cumulative

7.57 Percent of transplant centers failing at least one or two proposed criteria for graft failure

- Observed / Expected > 3
- Observed / Expected > 1.5

7.58 Comparison of proposed CMS rule for approval of transplant centers with a Bayesian modeling approach

- CMS proposal
- Bayesian approach

7.59 Comparison of CMS proposed standardized graft failure ratios with Bayesian graft failure ratios

- Observed / Expected > 3
- Observed / Expected > 1.5

7.60 Percent of centers failing by the proposed CMS rule &/or the Bayesian approach

7.61 Odds of transplant center failure based on transplant center size, by method
Figure 7.4 Men are transplanted relatively more frequently than women, and whites more often than people of color. Figure 7.8 Median waiting times for those who have received a kidney transplant have increased. Median waiting times are similar for men and women, but shorter for whites compared to people of color. Figure 7.11 Donation rates for deceased donor kidneys have declined slightly, while donation rates for living donor kidneys have increased.

Figures 7.14–15 One-year patient and graft survival rates have improved in the past eight years, for both deceased donor and living donor transplants. There has been little improvement in late kidney allograft survival, as measured by one-year conditional half lives. Figure 7.20 The rate of graft failure is 7.4 per 100 patient years. Figure 7.23 About half of the patients who returned to dialysis after a kidney transplant eventually receive another kidney transplant, while about half die.

Figure 7.24 Cardiovascular disease is the most common cause of death after kidney transplantation. Figure 7.26 Donor factors expected to be associated with reduced kidney function after transplantation are also associated with higher mortality. Figure 7.27 Use of an Expanded Criteria Donor kidney is associated with higher mortality. Figure 7.32 Transplanting kidneys from donors with hepatitis C is associated with an increased risk of graft failure and death from infections.

Figure 7.34 More than half of transplant centers reported to UNOS that their center provides followup care after kidney transplantation. Figure 7.40 Among those transplant patients who have diabetes and Medicare as primary insurance, the number who receive hemoglobin A1C measurements has grown, and exceeds that in the general Medicare population. Figure 7.42 Among transplant patients with Medicare as primary payor, 87 percent have at least some screening for dyslipidemias. Figure 7.46 Fifty-eight percent of women age 18–61 and with Medicare for primary insurance have Pap tests within three years of transplantation. Figure 7.47 Fifty-nine percent of women age 50–67 and with Medicare for primary insurance have mammograms within three years of transplantation.

Figures 7.49–55 There have been dramatic changes in the immunosuppressive medications used immediately after kidney transplantation. Figure 7.55 In 2000–2003 the most common immunosuppressive medication regimens included tacrolimus and mycophenolate mofetil.

Figure 7.59 Proposed CMS criteria for review will result in a disproportionate number of small centers being identified as having poorer outcomes.