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## Renal (Kidney) Transplantation

### *Definition:*

A kidney transplant is the organ transplant of a kidney into a patient with end-stage renal disease (ESRD). Kidney transplantation is typically classified as deceased-donor (formerly known as cadaveric) or living-donor transplantation depending on the source of the donor. Living donor renal transplants are further characterized as genetically related (living-related) or non-related (living-unrelated) transplants, depending on whether a biological relationship exists between the donor and recipient.

### *History:*

The first documented kidney transplant in the United States was performed June 17, 1950, on Ruth Tucker, a 44 year old woman with polycystic kidney disease, in Illinois. Although the donated kidney was eventually rejected because no immunosuppressive therapy was available at the time – the development of anti-rejection drugs was years away – Tucker’s remaining diseased kidneys began working again and she lived another 5 years before dying of an unrelated illness. Thereafter, successful kidney transplantations were undertaken in 1954 in Boston and Paris. Tissue typing was essential to success: early attempts in the 1950s on sufferers from Bright’s disease (kidney failure) had been very unsuccessful because of the lack of tissue typing. In 1954, at Brigham Hospital Dr. Joseph E. Murray and Dr. J. Hartwell Harrison performed the world’s first successful renal transplant between genetically identical patients for which Dr. Murray received the Nobel Prize for Medicine in 1990. The donor is still alive as of 2005; the recipient died eight years after the transplantation.

The major barrier to organ transplantation between genetically non-identical patients lay in the recipient’s immune system, which would treat a transplanted kidney as a “non-self” entity and immediately or chronically, reject it. Thus, having medications to suppress the immune system was essential. However, suppressing an individual’s immune system places that individual at greater risk of infection and cancer (particularly skin cancer and lymphoma), in addition to the side effects of the medications. Until the routine use of medications to prevent and treat acute rejection, introduced in 1964, deceased donor transplantation was not performed. The kidney was the easiest organ to transplant: tissue typing was simple, the organ was relatively easy to remove and implant, live donors could be used without difficulty, and in the event of failure, kidney dialysis was available from the 1940s.

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***Indications:***

The indication for kidney transplantation is end-stage renal disease (ESRD), regardless of the primary cause. This is defined as a drop in the glomerular filtration rate (GFR) to roughly 10-15% of normal. There are many causes of ESRD but the most common cause in the United States is diabetes. It accounts for 25% of renal transplants in the United States. The majority of renal transplant recipients are on some form of dialysis – hemodialysis or peritoneal dialysis – at the time of transplantation. However, individuals with chronic kidney disease who have a living donor available may undergo pre-emptive transplantation before dialysis is needed.

***Contraindications and Requirements:***

Patients may be excluded from getting kidney transplants if they have heart, lung, or liver disease. Current tobacco use and significant obesity are also reasons a patient may not qualify for kidney transplant because they put patients at higher risk for surgical complications.

Kidney transplant requirements vary from program to program and country to country. Many programs place limits on age (e.g. the person must be under a certain age to enter the waiting list) and require that one must be in good health (aside from kidney disease). Significant cardiovascular disease, incurable terminal infectious diseases, and cancer are often transplant exclusion criteria. In addition, candidates are typically screened to determine if they will be compliant with their medications, which is essential for survival of the transplanted kidney. People with mental illness and/or significant ongoing substance abuse issues may be excluded.

HIV was at one point considered to be a complete contraindication to transplantation. There was a fear that immunosuppressing someone with an already depleted immune system would result in progression of the disease. However, current research does not support this fear. In fact, there are findings that immunosuppressive drugs and anti-retrovirals may work synergistically to help reduce HIV viral loads, maintain CD4 cell counts, and prevent kidney rejection.

***Sources of Kidneys:******Living Donors:***

The percentage of transplants from living donors is increasing. Potential donors are carefully evaluated on medical and psychological grounds. This ensures that the donor is fit for surgery and has no disease which brings undue risk or likelihood of a poor outcome for either the donor or recipient. The psychological assessment is to ensure the donor gives informed consent and is not coerced. In countries where paying for organs is illegal, the authorities may also seek to ensure that a donation has not resulted from a financial transaction. There is good evidence that kidney donation is not associated with long term harm to the donor.

Traditionally, the donor procedure has been through a single incision of 4-7 inches (10-18 cm), but live donation is being increasingly performed by laparoscopic surgery. This reduces pain and accelerates recovery for the donor. Operative time and complications decreased significantly after a surgeon performed 150 cases. Live donor kidney grafts tend to perform better than those from deceased donors. The advent of laparoscopic surgery has increased the numbers of live donors.

In 2004 the FDA approved the Cedars-Sinai High Dose IVIG therapy which reduces the need for the living donor to be the same blood type (ABO compatible) or even a tissue match. The therapy reduced the incidence of the recipient's immune system rejecting the donated kidney in highly sensitized patients.

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### *Deceased Donors:*

Deceased donors can be divided in two groups:

- Brain Dead (BD) donors
- Donation after Cardiac Death (DCD) donors

Although “Brain Dead” (or heart-beating) donors are considered dead, the donor’s heart continues to pump and maintain circulation. This makes it possible for surgeons to start operating while the organs are still being perfused. During the operation, the aorta will be cannulated, after which the donor’s blood will be replaced by an ice-cold storage solution. Depending on which organs are transplanted, more than one solution may be used simultaneously. Due to the temperature of the solution, and since large amounts of cold sodium chloride-solution are poured over the organs for a rapid cooling, the heart will stop pumping.

“Donation after Cardiac Death” donors are patients who do not meet the brain-dead criteria but, due to the small chance of recovery, have elected via a living will or through family to withdraw support. In this procedure, treatment is discontinued (mechanical ventilation is shut off). After a time of death has been pronounced, the patient is rushed to the operating room where the organs are recovered. Storage solution is flushed through the organs. Since the blood is no longer being circulated, coagulation must be prevented with large amounts of anti-coagulation agents such as heparin. Several ethical and procedural guidelines must be followed; most importantly, the organ recovery team should not participate in the patient’s care in any manner until after death has been declared.

### *Expanded Criteria Donors (ECD):*

ECD kidneys are transplantable deceased donor kidneys for which the average patient, kidney survival, and kidney function are inferior when compared to standard criteria deceased donor kidneys. A kidney is considered to be an ECD organ if the donor is older than 60 years of age, or is age 50-59 and has two of the following: a cerebrovascular accident as the cause of death, pre-existing hypertension, or a terminal serum creatinine greater than 1.5mg/dl. Recipients of ECD kidneys have improved survival compared to ESRD patients on the kidney transplant wait list. However, the transplanted kidneys tend to do worse than standard deceased donor kidneys. Of note, patients less than 40 years of age, African Americans, and some Asian patients receive no survival benefit from ECD kidney transplantation. The benefit of choosing to accept an ECD kidney is the expansion of the donor pool that it results in, and therefore a higher likelihood of receiving a kidney transplant, sooner.

### *Compatibility:*

If plasmapheresis or IVIG is not performed, the donor and recipient have to be ABO blood group compatible. Also, they should ideally share as many HLA and “minor antigen” as possible. This decreases the risk of transplant rejection and the need for another transplant. The risk of rejection may be further reduced if the recipient is not already sensitized to potential HLA antigens, and if immunosuppression levels are kept in an appropriate range. In the US up to 17% of all deceased donor kidney transplants have no HLA mismatch. However, HLA matching is a relatively minor predictor of transplant outcomes. In fact, living non-related donors are now almost as common as living (genetically)-related donors.

Additionally, with the advent of better immunosuppression and plasmapheresis, a number of programs are even transplanting ABO-incompatible transplants on a routine basis.

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***Procedure:***

In most cases the barely functioning kidneys are not removed, as this has been shown to increase the rates of surgical complications. Therefore the kidney is usually placed in a location different from the original kidney, often in the iliac fossa. It is therefore necessary to use a different blood supply than the one that supplies the original kidneys. Since the kidney sits front and low in the abdominal cavity, it can often be felt on routine physical exams. This position also makes the kidney easy to get to in case future surgeries are needed or renal biopsies need to be done to assess for rejection. The ureter of the transplanted kidney is stitched to the bladder and the kidney's blood supply is sewn to the patient's external iliac system.

***Post-operation:***

Depending on its quality and if there were any difficulties during the surgery, the new kidney begins functioning immediately. Living donor kidneys normally require 3-5 days to reach maximal function, while deceased donor kidneys can take 7-15 days to reach maximal function. The hospital stay is typically 4-7 days, though complications post-operatively will extend that time period.

***Immunosuppression:***

Immunosuppressant drugs are used to keep the immune system from rejecting the donor kidney. These medicines must be taken for the rest of the transplanted kidney's life. The most common medication regimen today is a cocktail of three drugs. These include cyclosporine or tacrolimus, cellcept, and prednisone (a steroid).

The basis for most immunosuppressive regimens is steroid therapy. Its long term use at higher doses however causes a multitude of side effects including impaired glucose tolerance, diabetes, weight gain, hypertension, salt retention, water retention, osteoporosis, muscle weakness, dyslipidemia, and cataract formation. Prednisone alone is not enough to prevent rejection of the transplanted organ so other non-steroidal agents are used in conjunction with prednisone and can allow for lower doses of prednisone to be used, to minimize the above side effects.

Other regimens with newer drugs are being studied as well. Ironically, cyclosporine can itself cause kidney toxicity so levels must be monitored carefully. If kidney function appears to be declining, than a biopsy of the transplanted kidney can sometimes distinguish between rejection of the organ or cyclosporine toxicity.

***Complications:***

Problems after a transplant may include:

- Transplant rejection (acute or chronic). Acute rejection can occur immediately or within the first 60 days of transplant. It occurs in about 10-25% of cases. Rejection does not necessarily mean loss of the organ, but may require additional treatment and/or medication adjustments. It is diagnosed by kidney biopsy.
- Infections and sepsis due to the immunosuppressant drugs that are required to decrease the risk of rejection.
- Post-transplant lymphoproliferative disorder (a form of lymphoma due to the immune system suppression).
- Other cancers, predominantly skin cancers.
- Electrolyte imbalances affecting potassium, calcium and phosphorus. The latter two can affect bone health, as can the steroids.
- Other side effects of medications including gastrointestinal inflammation and ulceration, hirsutism (excessive hair growth in a male pattern distribution), hair loss, obesity, acne, diabetes type 2, dyslipidemia, hypertension, and others.

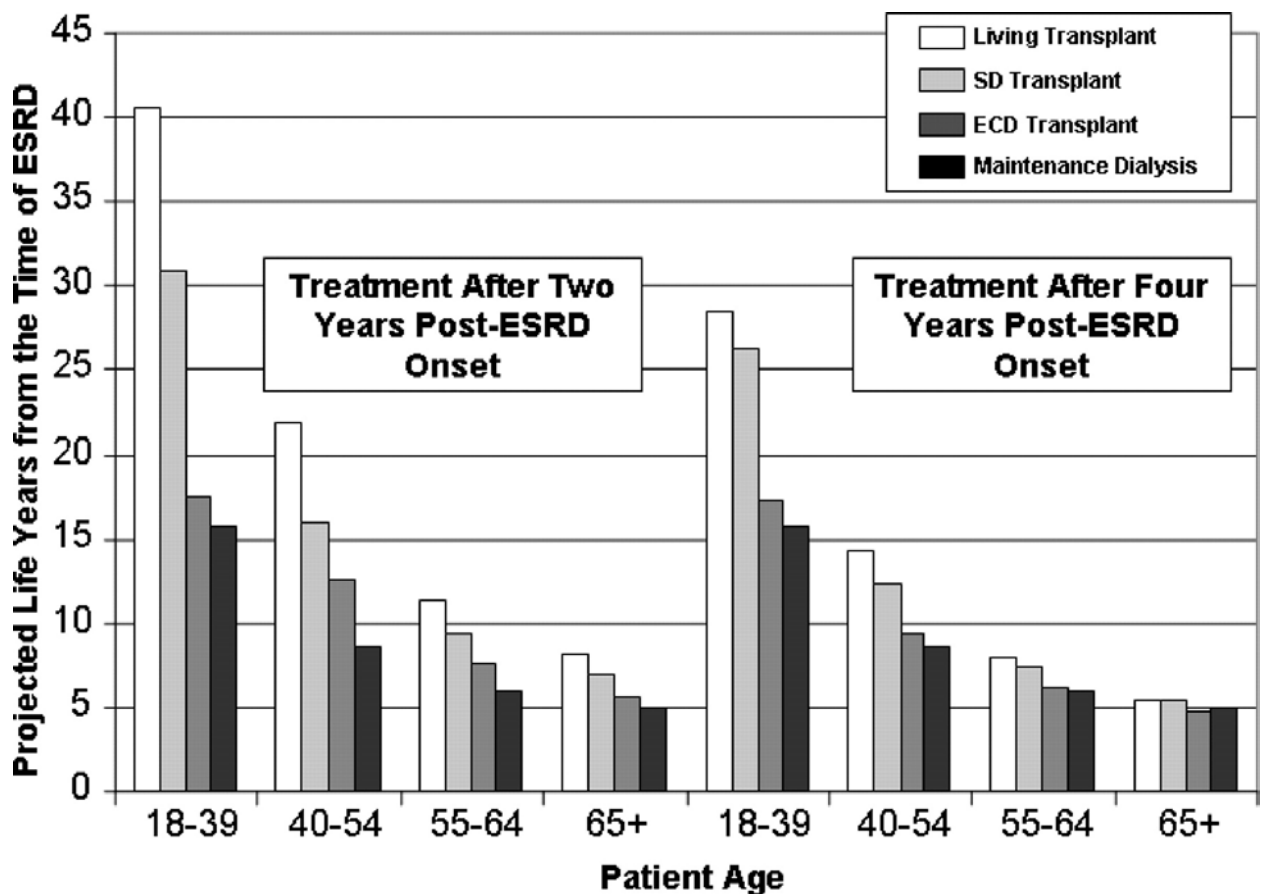
- The average lifetime of a donated kidney is 5-10 years. When a transplant fails a patient may opt for a second transplant or may need to start dialysis.

**Prognosis:**

Kidney transplantation is a life-extending procedure. The typical patient will live 10 to 15 years longer with a kidney transplant than if kept on dialysis. The years of life gained is greater for younger patients, but even 75 year old recipients (the oldest group for which there is data) gain an average of four more years of life. People generally have more energy, a less restricted diet, and fewer complications with a kidney transplant than if they stay on conventional dialysis.

Some studies seem to suggest that the longer a patient is on dialysis before the transplant, the less time the kidney will last. It is not clear why this occurs, but it underscores the need for rapid referral to a transplant program. Ideally, a kidney transplant should be pre-emptive, i.e. take place before the patient begins dialysis.

As shown below, once patients have started dialysis, life expectancy is best with a living transplant, followed by a deceased donor kidney, followed by an ECD kidney, with maintenance dialysis being the worst option for increasing life expectancy.



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At least four professional athletes have made a comeback to their sport after receiving a transplant: New England rugby union player Jonah Lomu, German-Croatian soccer player Ivan Klasnic, and NBA basketball players Sean Elliott and Alonzo Mourning.

**Statistics:**

Since medication to prevent rejection is so effective, donors need not be genetically similar to their recipients. Most donated kidneys come from deceased donors, however the utilization of living donors in the United States is on the rise. In 2006, 47% of donated kidneys were from living donors though this varies by country. For example, only 3% of kidneys transplanted during 2006 in Spain came from living donors. More than one in three donations in the UK is now from a live donor, and almost one in three in Israel.

**Statistics by country, year**

<b>Country</b>	<b>Year</b>	<b>Total transplants</b>
<b>Canada</b>	2000	1,112
<b>France</b>	2003	2,127
<b>Italy</b>	2003	1,624
<b>Spain</b>	2003	2,051
<b>United Kingdom</b>	2003	1,736
<b>United States</b>	2008	16,517
<b>Pakistan - SIUT</b>	2008	1,932

In addition to nationality, transplantation rates differ based on race, sex, and income. A study done with patients beginning long term dialysis showed that the sociodemographic barriers to renal transplantation present themselves even before patients are on the transplant list. For example, different groups express different interest levels and complete pre-transplant workup at different rates.

Barriers to individuals being accepted for evaluation and transplant by transplant programs in the US include lack of adequate insurance. Transplant recipients must take immunosuppressive anti-rejection drugs for as long as the transplanted kidney functions. The routine immunosuppressive regimen can cost USD \$1,500 per month. In 1999, Congress passed a law that restricts Medicare from paying for more than three years for these drugs, unless the patient is otherwise Medicare eligible. Transplant programs may not transplant the patient unless there is a reasonable plan in place to pay for medication after Medicare expires. However, patients are almost never turned down for financial reasons alone. 50% of patients with ESRD only have Medicare coverage and many still get kidney transplants.

In March of 2009, a bill was introduced in the Senate which would extend Medicare coverage of the drugs for as long as the patient has a functioning transplant. If it passes, it means that transplant patients who have lost their jobs and insurance will not also lose their kidney and be forced back on dialysis.

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