Renal Transplantation: Surgical Procedure and Complications

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Cover Illustration by mb cunney
INTRODUCTION

This manual is the second in a 2-part review of renal transplantation. The discussion began with a review of renal transplant recipient criteria and evaluation, kidney donation, and transplant immunology. It continues here with an overview of the surgical procedure and the complications inherent in renal transplantation and immunosuppression.

The results of kidney transplantation have improved over time (Figure 1). According to transplant data collected in the United States between 1992 and 2001, 1- and 5-year patient survival rates following renal transplantation are 94% and 80%, respectively, for deceased donor transplants and 98% and 90% for living donor transplants. In addition, 1- and 5-year graft survival rates are 88% and 63%, respectively, for deceased donor transplants and 94% and 76% for living donor transplants.

Despite improving graft and patient survival rates, surgical complications of renal transplantation and post-transplantation graft dysfunction remain important clinical concerns. Renal transplantation is a complex vascular and urologic surgical procedure that requires expertise to perform the operation successfully and to adequately manage its surgical and nonsurgical complications. In-depth knowledge of renal transplantation and postsurgical complications is important for urologists, who perform a large fraction of renal transplantation procedures and often are called upon to address the many urologic complications of the procedure. In addition, as transplantation has become commonplace, more renal transplant recipients are being treated for nontransplant–related urologic disease.

RENAI TRANSPLANTATION PROCEDURE

The standard renal transplantation procedure involves placement of the donor kidney in the iliac fossa. A curved flank incision typically is made from the pubic tubercle to a point 2 to 3 finger-breaths inferior to the costal margin. For recipients of a third or fourth renal transplant or for pediatric transplant recipients, a midline abdominal incision can be used to provide maximal access to the vasculature for graft implantation. The retroperitoneum is entered by carefully dividing the lateral abdominal wall muscles while avoiding the peritoneal lining. The iliac vessels are dissected free of their investing lymphatic tissue. The lymphatic tissue is carefully ligated to prevent a subsequent lymphocele.

Once the vascular structures are exposed, the donor renal vein is sewn end-to-side to an iliac vein, and the donor renal artery is sewn end-to-side to an iliac artery (Figure 2). If there are multiple renal veins (a common occurrence, since the veins within the kidney are nonsegmental and anastomose with one another), the accessory renal veins can be safely ligated. Even if 2 large veins exist, one can be ligated. Alternatively, the veins can be implanted separately or can be sewn together and then implanted. For cadaveric donor kidneys, a Carrel patch of donor aorta is used to facilitate the arterial anastomosis. For multiple renal arteries (also common), the arteries can be sewn together for a single anastomosis or implanted separately. Separate renal arteries supply separate renal segments; thus, ligation of a renal artery will create a zone of ischemia. Nevertheless, a small upper pole accessory artery can be ligated with no significant clinical consequence to the recipient. Lower pole arteries, however, may provide important arterial flow to the ureter and must be maintained. Once the vascular anastomoses are complete, the clamps are removed and the kidney is reperfused.

The donor ureter is attached to the recipient bladder via the Liche technique, in which a running mucosa-to-mucosa anastomosis is created using an absorbable monofilament suture. The anastomosis can be bolstered with a few interrupted detrusor muscle sutures, being careful not to constrict the ureter. If necessary, a donor-to-native ureteroureterostomy may be performed instead of anastomosing the transplant ureter to the bladder. A stent may be placed across the anastomosis, according to preference. For uncomplicated ureteral attachments, the stent can be sutured.
to the Foley catheter to allow for removal of the stent with the Foley.

EARLY COMPLICATIONS

VASCULAR COMPLICATIONS

Hemorrhage

Significant postoperative hemorrhage can develop due to the extensive vascular surgery involved in renal transplantation. Bleeding can occur at anastomotic sites, from the graft itself, or from the areas of dissection and may be the result of severely increased blood pressure following recovery from anesthesia or from the release, upon warming, of vasospastic divided vessels. Uremic platelet dysfunction, which can be treated with desmopressin acetate, increases the risk for bleeding, as does preoperative anticoagulation. Significant postoperative hemorrhage can be life threatening and requires surgical reexploration and attainment of hemostasis.

Graft Thrombosis

Graft thrombosis is a devastating complication of renal transplantation, which not only causes graft loss but also increases mortality. Vascular thrombosis should be suspected if urine output ceases or declines sharply after transplantation. If graft thrombosis is detected early enough, particularly if it is incomplete, graft salvage can be achieved upon surgical reexploration. Doppler ultrasonography or technetium 99m perfusion scintigraphy

Figure 1. Kaplan-Meier graph showing renal graft survival rates in the United States from 1994 through 2000. Adjusted survival is survival after confounding variables, such as donor age, have been accounted for. (Adapted from United States Renal Data System. USRDS 2002 annual data report: atlas of end-stage renal disease in the United States. Bethesda [MD]: National Institutes of Health; 2002. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author[s] and in no way should be seen as an official policy of the U.S. government.)

Figure 2. Diagram illustrating standard right renal transplantation. (Adapted with permission from Sollinger HW, D’Alessandro AM, Belzer FO. Transplantation science and immunology. In: Polk HC, Gardner B, Stone HH, editors. Basic surgery. 5th ed. St. Louis [MO]: Quality Medical Publishing; 1995:304–22.)
Occasionally, rejection or external scarring in the vicinity of the ureter can compromise the ureteral lumen. Early postoperative strictures typically are the result of a technical problem.

The diagnosis of ureteral stenosis is suggested by the presence of significant hydronephrosis on ultrasonography. In the absence of other obvious causes for the hydronephrosis (eg, poor bladder emptying, a lymphocele, or an obstructing renal calculus), a percutaneous nephrostomy is required. Ureteroarteriography is then performed to establish the location and length of the obstruction. If questionable, a Whitaker flow-pressure test can help delineate the pathophysiologic effect of the stricture. If the stricture is short, balloon dilation can be attempted, followed by placement of a stent.

Dilation and stenting typically is not effective for long strictures, and a surgical repair must be performed. There are 2 surgical approaches: the transplant ureter can be reimplanted into the bladder, or a ureteroureterostomy can be performed using the ipsilateral native ureter. In the latter approach, the proximal native ureter is ligated and divided, usually without consequence, and the distal native ureter is used to create a spatulated end-to-end anastomosis to the proximal transplant ureter (over a stent) using nonabsorbable suture. If no native ureter is available for repair, a Boari flap may be used.

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Urinary Retention

Urinary stasis can jeopardize the new ureterovesical anastomosis and contribute to urinary tract infection (UTI). Urinary retention, common in diabetic patients and in older male patients with benign prostatic hyper trophy (BPH), is initially treated using intermittent catheterization. For diabetic neuropathic bladder or other functional problems, a cholinergic agent can be added. If the problem is BPH, medical or surgical treatment may be required. A pathologically small bladder may need to be augmented prior to renal transplantation. An ileal conduit is not a contraindication to transplantation, as the ureter can be successfully sewn to the conduit.

Hematuria

Significant and persistent hematuria is an unusual complication of renal transplantation. Hematuria occurring early after transplantation may suggest an outflow problem from the renal vein. Typically, it is mild and self limited and related to bleeding from the bladder anastomosis. Later-occurring hematuria may suggest a UTI. Occasionally, hematuria is severe and should be evaluated and treated cystoscopically and with bladder irrigation.

URINARY COMPLICATIONS
Urinary Leak

Urinary leaks are an uncommon complication of renal transplantation. The diagnosis of urinary leak can be made by technetium 99m perfusion scintigraphy or by measuring the creatinine level of a perirenal collection observed via CT or ultrasonography (the level will be much higher than the serum creatinine concentration). Treatment for urinary leaks may be as simple as bladder decompression with prolonged Foley catheterization to allow for healing of the defect or, for bigger leaks, stenting or (preferably) surgical repair.

Ureteral Stenosis

Ureteral stenosis is uncommon and most often caused by ureteral ischemia. Because the blood supply to the transplanted ureter emanates from the hilar renal vessels, stenosis typically occurs in the distal ureter. Occasionally, rejection or external scarring in the vicinity of the ureter can compromise the ureteral lumen. Early postoperative strictures typically are the result of a technical problem.

Renal artery thrombosis is uncommon and may result from technical difficulties such as partial occlusion of the vessels due to kinking, atherosclerosis, or a poorly accomplished anastomosis. Renal vein thrombosis is more common and typically is not technical in origin, although it also can result from difficulties with the anastomosis or kinking. Renal vein thrombosis usually manifests as oliguria and hematuria. Doppler ultrasonography will show a high (> 80%) resistive index or reversal in diastolic flow. Some patients with prothrombotic states, especially those with a mutation in the coagulation factor V gene (factor V Leiden mutation) or antiphospholipid antibodies, are at greater risk for graft thrombosis. Retransplant recipients, pediatric transplant recipients, grafts with multiple renal arteries, and pediatric donor kidneys also are at greater risk for early graft thrombosis. Anticoagulants, including aspirin, can be successfully used in patients at increased risk for thrombosis.

Early renal artery stenosis causes poor graft function and can lead to graft thrombosis. Over the long term, renal artery stenosis not only will impair graft function but also can produce severe renovascular hypertension. Renal artery stenosis is suggested by low resistive indices on Doppler ultrasonography and can be diagnosed via standard angiography, computed tomography (CT) angiography, or MRA. Renal artery stenosis usually requires a surgical or endovascular intervention.
Lymphocele

Lymphoceles are fluid collections caused by leaks from divided iliac lymphatic vessels; they occur uncommonly. Lymphoceles usually lie anteromedial and inferior to the renal graft and often compress the transplant ureter, causing hydroureteronephrosis and consequent deterioration in graft function. As lymphoceles rarely respond to simple percutaneous drainage, the usual treatment is drainage into the peritoneal cavity through a wide peritoneal window, created either laparoscopically or via open surgery. The peritoneum, unlike the retroperitoneum, can easily absorb the fluid. Some centers successfully use sclerotherapy.

GRAFT INJURY OR REJECTION

Acute Tubular Necrosis

Acute tubular necrosis (ATN) is the generic name given to injury to the renal graft. Typically, ATN arises from a variety of accumulated insults, including hemodynamic instability in the brain-dead donor, warm ischemia (from recovery and implantation), cold ischemia (during preservation), rejection, and infection (severe pyelonephritis). Injury from the entire process of graft recovery, storage, and transplantation is called ischemia-reperfusion injury. Preservation solutions, such as the University of Wisconsin solution, minimize ischemia-reperfusion injury. Kidneys from older donors are at greatest risk for ATN occurring from ischemia-reperfusion injury.

Profound ischemia-reperfusion injury can result in renal grafts that never function (primary nonfunction). Less severe injury produces delayed graft function, which manifests as anuria or oliguria and is associated with the need for dialysis following transplantation. Because of the recent surgery, hemodialysis, not peritoneal dialysis, is used in such cases to remove fluid and potassium. Less severe ATN, called slow graft function, produces mild oliguria and a slow decline in serum creatinine from divided iliac lymphatic vessels; they occur uncommonly. Lymphoceles usually lie anteromedial and inferior to the renal graft and often compress the transplant ureter, causing hydroureteronephrosis and consequent deterioration in graft function. As lymphoceles rarely respond to simple percutaneous drainage, the usual treatment is drainage into the peritoneal cavity through a wide peritoneal window, created either laparoscopically or via open surgery. The peritoneum, unlike the retroperitoneum, can easily absorb the fluid. Some centers successfully use sclerotherapy.

Acute Rejection

Acute rejection can involve either a humoral (antibody-mediated) or cellular (T cell-mediated) immune response to the renal graft. Humoral rejection is the most dangerous and most difficult to treat. Humoral rejection can occur within minutes of transplantation (hyperacute rejection), due to an attack by preformed antibodies against the graft, or within the first 1 to 3 days post-transplantation (delayed hyperacute rejection), due to injury by memory cell–produced alloantibodies. More often, rejection reactions are due to a cellular immune response. Cellular rejection usually takes 5 to 7 days to develop but can occur at any time after transplantation, especially within the first 6 months.

INFECTIOUS COMPLICATIONS

In addition to the effects of immunosuppression, renal transplant recipients have several risk factors (eg, diabetes) that increase their susceptibility to infection.

Bacterial Infection

Wound infections are common in renal transplantation. Wound infections are more prevalent in obese and diabetic renal transplant recipients. Dehiscence and incisional hernias also complicate renal transplantation, especially as a consequence of wound infection, so care must be taken with the abdominal wall closure.

To reduce the rate of wound infection, systemic perioperative prophylactic antibiotics usually are given, many centers also irrigate the bladder with antibiotic solution after placing the Foley catheter. Staphylococci and streptococci are common causes of transplant wound infection. Thus, cefazolin or ampicillin plus sulbactam (for coverage of enterococci) are good choices for prophylaxis. For patients who are allergic to β-lactam antibiotics, vancomycin and a fluoroquinolone can be used. Although Pseudomonas is a common transplant pathogen, antipseudomonal coverage is best reserved for documented pseudomonal infections or high-risk situations. Similarly, coverage for coagulase-negative staphylococci with vancomycin should be reserved to minimize the development of vancomycin-resistant enterococci.

Perioperative UTI can be a problem for renal transplantation patients with preoperative urinary stasis due to minimal urine production or diabetic neuropathic bladder (from autonomic neuropathy). The risk for UTI is exacerbated by the use of stents and Foley catheters. The most common organisms producing UTI are the Enterobacteriaceae, such as Escherichia coli and enterococci. The use of trimethoprim-sulfamethoxazole helps prevent UTIs.

Perioperative pneumonia should be treated aggressively with antibiotics to cover both standard pathogens and Legionella, until the latter has been ruled out as a cause.

Fungal Infection

Fungal infections of the urinary tract are common and usually caused by Candida albicans or the more difficult to treat Torulopsis (Candida) glabrata. An azole antifungal agent often is adequate to treat candidal urinary
infections. It is important to note that these agents will increase calcineurin inhibitor blood levels. Amphotericin B may be needed for T. glabrata and may be administered systemically (preferably using lipid-based preparations) or via bladder irrigation. The newer antifungal agent caspofungin also may be used systemically.

Opportunistic fungal infections also can be a problem, particularly within the first 6 months post-transplantation. In the Mississippi River basin, renal transplant recipients are at greater risk for Histoplasmosis infection. Similarly, immunosuppressed patients in the southwestern United States are at greater risk for coccidioidomycosis. Aspergillus and Cryptococcus can be especially virulent in the immunocompromised patient; a high index of suspicion must be maintained for these pathogens, and if present the infections must be treated aggressively. Transplant recipients are at increased risk for Pneumocystis carinii pneumonia (PCP); thus, most centers use trimethoprim-sulfamethoxazole (or pentamidine) prophylaxis for several months post-transplantation. Candidal pharyngitis and esophagitis are common in the early post-transplantation period; most centers provide prophylaxis with an oral antifungal agent (typically clotrimazole or nystatin) for a few months after transplantation.

Opportunistic Viral Infection

Viral infection, particularly by members of the human herpesvirus (HHV) family, is a significant problem for the renal transplant recipient, especially during the first 6 months post-transplantation. Herpesviruses. Cytomegalovirus (CMV; HHV 5) is the most common viral pathogen in renal transplant recipients. CMV is a ubiquitous virus that can produce infection in up to two-thirds of recipients. Therefore, most centers give prophylactic ganciclovir or the more readily absorbed prodrug, valganciclovir, for several months post-transplantation. Prophylaxis is especially important for recipients at highest risk for CMV infection (ie, those who were serologically negative for CMV prior to transplantation and who received a kidney from a CMV-positive donor). CMV infection typically presents as low-grade fever, malaise, and leukopenia. Although CMV can attack any organ, gastrointestinal symptoms such as colitis (diarrhea) or esophagitis are most common. CMV also can cause hepatitis. Pneumonitis is the most dangerous manifestation of CMV infection. Both symptomatic and asymptomatic CMV infection should be treated with ganciclovir. For severe cases, anti-CMV antibody–enriched hyperimmune globulin can be added.

Other members of the HHV family are common causes of infection after renal transplantation, paricularly herpes zoster virus (HHV 3) but also herpes simplex viruses 1 and 2 (HHV 1 and HHV 2), Epstein-Barr virus (EBV; HHV 4), HHV 6, HHV 7, and HHV 8 (the cause of Kaposi’s sarcoma). All of these viruses are susceptible to acyclovir and ganciclovir and to their significantly more bioavailable prodrugs, valacyclovir and valganciclovir. Herpes zoster virus reactivation (shingles) is not uncommon in the transplant recipient and can produce herpes encephalitis; thus, most centers provide acyclovir or ganciclovir prophylaxis for several months post-transplantation as well as after treatment for rejection. EBV infection can drive B cell proliferation, producing post-transplantation lymphoproliferative disease (PTLD) or frank lymphoma. PTLD is a potentially devastating problem that occurs in approximately 2% of kidney transplant recipients. The cornerstone of treatment for PTLD is reduction in immunosuppression. Some centers also use the anti–B cell agent, rituximab. Once a monoclonal lymphoma develops, chemotherapy or radiotherapy is required.

Other viruses. Human polyomavirus BK has become an important pathogen in the transplant population. This ubiquitous urinary tract virus reemerges with excessive immunosuppression. It is now clear that re-emergence of polyomavirus BK is responsible for a significant proportion of renal graft losses. The virus can directly injure the kidney (interstitial nephritis) or cause ureteral strictures. Difficult to treat, active infection with polyomavirus BK mandates a reduction of immunosuppression. Influenzaviruses also can cause serious infection in renal transplant recipients, and most centers recommend vaccination.

LATE COMPLICATIONS

CHRONIC ALLOGRAFT NEPHROPATHY (CHRONIC REJECTION)

Like normal native kidneys, transplant kidneys lose function with age. In the case of renal grafts, the aging process is significantly accelerated and referred to as chronic allograft nephropathy (previously called chronic rejection). Extensive work is progressing in this poorly understood area.

Chronic allograft nephropathy is a complex process that varies from recipient to recipient and is the result of the combined effects of multiple insults. Graft injury may occur during the period of brain death or as a result of ischemia-reperfusion injury, rejection, chronic low-grade immunologic and inflammatory processes, infection, hypertension, or recurrent disease.
rejection, usually due to noncompliance with the immunosuppression regimen, also is an important cause of accelerated late graft loss. In addition, calcineurin inhibitor nephrotoxicity remains one of the most important causes of accelerated late graft loss. Recurrent glomerulonephritis also can play an important role in late graft loss. The end result of the multiple graft insults is renal tubular atrophy, interstitial fibrosis, and arteriopathy (intimal hyperplasia).

**RECURRENT RENAL DISEASE**

Clinically significant recurrent renal disease occurs infrequently but can be devastating. Its significance varies from disease to disease. For example, recurrent type II membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis often result in graft loss. In contrast, chronic allograft nephropathy generally supersedes the typically indolent effect of recurrent diabetic nephropathy.

**MEDICAL Complications IN THE RENAL TRANSPLANT Recipient**

With the significant improvement in short-term renal graft survival, attention is now being directed to the long-term well-being of the renal transplant recipient. Despite assiduous monitoring for cardiovascular disease and aggressive treatment for hypertension, hyperlipidemia, and smoking, premature death with a functioning graft (DWFG) remains an important complication of renal transplantation. Thus, the need for work in the area of long-term care of the renal transplant recipient has assumed elevated importance.

**Cardiovascular Disease**

Cardiovascular disease is the primary cause of DWFG. Although the cardiovascular risks related to end-stage renal disease are eliminated after transplantation, other cardiovascular risk factors (diabetes, hypertension, hyperlipidemia) are significantly increased after transplantation. Occurring in 10% to 30% of nondiabetic renal transplant recipients, post-transplantation diabetes is a common complication associated with significant morbidity and mortality. Several factors contribute to hyperglycemia after transplantation, including the hyperglycemic effects of corticosteroids and the toxic effects of calcineurin inhibitors on pancreatic islet cells.

Hypertension also is common post-transplantation. It is primarily due to the renal microvascular constricting effects of the calcineurin inhibitors and to the salt-retaining effects of corticosteroids. Calcineurin inhibitors also cause hypercholesterolemia, while sirolimus produces significant hypertriglyceridemia and hypercholesterolemia. In addition, CMV infection may contribute to accelerated atherosclerosis following transplantation. Thus, aggressive treatment of hypertension and hyperlipidemia is required in the renal transplant population.

**Infectious Disease**

Infectious diseases are the second most important cause of DWFG. The native kidneys can be the source of recurrent infections, especially in the presence of renal calculi or polycystic kidneys. When in doubt, a white blood cell scan can help identify the kidney that is producing the infections. The treatment is to remove the source of infection, which may require native nephrectomies (open or laparoscopic).

Recurrent UTIs also are somewhat common and usually develop after the withdrawal of the recommended trimethoprim-sulfamethoxazole or ciprofloxacin prophylaxis following transplantation. The work up for recurrent UTIs includes cystoscopy to look for foreign bodies or calculi and a CT scan to rule out renal calculi and intranephric or perinephric abscesses. Nonabsorbable suture may be a nidus for infections and calculi.

**Osteoporosis**

Osteoporosis is another significant medical complication in the renal transplant population. Renal transplant recipients are already at increased risk for bone disease because of renal osteodystrophy and secondary hyperparathyroidism. Because of the long-term stimulation of the parathyroid gland from renal disease, some patients with secondary hyperparathyroidism will continue to be hyperparathyroid long after calcium and phosphorus metabolism are returned to normal by the renal allograft (tertiary hyperparathyroidism). With transplantation, osteoporosis risk is significantly worsened by the synergistic bone-depleting effects of corticosteroids and calcineurin inhibitors. Therefore, renal transplant recipients must be aggressively monitored for bone disease and treated with bisphosphonates, vitamin D, and calcium.

**Malignancy**

The primary post-transplantation malignancies are skin cancer and PTLD. Renal transplant recipients are at an estimated 200-fold increased risk for the development of skin cancer. The decreased use of azathioprine may reduce the incidence of skin cancers, but this remains to be demonstrated. Besides PTLD, other virally related cancers, such as those from the
human papillomaviruses (skin, uterine, and peroneal neoplasms) and Kaposi’s sarcoma also occur with increased frequency in the renal transplant population. Interestingly, there does not appear to be an increased risk for breast, lung, colorectal, or prostate cancer after transplantation.

Renal cell cancer can occur in the renal allograft. It should be treated like any other renal cell malignancy. It may require nephrectomy, or for small tumors, a partial nephrectomy may suffice.145

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