Kidney Transplantation: A Guide to the Care of Kidney Transplant Recipients

Dianne B. McKay · Steven M. Steinberg
Editors

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Springer

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To my father Barry, who inspired my journey into the world of medicine and to Andy and our children Liam, Nora and Danny who inspire life's endless possibilities.

Dianne B. McKay, M.D.

To Stephanie and the kids, who make me want to be a better man.

Steven M. Steinberg, M.D.

Preface

Kidney transplantation improves the length and quality of life for many patients with end-stage renal disease. Successful transplantation is ensured by specialists trained to recognize and manage both the immediate pre- and post-transplant issues and the initial decisions regarding immunosuppression. Of course, early expert medical and surgical care is paramount to the successes of transplantation.

Immediately after the transplant, particularly trained specialists at the medical center manage the post-transplant care. However, after discharge from the transplant center, long-term care of the transplant recipient often falls on the shoulders of the community nephrologist or the general internist, who may or may not be experienced with transplant care. This guide to the care of the kidney transplant recipient aims to provide practical guidelines for management of the post-transplant recipient and is targeted at community nephrologists and general internists who care for the patient with a kidney transplant.

Although this book outlines many aspects of transplant specialty care, it is not intended to replace textbooks directed at transplant physicians. The aim is to provide practical advice for the continuation of long-term care of the patient after they leave the transplant center. Our ultimate goal is to provide informed, consistent, and multidisciplinary care guidelines for recipients of kidney transplants. We hope that this text contributes to that process.

Dianne B. McKay
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Chapter 1
Ten Things Not to Do

Dianne B. McKay and Steven M. Steinberg

Introduction

The purpose of this *Guide to the Kidney Care of Transplant Recipients* is to provide practical up-to-date information for practitioners who care for transplant recipients. This guide is also helpful for the transplant physician, including physicians in training, who through this guide will obtain an appreciation for the complexities of caring for the transplant recipient outside of the transplant center. While much of this guide focuses on specific medical and surgical topics, we would like to begin with a brief chapter of some of the "takeaway" messages of this guide. These messages rely on the art of medicine, as well as the science, and it is hoped that the reader will indulge us in this pursuit. The following "Ten Things Not to Do" are mostly directed at the community nephrologist and the internist who, although not the primary caregiver at the time of transplant, soon becomes the major caregiver of these patients, often with limited guidelines for assistance.

1. Do NOT forget to refer your ESRD patients for transplantation early, encourage them to find a living donor and pay attention to the pretransplant workup.

Encourage your ESRD patients to present to the transplant center before they begin dialysis and get eligible patients listed for a deceased donor organ or worked up for a preemptive transplant as soon as possible. Renal transplantation is the treatment modality of choice for nearly all suitable candidates with end-stage renal disease. Transplantation improves both patient survival and quality of life. The longer the patients are on dialysis the poorer their overall health.

For many reasons, a live donor is preferable to a deceased donor. Encourage your patients to speak to family members, friends, and altruistic donors. If the patient feels uncomfortable advocating for himself/herself, enlist a family member

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or friend to speak to others on behalf of the patient. Do not encourage your patient to participate in transplant tourism, for it is illegal and often results in bad outcomes. Do encourage your patient to consider a paired donor swap if a blood type mismatch is preventing a willing donor from donating to your patient.

If the patient has no donor, encourage him/her to quickly fulfill the requirements of the pretransplant evaluation so that they can be listed as soon as possible. The waiting times are lengthy and many patients fall ill and become ineligible for transplantation during the lengthy waiting process. Encourage the patient to ask about listing for expanded donor (ECD) or donation after cardiac death (DCD) kidneys if they are older, have diabetes mellitus, or have poor general health and need to shorten their waiting time.

The pretransplant workup will likely identify issues that need clarification before the patient can be listed for transplantation. Be sure to address all requests promptly to avoid excessive downtime before your patient is placed on the deceased donor transplant waiting list. Be sure to administer all needed vaccinations before transplantation because post-transplant immunosuppression prevents adequate antibody responses to vaccines. Live virus vaccinations are contraindicated after transplantation.

The following chapters detail important information specific to these take-home points:

Chapter 5 – describes how donor organs are allocated
Chapter 6 – describes the live donor workup
Chapter 8 – describes the paired donor-swap program
Chapter 13 – describes the pretransplant workup
Chapter 15 – details the survival advantage offered by transplantation over dialysis
Chapter 16 – details information regarding vaccinations in transplant recipients

2. Do NOT underestimate the clinical clues provided in the transplant center report! Be sure that a full report accompanies the patient on return to your office.

Request a summary from the transplant center that summarizes the transplant surgery, perioperative surgical and medical events, the hospital course, and the first few post-transplant months. Transplant centers vary in length of acute post-transplant follow-up, from a month at some centers to over a year at others. As you might have a lot of information to synthesize regarding the acute post-transplant course of your patient, schedule plenty of time to go through the transplant center report! Table 1.1 summarizes the information that you need to know about the transplant surgery, hospitalization, and acute post-transplant follow-up.

If you do not understand the peritransplant events or the therapeutic rationale prescribed by the transplant center you cannot adequately care for the transplant recipient. If the information you need is not available you must speak to the transplant physician who took care of your patient. The transplant coordinator provides an excellent, additional source of information. Communication with the transplant center is KEY!

Table 1.1 Information to be obtained from the transplant center

1. *Donor information*
   a. Type of donor: live donor, deceased donor
      - Live donor organs generally last long longer than deceased donor organs
      - Live donor organs might be less immunogenic

   b. Size incompatibility
      - Small kidneys transplanted into a large person may result in hyperfiltration and might benefit from ACEI or ARB therapy

2. *Hospitalization information*
   a. Length of hospitalization
      - You need to know if the transplanted kidney had delayed graft function or prolonged ATN

   b. Ureteral stent
      - Make sure you know when the ureteral stent should be removed if it was not already removed at the transplant center

   c. Post-transplant biopsy/biopsies
      - You need to know all post-transplant biopsy results to help guide the immunosuppressive therapy
      - Early rejection places the patient at high immunologic risk for another later rejection
      - Your patient might need surveillance for development of anti-DSA antibodies

   d. Hospital readmissions
      - Why was the patient readmitted – rejection, surgical complications, etc.

   e. Naidir creatinine and baseline creatinine
      - You need to know what the transplant center thinks is the BEST creatinine the patient will have.

3. *Immunologic information*
   a. Information that suggests your patient is at *high* immunologic risk (high risk of rejection)
      - Elevated pretransplant antibody titers (PRAs)
      - Development of donor-specific antibodies (DSAs)
      - Multiple HLA mismatches
      - Early acute rejection
      - Prior transplantation (second, third, etc.)

   b. Information that suggests your patient is at *low* immunologic risk (low risk of rejection)
      - Zero HLA donor/recipient antigen mismatch

4. *Immunosuppressive medication information:*
   a. What is the prescribed combination of maintenance immunosuppressive medications?
      - What are the target doses and target therapeutic blood levels?
      - How often should you measure immunosuppressive drug levels?

   b. Is the patient on an experimental drug protocol and what is it?
      - You need to know the protocol drugs and the requirements of the protocol if any

Table 1.1 (continued)

c. Induction therapy (especially Thymoglobulin)

- Increases risk for infections (e.g., CMV) and possibly malignancies [post-transplant lymphoproliferative disease (PTLD)]

5. *Information about infectious risks*
   a. CMV status of the donor and recipient
      - CMV positive donor places the patient at high risk of CMV disease
      - Be sure the patient is receiving adequate CMV prophylaxis

   b. EBV status of the recipient
      - EBV negative recipient should be monitored for seroconversion
      - Seroconversion increases risk for PTLD

   c. History of TB exposure (+PPD or + QuantiFERON-TB)
      - Find out if patient was treated before transplant if not start empiric therapy

   d. Received a HBV+ or HCV+ kidney
      - Higher risk of cirrhosis and hepatocellular carcinoma
      - Follow LFTs q 3 months, consider annual liver ultrasound and alpha-fetoprotein level

   e. Prior graft loss associated with BK virus
      - Check BKV-DNA by PCR q months x 6 months then at 9 months, 12 months, and yearly.

   f. Prophylaxis for Candida, *Pneumocystis jiroveci*, CMV, herpes, EBV, etc.
      - Know when you should stop these agents

6. *Information about malignancy risks*
   a. Did your patient have any pretransplant malignancy or premalignant lesions?
      - All transplant recipients have increased lifetime risk of malignancy
      - Be sure to follow closely for common post-transplant malignancies, e.g., non-melanoma skin cancer, cervical cancer, Kaposi's sarcoma, non-Hodgkin lymphoma, kidney cancer, thyroid cancer, and others

7. *Other essential issues*
   a. New proteinuria
      - Suggests recurrent disease (especially FSGS)
      - Might need to avoid sirolimus conversion

   b. Post-transplant specialty consults
      - Gives clues about peritransplant morbidities (e.g., CVD)

The following chapters detail important information specific to these take-home points:

Chapter 2 – describes the surgical procedure
Chapter 5 – describes how donor organs are allocated
Chapter 7 – describes laparoscopic donation
Chapter 14 – describes the acute post-transplant care

Chapter 17 – describes infections in the transplant recipients
Chapter 18 – describes malignancies in the transplant recipients

3. Try NOT to do more than you can at the local level. Do not get in over your head!

Physicians should NOT be optimistic with transplant patients. Usually what can go wrong will go wrong. Treating an unknown illness, new unexplained elevation in serum creatinine, new proteinuria, and so on without the input of the transplant center can be unwise. Admitting a newly transplanted patient to a hospital not affiliated with the transplant center usually leads to a compounding of delay in diagnosis and to a critical delay in treatment, especially if the patient eventually has to be transferred.

We recommend that organ transplant recipients with anything more than the simplest of illnesses be referred to a transplant center experienced in their care. This is nearly mandatory in patients with surgical issues, as many community surgeons have almost no experience with operating on organ transplant recipients. This is especially true for combined kidney–pancreas recipients.

Do not treat or admit a patient with newly altered renal function to a place where a transplant surgeon or a transplant biopsy is not available!

The following chapters detail important information specific to these take-home points:

Chapter 11 – describes evaluation of renal function in transplant recipients
Chapter 17 – describes infections in the transplant recipients
Chapter 18 – describes malignancies in the transplant recipients

4. Do NOT underestimate nonadherence – it is a common and REAL PROBLEM!!

Nonadherence is defined as "any deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect." Nonadherence is very common in both adult and pediatric kidney transplant recipients. In adults, 25% of graft losses are due to nonadherence and in pediatric recipients it is even higher (44%). There are many reasons for nonadherence, including socioeconomic, patient and disease and treatment-related factors, as well as health-care team-related factors. You MUST have high suspicion and maintain vigilance to avoid graft loss due to nonadherence!

There are several important clues that should raise your suspicion of nonadherence:

1. Missed office appointments or blood draws
2. Fluctuating drug levels (especially CNI levels)
3. Age: especially teenagers and young adults

4. Preemptive LRD, never before on dialysis
5. Late acute rejection (>6 months post-transplant)

It is difficult to be a transplant patient and the physician and staff must be cheerleaders and coaches for their patients. Would you let a dialysis patient miss appointments without some type of intervention and follow-up by the dialysis team? Members of the staff – nurses and medical assistants – are the primary effectors of this strategy and must be trained in the importance of insuring follow-up.

Medication drug levels provide an important clue to nonadherence, but they do not necessarily need to be low for a patient to be nonadherent. There is a unique type of "white coat syndrome" in which patients prepare for the MD visit by taking their medications correctly for a few days so as to have good drug levels, but are nonadherent in the interim. Some pharmacies offer compliance tracking programs and these should be utilized if available.

A particularly risky time for nonadherence is the time of transition from the pediatric to the adult transplant clinic. During this time, the teenager/young adult is at risk of losing medical insurance coverage. Usually their coverage stops at age 23, although it can stop before if they are not a full-time student. If they receive Medicare benefits only because of renal disease, their medical coverage will cease 3 years after transplantation. Patient assistance programs will pay for medications, but usually not laboratory work, office visits, and procedural examinations. You need to prepare ahead. You need to enlist the social worker to formulate a plan for these young, vulnerable patients. Teenagers and young adults are a particularly difficult group for other reasons. They may have altered sleep patterns (e.g., stay up late at night, sleep in and miss their AM medications), and they are concerned with cosmetic side effects and the effect of the medications on their body image and their sexuality. Be careful with pregnancy in female transplant recipients (not necessarily related to nonadherence).

Preemptive live donor recipients do not know what it is like to be on dialysis and might be prone to think that if they reject they can just get another transplant if they want one. As they have not experienced dialysis they see the medications, not the disease, as the problem.

Rejection rates in the 6 months immediately post-transplant are 5–10% at most centers. Why would someone reject at 6 months or later? Please investigate for partial adherence or full nonadherence in these patients. These patients often do not admit to nonadherence despite rejection episodes or undetectable levels of CNI.

The following chapters detail important information specific to these take-home points:

5. Do NOT change immunosuppressive medications without talking to the transplant center and seriously considering that you might precipitate either acute or chronic rejection. Respect the recipient's immune system!

When medication side effects or toxicities occur, you will likely be pressured to reduce or change immunosuppressive dosing. Do not make major changes to immunosuppressive medications without talking to the transplant center! Only clinicians familiar with the patient's immune history should be manipulating the immunosuppressive therapy.

Immunosuppressive drug levels can be falsely high, falsely low, or falsely normal in the case of nonadherence, unexpected drug interactions, or food–drug interactions (e.g., grapefruit juice). Drug levels may also be erroneous due to laboratory errors or sample timing.

If the immunosuppressive medication level is low, e.g., in the case of calcineurin inhibitors ACT ON IT!! Do not have the patient come back in a week or so to repeat serum creatinine and CNI levels, they need to come back immediately! Ineffective immunosuppression will precipitate rejection and the development of anti-DSA antibodies. DSA antibodies can appear anytime after transplantation when immunosuppressive medication levels have been allowed to remain low. You can also count on the fact that you may not detect rejection right away – there may be a slow rise in creatinine that is easy to miss (see creatinine creep below).

Just because a patient has intolerable side effects/toxicity from an immunosuppressive agent does not mean that they need less of it to prevent rejection. Toxicity and efficacy are two different and often unrelated properties. Over the years, many physicians continuously decrease immunosuppression based on their patient's request and perceived side effects without regard to immunological need.

A good example is prolonged reduction of mycophenolate mofetil (MMF) in patients for gastrointestinal symptoms who later demonstrate evidence of under-immunosuppression (i.e., acute or chronic rejection or development of donor-specific antibodies). If you must reduce a dose of one medication, increase the dose of another unless toxicities prevent this maneuver. If you reduce the dose of a medication you must have the patient return to your office for repeat laboratory evaluations, within at least 2 weeks, if not sooner. The sooner you catch a rise in creatinine, the better. Ask the transplant center for advice if considering individual tailoring of immunosuppressive medications.

Withdrawing steroids late, in our opinion, is NOT advisable. Actually, even for early steroid avoidance, it is not clear if steroid withdrawal is safe for all, is safe for the long term, or if it is associated with more chronic fibrosis in the transplant. Late withdrawal of steroids is not without risk of acute or chronic rejection and is of no clear benefit.

The following chapters detail important information specific to these take-home points:

Chapter 3 – describes the basics of transplantation immunology
Chapter 4 – describes tissue typing and HLA matching

Chapter 9 – describes immunosuppressive medications, dosing, and their side effects
Chapter 10 – describes minimization strategies for immunosuppressive medications

6. Do NOT delay the diagnosis or treatment of creatinine creep. There may be many reasons for a slow decline in renal allograft function.

Creatinine creep is the descriptive term for the slow, insidious rise in serum creatinine that occurs in some patients after transplantation. While most nephrologists are appropriately alarmed by a sudden and rapid decline in renal function, creatinine creep is often undertreated and certainly underinvestigated.

With the elevation of the serum creatinine in a transplant patient, the default or fallback strategy is often to lower the calcineurin inhibitor (CNI) without much diagnostic evaluation in order to see what happens. This is especially true in practices where a renal biopsy is difficult to obtain or the local pathologist has limited experience in renal transplantation.

Certainly, the creatinine may go down initially after the CNI dose is reduced, but this is often just the effect of less renal vasoconstriction, and then it frequently will rise again. Time lost in the delay in diagnosis cannot be recovered. Often this dose lowering "guess" is paired with the other errors of omission including reordering the labs, waiting, and hoping that the creatinine elevation is a laboratory error. There are numerous reasons for an elevation in creatinine and a full serologic, radiologic, and pathologic interpretation is mandatory.

Unfortunately, the optimal therapy for a slowly rising creatinine is not defined. If the transplant ultrasound shows new obstruction, a urologic consultation should be obtained and BK virus DNA should be measured in the blood; BK nephropathy can present as a late ureteral obstruction. Be careful interpreting the transplant ultrasound as mild to moderate calyceal distention can be normal in transplanted kidneys; you need to make a comparison to the baseline post-transplant renal transplant ultrasounds.

If the transplant biopsy shows acute rejection, IMMEDIATELY consult the transplant center for advice on optimal treatment! After acute rejection is treated, intensify the baseline immunosuppression, and address nonadherence. A frequent finding in the biopsy of a transplanted kidney with a slowly rising creatinine is interstitial fibrosis and hyaline arteriolopathy. It is difficult to distinguish CNI toxicity from chronic alloimmune injury of the kidney allograft and therefore clinical judgment needs to be applied to interpretation of the biopsy findings (e.g., if the CNI levels are chronically low you probably have rejection rather than CNI toxicity). The capability for C4d (to detect BK virus) and SV-40 (to detect humoral rejection) staining is essential.

Do not forget that there are other causes of allograft dysfunction besides rejection. Transplant biopsies done greater than 6–12 months post-operatively should include immunofluorescence and electron microscopy due to the possibility of recurrent disease. Failure to remember this may lead to a second biopsy. Other late causes of allograft dysfunction include transplant artery stenosis, often associated

with difficult to control hypertension, and sometimes with a bruit over the transplant artery. Ureteral stenosis, especially in those patients with a history of previous acute rejection, urine leak, or BK virus nephritis are other late causes of allograft dysfunction.

The following chapters detail important information specific to these take-home points:

Chapter 11 – describes evaluation of renal function in transplant recipients
Chapter 12 – describes the pathologic findings of kidney transplant biopsy
Chapter 14 – describes the acute care of the transplant recipient

7. Do NOT drop your vigilance regarding drug interactions. Be careful of generic immunosuppressive medications!

There are important interactions between immunosuppressive drugs and other medications that might be prescribed to your patient. Vigilance is needed to avoid serious drug interactions! A common example is the interaction between calcineurin inhibitors (CNIs) and drugs that regulate the cytochrome P450 3A enzyme system located in the liver and gastrointestinal tract. Non-dihydropyridine calcium channel blockers (CCB) (diltiazem and verapamil) increase CNI levels and therefore you need to monitor CNI levels with any CCB dose change; some transplant programs prescribe CCBs to purposely lower the required dose of CNIs and decrease patient expense. There are many drugs that alter the P450 system and common interactions with immunosuppressive medications are described in later text. Your patients should be told that only their nephrologist should modify the dose of medications that might influence immunosuppressive drug levels.

Generic immunosuppressive medications may not have the same bioavailability as the parent drug due to differences in the manufacturing process. Of particular concern with regard to immunosuppressive medications is that immunosuppressive drugs have a narrow therapeutic range. Be sure to know if your patient's pharmacy has substituted a generic immunosuppressive medication, and if so realize that you will need to perform more frequent immunological monitoring. It is important to also realize that not all generic medications have the same bioavailability and there might be significant variability in effective immunosuppression. If your patient is taking a generic substitute you will need to follow the patient closely because there are serious consequences to overdosing or underdosing. If you permit their use, you will need to consider generic drugs as an important variable in the management of your patient's immunosuppressive medications.

The following chapters detail important information specific to these take-home points:

Chapter 9 – describes immunosuppressive medications and their side effects
Chapter 14 – describes acute care of the transplant recipient

8. Do NOT forget your patients are living in the real world.

Transplantation is the gift of life and with that gift comes the opportunity to resume active, productive lives. An active life usually involves employment, lifting of dietary restrictions, and renewed sexuality.

Employment is the key to your patient's economic viability and probably a major factor in their ability to adhere to post-transplant medical advice. Patients who have been under the umbrella of a relatively secure medical system (Medicare) while on dialysis are suddenly faced with economic challenges after transplantation (e.g., co-pays for immunosuppressive medications, office visits). If a person has Medicare only based on kidney disease, coverage will end 3 years after transplantation. You need to plan ahead so that your patients do not find themselves at serious financial risk. Ask for help from your social worker or other patient advocate. Be sure you do not let your patient's insurance coverage lapse!

After transplantation, dietary restrictions are lifted and patients become hungry. A healthy lifestyle should be encouraged, including a healthy diet and regular exercise. Up to 29% of transplant recipients have a BMI > 30 kg/m^2 and even more are overweight (BMI > 25 kg/m^2). Overweight patients often become obese after transplantation and so you need to plan ahead by recommending a formal dietary program and a diet support group. Steroid reduction for obesity must be carefully weighed against the risk of allograft rejection and loss. Do not use pharmacologic medications to reduce weight, do consider gastric bypass in morbidly obese patients. An exercise program is mandatory and might involve referral to a physical therapist to initiate a safe exercise regimen.

Most ESRD patients are sexually inactive. That changes after transplantation! Women of reproductive age can easily become pregnant. You need to be sure that your female transplant patients are using effective contraception, e.g., oral contraceptives, not barrier methods. Be sure if your female transplant recipient wants to become pregnant that she is not taking CellCept or Myfortic or sirolimus. If so, you need to send her back to the transplant center to change her immunosuppressives. Male transplant recipients wishing to father a child should not be placed on sirolimus as there is an increased risk for infertility with sirolimus.

Please also remember that your patients have families that might also be affected by your patient's illness. The transplant social worker and other patient advocates are an excellent source for help.

The following chapters detail important information specific to these take-home points:

Chapter 9 – describes immunosuppressive medications and their side effects
Chapter 20 – describes sexuality and reproduction
Chapter 22 – describes social and socioeconomic issues of the transplant recipient

9. Do NOT forget the general medical problems of the transplant recipient – some of these are accelerated by the transplant medications. The most common cause of graft loss is death with a functioning graft!

All transplant recipients have comorbidities, many of which are compounded by immunosuppressive medications. Common comorbidities include hypertension, hyperlipidemia, anemia, new-onset diabetes, cardiovascular disease, and bone disease. Detailed information on each of these conditions is found in the text, but we will briefly describe some of the "take-home lessons."

Hypertension is common and blood pressures should be measured at every office visit. The goal is to reduce blood pressure to <130/80, but in proteinuric renal transplant recipients, the goal is less than 125/75 mmHg. There is no contraindication to any type of antihypertensive agent – even ACEI or ARBs. The CCBs diltiazem and verapamil increase CNI levels and therefore must be used with caution and CNI levels followed closely.

Hyperlipidemia is common and needs to be aggressively managed after the first six post-transplant months. Most patients will require pharmacotherapy. Be careful with the dose of statins because they interact with CNIs; CNIs cause a several-fold increase in statin blood level and increase the risk for myopathy and rhabdomyolysis. If statins do not work or cannot be tolerated try fibrates. Target low-density lipoprotein (LDL) concentrations should be less than 100 mg/dl (optimal <70 mg/dl), high-density lipoproteins (HDLs) >40 mg/dl for men and >50 mg/dl for women. A fasting lipid profile should be measured at least annually.

Anemia is commonly associated with azathioprine, mycophenolate, sirolimus, and ACEIs and ARBs. The goal for anemia correction, based on the KDOQI guidelines, is to achieve hemoglobin levels in the 11–12 g/dl. Erythropoiesis-stimulating agents are often used in transplant recipients to treat anemia. Be sure to evaluate for other causes of anemia though, such as PTLD. Erythrocytosis is also common and can be treated with angiotensin blockade and phlebotomy.

Cardiovascular disease is the norm in renal transplant recipients. Cardiovascular risk reduction strategies such as stopping smoking, losing weight, controlling blood pressure, and dyslipidemia are a mainstay of treatment. Proteinuria is an independent risk factor for CVD and so ACEI or ARBs should be considered in patients with microalbuminuria or proteinuria. Annual cardiac stress testing is recommended for high-risk patients (e.g., those with a history of MI, diabetes mellitus, known or symptomatic coronary artery disease).

New-onset diabetes after transplantation (NODAT) is common; it occurs in as many as 30% of post-transplant patients. The criteria for diagnosis follow the World Health Organization and American Diabetes Association Guidelines of a plasma glucose $\geq$200 mg/dl, fasting plasma glucose $\geq$126 mg/dl, or 2 h glucose tolerance test (after a 75 g glucose load) of $\geq$200 mg/dl. There are several risk factors, including family history of DM, obesity/metabolic syndrome, HCV, and pretransplant impaired glucose tolerance testing. If the patient develops NODAT the management should follow the conventional approach for patients with type 2 diabetes mellitus.

Bone disease is common in patients before and after kidney transplantation. During the first 6 months after the transplant, most patients experience a rapid decline in bone mineral density due to immunosuppressive medications and immobilization. Fall risk is also increased and fracture rates are high. Screening for bone disease is imperfect, but until better screening tools are available, bone mineral density screening should be performed within the first 3 months after transplantation if the GFR > 30 and if the patient is taking corticosteroids or has other risk factors for bone loss. Assessments should also be made for 25-hydroxy vitamin D deficiencies and treatment instituted if necessary.

The following chapters detail important information specific to these take-home points:

Chapter 15 – describes cardiovascular disease in renal allograft recipients
Chapter 16 – describes new-onset diabetes mellitus in renal allograft recipients
Chapter 19 – describes bone disease in renal allograft recipients

10. Do NOT forget that kidney transplantation is a temporary treatment for ESRD (not a cure) and that even the most successful kidney transplant recipient does not have normal glomerular filtration rate and has CKD.

Transplant patients should be classified with a "T" after the chronic kidney disease (CKD) as CKDT 2-3-4. Please bear in mind that your patient should be managed like a CKD patient, with all their associated comorbidities. CKDT tend to have a slower progression toward ESRD but a longer burden of cardiovascular risk due to the patient's previous history of advanced CKD, with or without accumulated dialysis time. Consider the cumulative vasculopathy including cerebral and peripheral vascular disease. Many successful transplants experience limb loss post-operatively. Not surprisingly, this is especially problematic in diabetics.

As you would monitor a patient with CKD, you should monitor renal allograft function at each office visit by measuring serum creatinine. Also screen for urinary protein and albumin excretion. Proteinuria is an early and sensitive marker of kidney damage in renal allograft recipients and persistent proteinuria is an important predictor of outcomes. Causes include allograft rejection and drug toxicity and also de novo and recurrent glomerular diseases (e.g., membranous glomerulonephritis, diabetic nephropathy, focal glomerulosclerosis). An allograft biopsy may be indicated to differentiate treatable causes of proteinuria. Albuminuria is increasingly being recognized as an indicator of poor renal allograft outcomes. Timed renal allograft biopsies are still outside the standard of care.

The following chapters detail important information specific to these take-home points:

Chapter 11 – describes evaluation of renal function in transplant recipients
Chapter 12 – describes the pathologic findings of kidney transplant biopsy
Chapter 14 – describes the post-transplant care of transplant recipients

A final consideration on the care of the kidney transplant patient is that it is easy to fall into the cognitive trap of trying to save the current allograft at all costs. All transplanted kidneys will eventually be lost to poorly defined processes that involve variable contributions from immunologic and nonimmunologic factors. Therefore, most patients will require multiple modalities for treatment of their ESRD. They may be on dialysis and then transplanted, return to dialysis and then receive a second transplant. The options are multiple and may be very unpredictable in any one patient.

In this spirit, it is preferred to minimize blood transfusions in order to decrease HLA sensitization, protect veins for AV fistula creation, and avoid excessive immunosuppression with repeated rejection therapies that increase malignancy and infection risk. For the patient it is sometimes better to "let the chronically diseased kidney allograft go" in the short term to protect their overall health for the long term and allow them to return to dialysis and later retransplantation. Of course this does not mean to discard a kidney that can be saved. But, if there is marginal kidney allograft function, you should not rely on heroics that might ultimately harm the patient.

There are many more things "not to do", which the reader will appreciate from the chapters in this guide. Hopefully, this introductory list will help the practitioner avoid common pitfalls and develop an overall strategy for the long-term care of the renal transplant recipient.

Chapter 2
The Transplant Procedure: Surgical Techniques and Complications

Barry J. Browne

Renal Transplantation

Introduction

Contrary to the way transplant surgery is portrayed on popular television shows, transplantation in the real world is less glamorous, less exciting, and when done correctly, quite routine. While the success or failure of the surgical procedure rests primarily on the shoulders of the transplant surgeon, the ingredients necessary to create a positive outcome rely on a team of specialists from a variety of fields. Matching the right patient with the right organ is an art developed by years of experience. The decisions involved in offering kidneys to patients, while highly regulated, are influenced greatly by nephrologists, surgeons, transplant coordinators, and social workers. Organ allocation is more fully discussed in Chapter 5.

There are four options for patients who reach end-stage renal disease (ESRD): death, peritoneal dialysis, hemodialysis, and transplantation. It is the responsibility of each nephrologist to discuss these options with each patient so that the correct path is chosen. Although we sometimes tend to look at care options as a single decision, many patients will bounce from modality to modality as their health and outlook change. This reality complicates the surgical care of patients with ESRD since each operation along the pathway from renal failure to eventual death can affect the next operation required.

The simplest surgical pathway involves pre-emptive living donor transplantation (LD). In this scenario, the list of pre-transplant operations is minimized and the operative choices are maximized. The transplant team has the opportunity to "tune up" the patient and best prepare him/her for a safe procedure. The anatomy and the quality of the donor's organ is well known before beginning and a positive outcome, while not assured, is expected. On the other hand, a patient with superior vena cava

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syndrome who dialyzes through a femoral AV graft being transplanted in the middle of the night with a cadaveric organ (CAD) procured by unknown surgeons in another state presents quite a different set of circumstances and may call for a different approach to have the best chance for success. It is the ability to predict, adapt, and modify both the medical and surgical approach to these complex patients that often separates good surgical outcomes from bad. In this chapter, I will address the most common scenarios encountered in the operating room and explain the surgical approaches that can be used to give the patients their best chance for long-term survival.

History

Alexis Carrel[1] and C.C. Guthrie[2] developed the surgical techniques required for organ transplantation at the turn of the twentieth century. The modern era of renal transplantation began with a series of unsuccessful CAD and LD kidney transplants carried out in Europe,[3–5] which were doomed due to poorly understood immunologic barriers. These obstacles were circumvented in the 1950s through the use of identical twin donors and led to the first successful kidney transplant at the Peter Bent Brigham Hospital in Boston in 1954.[6] Introduction of the antimetabolite azathioprine by Roy Calne[7] and Joseph Murray[8] coupled with the empirical addition of corticosteroids by Goodwin[9] in the early 1960s ushered in the era of widespread clinical transplantation. While surgical techniques have undergone refinement over the years, the basic procedure has changed little over the last 50 years.

Building on Carrel's descriptions of vascular anastomotic techniques Ullman[10] and Unger[11] first described experimental autotransplantation and allotransplantation of kidneys in dogs over 100 years ago. By 1914, technical progress in animal models was so successful that Carrel boasted that little work remained to perfect transplantation techniques.[12] The Ukrainian surgeon, Yu Yu Voronoy, transplanted six patients between 1933[13] and 1946[14] but without a good understanding of immunology, all of the grafts were lost and he abandoned clinical transplantation. Prior to Murray's historic transplant in 1954, the closest anyone came to clinical success was David Hume in 1945. While serving as a surgical resident at the Brigham, he sewed a CAD kidney at bedside to the brachial vessels of a woman with acute post-partum renal failure. Although this brief treatment likely played little role in the patient's recovery and the results were never published, it nonetheless kindled the interest of many surgeons[15] and ultimately led to the creation of the clinical transplant program at the Brigham. The modern technique of placement of the kidney in the pelvis with vascular anastomoses to the iliac vessels and ureteral drainage into the bladder was first described by Kuss.[16] Murray's team modified this procedure slightly by changing from Kuss' intraperitoneal approach to the preperitoneal approach used today for most kidney transplants.[17]

Living Donors

Every effort should be undertaken to identify willing living donors. Not only does this decrease the time that the recipient must wait for an organ, it also converts the procedure from an emergency to an elective basis. As mentioned earlier, the LD facilitates pre-emptive transplantation and eliminates the need for dialysis. There are three medical advantages to the use of LDs: (1) decreased risk of acute tubular necrosis (ATN) due to the shortened cold ischemia time, (2) increased potential for HLA matching, and (3) opportunity to initiate and optimize immunosuppressive therapy pre-operatively, thereby reducing risk of early acute rejection episodes. However, living donor nephrectomy subjects a healthy volunteer to a potentially lethal operation with no physical benefit to the donor. Thus it is the transplant center's responsibility to insure that (a) the physical risks of the procedure are acceptably low and (b) the donor has exerted informed consent of his/her own volition. The evaluation of living donors is described by Dr. Steiner in Chapter 6 while the technical aspects of donor nephrectomy are described by Dr. Martinez in Chapter 8.

Although the functional quality of LD kidneys is generally superior to CAD kidneys, this is no longer universal due to the shift over the last 10 years toward minimally invasive surgery for the donors. While delayed graft function (DGF) was rare in the past, it has become more common since the advent of laparoscopic nephrectomy for a number of reasons. First, the pneumoperitoneum required for laparoscopy decreases renal blood flow. Second, manipulation of the kidney often causes the renal artery to go into spasm. Third, removal of the kidney through a small incision can result in mechanical trauma to the organ. And finally, technical delays in extracting the kidney from the abdomen can result in prolonged warm ischemia time. In the most extensive single center review to date from the University of Maryland, laparoscopic nephrectomy was associated with an increase in DGF and a decrease in long-term outcome.[18] A recent meta-analysis, however, showed no difference in long-term outcome[19], so each center must continuously evaluate its outcomes to assure that transplant strategies are being optimized.

LD kidneys can also present technical problems for the surgeon during implantation. Because the donor's safety is paramount, the lengths of the renal arteries and veins are shorter in kidneys procured from LDs. In patients with multiple renal arteries, backtable reconstruction can be quite challenging and time consuming. In some cases, surgeons have resorted to using recipient saphenous vein grafts in order to simplify transplantation although I have not yet found this to be necessary in my practice.

Cadaver Kidneys

Kidneys from donors between the ages of 1 and 80 years may be acceptable under the right circumstances although special care should be taken at each end of the age spectrum. Following pronouncement of brain death and authorization for organ donation, the care of the donor is transferred to the organ procurement coordinator

whose goal is maintenance of adequate renal perfusion up until the time the donor is taken to the operating room. In the early days of transplantation, the procuring team and transplanting team were one and the same. Today, however, it is most common to have different teams procure and implant the organs. Since most CAD procurements involve the removal of extra-renal organs, the kidneys are usually removed by the surgical team responsible for removal of the liver. In situations where kidneys are the only solid organs being procured, the procuring team may consist of transplant surgeons, transplant urologists, or even local surgeons recruited at the last moment to help out.

There are many variables that affect the quality of the organ which ultimately arrives in a sterile container packed in ice. The single most important factor is the baseline condition of the kidneys prior to the event leading to the donor's presentation to the hospital. The old adage that you cannot make a silk purse from a sow's ear is never more true. Older patients presenting with elevated creatinines rarely go on to successful donation. Conversely, young adults with normal creatinines who go on to become donors usually yield high-quality organs, despite transient, reversible events which often occur during the hospitalization in failed attempts to save their lives. Following the declaration of brain death and obtaining consent to donation, the care of the donor is transferred to the organ procurement organization. Its coordinators endeavor to optimize perfusion to the kidneys, liver, and other transplantable organs prior to proceeding into the operating room for procurement.)

Once in the operating room, the surgical team's job is to remove the organs in a timely fashion after they have been flushed with chilled perfusion solution and then package them for distribution. Although there have been many attempts to standardize procurement techniques, every procurement is different. In the situation where the kidneys are the only organs being procured, the operation is straightforward and quick. If extra-renal organs are being procured, the kidneys are always removed last. Unless care is taken to keep ice on the kidneys while the heart, lungs, liver, and pancreas are removed, the quality of the kidneys can be compromised by what effectively becomes warm ischemia time. Additionally, it is not uncommon to receive kidneys obtained during multiorgan procurements with surgical damage to either the renal artery or vein. For this reason, I always examine kidneys sent to me from unknown surgeons before beginning the recipient operation.

Organ Implantation

The operative procedure can be divided into five separate parts: preparation, exposure, vascular anastomoses, ureteral anastomosis, and closing. A schematic representation of the completed implantation is shown in Fig. 2.1.

Preparation

Although regional anesthesia can be used, nearly all patients today undergo general anesthesia. If not begun pre-operatively, this is a good time for the surgeon to discuss

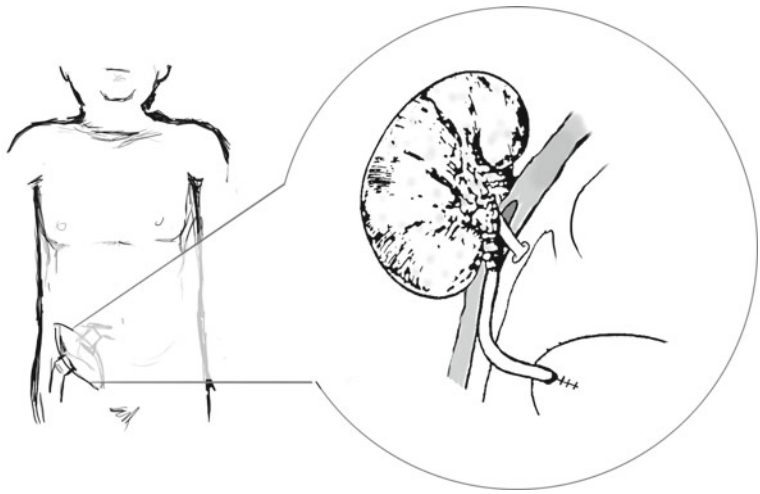

Fig. 2.1 Most common technique of heterotopic renal transplantation. Kidney is lying in the *right* iliac fossa in the retroperitoneal space. Patch of aorta containing renal artery applied directly to side of external iliac artery and external (Lich) ureteroneocystostomy. Venous anastomosis is end renal to side external iliac. Veins are *shaded* while arteries and graft ureter are not

intra-operative management with the anesthetist and prepare for anything special the surgeon might request. I nearly always ask for a central line as this is the most reliable way to assess fluid status and it also simplifies post-operative care. Most patients are given a steroid bolus at this time followed by an induction agent if warranted. I take this opportunity to discuss blood pressure parameters, depth of anesthesia, and other medications that I will ask for later in the operation. I confirm that the peri-operative antibiotic has been given and participate in the mandatory "time out" to assure that we are operating on the correct patient and have the correct kidney in the room. A Foley catheter is placed. Clot retention can complicate post-operative management so it is best to place the largest catheter possible. I prefer to use a 22F catheter unless restricted by a small urethral opening. Antibiotic solution can be instilled into the bladder at this time or just before beginning the ureteral anastomosis. This maneuver facilitates rapid identification of the bladder within the pelvis and in some circumstances gives the surgeon a nudge toward utilizing ureteroureterostomy when the bladder appears hostile to intra-operative manipulation.

Exposure

After prepping and draping the patient, an incision is made in either the right or left lower quadrant of the abdomen. The site of implantation is chosen based on the degree of peripheral vascular disease. In general, the right iliac fossa is preferred because the external iliac vein tends to have a more superficial and direct course and the sigmoid colon does not interfere with exposure of the bladder. Tissues are

divided and the retroperitoneal cavity is converted from a potential space into a workable cavity. The epigastric vessels are divided between ties because attempts to spare them are not uncommonly associated with undetected injury and delayed hemorrhage. In cases of multiple renal arteries, a healthy epigastric artery can be mobilized for later use as one of the inflow conduits. The round ligament may be safely divided in women while the spermatic cord is best retracted medially. Lymphatic tissues overlying the iliac artery and vein are divided between ties in order to reduce the risk of post-operative lymphocele formation. Historically, the preferred inflow vessel was the internal iliac artery because this minimized the risk of ischemia to the ipsilateral leg. Most surgeons today, however, use the external iliac artery because it is easier and safer to dissect. The internal iliac is also more commonly diseased due to an aging recipient population and increased incidence of diabetes. The external iliac vein is nearly always used for venous return. The hypogastric veins can be sacrificed if necessary in order to mobilize the iliac vein and simplify the venous anastomosis. If the iliac vein is absent, thrombosed, or very small, any suitably sized vein in the area can be utilized.

Vascular Anastomoses

In a straightforward operation, the venous anastomosis is usually completed first and the arterial anastomosis done last. This is due to the geometry of the vessels in the pelvis, in that the vein lies posterior to the artery. During this part of the operation, care is taken to keep the kidney chilled and topical ice is used liberally. Once the venous portion of the operation is complete, a small clamp can be placed across the renal vein and the clamps removed from the iliac vein. This releases the venous congestion in the leg and may lessen the risk of deep venous thrombosis. The arterial anastomosis is then rapidly accomplished, being careful to choose a site on the recipient artery as free of plaque as possible because endarterectomy carries the risk of raising a distal flap that may compromise flow to the leg. During the anastomoses, I usually ask the anesthetist to give 12.5 g albumin, 25 g mannitol, and 80 mg furosemide to promote immediate diuresis. Mottling of the graft surface due to arterial spasm is not uncommon, but generally resolves within 30 min as long as there is adequate perfusion pressure. Following reperfusion of the graft, meticulous hemostasis is achieved as manipulation of the kidney becomes more difficult once the ureteral anastomosis is complete. In patients given systemic heparin due to a known hypercoagulable state, protamine can now be safely administered.

Ureteral Anastomosis

Ureteroneocystostomy is the preferred method to establish urologic continuity. Both transvesicle (Politano and Leadbetter[20]) and extra-vesicle (Lich[21]) anastomotic techniques yield excellent results. Although the merits of various techniques will continue to be argued by their evangelical supporters, there does not appear to be any one superior or inferior method. Provided that a ureteral stent is used and an adequate blood supply to the ureter has been preserved, nearly all techniques