7 Kidney and pancreas transplantation

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In 2004, the international transplant community celebrated the fiftieth anniversary of the first successful kidney transplantation performed between identical twin brothers by Dr Joseph Murray and colleagues at the Peter Bent Brigham Hospital in Boston. Since that time, remarkable strides have been made to increase the success of kidney transplantation and to prolong the lives of patients with end-stage renal disease (ESRD). General advances in medical science, including improvements in surgical techniques and the development of effective antimicrobial agents, have undoubtedly played a role in this success story. However, the current success of kidney transplantation has been related more directly to an improved understanding of the mechanisms resulting in allograft rejection and the development of immunosuppressive drugs capable of preventing or reversing these processes. The introduction of cyclosporine in the early 1980s was associated with dramatic improvements in kidney transplant outcomes, a proliferation of transplant centers, and the serious development of extrarenal organ transplantation. The introduction of newer and more potent immunosuppressants since the mid-1990s has been associated with further improvements in traditional short-term benchmarks of success in kidney transplantation, as discussed below.

Pancreas transplantation is appropriately discussed in parallel with kidney transplantation because the diabetic patients who are candidates for this procedure almost always have chronic kidney disease (CKD) resulting from diabetic nephropathy. In the USA, most whole organ pancreas transplantations are performed as simultaneous pancreas–kidney (SPK) transplantations using organs from a common deceased donor. Pancreas after a previous kidney transplantation (PAK) is another approach. Pancreas transplantataion alone (PTA), performed before the need for kidney transplantation, is the least common modality. Islet cell transplantation is being performed increasingly but arguably remains experimental. This chapter will focus on the evaluation and selection of kidney transplant recipients and donors, their surgical and medical management, and their long-term outcomes and complications. Where appropriate, pancreas and islet cell transplantation are considered separately.

Patient and allograft outcomes

The number of patients wait-listed for a deceased donor kidney transplant has grown steadily over the past two decades. During the same time period, the number of deceased donor grafts available has grown only modestly. According to the Organ Procurement and Transplantation Network (OPTN) data 8097 deceased donor renal transplants were performed in the USA in 2006, a marginal increase from 7730 a decade ago. As discussed below, the largest proportion of the increase in deceased donors over the past few years can be attributed to the increased use of expanded criteria (ECD) and donor after cardiac

Primer on Transplantation, 3rd edition.
Edited by Donald Hricik.

death (DCD) donors. The demand for organs, with 24 077 new kidney waiting list registrations in 2006 alone, far exceeds the increase in donors. For the wait-listed patient between the ages of 35 and 64 years, this shortage translated to a median wait time of 3.2 years in 2001. Since that time, it has been difficult to calculate median waiting times because of substantial regional variations in waitlist times. Eleven percent of candidates can expect to wait more than 5 years. The average age of wait-listed patients is rising, and currently over 15% of candidates on the waitlist are aged >65 years. Not surprisingly, there has been a progressive increase in the number of patients dying while waiting for a kidney transplant. White people have significantly shorter wait times (mean 1255 days) than African–American (1782 days), Hispanic, (1617 days) or Asian individuals (1787 days). The longest wait times are for patients with blood types B and O (1967 and 1764 days, respectively), with shorter wait times for patients with blood type A (1084 days) or AB (596 days). The number of living donor transplants performed in the USA rose from 3886 in 1996 to 4905 in 2006. Since 2001 the number of living donors has exceeded the number of deceased donors (Figure 7.1), though the rate of increase in living donors has actually decreased in recent years.

It is now well recognized that kidney transplantation offers a survival advantage and improved quality of life for eligible patients with ESRD when compared with dialysis-based renal replacement therapy. Compared with wait-listed patients who are maintained on dialysis, projected years of life are greater with transplantation, irrespective of age and the presence or absence of diabetes mellitus (Table 7.1). As discussed below, this survival advantage holds true even for recipients of kidneys from marginal or expanded criteria donors (ECDs). The traditional short-term benchmarks of success in kidney transplantation, i.e., 1-year allograft survival rate and the incidence of acute rejection in the first year post-transplantation, have improved steadily over the past five decades (Figure 7.2). As noted above, the most significant breakpoints occurred in association with the development of cyclosporine in the early 1980s and with the introduction of tacrolimus and mycophenolate mofetil (MMF) in the mid-1990s. Currently, irrespective of donor source, most transplant centers achieve 1-year graft survival rates of >90% and a 1-year incidence of acute rejection of <20%. As discussed below, recipients of living donor renal allografts experience both short- and long-term outcomes that are superior to those of patients who received deceased donor grafts.

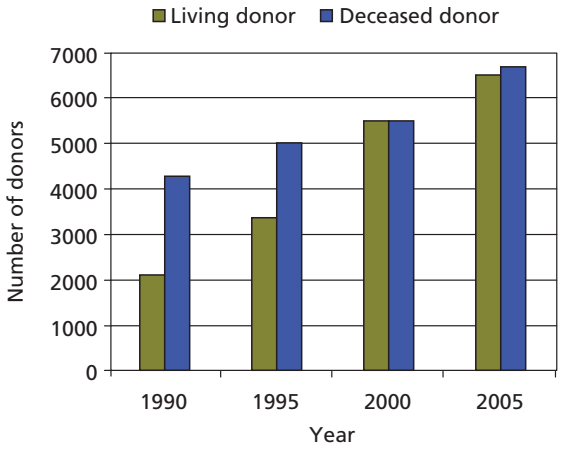

Figure 7.1 Numbers of living and deceased donors in the USA from 1990 TO 2005. (From www.OPTN.org.)

Table 7.1 Projected years of life based on retrospective analysis of patients receiving deceased donor kidney transplants versus waitlisted patients

Age and diabetic status	Projected years of life	
	With a kidney transplant (n = 46 164)	Without a transplant (n = 23 275)
20–39 years, no diabetes	31	20
20–39 years with diabetes	25	8
40–59 years, no diabetes	19	12
40–59 years with diabetes	22	8
60–74 years, no diabetes	12	7
60–74 years with diabetes	8	5

Adapted from Wolfe RA Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;**341**:1725–30.

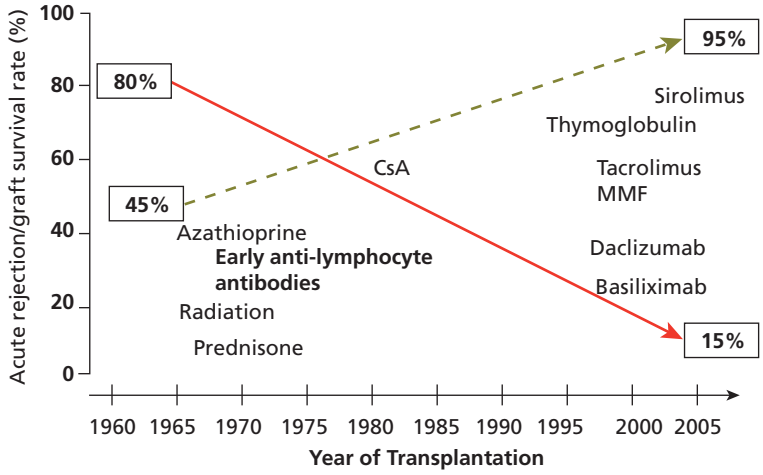

Figure 7.2 Changes in 1-year graft survival rates (dashed line) and in the incidence of acute rejection during the first transplant year (solid line) in deceased donor kidney transplant recipients during the past 50 years. CsA, cyclosporine; MMF, mycophenolate mofetil.

Improvements in the short-term outcomes of kidney transplant recipients have not been paralleled by robust improvements in long-term outcomes. There are a number of potential explanations for this disparity. The most common causes of long-term graft loss are "chronic allograft nephropathy" and death with a functioning graft. Immunosuppressive medications are expensive and non-compliance with medications based on inability to pay for the drugs tends to increase with time after transplantation. Although the calcineurin inhibitors (cyclosporine and tacrolimus) have served as the cornerstones for modern immunosuppression protocols, their nephrotoxic effects probably contribute to long-term allograft loss in a substantial minority of kidney transplant recipients and certainly do so in recipients of extrarenal organs. The epidemic of BK polyoma nephropathy was not anticipated 20 years ago and certainly has contributed to poor long-term outcomes after kidney transplantation in some patients. Although acute rejection is not common in the modern era, there is evidence to suggest that even a single episode of acute rejection has an even greater impact on long-term graft survival than was true in an earlier era. The importance of high titers of preexisting anti-donor antibodies as a risk factor for hyperacute rejection has long been recognized. However, it has only recently been recognized that low titers of such antibodies detected either before or new after transplantation may contribute to allograft rejection even many years after transplantation. Finally, it is also possible that death with a functioning graft is related directly to the toxicities of the very immunosuppressants that have yielded such impressive short-term outcomes. The available maintenance drugs variably contribute to the risks of cardiovascular disease, infection, and malignancy – the main causes of late mortality in transplant recipients.

Key points 7.1 Common causes of late mortality after kidney transplantation

Cardiovascular disease

Infection

Malignancy

A discrepancy between supply and demand has also characterized pancreas transplantation in the past decade. The number of pancreata recovered increased by 53% between 1997 and 2006. However, the number of people waiting for pancreas transplants during that time period doubled to approximately 4000 during the same time period, resulting in increased waiting times for all types of pancreas candidates. The median waiting time for a PAK transplant increased from about 220 days in the late 1990s to 562 days in 2004. The median waiting time for an SPK rose from 380 days in 1997 to 451 days in 2005.

On the other hand, there have been recent downward trends in the number of SPK, PAK, and total pancreas transplant registrations. The total number of new pancreas waiting list registrations grew from 1740 in 1997 to a high of 2796 in 2000, and then fell to 2548 in 2006. Only PTA registrations showed a consistent increase from 1997 to 2006, growing from 187 to 404.

The most recent data from the Scientific Registry for Transplant Recipients (SRTR) indicates that patient survival rates are similar for PAK, SPK, and PTA recipients at 1 year (ranging from 95% to 97%), 3 years (ranging from 91% to 92%), and 5 years (ranging from 84% to 88%). However, the 10-year patient survival rate was lowest for PAK recipients at 64%, and similar for SPK and PTA recipients, with rates of 70% and 71%, respectively. Among pancreas recipients, those with SPK transplants experienced the best pancreas graft survival rates (86% at 1 year and 54% at 10 years). Pancreas graft survival rates for PAK and PTA recipients were similar to each other, with 1-year rates of 79% and 80%, respectively, and 10-year rates of 29% and 27%, respectively (Figure 7.3). Both registry analyses and single center experiences suggest that patient survival for SPK recipients is superior to that of patients with type 1 diabetes receiving deceased donor kidneys alone and possibly superior to that of patients with diabetes receiving HLA-mismatched living donor kidneys. However, in the absence of randomized trials, such analyses should be viewed with caution because of likely bias in the selection of healthier candidates for the combined transplants. As a result of early technical complications including thrombosis of the pancreas (in 5–10% of cases), 1-year pancreas graft survival is lower than 1-year kidney graft survival in SPK recipients. However, some studies suggest that, in SPK recipients in whom both organs are functioning at 1 year, the subsequent half-life of the pancreas allografts exceeds the half-life of the renal allografts. In SPK recipients, the incidence of acute rejection in the renal allograft is higher than that observed in comparable patients receiving kidney transplants alone. This is an intriguing observation that differs from the experience with other combined organ transplants (e.g., liver–kidney, heart–kidney) in which the non-renal organ appears to exert an immunoprotective effect manifested by relatively low rates of renal allograft rejection.

The major proven benefits of a technically successful pancreas transplantation are insulin independence and normal or near-normal control of blood glucose concentrations. Whether a pancreas transplantation prevents or retards the progression of microvascular complications of diabetes mellitus has been more difficult to prove, in part because many patients receive their pancreas allografts when these complications are already far advanced. Evidence suggesting improvements in diabetic retinopathy, enteropathy, or peripheral and autonomic neuropathy after pancreas transplantation is mixed at best, and there is little evidence for improvement in macrovascular disease. Nevertheless, anecdotal reports of improvements in all of these complications, together with the observation that glycemic control generally retards the development of diabetic complications in the general population, underscore the need for additional long-term studies and continue to provide motivation for whole organ pancreas transplantation among both patients and transplant professionals.

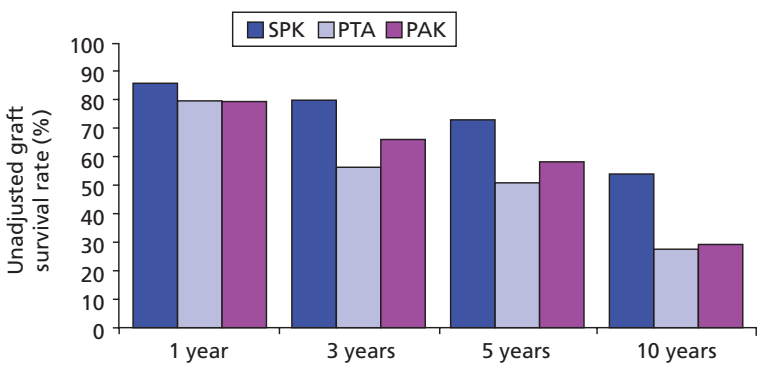

Figure 7.3 Pancreas graft survival by transplant type. SPK, simultaneous pancreas and kidney; PTA, pancreas transplant alone; PAK, pancreas after kidney transplantation. (From www.OPTN.org.)

Key points 7.2 Important facts regarding simultaneous pancreas kidney transplantation (SPK)

Most pancreas transplants are performed simultaneously with a kidney transplant from the same deceased donor

After SPK transplantation, short-term pancreas graft survival is lower than kidney transplant survival owing to early technical problems including thrombosis

Acute renal allograft rejection occurs more commonly after SPK transplantation than in diabetic patients receiving a kidney transplant alone

Non-randomized studies suggest that patient survival after SPK transplantation is superior to that of diabetic patients receiving a kidney transplant alone

Key points 7.3 Timing of kidney transplantation

Listing for deceased donor transplantation generally allowed only when glomerular filtration is <=20 mL/min

Long-term graft survival is optimized in patients who are transplanted pre-emptively (before the need for dialysis)

Pre-emptive transplantation for asymptomatic patients is generally performed when the glomerular filtration rate is <15 mL/min but can be performed with higher levels in patients with symptomatic uremia

Recipient selection and evaluation

Evaluation of kidney transplant recipients

In view of the survival advantage offered by kidney transplantation, all patients with advanced CKD should be considered as potential transplant recipients until deemed not suitable, or unless a pre-existing absolute contraindication is identified, as discussed below. In fact, referral of the patient for evaluation should be considered in advance of starting dialysis, because several studies have suggested a decreased risk for graft failure and death when transplantation is performed *pre-emptively*. Patients are generally not listed for deceased donor transplantation until the glomerular filtration rate (GFR) has fallen to <=20 mL/min. When pre-emptive transplantation is possible (most often in the setting of living donor transplantation), transplantation is generally performed when the GFR is <15 mL/min unless the patient is symptomatically uremic with higher values. Whenever possible, evaluation of the potential kidney transplant recipient should begin before the GFR falls to a level mandating initiation of dialysis.

Medical evaluation

Evaluation starts with a detailed medical history and physical examination. Standard laboratory testing varies from one center to another but generally includes ABO blood typing, a complete blood count, comprehensive metabolic panel, coagulation screen, and urinalysis. Additional studies include an EKG, chest radiograph, colonoscopy for patients aged >50 years, pap smears for women of reproductive age, mammography in women aged >40 years, a PPD (purified protein derivative) skin test, prostate-specific antigen for men aged >50 years, a urine drug screen, and serologic studies to determine prior exposure to human immunodeficiency virus (HIV), hepatitis B and C, cytomegalovirus (CMV), Epstein–Barr virus (EBV), varicella-zoster, and syphilis. Further evaluation is determined on a case-by-case basis and may include urodynamic evaluation, cystoscopy, and non-invasive imaging of the aortofemoral vasculature. These latter studies are protocol driven in some centers, or may be precipitated by findings elicited from the history or physical examination in others. At any step during the process, an absolute or relative contraindication may be identified and result in either a delay in listing the patient, or declaration that the patient is permanently ineligible for transplantation.

Contraindications to transplantation

Absolute contraindications to kidney transplantation are listed in Table 7.2 and generally include conditions that represent an ongoing threat to life, or conditions that are associated with high short-term mortality rates. There are many relative contraindications discussed below.

Cardiovascular disease Cardiovascular disease is the major cause of death among dialysis patients, and remains the major cause of mortality after transplantation, albeit at a much lower incidence. Risk factors for cardiovascular disease among patients with ESRD include increased age, hypertension, diabetes mellitus, dyslipidemia, smoking history, family history of premature cardiovascular disease, and prolonged

Table 7.2 Absolute contraindications to kidney transplantation

Chronic medical disease with life expectancy <2 years:
severe cardiomyopathy or irremediable ischemic heart disease
severe chronic obstructive pulmonary disease
hepatic cirrhosis
diffuse, pronounced vascular disease
Active malignancy, other than basal cell skin cancer
Active sepsis or other life-threatening infectious disease
Active substance abuse
Active peptic ulcer disease
Psychiatric illness impeding upon patient's compliance

duration of dialysis (>2 years). Pretransplantation evaluation for cardiovascular disease has become a subject of increasing controversy. Nuclear and echocardiographic stress testing predict myocardial infarction and cardiac death after transplantation, particularly in patients with diabetes. However, the sensitivity of non-invasive testing may be reduced in the ESRD population, and some have advocated cardiac angiography in higher-risk transplant candidates. That being said, there is little evidence supporting the benefit of intervention in otherwise asymptomatic patients in the absence of left main coronary artery disease, at least in the general population. In the Coronary Artery Revascularization Prophylaxis trial, 510 patients undergoing major vascular surgery were randomized to revascularization versus medical management. No survival benefit was demonstrated in either group, prompting guidelines from the American College of Physicians against revascularization in asymptomatic patients before non-cardiac surgery. For transplant candidates, preoperative cardiac stenting can be particularly problematic when antiplatelet agents such as clopidogrel are required for an extensive period, increasing the risk of bleeding or delaying transplant surgery. With these caveats in mind, most centers continue to perform screening studies in patients deemed to be at high risk based on age >50 years, presence of diabetes mellitus, or multiple conventional risk factors. Screening of such patients consists minimally of an EKG, echocardiogram, and a stress test with myocardial perfusion imaging. Coronary angiography should be considered when stress tests are positive or in any patient with symptomatic heart disease. Revascularization is generally recommended before transplantation in patients with critical coronary lesions. Inoperable coronary disease and/or advanced heart failure is a contraindication to transplantation.

As there is an increased prevalence of carotid artery disease among patients with ESRD, duplex imaging of the carotids should be considered in patients with asymptomatic carotid bruits and in those with a prior history of stroke or transient ischemic attack. Patients with adult polycystic kidney disease have an increased incidence of cerebral aneurysms. Screening with magnetic resonance (MR) angiography should be considered for such patients if they have a family history of cerebral aneurysms or unexplained stroke, or if they suffer from unexplained headaches.

Peripheral vascular disease occurs in 2.0–3.2% of renal transplant candidates. Traditional risk factors include diabetes mellitus, cigarette smoking, hypertension, dyslipidemia, older age, and male gender. For patients who manifest either clinical symptoms or physical findings consistent with aortoiliac disease, angiography and surgical intervention may be required before proceeding with transplantation.

Malignancy Immunosuppression may promote growth of existing malignant cells, so that all potential kidney transplant recipients should be screened for common cancers. In a review of more than 900 renal transplant recipients from the pre-cyclosporine era, Penn noted a 53% recurrence rate for all tumors when patients were transplanted within 0–24 months following their cancer treatment course, a 34% rate of recurrence when treatment finished 25–60 months before transplantation, and a 13% rate when treatment was completed >60 months pretransplantation. These observations led to the general concept that pre-existing cancer mandates treatment, complete remission, and a period of waiting before proceeding with transplantation. However, the recommended period of waiting varies depending on the type of tumor, its size, and the presence or absence of metastases before achievement of remission. No waiting may be necessary when a tumor is small and completely resected surgically (e.g., some renal cell or

prostate cancers). For most solid tumors, a waiting period of 3–5 years is generally recommended.

Infection Active infection should be viewed as a contraindication to transplantation until the infection has been adequately treated. Transplantation of HIV-positive patients was not considered before the introduction of highly active anti-retroviral therapy (HAART). With the advent of HAART, acceptable graft and patient survival rates are now being achieved among selected patients. In the USA, transplantation of HIV-positive patients has been aided by an ongoing collaborative multicenter study sponsored by the National Institute of Allergy and Infectious Disease. Hepatitis C infection is common among hemodialysis patients with a reported prevalence 7.8% in the USA in 2002. As routine liver function tests are normal in most hepatitis C virus (HCV)-positive dialysis patients, many transplant centers recommend a liver biopsy before kidney transplantation in order to rule out chronic active hepatitis or cirrhosis. Antiviral therapy with interferon and/or ribavirin may be tried in an attempt to eradicate the virus before transplantation. Overall, HCV-positive transplant recipients enjoy better long-term survival rates than their dialysis counterparts, so that, in the absence of severe hepatitis or cirrhosis, a positive test for hepatitis C in itself is not a contraindication to transplantation. Patients testing positive for hepatitis B surface antigen (HBsAg) should undergo additional evaluation including tests for evidence of active viral replication and possibly a liver biopsy to rule out chronic active hepatitis. If either is present, kidney transplantation is contraindicated because of an increased risk of death from liver failure with initiation of immunosuppression. In the absence of evidence for active viral replication, the HBsAg-positive patient may proceed with transplantation, although liver function tests should be monitored regularly thereafter.

Patients with negative serologic tests for CMV or EBV should be informed of the potential risk for acquiring these viruses from seropositive donors. Varicella immunization should be performed before transplantation in patients who are seronegative for this virus. Patients with a positive PPD skin test and a normal chest radiograph are generally treated with isoniazid, although the timing of treatment (i.e. pre- or post-transplant) varies and depends on the likelihood and expected timing of transplantation.

Case

A 53-year-old man with ESRD from hypertension is being evaluated as a potential kidney transplant recipient. His pretransplant evaluation is unremarkable except for a past history of intravenous drug abuse that was discontinued 12 years ago. In addition, serologic studies indicated the presence of hepatitis C antibody. Polymerase chain reaction (PCR) studies confirm a positive, albeit low, viral load. A liver biopsy is performed and shows mild hepatitis without evidence for chronic active hepatitis or cirrhosis. Liver ultrasonography shows no evidence of hepatocellular carcinoma. The man is advised that his risk for severe liver disease after kidney transplantation will not be appreciably different than expected if he remains on dialysis. The patient opts to proceed with transplantation and is added to the center's waiting list.

Other relative contraindications As discussed in Chapter 5, the influence of obesity on post-transplant outcomes remains controversial, but most studies suggest an adverse effect on death-censored graft survival. In addition, obesity increases the risk of perioperative complications, including impaired wound healing and wound infection. The upper threshold of acceptable body mass index (BMI) varies from 35 kg/m^2 to 40 kg/m^2 across centers, and patients above those thresholds are encouraged to lose weight before proceeding with transplantation. Most centers have abandoned upper age limits for kidney transplantation and individualize decisions about transplantation of patients aged >65 years based on their overall health status. Use of tobacco products is, of course, frowned upon, but centers differ in opinions about smoking as a contraindication to kidney transplantation. Although smoking is considered an absolute contraindication in some centers, others consider smoking a contraindication only in patients with proven vascular disease.

A number of renal diseases are known to recur in transplanted kidneys (Table 7.3). The risk of recurrence should always be discussed with the potential recipient. However, the possibility of recurrent disease should only rarely preclude kidney transplantation. Exceptions to this rule include primary oxalosis for which prior or simultaneous liver transplantation may be required to prevent recurrence, and focal and segmental glomerulosclerosis in a patient who has lost a previous allograft from recurrence of this

Table 7.3 Approximate risk of recurrent disease after kidney transplantation

Recurrent disease	Risk (%)
Primary oxalosis	80–100
Membranoproliferative glomerulonephritis type 2 (dense deposit disease)	80–100
Diabetic nephropathy	80–100
Idiopathic hemolytic–uremic syndrome	50–75
IgA nephropathy	40–50
Focal and segmental glomerulosclerosis	30–50
Membranoproliferative glomerulonephritis type 1	30–50
Membranous nephropathy	10–30
Wegener's granulomatosis	20
Systemic lupus erythematosus	10
Fabry's disease	5

disease. For certain systemic immune disorders associated with ESRD (e.g., systemic lupus erythematosus, Goodpasture's disease, or Wegener's granulomatosis), it is generally agreed that recurrence in the transplanted kidney can be minimized by postponing transplantation until the systemic disease is in remission. It is less clear whether the risk of recurrence is higher when transplantation is performed in the face of persistent serologic activity (e.g., positive anti-DNA antibodies in lupus or positive anti-neutrophil cytoplasmic antibodies in Wegener's granulomatosis) in patients with clinically quiescent disease.

Wait-list management

The imbalance between supply and demand for kidney allografts has resulted in growth in the size of the waiting list, longer waiting times, and increased death rates among wait-listed patients. Particularly because prolonged exposure to dialysis is associated with a number of morbidities, most transplant centers have developed protocols for re-evaluation of wait-listed candidates on at least an annual basis. The protocol varies between centers but usually includes an interim medical history, and an update on viral serologies and cancer screening. Many centers repeat cardiovascular screening for high-risk patients on an annual basis. Patients with new, reversible contraindications to transplantation should be placed on "status 7" or "hold" status until the problem is rectified. Those with irreversible contraindications should be removed from the list.

Evaluation of pancreas transplant recipients

Patients referred for pancreas transplantation should fulfill the general eligibility criteria for kidney transplantation. However, many centers impose stricter limits on age (often excluding patients aged >55 years) and BMI (excluding patients with BMI >30 kg/m^2). Most centers perform pancreas transplantation only on patients with type 1 diabetes mellitus, defined by undetectable blood C-peptide levels. However, a number of studies have shown that pancreas transplantation can be successful in selected patients with type 2 diabetes mellitus, so that the presence of type 2 diabetes is no longer considered an absolute contraindication at some centers. As patients with diabetes, potential pancreas recipients are considered to be at high risk for cardiovascular disease so that, irrespective of age, most centers aggressively perform cardiovascular screening at the time of the initial evaluation and at least annually for waitlisted patients. For PAK or PTA candidates, renal function should be stable (GFR >40 mL/min for PAK on calcineurin inhibitor, >60 mL/min for PTA). Otherwise, an SPK should be considered.

Donor selection and evaluation

Deceased kidney donation

Donor factors affecting outcome

The outcomes of deceased donor allografts are influenced by the quality and function of the graft at the time of harvest. The age of the deceased donor has a significant impact on long-term graft survival. The 5-year graft survival rate is 72% when the deceased donor is aged between 18 and 34 years, and 61% when between 50 and 64 years. Prolonged cold ischemia time and HLA mismatching have a relatively smaller impact. The difference in graft survival between zero-mismatched kidneys and 6-antigen-mismatched kidneys is only 10% at 5 years post-

transplantation. Similarly, graft survival in transplants with a cold ischemia time of <11 h versus those with a cold ischemia time of 32–41 h differs by only 6%. Through the use of variables including age, cold ischemia time, donor race, cause of death, history of hypertension or diabetes, and HLA match, computer models can provide relatively precise projections of graft half-life.

Organ evaluation and procurement

Once accepted to a waiting list, patients in the USA are registered with the United Network for Organ Sharing (UNOS), where a centralized computer network links all organ procurement organizations (OPOs) and transplant centers. OPOs are non-profit, federally funded organizations that are assigned to distinct geographic areas within the USA. They provide an integral link between donor and recipient, and are responsible for the retrieval, transportation, and preservation of organs nationwide. Inclusion and exclusion criteria for deceased donation, as well as medical evaluation and management of the deceased donor, are discussed in detail in Chapter 3. As noted in that chapter, infection with HIV is an absolute contraindication to deceased donation. In addition, the Center for Disease Control has generated criteria for behavior considered to represent a high risk for transmission of HIV, irrespective of the results of HIV testing (Table 7.4). Organs should not be accepted from donors meeting these criteria unless the transplant center deems that the benefits of transplantation outweigh the small risk of transmitting HIV. Under those circumstances, the center is obliged to notify the potential recipient about the high risk behavior.

In addition to providing help in obtaining consent, OPOs are responsible for obtaining the donor medical history, blood type, tissue type, size of the organ, and distance between donor and recipient. All of these factors are entered into a national database. A list of potential recipients is generated, ranked based on blood and tissue match and distance from the recipient. The computer will search nationally for a recipient who matches the donor at all identified HLA loci. Historically, almost 15% of transplanted kidneys have been allocated on the basis of a "perfect" match or zero mismatches. However, recent changes in UNOS bylaws now limit exportation of zero-mismatched kidneys to highly sensitized patients. With that exception, the kidney is usually allocated to a patient in the local area of the OPO according to an algorithm that takes into account waiting time, HLA-DR matching, panel reactive antibody (PRA) status, pediatric status, and geographic factors using the UNOS "points" system. It is important to note that, over the years, UNOS has modified the number of points assigned to each of these variables in an effort to improve the equity of allocation. Ethnicity, gender, religion, and financial status currently are not part of the point system. The transplant center caring for the top-ranked patient determines if the organ is suitable. If not, the next listed individual's transplant center is contacted, and so on.

Table 7.4 Center for Disease Control guidelines for high-risk behavior that must be considered in all potential kidney transplant donors

1. Men who have had sex with other men in the preceding 5 years
2. People who report non-medical intravenous, intramuscular, or subcutaneous injection of drugs during the preceding 5 years
3. People with hemophilia or related clotting disorders who have received human derived clotting factor concentrates
4. Men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years
5. People who had had sex in the previous 12 months with any person described in items 1–4 above or with a person known or suspected to have HIV infection
6. Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membranes
7. Inmates of correctional systems

Special considerations for pancreas donors

Most of the inclusion and exclusion criteria applying to potential donors for kidney transplantation are relevant to pancreas transplantation as well. However, donors with a history of diabetes mellitus are generally excluded. Elevations of pancreatic enzymes occur

commonly in the hemodynamically unstable donor, may reflect ischemic injury to the organ, and often preclude acceptance of the pancreas for transplantation. Finally, transplant surgeons generally prefer younger, non-obese individuals for pancreas donation, so that potential donors aged >55 years and those with BMIs >35 kg/m^2 are often excluded. In some cases, a preliminarily accepted pancreas may be rejected during the harvesting procedure when visual inspection of the pancreas reveals evidence of fat necrosis or other injury.

New trends in deceased donor transplantation

Expanded criteria donors The ECD program was specifically developed to increase the pool of deceased donors, taking advantage of kidneys that previously were discarded. ECD kidneys are defined by donor characteristics associated with a 70% greater risk of kidney graft failure, at any point in time following transplantation, when compared with a reference group of "standard criteria" donors (SCDs) (Table 7.5). In the first 18 months after implementation of the ECD kidney allocation policy, there was an 18% increase in ECD kidney recovery and a 15% increase in ECD kidney transplantations. The ECD donor population currently constitutes about 20% of the donor pool. Inpatient costs are about 10% greater for ECD compared with SCD recipients, largely reflecting higher rates of delayed graft function and the accompanying need for dialysis and extended length of hospital stay.

Wait-listed patients must provide informed consent before consideration for an ECD kidney. Patients should understand that consenting for an ECD kidney does not influence waiting time for an SCD kidney. However, the increasing age of the donor population makes ECD kidneys more likely to be available. Thus, the main reason to consider ECD grafts is to decrease waiting time for transplantation. This may be particularly appealing for patients with shortened life expectancies on dialysis (e.g., patients with diabetes, older patients) or for any patient anticipating extended waiting times for standard kidneys (e.g., highly sensitized patients). An ECD kidney that is thought to be non-transplantable as a single allograft may provide sufficient renal function when both donor kidneys are transplanted together into one recipient. Almost always, dual transplants of this kind involve elderly donors and recipients. Reported outcomes have been at least equivalent to those of single ECD kidneys.

Table 7.5 Defining characteristics of expanded criteria donors for deceased donor kidney transplantation

Age >60 years
or
Age >50 with at least two of the following 3:
History of hypertension
Cerebrovascular accident as the cause of death
Terminal serum creatinine concentration >1.5 mg/dL

Donation after cardiac death Transplantation of kidneys from non-heart-beating donors (i.e., DCDs) has increased markedly over the last decade. A comparison of all DCD to brain-dead donor kidney transplants in the USA between January 1993 and June 2000 found elevated rates of delayed graft function after DCD transplantation, but equivalent graft and patient survival rates at 1, 6, and 10 years. Currently in the USA, fewer then half of OPOs perform the majority of DCD kidney transplantations. Many centers remain reluctant to transplant DCD kidneys for a variety of reasons. However, UNOS recently mandated that all OPOs develop protocols for harvesting organs from DCDs. It has been estimated that increasing the utilization of DCD grafts represents an opportunity to increase the supply of kidneys, by as much as 25%.

Allocation according to net survival benefit Although there have been trends toward older recipients receiving older organs, the current allocation system does not mandate who should receive a given organ based on its quality. There is concern that significant graft years may be lost by transplantation of younger donor kidneys into older recipients with potentially shorter lifespans. Such concern has led to the idea of a utility-based "net lifetime survival benefit" allocation system, similar to that seen for lung and heart transplants. In proposed models, the incremental survival benefit (i.e., the difference between estimated transplant lifespan with a given kidney minus predicted waiting list lifespan without a transplant) is determined from statistical modeling of donor and recipient factors. The model assumes that transplan-

tation increases the overall life expectancy compared with remaining on the waiting list for most candidates. New allocation policies based on net survival benefit are currently being scrutinized by UNOS.

Living kidney donation

Donor trends

The number of living donor kidney transplants has increased over time, and in the USA the number of live donor transplants surpassed that of deceased donors for the first time in the year 2000, when over 5000 transplantations from each donor source were performed. However, since 2005 this trend has reversed. As the waiting list has grown, an increased demand for donor kidneys has fueled an increase in living donation. Short- and long-term outcomes in kidney transplantation have been consistently superior with living versus deceased donors (Figure 7.4), further increasing the demand for living kidney donation. In addition to the obvious advantage of avoiding long wait-list times, recipients of living donor transplants have longer graft half-lives and patient survival than recipients of deceased donor grafts. One-year and 5-year graft survival rates for living versus deceased donor grafts is 95% versus 89%, and 80% versus 67%, respectively. Patient survival rates at 1 and 5 years for living donor recipients is 98% and 90%. By comparison, for deceased donor recipients, 1- and 5-year patient survival rates are 95% and 82%, respectively. Living donors must go through a rigorous evaluation program to ascertain their eligibility for donation, and tend to be healthier than age-matched individuals in the general population. Also, living donor allografts avoid the cold ischemia time and subsequent ischemia–reperfusion injury typical of deceased donor transplantation. In contrast, most deceased donors have comorbid conditions around the time of death.

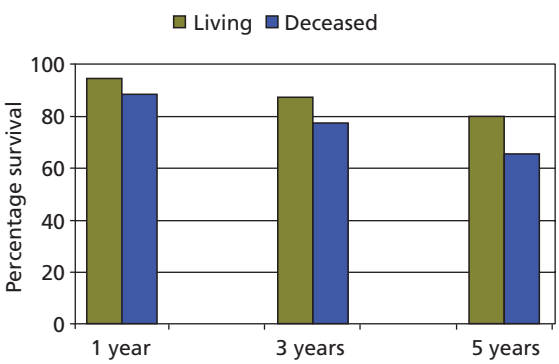

Figure 7.4 Comparison of graft survival rates in living versus deceased donor kidney transplant recipients from 1997 to 2004. (From www.OPTN.org.)

Laparoscopic donor nephrectomy has become a standard of practice for live donor nephrectomy at most centers, and decreased morbidity associated with the laparoscopic technique has also contributed to the increase in living donor transplants. The laparoscopic approach has been associated with less postoperative pain, less blood loss, quicker convalescence, and quicker return to work compared with open nephrectomy. Laparoscopic nephrectomy is a longer, more technically challenging procedure, and for this reason concern has been raised that the donor kidney may be at risk for more ischemic injury before implantation. However, long-term renal function in recipients appears to be comparable when the laparoscopic and open donor techniques have been compared.

The number of unrelated living donor transplants has also increased in the past 20 years and represents the greatest percentage increase among donor types. In the 1980s to 1990s, less then 10% of living donor kidneys came from unrelated donors and, at that time, were primarily from recipient spouses. Recently, unrelated donors have more commonly included friends, workmates, members of places of worship, and even strangers. In the era of modern immunosuppressive therapy, living unrelated donor kidneys have had a survival rate similar to that of living related kidneys, and allograft survival with unrelated donors remains superior to that with deceased donors.

Occasionally, transplant centers will receive requests from those who want to donate a kidney anonymously, with no specific target recipient. A series of ethical considerations and practice guidelines for so-called non-directed donation has been published. Most experts agree that non-directed donors should not be solicited but may be considered for donation after initiating contact with a transplant center. Most also agree that centers should choose a recipient in a similar manner to a deceased donor recipient, through the UNOS points system. Additional attention may be given to matching of donor and recipient age and body size, while avoiding any medically irrelevant biases that may exist from the donor or the transplant center itself.

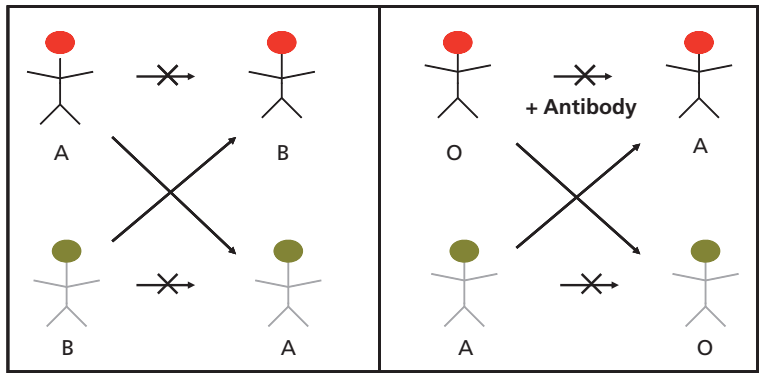

Figure 7.5 Examples of the potential utility of a paired donor exchange program. In the left panel, two ABO-incompatible donor recipient pairs exchange to facilitate two ABO-compatible transplants. In the right panel, transplantation is precluded in the upper pair by a positive cross-match and in the lower pair by ABO incompatibility. If the recipient in the upper panel has a negative cross-match to the donor in the lower panel, exchange between the couples facilitates two successful kidney transplants.

Many potential non-directed donors do not pursue further work-up after initial contact with transplant centers, particularly after learning about the extent of the donor work-up required. However, if such prospective donors do continue to request evaluation, psychological evaluation is a key component of the work-up. A significant percentage of such donors have been found to be unsuitable, not only on physical grounds, but also on psychological or motivational grounds. Centers must be wary of a desire from such donors to relieve a psychological burden or to look for secondary gain either from the media or through a relationship with the recipient or others. Ultimately, only a small percentage of applicants progress to non-directed donation, and donors who are deemed suitable typically exhibit a rational desire to improve the well-being of others and have a pre-existing pattern of benevolent and charitable behavior.

Non-directed donation may also be used to benefit a loved one or friend through a policy of donor exchange. A live-donor exchange involves a living donor–recipient pair who are incompatible due to either blood-type mismatch or a positive antibody cross-match. The donor agrees to donate to a second compatible recipient in exchange for a donation from a second donor to the primary recipient. Recipients with type O blood may be disadvantaged by this system because donors with type O typically donate regardless of recipient blood type. Therefore recipients with type O who participate in a living donor exchange must rely on a type O donor who elicits a positive cross-match in the primary recipient (Figure 7.5). One-year patient and graft survival rates were excellent in a recent series of living donor or exchange recipients that included patients who were highly sensitized.

Some UNOS regions have also developed a live-donor/deceased donor exchange program. In such a system, an incompatible living donor agrees to donate to a transplant candidate on the waiting list. Selection is based on points akin to selection of a deceased-donor recipient. In exchange, the incompatible recipient becomes a candidate for the next ABO-identical or O-type deceased donor kidney. One criticism of this policy is that it may deplete O-type donors from the deceased donor pool, and further disadvantage type O recipients on the waiting list.

Another recent approach aimed at increasing the number of living donor kidney transplants involves the use of antibody desensitization protocols. Such protocols have used plasmapheresis and intravenous immunoglobulin (IVIG)-based therapies to decrease the concentration of circulating antibodies against HLA, allowing transplantation despite an initially positive cross-match. High dosage of IVIG alone (2 mg/kg) given monthly until a cytotoxic cross-match becomes negative has been used with some success in

highly sensitized patients. Other groups have found greater success using plasmapheresis, IVIG at lower dosages, ± treatment with an anti-CD20 antibody (rituximab). Success appears to depend on the antibody titer before therapy. Most studies show high rejection rates of 30–50% despite recipient conversion to a negative cross-match, and aggressive and costly desensitization treatment is frequently continued after transplantation. Even with successful conversion to a negative antibody cross-match, alloantibodies tend to persist and may potentially contribute to chronic rejection post-transplantation. Similar protocols have been used to allow transplantation in the presence ABO blood type incompatibility. One center used pre- and post-transplant plasmapheresis with either splenectomy or rituximab in 40 ABO-incompatible recipients. Recipients with an ABO titer of <1 : 8 proceeded with transplantation. Rejection rates were high at 3 months (30%) but the 1-year graft survival rate was excellent at 95%, likely due to aggressive post-transplant monitoring and treatment with ongoing plasmapheresis, steroids, and/or rituximab after either rejection or a rise in ABO titers.

Most agree that donor exchange programs are superior to desensitization protocols in that the cost of therapy is significantly reduced and rejection rates are substantially lower. However, broadly sensitized patients and patients with blood type O may not find success with donor exchange programs and may benefit from desensitization protocols. Further analyses of such protocols are required, because both treatment regimens and outcomes remain variable between transplant centers.

Donor evaluation

The medical evaluation of the living kidney donor consists of basic tests to confirm adequate renal function in the absence of kidney disease, as well as excellent overall health in the donor. Most centers demand that a donor be of legal adult age (18 years) and able to provide informed consent. The upper limit of age for the donor varies among institutions and may not be as important as the donor's overall health status. However, the realization that renal function declines with age may make an older donor less desirable.

A history and physical examination are key components of the donor evaluation. Any history of major illness, including cardiovascular, pulmonary, or liver disease is noted, and donor candidates with significant comorbidities are typically excluded. Active malignancy and infection are usually also contraindications. Screening for syphilis and tuberculosis is performed, and donors are screened for viral infections such as hepatitis B, hepatitis C, and HIV, and excluded if active infection is present. Titers of antibodies against CMV and EBV are also measured to assess the risk of transmission of these viruses to the recipient.

Renal functional impairment and/or proteinuria is a contraindication for kidney donation. Some centers rely on 24-hour urine collections for both creatinine clearance and proteinuria. Others use more accurate assessments of GFR based on clearances of various isotopes, most commonly iothalamate. A GFR of 80 mL/min per 1.73 m^2 is the typical lower cut-off value for donation. Albumin:creatinine ratios are effective and accurate in ruling out abnormal albumin excretion, and total protein:creatinine ratios will also capture non-glomerular protein excretion.

Urinalysis is used to rule out pyuria or hematuria. Hematuria typically requires evaluation of the urogenital tract to look for mucosal abnormalities or kidney stones. A history of multiple kidney stones is generally a contraindication for donation. Occasionally patients with a history of a remote solitary kidney stone or with small microcalcification found on renal imaging will undergo a metabolic work-up for kidney stones. If such a work-up is unrevealing or can be corrected over time with medical therapy, donation is allowed at many centers.

If the potential donor has hematuria and no source of bleeding is found with renal imaging and cystoscopy, one must also consider glomerular hematuria, which may be associated with defects in the glomerular basement membrane. Potentially deleterious kidney diseases such as Alport's syndrome or IgA nephropathy must be considered in such patients. Even thin basement membrane disease, a condition once thought benign, has recently been associated with deteriorating kidney function over time. Risk of familial kidney diseases in a living related donor must be considered when the recipient has kidney failure due to polycystic disease, Alport's syndrome, or nephrotic syndrome. Polycystic kidney disease in the donor can be ruled out with renal ultrasonography, which serves as a highly sensitive screening test if the donor is aged >30 years.

Blood pressure measurement is a key component of the donor work-up, and patients with hypertension are generally excluded. There is no clear evidence that hypertension predisposes to kidney failure in patients with a solitary kidney, but there is an association with higher blood pressure and progression to kidney failure in the general population. A cut-off of ≥140/90 mmHg in the office and/or the need for blood pressure medication is generally used as an exclusion criteria. However, a significant percentage of patients with mild elevations in blood pressure in the office will have normal readings using ambulatory blood pressure monitoring, and such home monitoring can be a valuable tool in evaluating the potential donor. Some centers have expanded living donor criteria to include subjects with mild hypertension, although most agree that this is probably not wise in African-American individuals.

Donor candidates are usually screened for diabetes mellitus. One challenge commonly encountered is a younger donor candidate with no evidence of diabetes mellitus, but with an extensive family history of the disease, sometimes including the recipient candidate. A glucose tolerance test may be performed in a donor with a family history of disease, and donors with glucose intolerance should be excluded. Donors with an extensive family history of diabetes mellitus, particularly if they have other risk factors such as obesity, may be excluded as well. A history of gestational diabetes in women is also a relative contraindication, because approximately a third will go on to develop type 2 diabetes mellitus.

Other tests such as a chest radiograph and EKG are standard in the donor evaluation. Donors should undergo age-appropriate screening for malignancy, such as mammograms and pap smears in women, prostate evaluation in men, and colonoscopy in age-appropriate adults. Specific findings on history and physical examination may prompt further studies, such as cardiac stress testing or pulmonary function studies. A history of clotting or deep venous thrombosis is a relative contraindication for donation, because surgery itself creates a risk for recurrent thrombotic events. Pregnancy is a contraindication for donation, but future planned pregnancy is not, as many case series of normal successful pregnancies have been reported after kidney donation. Two recent studies suggest a slightly increased risk of pre-eclampsia in women who have previously donated a kidney. Finally, the donor medical evaluation includes a study that details the anatomy of both kidneys and their vascular supply. Angiography was once the norm, but less invasive modalities such as CT, MR, or digital subtraction angiography have largely supplanted conventional angiograms. These imaging studies are critical to rule out any anatomic abnormality that may exclude a donor. Identification of multiple renal arteries may make vascular implantation more challenging or lead to the harvesting of the right kidney despite the increased technical challenge of right nephrectomy.

A careful psychosocial evaluation is necessary to ensure that the donor is free from psychiatric illness and appropriately motivated. A donor seeking secondary gain through either financial reimbursement or improvement in social status should be excluded. It is also critical that the donor be highly motivated and willing to undergo some degree of risk to benefit the recipient. Donors should be screened in the absence of family members or the recipient. They should not feel overt pressure or undue anxiety about proceeding, and must be allowed to stop the evaluation process at any time. Finally, donors must be counseled on the fact that recipient outcomes may not always be optimal. Under recent UNOS mandates, each transplant center is obliged to identify a living donor advocate whose purpose is to objectively assess and counsel potential donors based on the above principles.

Case

A 29-year-old woman was being evaluated as a potential donor to her 61-year-old father who has ESRD from diabetic nephropathy. Her older brother and two paternal uncles have type 2 diabetes mellitus. She has a history of gestational diabetes during an otherwise uncomplicated pregnancy 2 years earlier. An oral glucose tolerance test was performed. Fasting blood glucose was normal but postprandial glucose was elevated, indicating impaired glucose tolerance. In view of concerns that the she was at high risk for developing overt diabetes mellitus in the future, she was advised against kidney donation.

Living kidney donor outcomes

Donor mortality after surgery is extremely low, but not absent. Mortality rates of 3 in 10 000 and complication rates of around 1% have been reported.

Long-term outcomes have been examined in living donors via retrospective analyses. Life expectancy in living donors exceeds that of the general population, due in part to the selection of healthy candidates for kidney donation. A recent survey from the University of Minnesota contacted donors 20 years after donation. Of 773 donors, information was gathered on 464 (60%), and serum creatinine was measured in 74 (9.5%). Mean serum creatinine was 1.2 ± 0.04 mg/dL (range 0.7–2.5 mg/dL). Proteinuria was seen in approximately 10% of donors, and hypertension was common, occurring in more than a third of those surveyed. However, the great majority with proteinuria had either trace or 1+ protein on a dipstick, with no impairment in renal function, and hypertensive rates were no different from aged-matched rates from the general population.

Long-term data are lacking on kidney donors who may be at higher risk, including obese donors. Obesity has increased in the general population and a higher percentage of modern-era kidney donors are obese. Donor nephrectomy in obese donors appears to be safe, with no increased risk of major complications or hospital length of stay after laparoscopic nephrectomy in one series. Obese donors in this study also had no increased proteinuria or renal dysfunction in the first year after donation. There is concern, however, that obese donors may be at greater risk for renal functional deterioration over time. Obesity is an independent risk factor for the development of proteinuria in the general population, and after non-transplant nephrectomy in one series. In kidney donors, higher BMI correlates with risk of developing hypertension, and hypertension correlates with a risk of developing proteinuria after donation.

Controversies in living donor transplantation

Soliciting for organ donation On a small scale, organ solicitation has likely gone on for years through local venues such as newspapers and places of worship. More recently, widespread solicitation has been made available through media sources such as the internet. New websites have been set up by third parties allowing wait-listed patients to advertise for organs and to communicate online with potential donors. Some worry that an unfair allocation of organs may result from such widespread solicitation. Recipients may not always be forthright in self-portrayals, and certain descriptions may be used to stimulate an emotional response from prospective donors. Whether portrayals are accurate or not, responses to such solicitation may lead to the bypassing of recipients with longer waiting times or better immunologic matching. Although some recipients may capitalize on such solicitation, others may not have the resources or the charisma to gain similar benefit.

Arguments supporting widespread organ solicitation describe a potential increase in the overall donor pool by increasing awareness of the unmet need for organ donation. With the current shortage of available donors relative to numbers on the waiting list, desperate patients will naturally pursue such means. Organ solicitation is not illegal, provided that it does not involve financial compensation. However, in an attempt to maintain fair allocation, some have recommended that anyone responding to such solicitation be offered the chance to donate in a non-directed fashion.

Financial compensation for organs Another concern about widespread donor solicitation is the potential for financial compensation and trafficking of organs. As a direct emotional link is often absent in this type of organ exchange, financial recompense may be used to fill the void. In the USA, the National Organ Transplant Act (NOTA) of 1984 contains a specific title prohibiting the sale of organs, although it does allow for reimbursement for donor travel and lodging expenses. Some argue that this law should be amended, and that a regulated system of reimbursement for organ donation in the USA is needed to combat the long and growing waiting list for deceased donor kidneys. A regulated system could eliminate kidney brokers, and may be superior to the black market trade in kidneys that exists in other countries and even in the USA.

One suggestion would allow for government-sponsored life insurance and life-long medical coverage for living donors, reimbursement for lost wages and travel expenses, and a modest cash compensation for "inconvenience, anxiety, and/or pain." Government-based compensation would eliminate the potential injustice of kidneys being purchased exclusively by wealthy recipients. A recent public poll found that a majority was in favor of some compensation for expenses, including medical costs and insurance coverage for living donors. Lifelong health insurance has been considered an appropriate

award for living donors; however, many believe that any cash compensation would attract an indigent population willing to donate for the money alone. Donors desperate to repay debt may be clouded in their judgment and may not give true informed consent.

Systematic reimbursement for organ donation has been described in other nations, and some studies have suggested the process as an effective way to reduce or even eliminate patients on the waiting list. Impoverished young men have been the primary targets for donation under one such system and, despite reimbursement, compensation for kidney donation has not resolved debt. In addition, although altruistic donors are lauded as heroes in the USA, paid donors in other countries have been ostracized. The vast majority of Iranian paid donors attempt to hide their history of donation, and describe organ donation as a form of "prostitution."

Some argue that kidney sales would actually diminish the number of altruistic donations from family and friends. This has been observed in Iran, where living unrelated donation for reimbursement has dominated over altruistic living donation. Surveys from paid donors have revealed that the great majority would not donate again if given the chance, with percentages roughly inverse to those from surveys from altruistic donors in the west. Nevertheless, the debate over donor compensation continues in the USA, where concerns for donor welfare and exploitation have been weighed against the goal of improving survival by increasing the number of living donor transplants and diminishing recipient waiting time.

Surgical techniques and complications

Kidney graft procurement

Deceased donor kidney graft procurement

Multiorgan retrieval from heart-beating, brain-dead donors is the most common scenario for deceased organ donation. A median sternotomy and midline laparotomy (see Figure 7.6a) allow for isolation of the great vessels in the chest, at the diaphragm, and at the iliac bifurcation. This exposure also permits rapid cannulation of the distal aorta in case of donor instability. Further dissection defines anatomic variations, assesses organ quality, and prepares the field for cold flush with preservation solution after aortic clamping. Elements essential for good organ preservation at the time of aortic clamping include previous intravenous bolus of heparin, rapid arrest of the donor metabolism by decreasing donor body temperature (aortic cold flush and ice slush packing of the peritoneal cavity), and complete removal of intragraft blood by flushing with preservative solution.

Grafts are removed in a standard order: first the heart, then the lung(s), liver. and pancreas, and finally the kidneys. When used, the intestine is removed with the liver and pancreas before the kidneys. The kidneys can be removed en bloc, attached to the aorta and vena cava (see Figure 7.6b), and then separated on

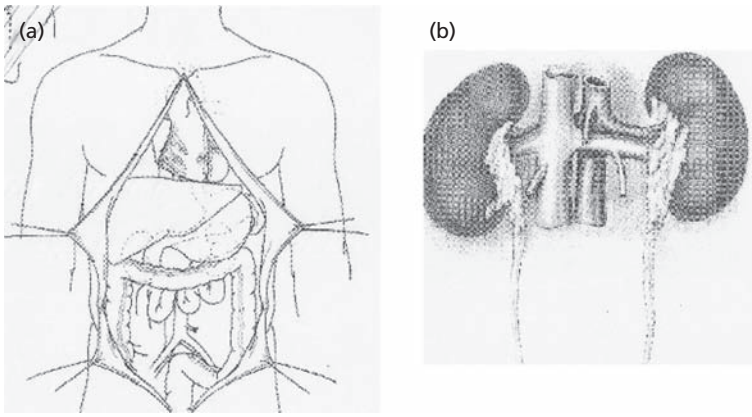

Figure 7.6 The multiorgan donor procurement operation. (a) Exposure is facilitated by a median sternotomy and midline laparotomy. (b) En bloc kidney removal. Note the piece of aorta and vena cava with attached renal vessels. The ureters are removed, retaining as much length as possible.

the back table. Alternatively, they can be separated *in situ* and then removed. Perinephric fat should be cleared to allow inspection for neoplastic lesions, and superficial cysts or masses should be opened and biopsied. Renal biopsy may be performed to evaluate histology in grafts deemed to be marginal on the basis of clinical parameters.

Organ retrieval from non-heart-beating donors follows the declaration of death using standard criteria after withdrawal of life support. The latter should be performed either in the operating room or in close proximity to the operating room in order to decrease warm ischemia time. Rapid organ cooling is accomplished by prompt laparotomy, placement of an aortic cannula for cold flushing of the organs, and installation of ice slush in the peritoneal cavity.

Live donor procurement

The goal in performing live donor nephrectomy, regardless of technique, is to safely procure the kidney while exposing the patient to the lowest chance for morbidity. Before renal artery occlusion, systemic anticoagulation is achieved by the administration of heparin. Generous administration of intravenous fluids during the procedure assures good diuresis. After removal, the kidney is immediately flushed with cold preservation solution and packed in ice until preimplantation preparation is performed.

Open and mini-incision nephrectomy Traditionally, open nephrectomy has been performed through a large flank incision (16–22 cm) that sacrifices the tip of the twelfth rib, and extends to the border of the rectus muscle. Smaller, less painful incisions are now preferred and often result in postoperative recovery times similar to those following laparoscopic nephrectomy. The kidney is dissected out of Gerota's fascia and the renal artery and vein are divided after transfixion sutures or staples are employed proximally. The site of ureter transaction is chosen to maximize length.

Laparoscopic nephrectomy Laparoscopic donor nephrectomy, first reported in 1995, was initially reserved for left kidneys with standard anatomy, and was associated with an increased risk for delayed graft function compared with open donors. More recently, successful recovery of right or left kidneys has been performed and transplant outcomes are comparable to kidneys procured using the open technique. Previous abdominal surgery may preclude the laparoscopic technique.

Appropriate positioning of the patient is essential. Pneumoperitoneum is accomplished through the placement of a 12-mm trocar using the open technique. Two other 5-mm trocars are placed under direct vision. This approach requires the use of both a 10-mm and a 5-mm laparoscopic camera at different times during the dissection. Inflation pressures are kept around 10–12 mmHg, and intravenous fluids are administered generously, to minimize renal dysfunction. The hand-assisted approach starts with a midline periumbilical incision (6–8 cm in length) to place the hand port and to establish pneumoperitoneum. Graft dissection is performed as described for the open technique; once it is completed a brief period of deflation is recommended to improve graft blood flow and to establish a brisk diuresis. The preferred technique is to gain control of the renal artery and vein by the use of staplers. Use of a single-three row stapler followed by section with scissors affords greater blood vessel length. The kidney is removed through the hand port. With the non-hand-assisted laparoscopic procedure, organ dissection is performed through the three ports with delay of the larger incision (midline or lower quadrant transverse) until the kidney is ready for removal. Similar periods of hospital recovery and return to normal activities have been observed with the laparoscopic approach when compared with the mini-incision approach.

Key points 7.4 Important facts regarding laparoscopic donor nephrectomy (compared with traditional open nephrectomy)

Higher cost, mostly related to longer operative time

Shorter length of hospital stay

Shorter period of rehabilitation

Higher rate of delayed graft function in the recipients, but no discernible effect on long-term outcomes

Organ preservation

Although kidneys may be preserved for up to 72 h, particularly when preserved by pulsatile perfusion,

most surgeons perform kidney transplantation in less than 24 h to minimize the risk of delayed graft function. University of Wisconsin solution (UW, Viaspan) or HTK solution (Custodiol) may be used. Although they differ significantly in their components, both are high in oncotic pressure and achieve similar periods of successful cold preservation. Preservation of kidney graft function for >24 h is best achieved by the use of a pulsatile preservation pump. This technique is associated with a decrease in the incidence of graft dysfunction and it may be used as a tool for assessing graft quality by observing the trends in perfusion pressure and perfusate flow and vascular resistance.

Kidney graft implantation

Adult transplantation

The extraperitoneal approach, using the iliac vessels for blood supply, has been the mainstay for single kidney transplantation since its inception (Figure 7.7). Arterial inflow to the graft is usually achieved by end-to-side anastomosis of the renal artery to the host common or external iliac artery. Alternatively, an end-to-end anastomosis to the hypogastric artery can be used. The recipient's saphenous vein can be used as a conduit to extend the renal artery if it is too short. Rarely, excision and replacement of the iliac artery with a prosthetic conduit can provide a location for anastomosis in patients with severe iliac artery atherosclerosis. Use of the proximal common iliac vessels or even the distal aorta and vena cava is occasionally necessary, especially in patients undergoing re-transplantation, or in patients with implantation of dual kidneys. Venous reconstruction is usually achieved by an end-to-side anastomosis between the renal vein and the external iliac vein. Venous length is rarely an issue when the left kidney is used. When necessary, the right renal vein can be lengthened by creating a venous conduit from the attached vena cava or by attachment of a hand-sewn segment of donor iliac vein.

The technique for ureteral implantation depends on the anatomy of the patient and the preferences of the surgeon. The anterior (Gregoir–Lich) ureteroneocystostomy is straightforward and therefore, more commonly used than the posterior (Ledbetter) approach. Use of a double J stents is a matter of surgical preference. In cases of a short ureter or small bladder, the use of the recipient ureter either as a pyeloureterostomy or ureter-to-ureter anastomosis can be used. Uncommonly, bladder augmentation, construction of an ileo-conduit, or a cutaneous ureterostomy may be necessary.

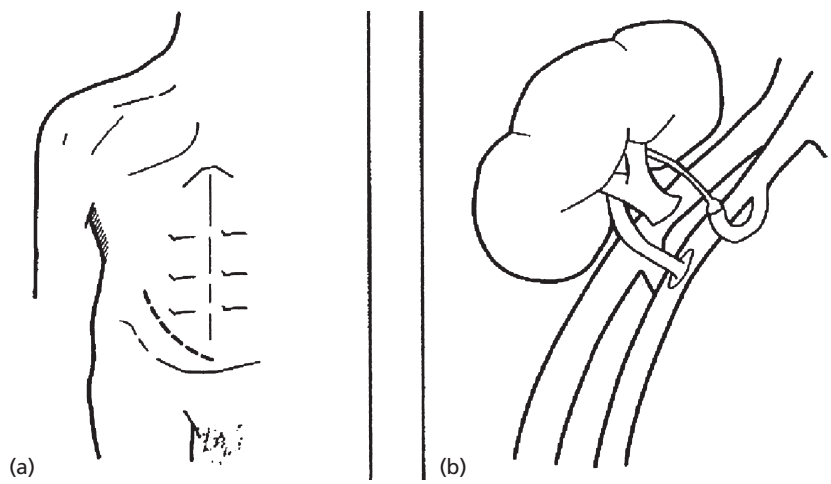

Figure 7.7 The recipient operation for kidney transplantation. (a) A lower abdominal incision is performed in an extraperitoneal approach. (b) The final anatomy of a revascularized renal allograft. Note the use of the internal iliac artery as a separate inflow for the polar renal artery.

Implantation of both kidneys from a deceased donor into a single recipient is an alternative strategy when donors exhibit marginal kidney function or histology. Transplantation of both kidneys can be performed on one side of the pelvis, if adequate recipient arterial supply exists. This approach avoids two incisions and leaves the contralateral iliac vessels intact, should future re-transplantation be needed.

Pediatric kidney transplantation

Transplantation using pediatric donors Kidneys from infant donors (<20 kg) have small renal vasculature that increases the risk of technical failure. In addition, transplantation of one small kidney may not provide adequate nephron mass for a large adult recipient. Such kidneys may be kept en bloc and transplanted into a single recipient, using the donor aorta and vena cava for the implantation. Some surgeons advocate suture pexy of the grafts in a position that preserves vascular inflow and outflow. The use of absorbable mesh for this purpose has been reported.

Transplantation into pediatric recipients Use of adult kidney grafts for pediatric recipients is standard procedure. In very small infants the graft is implanted intraperitoneally on the right side through a midline incision, using the recipient aorta and vena cava for revascularization. In children weighing >10 kg, the retroperitoneal approach can be used. Again, preference is for the right side. Care should be exercised at the time of reperfusion because a large kidney can take up to 30% of the total blood volume of a child. Graft hypoperfusion and subsequent risk of delayed graft function may be decreased by keeping the central venous pressure at ≥15 mmHg, particularly at the time of reperfusion. Bladder reconstruction before or at the time of transplantation may be necessary in children with very small bladders.

Kidney re-transplantation

A second transplantation is usually accomplished by placement of the kidney on the contralateral, unused side. Third and further re-transplants require both dissection in a reoperative field and removal of the previously failed graft in order to accommodate the new kidney. Immunosuppression, prior infections, fluid collections, and the occurrence of other surgical complications make the degree of scarring unpredictable. In rare occasions, an intraperitoneal approach is required with placement of the vascular reconstruction at the aorta and vena cava level.

Kidney transplantation in combination or after other abdominal organs

Simultaneous deceased donor kidney and pancreas transplantation is routine, and is usually accomplished through a midline, intraperitoneal approach. Most surgeons place the kidney graft on the left side and the pancreas graft on the right side of the pelvis using the iliac vessels as previously described. Portal venous drainage of the pancreas moves the graft to the mid abdomen, away from the pelvis, affording greater options for kidney placement (Figure 7.8). Compared with systemic venous drainage into the iliac venous system, portal drainage mimics normal physiologic drainage of the pancreas into the portal system. Although there has been some debate regarding the immune and metabolic advantages of systemic versus portal venous drainage, there is no clear consensus about clinically meaningful differences, and the approach has been left to surgeon discretion. With the portal drainage approach, the use of an additional

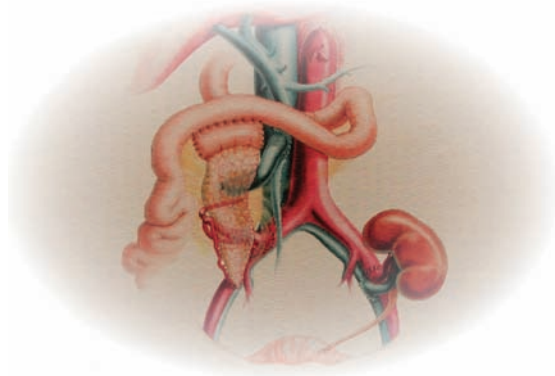

Figure 7.8 Simultaneous kidney and pancreas transplantation. Typically, the kidney graft is implanted on the left side of the pelvis. The pancreas graft is usually implanted on the right side using the iliac vessels or, as in this case, using the iliac artery for the arterial reconstruction and the portal vein for the venous implantation. Note the conduit to the portal vein. The exocrine pancreas is enterically drained using an anastomosis of the donor duodenal cuff with the recipient's small intestine.

conduit to the portal vein is usually necessary (Figure 7.8). Currently, drainage of the exocrine pancreas is accomplished most often by anastomosis of the donor duodenal stump to the small intestine of the recipient. However, some surgeons still prefer the older technique in which the duodenal stump is anastomosed to the recipient bladder. Kidney transplantation together with liver transplantation is usually performed through a separate standard iliac fossa approach.

Surgical complications

Fluid collections – vascular

After kidney transplantation, fluid collections may form due to bleeding or leakage of lymph. Significant postoperative hemorrhage should be addressed by re-exploration. Large, stable hematomas may cause pain, become infected, or cause compression symptoms, and should be evacuated. Although mycotic aneurysm formation is rare after renal transplantation, the condition will lead to hemorrhage and carries a high mortality rate (>50%) if not repaired expeditiously. Complete excision of the arterial anastomosis and vein patch repair of the iliac artery are mandatory. When treating severe vascular infections, the limb and life of the patient are always the priority. Infrequently, severe bleeding may occur as a result of parenchymal fracture due to acute rejection. If difficult to control it may require graft removal.

The rich lymphatic network surrounding the iliac vessels is routinely divided at the time of transplantation. Suture ligation of these channels is routine, but leakage of lymph fluid occurs in 5–15% of patients. Although incidental asymptomatic collections do not require intervention, lymphoceles that partially occlude the ureter or renal vein, leading to renal dysfunction or ipsilateral leg swelling (by compressing the iliac vein), require drainage. Percutaneous drainage can be used to confirm the presence of lymphocytes, establish the association with infection, and drain the collection. In up to 30% of cases a more definitive approach is required. This is usually achieved by marsupialization of the lymphocele into the peritoneal cavity by a laparoscopic or open approach.

Fluid collections – urologic

Early urine leak occurs in 1–3% of cases. With small leaks, prolonged bladder catheterization, percutaneous drainage of the urinoma, and ureter stenting may lead to spontaneous healing. When repair is necessary, repeat implantation into the bladder is the preferred technique, but a ureter-to-ureter reconstruction utilizing the distal recipient ureter, or a bladder flap, may be required. Ureter implantation into a very small, spastic bladder may increase the risk of a high-output leak and surgical repair is required. Bladder augmentation in addition to prolonged drainage (J stent and nephrostomy tube) will provide a low-pressure system that will enhance healing.

Key points 7.5 Most common causes of perinephric fluid collections after kidney transplantation

Seromas

Hematomas

Lymphoceles

Urinomas

Case

A 49-year-old man received a deceased donor kidney transplant after being on hemodialysis for 12 years. The bladder was atrophic but a standard ureteral anastomosis was performed. A Jackson–Pratt drain was placed adjacent to the transplanted kidney. The allograft functioned immediately and serum creatinine concentration fell from 8.2 mg/dL to 2.3 mg/dL by postoperative day 3. The patient's Foley catheter was removed 4 days after transplantation. During the next 12 h, there was an abrupt increase in output of the drain and laboratory analysis of the drainage fluid indicated that the concentration of creatinine was threefold higher than a simultaneous serum creatinine concentration, confirming a urine leak. The Foley catheter was replaced with prompt reduction in output from the drain. The patient was discharged; 10 days later the Foley catheter was removed. Drainage from the Jackson–Pratt drain remained low and the drain was removed 2 days later with no further evidence of a urine leak.

Decreased diuresis – vascular

Early arterial thrombosis occurs in 1–2% of patients; it may be caused by technical errors, hypercoagulable

states, or poor inflow from a stenotic/thrombosed native vessel used for reconstruction. Immediate recognition is paramount for successful salvage of the graft. Sudden development of anuria is highly suggestive of arterial thrombosis and must be investigated immediately. As delayed graft function or acute cellular rejection can have a similar presentation, an ultrasound evaluation is readily indicated. If ultrasonography is not available, return to the operating room should be considered because arterial thrombosis requires urgent thrombectomy, infusion of thrombolytic agents, and correction of any technical error. In most cases, renal function will not be restored, and transplant nephrectomy will be necessary. Isolated renal vein thrombosis may present initially with hematuria before anuria ensues. Similar to arterial thrombosis, it is rarely reversible and will often mandate allograft nephrectomy.

Decreased diuresis – urologic

Decreased urinary output may also be caused by external compression of the ureter, urinary leak, or obstruction of the urinary track at any level. If the urinary catheter is in place, it should be flushed to clear it of any obstruction. If the urinary catheter has been removed an "in-and-out" bladder catheterization may prove to be useful. High residuals may be due to bladder dysfunction or prostatic hypertrophy. Urinary stents, if used, are removed 2–4 weeks after transplantation. Late ureter stenosis may be due to ischemia, cellular or humoral rejection, or scarring from prolonged stenting, or as a consequence of a technical error. This is manifested by renal dysfunction associated with hydronephrosis. Anatomic definition of the stenotic segment is accomplished by percutaneous antegrade contrast study or by endoscopic ureterography. Focal stenoses may be amenable to transluminal dilation and stenting although long stenotic segments usually require surgical reconstruction. The latter is usually corrected by native ureter-to-graft pyelostomy.

Infectious surgical complications

Surgical site infections after kidney transplantation are not common. However, when they occur, recognition may be delayed because the inflammatory manifestations of the infection may be blunted by immunosuppressive therapy. The use of sirolimus as an immunosuppressant may compromise wound healing and promote infection due to its antiproliferative and antiangiogenic properties. Wound infections above the fascia are treated by opening of the wound, administering systemic antibiotics, and local wound care. Deep space infection must be adequately drained and aggressively controlled to avoid breakdown of any of the vascular anastomoses. Usually this requires surgical debridement and drainage.

Transplant nephrectomy

Kidney graft removal early after transplantation is rarely required. Uncontrolled accelerated/acute rejection, unremitting graft hemorrhage, arterial/venous thrombosis, and mycotic aneurysm formation are the most common indications. Late transplant nephrectomy, after the patient has returned to dialysis, is performed most often because of severe pain, persistent fever, chronic infection, hematuria, proteinuria, and/or difficult management of hypertension. Nonfunctioning renal grafts may also be removed to accommodate a new transplant or to prevent the formation of antibodies in patients who stop immunosuppression. The development of a neoplasm in the graft is a rare reason for graft removal.

Late transplant nephrectomy is best accomplished through a limited incision directly over the allograft. The renal capsule is entered and the graft is shelled out to the hilum. Significant hemorrhage is occasionally encountered, and expeditious cross-clamping at the hilum allows for rapid excision of the kidney. Vessels are individually sutured when possible. Intracapsular dissection avoids injury to the iliac vessels and other recipient structures.

Immunosuppression

Antibodies used for induction therapy

The incidence of acute rejection is greatest in the first few months after transplantation. Thus, the intensity of immunosuppression delivered is typically highest during the perioperative and early postoperative periods. An immunosuppressive strategy known as "induction therapy" is employed when the early post-transplant protocol includes antibodies against specific or multiple antigenic targets. The benefits of using such induction antibodies to reduce the risk of

early acute rejection must be weighed against the cost of these agents and the potential risk of over-immunosuppression, manifested by infection or malignancy. Induction antibodies can generally be classified as either lymphocyte depleting or non-depleting agents. Within each category, there are both monoclonal agents directed against specific antigenic targets of lymphocytes and polyclonal agents containing a pool of antibodies directed against multiple antigens. Monoclonal antibodies are created with murine hybridoma techniques and are sometimes genetically engineered to create chimeric or humanized modifications. Polyclonal agents are generally produced by harvesting serum from animals previously inoculated with human thymocytes or lymphocytes. The use of induction antibody therapy varies around the world but has become increasingly popular in the USA over the past 15 years, such that more than 70% of patients currently receive one of the agents described below.

Lymphocyte-depleting antibodies

Over the years, a number of polyclonal anti-lymphocyte antibodies have been generated using a variety of animals. The only polyclonal agents currently used in the USA are rabbit antithymocyte globulin (rabbit ATG; Thymoglobulin) and ATGAM, an agent produced in horses. As Thymoglobulin proved to be superior to ATGAM for the treatment of acute rejection in a randomized trial, it has become the predominant polyclonal agent used in the USA. However, it is important to note that rabbit ATG is approved by the Food and Drug Administration (FDA) only for treatment of rejection and is technically used off-label as an induction therapy. When compared with no induction antibody therapy, this and other polyclonal agents have been shown to reduce the incidence of acute rejection and to prolong graft survival. Moreover, a randomized trial suggested that rabbit ATG is superior to basiliximab, a non-depleting antibody, in preventing acute rejection in patients deemed to be at high risk for immune graft injury. Lymphocytes are cleared from the circulation during active administration of the drug, which is usually slowly infused daily for 3–10 days post-transplantation. Thrombocytopenia and leukopenia are common side effects, often resulting in the need for dose modification. Fever, chills, and myalgias are commonly observed with the initial infusion, but can be mollified by concomitant administration of corticosteroids. Anaphylactic reactions occur rarely.

Alemtuzumab (Campath-1H) is an anti-CD52, humanized, monoclonal antibody that binds to all T and B lymphocytes, as well as most macrophages, monocytes, and natural killer cells. It was approved in the 1980s as an agent for the treatment of B-cell chronic lymphocytic leukemia and is currently used off-label in transplantation. Alemtuzumab produces significant leukopenia, probably by antibody-dependent lysis of the lymphocytes that leads to depletion of T and B cells in the peripheral circulation for >12 months. The drug is easily administered peripherally, given in a single (30 mg) or double dose in the perioperative period. Some centers have reported a relatively high incidence of humoral (antibody-mediated) acute rejection in patients treated with alemtuzumab, and repeated courses of therapy have been associated with the emergence of autoantibodies and autoimmune disorders.

Another depleting monoclonal antibody, OKT3 (Orthoclone Muromonab-CD3), targets the CD3 complex of T cells causing endocytosis of its constituent peptides and profound impairment of both T-cell activation and proliferation. Although this drug proved to be useful as an induction agent in the 1980s, it is rarely employed for induction in the USA in the modern era, mostly because of its cost and toxicities.

Non-depleting antibodies

The major agents in this category are the monoclonal antibodies directed against the α chain of the interleukin-2 (IL-2) receptor (also known as CD25). Binding to this receptor blocks the proliferative signals normally mediated by IL-2 without causing profound depletion of lymphocyte counts. Basiliximab (Simulect) is a chimeric anti-CD25 antibody (30% murine, 70% human). Daclizumab (Zenepax) is a humanized version (10% murine, 90% human). Together, the anti-CD25 antibodies are currently the second most frequently prescribed induction antibodies in the USA. However, Zenepax is no longer be produced. When compared with placebo, treatment with either of these antibodies has been associated with lower rates of early acute rejection. Basiliximab is typically administered intraoperatively and again on the fourth postoperative day.

Maintenance immunosuppression

Herein we describe the mechanisms of action and dosing strategies for maintenance immunosuppressants commonly prescribed to kidney and pancreas transplant recipients. The pharmacokinetics and side effects of these agents are discussed in greater detail in Chapter 2.

Corticosteroids

Corticosteroids exert two principal effects on the immune system. First, within 4–8 hours of administration, they alter the distribution of lymphocytes, causing their sequestration in the reticuloendothelial system. Second, corticosteroids inhibit the proliferation and function of lymphocytes by blocking the expression of various lymphokines and cytokines. Glucocorticoids easily diffuse into cells and bind to cytoplasmic receptors that exist in association with a heat shock protein. Corticosteroids also inhibit the action of transcription factors such as activating protein-1 (AP-1) and nuclear factor-κB (NF-κB). In the case of NF-κB, activated glucocorticoid receptors may bind to activated NF-κB and prevent it from binding to κB sites on proinflammatory genes. The major consequence of these intracellular effects of corticosteroids is an inhibition of the production of IL-1 and IL-6 by antigen-presenting cells such as macrophages and monocytes. As IL-1 is a primary costimulus for helper T-cell activation and IL-6 is a major inducer of B-cell activation, corticosteroid administration has the potential to inhibit both the cellular and humoral arms of the immune response.

Corticosteroids are most often prescribed according to fixed and empiric dose-tapering schedules. In the modern era, many centers use doses of prednisone as low as 5 mg daily beyond the several months after transplantation. These agents have been employed to prevent and treat acute allograft rejection for more than 40 years. However, the well-known side effects of steroids have led to steroid-sparing regimens and, although somewhat controversial, complete withdrawal of these agents in low-risk patients has become the standard of practice in many transplant centers.

Calcineurin inhibitors

Calcineurin inhibitors (CNIs) have formed the backbone of solid-organ transplant immunosuppressive regimens since the introduction of cyclosporine in the early 1980s. Cyclosporine is a small cyclic polypeptide of fungal origin. The other available CNI is tacrolimus, a macrolide antibiotic compound that became available in the USA in the mid-1990s. Tacrolimus has emerged as the most commonly used CNI in the USA. As described below, cyclosporine and tacrolimus have different side effects. Whether the two agents are comparably efficacious in preventing rejection or prolonging graft survival remains a subject of great debate. Calcineurin is an intracellular phosphatase that is found in T cells and functions to dephosphorylate certain nuclear regulatory proteins, allowing them to pass through the nuclear membrane. These regulatory proteins then activate the transcription of several cytokines (IL-2, IL-4, IFN-α and tumor necrosis factor α [TNF-α]) that promote T-cell activation. Cyclosporine binds to the cytoplasmic receptor, cyclophilin, whereas tacrolimus binds to the cytoplasmic receptor, FK-binding protein (FKBP) (Figure 7.9). Both the cyclosporine–cyclophilin and tacrolimus–FKBP compounds bind to calcineurin, preventing its normal function and thereby blocking T-cell activation.

The original oral formulation of cyclosporine was Sandimmune, which exhibits relatively poor bioavailability with great within- and between-patient pharmacokinetic variability. A newer microemulsion formulation, Neoral, was later developed to improve absorption and minimize variation in bioavailability. Several generic forms of cyclosporine are now available. Tacrolimus is currently available as Prograf, but generic forms of tacrolimus are now available. As a result of variations in absorption and genetic differences in the expression and function of the cytochrome P450 3A4 (CYP3A4) system responsible for metabolism of CNIs (see below), drug level monitoring is still considered necessary for optimal management of all the available CNIs. Due to subtle variations in pharmacokinetics between different formulations, it is best to avoid switching from brand name compounds to generics. However, if conversion is necessary, close monitoring of drug levels and renal function is suggested in the short term. Both CNIs are excreted in the bile with minimal renal excretion, so there is no need for dose adjustment in the presence of renal impairment. Cyclosporine can be administered intravenously, generally using 30% of the oral dose as a constant infusion over 24 h. Intravenous

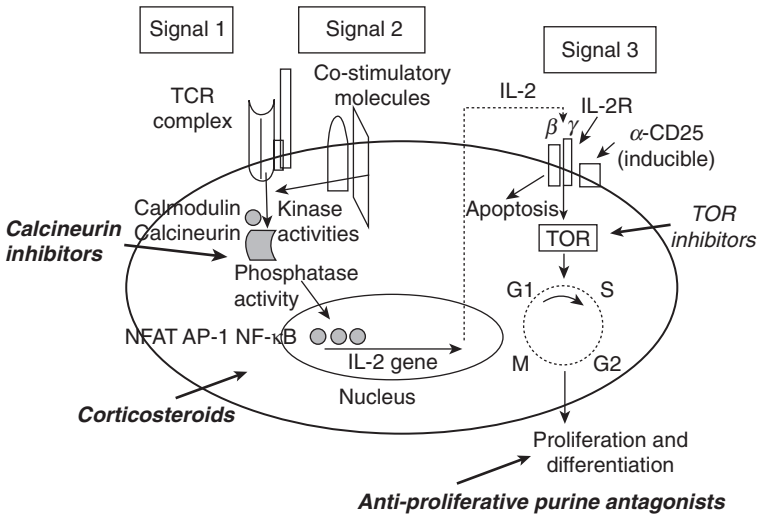

Figure 7.9 Schematic representation of intracellular signaling events associated with T-cell activation, organized according to three sets of signals: (1) antigen recognition, (2) co-stimulation, and (3) cell cycle progression. The sites of action of immunosuppressive drug classes are shown in italics. AP, activator protein; CTLA4-Ig, cytotoxic T-lymphocyte antigen 4-immunoglobulin; IL, interleukin; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor-κB; TCR, T-cell receptor; TOR, target of rapamycin.

tacrolimus is extremely toxic and should be used with great caution.

Typical starting dose of cyclosporine is 8–12 mg/kg per day with maintenance dose of 3–5 mg/kg per day in twice daily doses. For tacrolimus, the typical starting dose is 0.15–0.3 mg/kg per day in twice daily doses. There is a reasonably good correlation between trough blood levels of tacrolimus and overall drug exposure. This correlation is less reliable with cyclosporine. Nevertheless, due to convenience and cost, trough drug levels are most commonly used in monitoring all CNIs. There are two general methods for measuring whole blood concentration of CNIs. High-performance liquid chromatography (HPLC) is the most specific method, but is also more expensive and labor intensive. Whole blood immunoassays are cheaper and more readily available for use in automated analyzers. Lower starting doses of CNIs and lower trough target levels are used when these agents are prescribed with a target for rapamycin (TOR) inhibitor, because the combination of agents increases the risk of nephrotoxicity.

CNIs are metabolized by CPY3A4 enzyme system located in the liver and gastrointestinal tract. As many drugs can up- or downregulate the cytochrome P450 enzyme system, vigilance is needed to avoid potential drug interactions between CNIs and commonly prescribed medications. Drugs that reliably decrease CNI concentration by inducing the cytochrome P450 enzyme system include rifampin and anticonvulsants such as barbiturates and phenytoin. If these drugs are required, the dose of CNI often needs to be increased to maintain therapeutic levels. Other drugs that decrease CNI levels less predictably include nafcillin, trimethoprim, imipenem, cephalosporins, and ciprofloxacin. St John's wort, a herbal mood enhancer, can also induce the cytochrome P450 enzyme system. Whenever any of these medications are used, CNI trough levels should be monitored closely. Lastly, corticosteroids are also inducers of the cytochrome P450 enzyme system. When steroids are tapered, CNI levels should be monitored closely to determine the need for dose reduction.

Drugs that increase CNI concentration by inhibiting cytochrome P450 activity include non-dihydropyridine calcium channel blockers, such as diltiazem and verapamil, the azole antifungal agents, such as ketoconazole, itraconazole, voriconazole, and fluconazole, and erythromycin and its analogs (except azithromycin). Drugs such as diltiazem and ketoconazole are occasionally prescribed together with CNIs in an effort to lower the CNI dose and reduce cost. Other medications that inhibit cytochrome P450 activity less predictably include isoniazide, oral contraceptives, amiodarone, and carvediol. With the advent of HAART, some centers are now providing organ transplants to HIV-positive patients. Therefore, it is worth noting that protease inhibitors

– particularly ritonavir – are potent inhibitors of the cytochrome P450 enzyme. Lastly, a special dietary concern for all patients on a CNI is grapefruit juice which can result in higher drug levels from increased absorption. Non-cytochrome P450 enzyme-related drug interactions can occur with cholestyramine and GoLYTELY which may interfere with absorption of CNIs. Concomitant use of CNIs and HMG-CoA (hydroxymethylglutaryl coenzyme A) reductase inhibitors alter the pharmacokinetics of the "statin," resulting in a longer half-life and a greater risk for rhabdomyolysis.

Key points 7.6 Drugs that exert predictable interactions with immunosuppressants metabolized by the cytochrome P450 3A4 enzyme system (cyclosporine, tacrolimus, sirolimus)

Drugs that increase levels:
- Erythromycin and its congeners (except azithromycin)
- Azole antifungals
- Diltiazem, verapamil
- Protease inhibitors

Drugs that decrease levels
- Phenytoin
- Barbiturates
- Rifampin

Antiproliferative agents

There are three available agents or classes of antiproliferative immunosuppressant medications: azathioprine, mycophenolic acid derivatives, and the TOR inhibitors.

Azathioprine The oldest of the antiproliferative agents is azathioprine, first introduced in the 1960s. Azathioprine is a metabolite of 6-mercaptopurine which is processed intracellularly into purine analogs that inhibit purine synthesis from both the direct and the salvage pathways. In so doing, the drug suppresses gene replication and cell proliferation via inhibition of RNA and DNA synthesis. Although it is more selective for T lymphocytes, it can also suppress promyelocytes in the bone marrow, resulting in leukopenia, thrombocytopenia, and/or anemia.

Azathioprine is available in both oral and intravenous formulations as Imuran or in generic formulation. However, only half of the orally administered azathioprine is absorbed; therefore, the equivalent intravenous dose is half that of the oral dose. The starting oral dose of azathioprine is 1–2 mg/kg administered once daily. There is no need for blood level monitoring because its effectiveness is not blood-level dependent. It is also not excreted by the kidney, so there is no need for dose reduction during episodes of acute renal insufficiency. Dose adjustments are based on toxicity. Azathioprine is metabolized by xanthine oxidase; treatment with allopurinol inhibits xanthine oxidase. Therefore, when combined with azathioprine, there can be prolonged azathioprine activity resulting in significant pancytopenia. To prevent this, the azathioprine dose should be reduced by 75–80% and blood counts should be followed closely.

Mycophenolic acid derivatives MMF (CellCept) is a prodrug of mycophenolic acid (MPA). It was approved for use in 1995 and has essentially replaced azathioprine as the antiproliferative agent of choice, given its relatively few side effects and superior effects in preventing acute rejection. An enteric-coated form of mycophenolate sodium (ECMPS or Myfortic) became available in 2004. MPA is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is a critical rate-limiting enzyme in new purine synthesis. MMF achieves its antiproliferative effect by blocking nucleic acid synthesis. However, its effect is relatively selective for lymphocytes, because not only do lymphocytes have a more susceptible isoform of IMPDH, but they also rely more heavily on new purine synthesis whereas other cell types have an alternative salvage pathway.

MMF is available as capsules in either 250 mg or 500 mg dosages. The standard dose when used together with cyclosporine is 1 g administered twice daily; African–American individuals may need a higher dose of 1.5 g twice daily to achieve adequate suppression when used with cyclosporine. ECMPS is available in 180 mg and 360 mg capsules and the standard dose is 720 mg administered twice daily, which is equivalent to 1 g twice daily of MMF. Only MMF is available as an intravenous formulation and intravenous dosing that is identical to the oral dose. MMF is hydrolyzed to MPA in the liver, producing an initial peak drug concentration in 1–2 h followed by a

second peak in 5–6 h through enterohepatic cycling. It is believed that the gastrointestinal side effects of MMF stem from this cycling. Therefore, not surprisingly, ECMPS has been shown to have a similar lower gastrointestinal side-effect profile as MMF. To minimize the side effects, the daily dose can be split into three to four doses a day. Similar to azathioprine, therapeutic drug monitoring is not mandatory, although some centers measure trough levels of mycophenolic acid in an effort to individualize dosing.

There are few significant drug interactions with MMF. However, concomitant administration of other antiproliferative agents, such as azathioprine or TOR inhibitors, should be done with caution to avoid excessive myelosuppression. Drugs that can decrease intestinal absorption of MMF include antacids, cholestyramine, and oral ferrous sulfate. Cyclosporine can also decrease MMF concentrations by interfering with the enterohepatic cycling, an effect not seen with tacrolimus. This explains the higher dose of MMF sometimes needed when used together with cyclosporine compared with tacrolimus.

TOR inhibitors The newest antiproliferative agents are the TOR inhibitors. Target of rapamycin is an important regulatory kinase involved in cell cycle progression. There are two medications in this class. Sirolimus (Rapamune), also known as rapamycin, is a macrolide antibiotic compound structurally related to tacrolimus. Everolimus (Certican or Zortress) is a chemical variant of sirolimus and was approved by the FDA in 2010. Initially, there was great enthusiasm for using sirolimus as an alternative to CNIs. However, as the side-effect profile of TOR inhibitors emerged, enthusiasm for new uses of this TOR inhibitor have waned. As sirolimus is structurally similar to tacrolimus, it also binds the FKBP. However, the sirolimus–FKBP ligand does not block calcineurin, but instead blocks the effects of TOR (see Figure 7.9). As mentioned, TOR is a key regulatory kinase in cell division, hence its blockade leads to the inhibition of cellular proliferation. The TOR pathway also has an angiogenic effect, so, unlike other antiproliferative agents, sirolimus has unique antiangiogenic properties.

Sirolimus was initially formulated as an oral solution but it has now been replaced by the more convenient oral form that comes in 1 mg and 5 mg capsules. Its usual dose is 2–5 mg daily. Sometimes an initial loading dose (up to 15 mg daily for 3 days) is used to more rapidly reach a steady state. Similar to the CNIs, sirolimus is metabolized by the cytochrome P450 enzyme and has the same variations in between- and within-patient bioavailability. Therefore, blood level monitoring is required. The target level ranges from 10 ng/mL to 20 ng/mL, with a lower target of 8–12 ng/mL in stable patients. As sirolimus has a long half-life, averaging 62 h, drug levels do not need to be checked until several days after a dose adjustment.

Given that both CNIs and sirolimus are metabolized by cytochrome P450, there is a potential interaction when these two classes of medication are given together. It has been shown that, when sirolimus is given with cyclosporine, there can be a significant increase in sirolimus levels. However, this effect can be avoided if the sirolimus is given 4 h after cyclosporine. A similar interaction has not been demonstrated with tacrolimus. And like CNIs, sirolimus has similar drug interactions with increased drug levels from concomitant use of non-dihydropyridine calcium channel blockers, azole antifungal agents, erythromycin, and grapefruit juice, whereas decreased drug levels are observed with anticonvulsants such as phenytoin and carbamazepine.

Maintenance drug combinations

It should be obvious that the increased number of available maintenance immunosuppressants for transplant recipients has greatly increased the number of potential drug combinations that can be used to prevent allograft rejection. The most popular combination of drugs currently used in the USA consists of tacrolimus and a mycophenolic acid derivative with or without prednisone. Cyclosporine-based regimens have declined in popularity. As mentioned above, donor use of sirolimus is no longer common, although some centers convert patients from a CNI to sirolimus several months after transplantation. Azathioprine is most often reserved for patients who are intolerant of the side effects or costs of the other antiproliferative agents.

Case

A 26-year-old man with diabetic nephropathy received a deceased donor kidney transplant 9 months earlier and has been maintained on tacrolimus, enteric-coated mycophenolic acid, and prednisone. Between 4 and 9 months

after transplantation, serum creatinine concentration rose from1.3 mg/dL to 2.1 mg/dL despite trough tacrolimus levels deemed to be in a therapeutic range. A 24-hour urine collection contained 320 mg protein. A biopsy was performed and showed patchy interstitial fibrosis and mild arteriolar hyalinosis. Based on the concern for chronic nephrotoxicity from his calcineurin inhibitor, he was converted from tacrolimus to sirolimus. Six months later, serum creatinine concentration is slightly improved (1.9 mg/dL) but repeat 24-hour urine protein has increased to 540 mg/day.

Treatment of acute rejection

Most centers prefer to obtain a percutaneous renal transplant biopsy to facilitate treatment decisions in patients with suspected rejection. Cases of acute cellular rejection that are deemed to be clinically or histologically mild are often treated initially with large "pulse" doses of corticosteroids (typically methylprednisolone in doses ranging from 250 mg to 1000 mg intravenously daily for 3–5 days, or oral prednisone 200–500 mg per day for 3–5 days). Patients who do not respond to pulse steroid therapy, and those with clinically or histologically severe rejection, are treated with anti-lymphocyte preparations including rabbit anti-thymocyte globulin or OKT3. The use of OKT3 for treatment of acute rejection has decreased greatly in the past decade, largely owing to its cost and significant first-dose side effects, including a "cytokine storm" syndrome consisting of fever, headache, flu-like symptoms, and, more rarely, acute respiratory failure. Traditional anti-lymphocyte antibodies are often employed to treat antibody-mediated rejection, based on the concern for simultaneous cellular rejection. However, treatment with plasmapheresis, anti-CD20 antibodies, and/or IVIG is now commonly used as either primary or adjunctive therapy for humoral rejection.

Diagnosis of allograft rejection

Although the cumulative incidence of early acute rejection has decreased dramatically in recent years, acute rejection continues to exert a detrimental impact on allograft survival. An episode of rejection – particularly if severe, recurrent, or late (>1 year post-transplantation) – significantly increases the risk of chronic allograft nephropathy, a major cause of long-term graft loss. Advances in molecular diagnostics, proteomics, and microarray analyses promise to generate non-invasive means for detecting early signs of immune injury. However, the diagnosis of renal allograft rejection currently continues to depend on the detection of changes in renal function (most often by changes in serum creatinine concentration) and on biopsy of the transplanted kidney. It is understood that deterioration of kidney function is a relatively late development in the course of an acute rejection episode, usually detected after significant histologic injury has already occurred.

Acute rejection

Acute cellular rejection

Acute cellular rejection occurs most commonly in the first few days to months after transplantation The immune events leading to this form of rejection center around activation and proliferation of T cells, and are described in detail in Chapter 1. Fever, allograft tenderness, oliguria, or hypertension may be present, but in the era of modern immunosuppression such symptoms are unusual. Often, the transplant recipient is asymptomatic during a rejection episode, and it is an increase in serum creatinine concentration that triggers concern.

The Banff consortium was established to standardize interpretation of renal allograft pathology in clinical trials. With further evolution, the Banff grading system has proved to be useful in guiding therapy and in establishing prognoses. According to revised Banff 2007 criteria, acute cellular rejection is characterized by the presence of tubulitis and arteritis. Leukocyte (usually lymphocyte) infiltration of the tubular epithelium is called "tubulitis," whereas disruption of the arterial intima is referred to as "arteritis." Both the intensity of interstitial infiltrate and the severity of tubulitis and intimal arteritis categorize the grade of rejection as either mild (I), moderate (II), or severe (III) (Table 7.6). Chronic allograft arteriopathy, which encompasses arterial intimal fibrosis and formation of neointima, is the hallmark of chronic cell-mediated rejection. Histopathologic findings suspicious for acute cellular rejection, but insufficient for a firm diagnosis, are deemed "borderline" or "suspicious." Decisions about treatment in these cases are based on the clinical setting.

Table 7.6 Banff 1997 classification system – revised in 2007

Category	Histology
Normal	Normal biopsy
Antibody-mediated rejection	
Acute	Type I: minimal inflammation, acute-tubular necrosis like (C4d positive)
	Type II: capillary–glomerulitis (C4d positive)
	Type III: arterial–transmural inflammation/fibrinoid change (C4d positive)
Chronic active	Glomerular double contours, lamellar peritubular capillary basement membrane, interstitial fibrosis, tubular atrophy, arterial fibrous intimal thickening (C4d positive)
Borderline	Findings suspicious for acute T-cell-mediated rejection, but non-diagnostic
T-cell-mediated rejection	
Acute	Significant interstitial inflammation (>25% of parenchyma) with:
	Type IA: moderate tubulitis (more than four mononuclear cells/tubular section)
	IIB: severe tubulitis (>10 mononuclear cells/tubular section)
	Type IIA: mild-to-moderate arteritis
	IIB: severe arteritis (>25% loss of luminal area)
	Type III: transmural arteritis/fibrinoid change, necrosis of medial smooth muscle in association with lymphocytic inflammation of the vessel
Chronic active	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration and formation of neointima)
Interstitial fibrosis and tubular atrophy	Grade I: mild (<25% of cortical area) Grade II: moderate (25–50% of cortical area) Grade III: severe (>50% of cortical area)
Other	

Adapted from Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int* 1999;**55**:713–23 and Solez K, Colvin RB, Racusen LC, et al. Banff '05 meeting report: Differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ("CAN"). *Am J Transplant* 2007;7:518–26.

Antibody-mediated rejection

As many as 25–30% of acute rejection episodes have an antibody-mediated component. In general, identification of antibody-mediated rejection (AMR) portends a worse prognosis, because such cases tend to be refractory to conventional treatment. Donor HLA antigens are the predominant targets. Endothelium-associated donor antigens or ABO isoagglutinins are involved less commonly. The mechanisms leading to antibody-mediated damage to the allograft are discussed in Chapter 1. The discovery that endothelial deposition of the complement split product, C4d, is a footprint for antibody-mediated rejection, has greatly aided the diagnosis of AMR.

Catastrophic rejection within minutes to hours of transplantation, termed "hyperacute rejection," is the result of transplantation across donor-incompatible blood groups or in the presence of high titers of pre-formed donor-specific antibodies. Recipient presensitization, from prior transplanta-

tion, pregnancy, blood transfusions, or other antigenic exposures, is required to form the donor-specific antibody so quickly and typically results in a positive complement-dependent cytotoxic cross-match before transplantation. Antibody-mediated endothelial injury leads to a cascade of complement activation, vascular thrombosis, and eventual ischemic necrosis. Grossly, the transplanted kidney is mottled and cyanotic. Marked edema and rupture of the allograft may occur, so that immediate nephrectomy is usually required.

An anamnestic immune response accounts for some cases of AMR that occur days to weeks after transplantation. Such patients usually have evidence of sensitization before transplantation. However, antibody titers are presumably low at the time of transplantation, resulting in a negative complement-dependent cytotoxic cross-match. Antibody titers rise post-transplantation in the presence of an antigenic stimulus (the donor allograft). Accelerated or acute vascular rejection may ensue, presenting as an acute rise in serum creatinine with or without allograft tenderness, oliguria, and hypertension.

AMR also can occur in non-sensitized patients. In most cases, the primary cell-mediated immune response serves as the mechanism for B-cell activation. The severity of the rejection episode varies with antibody titer and relative binding affinity, as well as with the intensity of expression of HLA and other donor-specific antigens within the allograft. Such episodes can occur at any time post-transplantation, particularly during periods of inadequate immunosuppression. Either accelerated or acute vascular rejection may result. Late in the post-transplant course, antibodies may play a role in the development of chronic allograft damage. Numerous studies have documented C4d deposition preceding biopsy findings of transplant glomerulopathy (see below), suggesting an important role for anti-donor antibody and complement activation. Notably, circulating new anti-HLA antibodies can precede renal allograft loss by many months or years.

The Banff classification outlines four features fundamental to the identification of AMR:

1. Allograft dysfunction

2. Morphologic evidence of tissue injury (from minimal inflammation/acute tubular necrosis-like histology to capillary glomerulitis to transmural arterial inflammation and fibrinoid change)

3. Immunopathologic evidence for antibody-mediated action (C4d deposition in the peritubular capillaries)

4. Serologic evidence of circulating antibodies to donor HLA or to other donor endothelial antigens.

Definitive diagnosis requires the presence of three of the four criteria (see Table 7.6). Chronic active AMR is suggested by C4d deposits and glomerular double contours and/or multilayering of the peritubular capillary basement membrane, with or without interstitial fibrosis, tubular atrophy, or arteriolar fibrous intimal thickening.

Case

A 56-year-old multiparous woman had a prior kidney transplant that failed 5 years earlier as a consequence of acute and chronic rejection. Thereafter she became highly sensitized with panel-reactive antibody levels consistently >60% for both class I and class II HLA antigens. Her 28-year-old daughter wished to donate a kidney and was haploidential to her mother. A standard CDC cross-match and anti-human globulin-augmented cross-match were negative but flow cytometry cross-matching revealed a strongly positive T-cell cross-match. The daughter is otherwise healthy and deemed to be a suitable donor. The mother was treated with three courses of plasmapheresis followed by infusions of IVIG. A repeat flow cytometry cross-match was negative, and the living donor transplant was performed with initial success and excellent allograft function. Four weeks after the transplantation, serum creatinine concentration rose and a percutaneous biopsy showed leukocytes in peritubular capillaries with heavy deposits of C4d. The patient was treated with three additional courses of plasmapheresis and IVIG and also received two doses of rituximab. Serum creatinine concentration decreased but never returned to baseline. One year later, a slow rise in serum creatinine concentration and the development of proteinuria (3.5 g/day) prompted a second biopsy that showed glomerular basement membrane duplication compatible with transplant glomerulopathy.

Chronic allograft nephropathy

Renal allograft failure is a common cause of ESRD, and accounts for up to 30% of patients awaiting renal transplantation The most common cause of renal allograft failure is a poorly understood entity, variably referred to as chronic allograft nephropathy,

transplant glomerulopathy, chronic renal allograft dysfunction, chronic rejection, or transplant nephropathy. The 2007 Banff consortium re-named chronic allograft nephropathy "interstitial fibrosis and tubular atrophy, without evidence of any specific etiology." Confusion surrounds this disorder because of its complex, multifactorial pathogenesis and the lack of universally accepted diagnostic criteria. In general, chronic allograft nephropathy is characterized by slowly progressive renal allograft dysfunction that usually begins 3 months or more after transplantation, in the absence of active rejection, acute drug toxicity, or another disease. Clinically, recipients develop slowly worsening azotemia, proteinuria (occasionally in the nephrotic range), and worsening hypertension.

Both immune and non-immune mechanisms of injury are implicated in the pathogenesis of chronic allograft nephropathy. The importance of cell-mediated and humoral immunity, HLA mismatch, inflammatory cytokines, anti-inflammatory cytokines, growth factors, and endothelin has been demonstrated both in vitro and in vivo. Hypertension, glomerular hyperfiltration, delayed graft function, ischemia–reperfusion injury, hyperlipidemia, proteinuria, and chronic CNI toxicity are also known contributors. Emerging data suggest that a number of donor factors (age, donor source, and comorbidities) also play a role. Histological changes are similarly diverse, involving all components of the renal parenchyma. Endothelial inflammation leading to fibrous intimal thickening is hypothesized to be one of the initial pathologic events. The glomerular capillary walls thicken with an occasional double-contour appearance, termed "transplant glomerulopathy." This is the most specific finding for chronic allograft nephropathy within the Banff classification scheme. Variable degrees of tubular atrophy and patchy interstitial fibrosis are present. Splitting and lamination of the tubular capillary basement membrane have also been described.

Although glomerular and vascular histologic findings may be more diagnostically specific, Banff criteria grades disease severity according to the amount of interstitial fibrosis and tubular atrophy (see Table 7.6), a better correlate of late graft failure. Another commonly cited index of disease severity is the chronic allograft disease index (CADI) score, which takes into account the percentage of sclerotic glomeruli and vascular change. In some studies, the CADI score from protocol renal biopsies at 2 years are predictive of graft function at 6 years.

Key points 7.7 Factors associated with the development of chronic allograft nephropathy

Immune factors
- Acute rejection episodes
- Recipient-donor HLA mismatching
- Pre-existing or new anti-HLA antibodies
- Inadequate immunosuppression

Non-immune factors
- Hypertension
- Glomerular hyperfiltration
- Ischemia–reperfusion injury
- Delayed graft function
- Hyperlipidemia
- Cytomegalovirus infection
- Calcineurin inhibitor toxicity
- BK polyoma infection

Protocol biopsies

As changes in serum creatinine tend to occur after histologic injury has been initiated, the benefit of surveillance biopsies at defined points after transplantation offers some appeal. Protocol biopsies attempt to identify pathologic changes before allograft dysfunction occurs, at a time when renal injury may be more amenable to treatment. Numerous studies suggest that detection of tubulitis (i.e., subclinical acute rejection) or chronic allograft nephropathy in early protocol biopsies predicts subsequent graft function and loss. Other studies suggest that prompt treatment of subclinical rejection may improve graft survival. However, there are few prospective data about the effect that increasing immunosuppression for subclinical rejection has on long-term clinical outcomes. Many aspects of the natural history of subclinical rejection are simply not known, e.g., the significance of persistent histologic but clinically resolved rejection, and the significance of C4d staining in patients with stable allograft function. In addition, the optimal timing of biopsies is unclear.

Moreover, early enthusiasm for protocol biopsies was based on studies from the cyclosporine era in which the incidence of subclinical rejection in the first 6 months after transplantation was as high as 30%. More recent studies in patients receiving tacrolimus-based immunosuppression suggest rates of <10%, raising serious questions as to whether the benefits of protocol biopsies outweigh their cost and risk. Nevertheless, protocol biopsies may still be valuable in high-risk populations (e.g., recipients with delayed graft function or patients in drug minimization protocols) and currently remain an important tool in research studies.

Molecular diagnosis of rejection

In the search for urinary or serum markers that allow non-invasive and rapid diagnosis of ongoing or imminent immune injury, advancements in molecular technology have allowed for the measurement of candidate molecules or their corresponding genes or messenger RNAs. The molecules studied most extensively are cytotoxic T-cell products such as perforin, granzyme B, and Fas ligand. Peripheral blood leukocyte cytokine production, recipient T-cell responses to donor-specific HLA antigens, and urinary proteomic profiling have all shown correlations with immune injury but require further validation in large scale studies. Quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and DNA microarray assays derived from peripheral blood, urine, or the allograft itself show great promise as non-invasive approaches to detect early immune injury. At this time, all of these assays are used primarily as research tools.

Pancreatic rejection

Pancreas allografts can fail for a variety of reasons. Early graft loss, occurring within hours to days of surgery, is usually secondary to technical failure (thrombosis, leak, bleeding, or pancreatitis). Acute rejection of the pancreas can occur at any time, but typically occurs in the same time frame as described for renal allografts. The diagnosis of acute pancreatic rejection can be difficult using non-invasive tests. Elevations in serum lipase and amylase are non-specific, whereas a rise in fasting serum glucose can occur under conditions of physiologic stress (e.g., infection) or as a late indicator of allograft dysfunction. In simultaneous kidney–pancreas transplantation, rejection of the pancreas allograft alone is uncommon (<15% of cases) and an increase in serum creatinine concentration is often relied on as the earliest indication of concomitant pancreas rejection. In recipients with bladder-drained pancreatic allografts, a serially decreasing urinary amylase has been used as a crude sign of rejection. Some but not all centers perform percutaneous pancreatic biopsies routinely as the definitive means for diagnosing pancreatic rejection. However, biopsy may be technically difficult in some patients, depending on the exact placement of the organ. After the first 6 months post-transplantation, the most common cause of pancreatic graft loss is chronic rejection, with progressive allograft sclerosis (increasing fibrosis and atrophy of the glandular components) secondarily leading to endocrine failure.

Long-term complications

Cardiovascular disease, diabetes mellitus, and hyperlipidemia

Cardiovascular disease remains highly prevalent in kidney transplant recipients and is the most frequent cause of late allograft loss. Traditional risk factors such as smoking and diabetes mellitus influence the risk of cardiovascular disease after transplantation. Additional risk is derived from the presence of CKD before transplantation, particularly in patients with prolonged exposure to dialysis. Some reduction of GFR is common after transplantation and further contributes to cardiac risk. Persistent proteinuria after transplantation is an independent risk factor for cardiovascular disease, and elevations in C-reactive protein and homocysteine are also associated with increased risk.

Specific immunosuppressive agents independently increase cardiovascular risk through an array of side effects that contribute to the metabolic syndrome (Table 7.7). Corticosteroids increase serum lipids, blood pressure, obesity, glucose intolerance, and vascular atherogenesis. Cyclosporine also increases lipids, blood pressure, and glucose intolerance, and can lead to progression of CKD. Tacrolimus appears to have a favorable side-effect profile relative to cyclosporine in terms of lipid elevation and endothelial dysfunction, but is associated with a greater risk

Table 7.7 Semiquantitative associations between various immunosuppressants and cardiovascular risk factors

	Hypertension	Diabetes mellitus	Hyperlipidemia	Nephrotoxicity
Corticosteroids	++	+++	++	–
Cyclosporine	++	+	++	++
Tacrolimus	±	+++	±	++
Sirolimus	–	+	+++	+

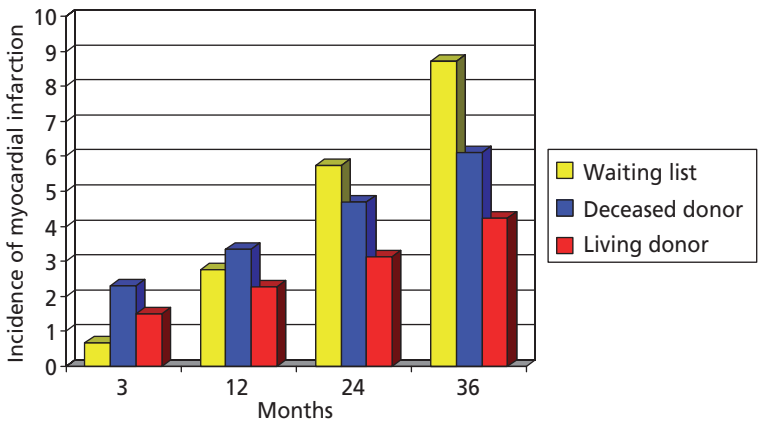

Figure 7.10 Incidence of myocardial infarction over time in wait-listed transplant candidates, deceased donor kidney transplant recipients, and living donor transplant recipients. (Adapted from Kasiske BL, Maclean JR, Snyder JJ. Acute myocardial infarction and kidney transplantation. *J Am Soc Nephrol* 2006;**17**:900–7.)

of glucose intolerance and diabetes mellitus. A randomized trial of 682 patients comparing tacrolimus and cyclosporine therapy found the incidence of new-onset diabetes after transplantation (NODAT) to be 34% versus 26% in *tacrolimus- and cyclosporine-treated* recipients, respectively ($p = 0.05$). However, low-density lipoprotein (LDL)-cholesterol and triglyceride levels were higher in the cyclosporine group.

Sirolimus increases total cholesterol, LDL-cholesterol, and triglycerides relative to other agents, related to a decrease in the metabolism of apoB100-containing lipoproteins. Emerging data have also linked sirolimus to increased insulin resistance and decreased insulin production. Therapy with this TOR inhibitor has also been associated with an increase in proteinuria, further contributing to cardiovascular risk. Despite these risks, sirolimus and other TOR inhibitors have putative antiatherogenic effects mediated, in part, by inhibition of vascular smooth muscle proliferation, as evidenced by the observation that sirolimus-coated stents decrease neointimal proliferation after coronary intervention. It remains to be proven whether systemic therapy with TOR inhibitors conveys protection against cardiovascular disease despite their negative influence on multiple risk factors.

Screening for cardiovascular disease is integral to the evaluation for kidney transplantation, although the benefit gained by preoperative revascularization is unclear (see "Recipient evaluation" above). Adverse cardiovascular events remain highly prevalent after transplantation relative to the general population, but the risk of disease declines over time relative to that of patients remaining on the transplant waiting list. When Kasiske et al. compared analyzed cardiovascular mortality rates after kidney transplantation to rates in wait-listed patients, the adjusted relative cumulative risk of myocardial infarction at 3 years post-transplantation was 0.83 ($p < 0.001$) (see Further reading). Living donor recipients had a greater benefit, with a relative risk of 0.69 ($p < 0.001$). However, the risk of myocardial infarction during the perioperative period exceeded the rate of wait-listed patients (Figure 7.10).

Transplant-associated hyperglycemia and NODAT are common and contribute to cardiovascular and overall mortality after transplantation. The risk of NODAT is roughly 15% in the first post-transplant year, and is followed by a roughly 5% incidence per year for subsequent years. In a Mayo Clinic experience, prediabetic hyperglycemia, defined as fasting glucose between 100 and 125 mg/dL, was present at 1 year in a third of patients who were euglycemic pretransplantation. Considering the significant percentage of transplant recipients with diabetes mellitus at baseline, glucose impairment after kidney transplantation is the norm rather than the exception, particularly in the USA. Pretransplant diabetes mellitus, NODAT, and even pretransplant hyperglycemia are all associated with an increased risk for cardiovascular disease after transplantation. NODAT is also a risk factor for mortality and death-censored graft failure post-transplantation.

Risk factors for NODAT have been elucidated and include non-modifiable and modifiable risks (Table 7.8). One key modifiable risk factor is weight gain, which is typical after transplantation and is associated with black race, poor socioeconomic status, female gender, and younger age. Weight gain is accelerated in the first year post-transplantation and may relate in part to higher steroid doses during this interval. One study of over 600 kidney recipients found that progression to obesity after transplantation increased the risk of diabetes mellitus, hypertension, cardiovascular disease, and deterioration of allograft function.

Table 7.8 Risk factors for development of new-onset diabetes after transplantation

Non-modifiable	Modifiable
Older age	Greater body weight/obesity
Race/ethnicity	Immunosuppressive therapy
Black	Corticosteroids
Hispanic	Tacrolimus
Native American	Cyclosporine
Asian Indian	Sirolimus
Genetic risk/family history	Hepatitis C infection
Impaired glucose tolerance pre-transplantation	
Time post-transplantation	

Adapted from Rodrigo E, Fernandez-Fresnedo G, Valero R, et al. New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol* 2006;**17**, S291–5.

Hyperlipidemia is common after transplantation and is associated with specific immunosuppressive agents as described above. Over 2000 cyclosporine-treated kidney transplant recipients from Europe and Canada were analyzed in the Assessment of Lescol in Renal Transplantation (ALERT) trial. This double-blinded study randomized patients to fluvastatin (40–80 mg/day) or placebo and monitored outcomes for 5 years. Fluvastatin effectively lowered LDL-cholesterol by a third. The primary endpoint of cardiac death, myocardial infarction, or coronary intervention was not significantly different between groups, but the risk ratio for cardiac death or myocardial infarction was 0.65 ($p = 0.005$) in the fluvastatin group. Treatment was well tolerated with no difference in side effects compared with placebo. In the placebo group, cholesterol level was an independent risk factor for myocardial infarction, further strengthening the argument for statin usage in the kidney transplant population.

Malignancy

Recent data indicate that most types of cancer occur at increased frequency after kidney transplantation compared with the general population. In particular, risk of malignancies related to certain viral infections is increased severalfold. These include EBV-related post-transplant lymphoproliferative disease (PTLD), as well as cervical, skin and lip cancers related to human papillomavirus (HPV). Kaposi's sarcoma is linked to human herpes virus 8 (HHV-8) and has a 10- to 20-fold incidence in transplant recipients relative to the general population (Table 7.9).

Certain cancers such as myeloma, and kidney or urinary tract malignancies are associated with kidney disease and thus are more prevalent in kidney transplant failure patients compared with the general population. Acquired cystic disease is common in ESRD and is a risk factor for renal cell carcinoma. One analysis of kidney recipients found a 1.2%

incidence of renal cell carcinoma at 2–7 years post-transplantation, a rate approximately 10-fold that of the general population.

PTLD represents a spectrum of disease ranging from benign polyclonal proliferation of EBV-positive lymphocytes to a monoclonal non-Hodgkin's B-cell lymphoma that requires aggressive chemotherapeutic treatment (see Chapter 5). PTLD occurs in 1–5% of kidney transplant recipients with the highest incidence observed within the first year after transplantation. It is more commonly seen in children due to the risk related to EBV antibody mismatch with a seronegative recipient. PTLD may present with fever, pharyngitis, and lymphadenopathy. Solid lymphomatous tumors may be found in the chest, gastrointestinal tract, or the kidney allograft. PTLD in the gastrointestinal tract may present with abdominal pain, bleeding, or obstruction.

One study of 25 000 Medicare kidney recipients transplanted between 1996 and 2000 found that PTLD developed in 344 (1.4%). Risk factors for PTLD included antibody induction therapy or rejection treatment with OKT3 or anti-thymocyte globulin, but not with IL-2 receptor antibody-induction therapy. Other risks included absence of serologic evidence for prior exposure to EBV, younger age, pre-transplantation malignancy, and maintenance therapy with tacrolimus.

Recent reports utilizing Medicare data forms have identified an increased risk for most cancers post-transplantation even in the absence of a known viral association (Table 7.9). Kasiske et al. examined US Renal Data System (USRDS) and Medicare data and found that common solid tumors including colon, lung, prostate, and breast cancers were increased roughly twofold within 3 years of transplantation (see Further reading). An analysis of the Canadian Organ Replacement Register database measured the standardized incidence ratio of malignancy, excluding non-melanoma skin cancers. The overall ratio was 2.5 relative to the general population, and no type of cancer was less common after transplantation. Risk of malignancy progressed over time, with a cumulative incidence of >10% after 15 years. A German analysis tracked patients up to 25 years post-transplantation and found a 49.3% incidence of malignancy, compared with a 21% rate for the general population matched for sex and age. Patients who survived longer on immunosuppressive therapy had a greater risk of new malignancy. In an Australian registry analysis, the average time to cancer after transplantation was 9.4 years.

Table 7.9 Relative risk of specific cancer types after kidney transplantation relative to the general population

>10–100	Non-melanoma skin cancer
	Lip cancer
	Non-Hodgkin's lymphoma
	Renal carcinoma
	Cervical and uterine cancer
	Penile cancer
	Anal cancer
	Kaposi's sarcoma
>1–10	Hodgkin's lymphoma
	Leukemia
	Melanoma
	Esophageal cancer
	Gastric cancer
	Hepatic cancer
	Biliary carcinoma
	Colon cancer
	Lung cancer
	Thyroid carcinoma
	Head and neck cancer
	Bladder cancer
	Pancreatic cancer
	Breast cancer
	Testicular cancer

Screening for malignancy in patients with reasonable life expectancy is clearly warranted after kidney transplantation. Skin surveillance with an annual examination by the transplant surgeon or a dermatologist is recommended. Women should have annual pelvic examinations and cytological studies, and women aged >40 or with a first-degree family history of breast cancer at age <50 should undergo yearly mammography and self-breast examinations. Colonoscopy is warranted in patients aged >50 or with a primary family history of malignancy. Digital rectal examination along with serum prostate specific antigen should be considered in all men aged >50 years. Annual chest radiographs may be considered in smokers. Lung cancer is increased approximately twofold in transplant recipients, and smoking cessation must be stressed. Patients with chronic liver

disease or viral hepatitis should be screened with liver ultrasonography every 6–12 months.

Increased risk of cancer is thought to be related to potent immunosuppressive therapy. However, sirolimus appears to have unique anti-neoplastic properties. The drug inhibits the TOR which prevents downstream activation of cellular translation through inhibition of Akt and p79S6 kinase, and secondarily inhibits angiogenic growth factors such as vascular endothelial growth factor (VEGF). Animal models have demonstrated a reduction in tumor progression of kidney cancer cells. A study of 33 249 deceased donor kidney recipients reported to the OPTN database showed that the incidence rates of malignancy were 0.6% with sirolimus-based therapy compared with 1.8% in patients on cyclosporine or tacrolimus-based treatment. Sirolimus may have a particular benefit in the treatment of Kaposi's sarcoma. Fifteen transplant recipients converted from cyclosporine to sirolimus showed complete resolution of Kaposi's sarcoma lesions. Other case reports have demonstrated similar success, although a recent series did not show uniform resolution, particularly in more severe cases.

Bone disease

Bone disease is common after kidney transplantation, and risk for fracture increases over time with a rate greater than that seen in dialysis patients. Risk is related in part to osteoporosis, with a higher incidence of fractures in postmenopausal women. Although guidelines exist for monitoring bone mineral density (BMD) after transplantation, low BMD does not consistently correlate with the risk of fracture. Risk factors for fracture after transplantation include older age, diabetic status, and previous fractures before transplantation. Steroid usage likely contributes to bone demineralization and low bone turnover after transplantation, although BMD has been shown to decline in a similar fashion early post-transplantation even in the absence of corticosteroids. Steroid usage has been clearly linked to the development of osteonecrosis, a severe adverse event that typically involves the femoral head and typically requires surgical repair.

Studies incorporating bone biopsy in kidney recipients show a mixture of low bone turnover disease and increased bone resorption, making treatment decisions difficult in the absence of histologic analysis. Although studies have used BMD as a surrogate outcome, few have analyzed fracture rates between groups. Vitamin D supplementation increases BMD, and can help control hyperparathyroidism early after transplantation. Bisphosphonates have also been shown to increase BMD, but their use may contribute to low bone turnover disease. Furthermore, is not clear whether bisphosphonates prevent fracture after kidney transplantation.

Post-transplant hyperparathyroidism is common, and parathyroid hormone (PTH) levels tend to fall gradually but remain elevated in most transplant recipients. The implications of persistent hyperparathyroidism after kidney transplantation are unclear. One report identified tubulointerstitial calcification of the renal allograft in 18% of protocol biopsies at 6 months, and patients with calcification had higher PTH and serum calcium levels. High PTH in the face of calcification also predicted inferior graft function at 1 year. However, over 60% of patients in this cohort received phosphorus supplementation, which may have contributed to the risk of calcium phosphate calcification in the allograft. A second study analyzed bone biopsy and urinary calcium in kidney recipients with high PTH and hypercalcemia. These patients had a surprising mix of high and low bone turnover disease, with most demonstrating low-to-normal levels of urinary calcium excretion, suggesting an increase in renal tubular calcium uptake. This study brings into question the benefit of parathyroidectomy, which may be inappropriate in patients with low bone turnover disease. Current guidelines recommend waiting 1 year for PTH levels to fall, and considering parathyroidectomy only when serum calcium levels remain >11.5 mg/dL. Calcimimetic therapy with cinacalcet has been used with some success after kidney transplantation. Both parathyroidectomy and cinacalcet have been associated with a reduction in renal allograft function, perhaps related to an increase in hypercalcuria.

Current status of islet cell transplantation

The field of islet cell transplantation was revolutionized in 2000 when investigators from the University of Alberta in Edmonton described a small group of

patients with type 1 diabetes who remained insulin independent for more than 1 year after receiving intrahepatic injections of islet cells.

Notably, the major indication for islet cell transplantation was hypoglycemic unawareness, and none of the patients in this landmark trial had advanced complications of diabetic microvascular disease at the time of transplantation. The success of this protocol was attributed to the use of advanced techniques for isolating and preparing islets from human pancreata, the fact that most patients in the series required islets from two or more separate donor organs, and the then novel immunosppressive protocol that completely avoided corticosteroids, but included an anti-IL-R antibody for induction and maintenance therapy with "low-dose" tacrolimus and sirolimus. The unexpected short-term success of this protocol spawned the initiation of a National Institute for Health (NIH)-sponsored multicenter study in the USA, originally intended to use the "Edmonton protocol" to facilitate successful islet cell transplantation. Outside the NIH study, a number of other centers were motivated to begin islet cell transplant programs based on the Edmonton experience.

However, long-term outcomes of islet cell transplant recipients treated with the Edmonton protocol or closely related protocols have been disappointing. Almost 80% of patients have returned to insulin dependence after 5 years. Some of these patients continue to show evidence of islet cell activity, as evidenced by the presence of detectable C-peptide levels, and may still be protected from hypoglycemic unawareness. Even more concerning, however, is the observation that the vast majority of islet cell transplants develop evidence of HLA sensitization, especially when the islets fail and immunosuppression is withdrawn. These high rates of sensitization could reflect both the use of multiple donors in most cases and the robust presence of antigen-presenting cells in islet cell preparations. As mentioned earlier in this and other chapters, both tacrolimus and sirolimus are diabetogenic, so it remains possible that some long-term islet cell failures may reflect drug toxicity and not immune injury. Whatever the mechanisms, investigators in the field are currently studying new immunosuppressants, including a number of new biologic agents, in an effort to improve long-term outcomes and to minimize the numbers of donor pancreata needed to acquire insulin independence. In the meantime, islet cell transplantation is regarded by many to remain an experimental treatment for type 1 diabetes mellitus.

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