CHAPTER

82 Clinical Aspects of Renal Transplantation

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INTRODUCTION

Since the first successful renal transplant over 50 years ago,[1] more than 500,000 patients with renal failure have had their lives prolonged with renal allografts. Renal transplantation is associated with improved longevity compared to dialysis[2] with increased quality of life,[3] and currently is the preferred treatment modality for eligible patients with chronic kidney disease (glomerular filtration rate [GFR] <20 mL per minute).

The progressive increase in the incidence and prevalence of severe chronic kidney disease (CKD) has led to a parallel increase in the number of patients waiting for a transplant. This increase substantially outpaces the supply of available organs (Fig. 82.1). The reported average waiting time for a deceased donor kidney transplant (DDKT) is more than 3.5 years (2009 Scientific Registry of Transplant Recipients [SRTR] Annual Report Table 5.2). For this reason, efforts have been made to increase living kidney donor transplantation. Unfortunately, living donation rates in the Unites States have not increased in recent years, and modest growth in kidney transplantation has occurred as a result of increased deceased donor use.[4,5] Worldwide, rates of kidney transplantation and use of living donors for kidney transplant vary widely due to societal differences in the perception of transplantation and of organ donation following brain death or cardiac death (Fig. 82.2).

Patient and graft survival after kidney transplant are affected by a large number of variables (Table 82.1). Primary factors include: age, sex, and race of the recipient and donor; type of donor (living versus deceased, expanded criteria versus standard criteria); tissue compatibility; prior sensitization to human leukocyte antigens (HLA); original renal disease, pretransplant health status, and concomitant extrarenal disease of the recipient; adherence of the recipient; donor factors, such as age, cold ischemia time, and nephron dosing effect; and choice of immunosuppressive agents (Figs. 82.3 and 82.4). Short-term outcomes have improved substantially over the past 15 years, with 1-year graft survival averaging 90% to 94% and patient survival averaging 94% to 97%; however, improvements in long-term graft survival have been more difficult to achieve. An analysis by Hariharan et al.[6] of graft survival for all 93,934 renal transplantations performed in the United States between 1988 and 1996, suggested that the estimated half-life for grafts from living donors increased steadily from 12.7 to 21.6 years, and that for deceased donor grafts increased from 7.9 to 13.8 years. However, in this analysis graft survival was calculated upon projected, not actual, graft survival. A later analysis of graft outcomes from 1988 to 1995 demonstrated that actual graft survival demonstrated far less improvement in graft half-life of 6.0 to 8.0 years for deceased donor grafts.[7] A recent analysis of transplants from 1989 to 2009 suggests slow improvements in graft survival over time, primarily in higher risk transplants (the expanded criteria donor, described later) (Table 82.2). For living donor kidney transplants, the estimated graft half-life did not change appreciably for transplants performed from 1989 to 2005 (11.4 years to 11.9 years).[8] With greater understanding of the causes of graft loss, it is hoped that this will translate into better outcomes in renal transplantation with improved long-term graft and patient survival. In the subsequent sections of this chapter, we will discuss each of the factors influencing outcomes of renal transplantation, the recipient and donor evaluation prior to transplantation, immunosuppressive drugs, posttransplantation management, and complications.

PATIENT SELECTION AND PRETRANSPLANT EVALUATION

General Philosophy in Recipient Selection

In general, patients with CKD stage IV through V (GFR <30 mL per minute) should be presented with information regarding dialysis modalities and transplantation. Patients who express an interest in undergoing kidney transplantation should be fully evaluated by the transplant team. This is typically as an outpatient during a clinic visit; however, some centers may provide this on an inpatient basis. Early referral prior to the onset of dialysis should be encouraged, because

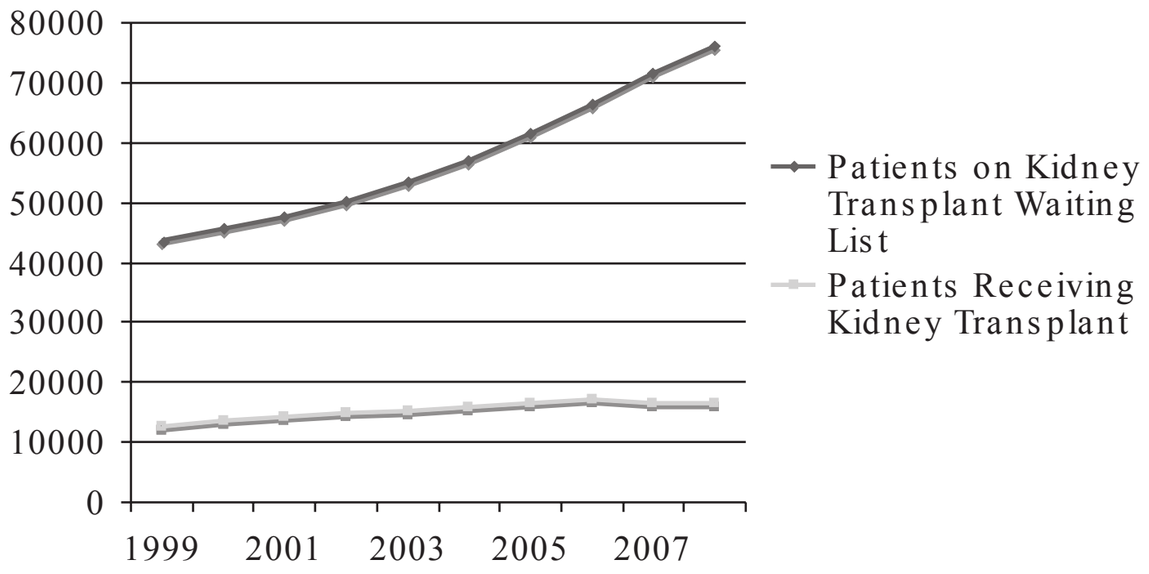


FIGURE 82.1 Counts of patients on the renal transplant waiting list and counts of renal transplants by year in the United States from 1999 to 2008. (From Scientific Registry of Transplant Recipients 2009 Annual Data Report, Ann Arbor MI, Tables 5.1a, 5.1b, 5.4, 5.4d, with permission.)

the degree of dialysis time prior to transplant has been associated with poorer graft survival following transplant.[9]

There are few absolute contraindications to kidney transplantation, and many of these contraindications are relative (Table 82.3). The current protocols for a transplant evaluation focus on ensuring the safety of undergoing surgery and the ability to assume the risks of immunosuppressive therapy in order to optimize successful kidney transplant outcomes. This evaluation is tailored to the individual candidate's risk for complications, and includes consideration of the patient's age, diabetes, and heart disease status. These factors are also associated with a higher risk of death in the general population and in patients with end-stage renal disease (ESRD) treated by dialysis.

Age

The adolescent patient (age 12 to 17) and the elderly recipient (age >65) have poorer graft survival than other age groups (SRTR Annual Report Table 5.8c). In the former, this is due primarily to difficulties in medication adherence, whereas in the latter, this is due to complications of immunosuppressive therapy leading to death or to nontransplant-related complications, in particular, cardiovascular disease in the elderly leading to death.[10,11]

In the United States, national kidney allocation policy prioritizes pediatric candidates to ensure a minimum of waiting time to promote the beneficial effects of transplantation, including growth and development. The challenge of ensuring appropriate medical support for young people with solid organ transplants as they move into adult-centered services has become a topic of significant interest in the field of organ transplantation. Proceedings from a consensus conference of the major transplant societies has outlined the need for collaborative transitional care between pediatric and adult providers and the need for research in this area.[12]

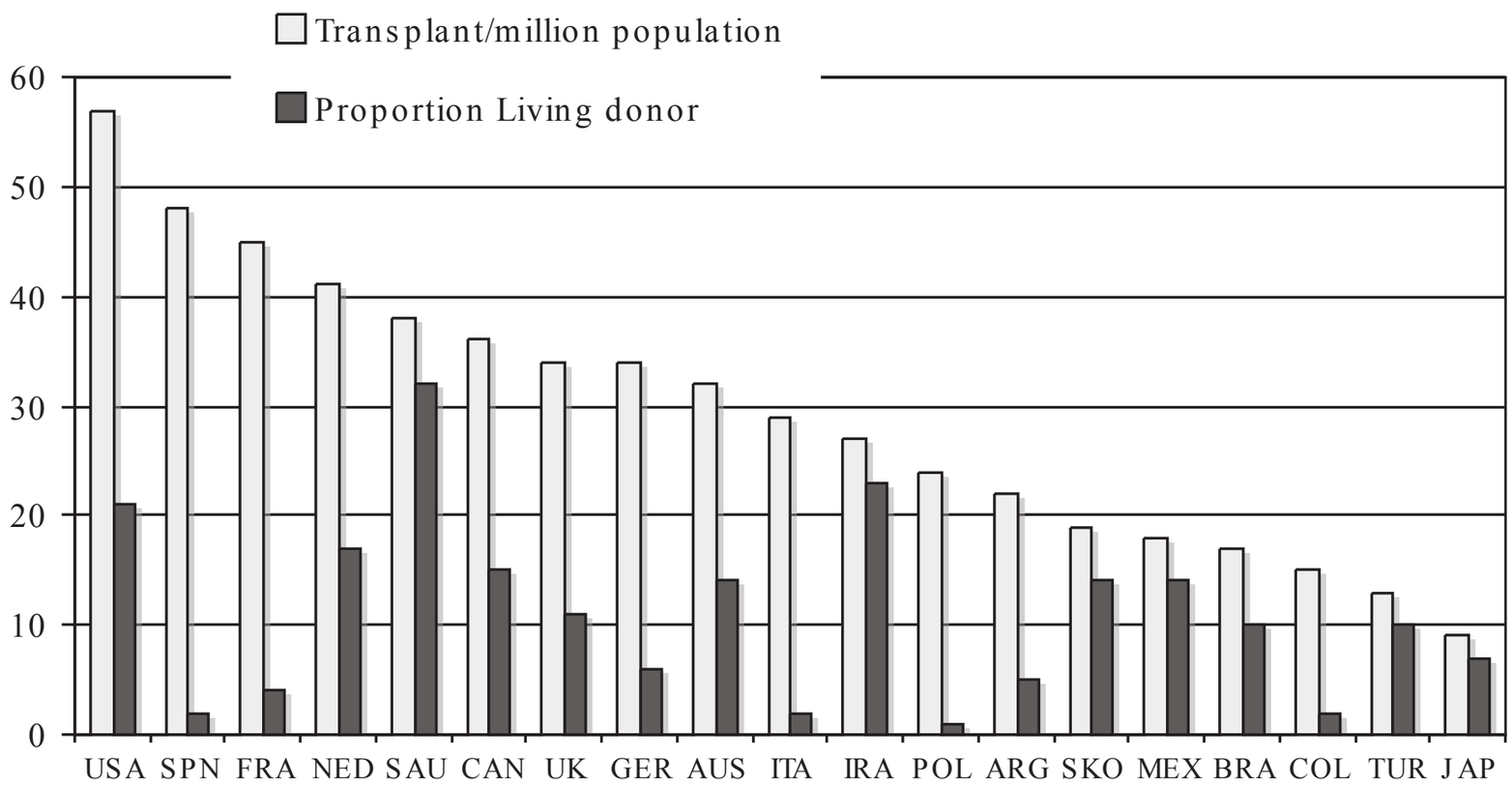


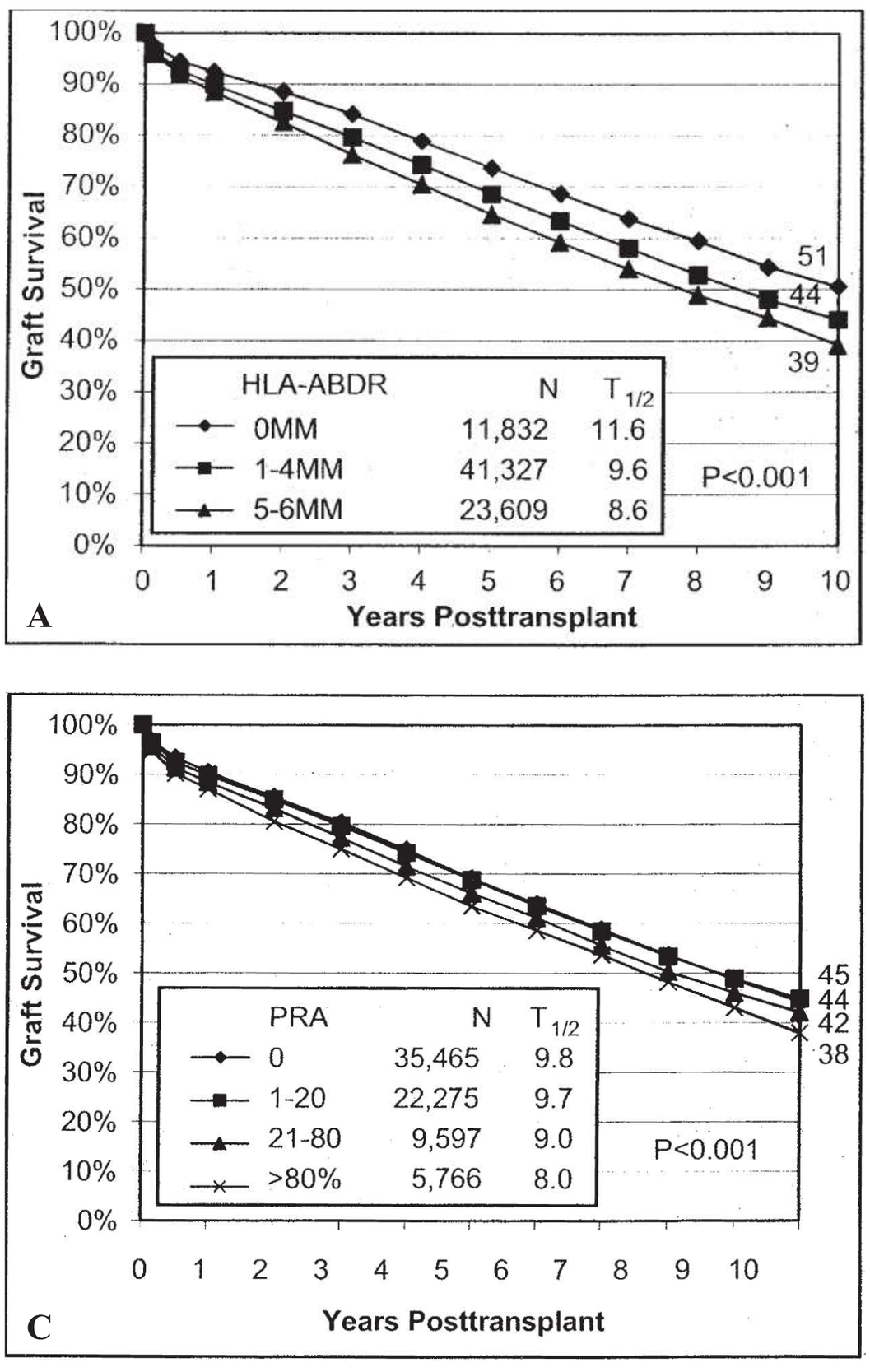
FIGURE 82.2 Transplantation rates for countries reporting more than 500 kidney transplants in 2006 (count of new renal transplants per million total population) and number of transplants arising from living donors. *SPN,* Spain; *FRA,* France; *NED,* Netherlands; *SAU,* Saudi Arabia; *CAN,* Canada; *UK,* United Kingdom; *GER,* Germany; *AUS,* Australia; *ITA,* Italy; *IRA,* Iran; *POL,* Poland; *ARG,* Argentina; *SKO,* South Korea; *MEX,* Mexico; *BRA,* Brazil; *COL,* Columbia; *TUR,* Turkey; *JAP,* Japan. (Data from Horvat LD, Shariff SZ, Garg AX. Global trends in the rates of living kidney donation. *Kidney International* 2009; 75:1088–1098.)

82.1 Factors Influencing the Outcome of Renal Transplantation

Immunologic	Nonimmunologic
Immunosuppressive protocol	Delayed graft function/ischemic time
Matching for HLA	Medication adherence
Sensitization	Cardiovascular disease
Rejection	Recipient age
	Nephron dose/donor and recipient gender

HLA, human leukocyte antigens.

With the improvements in perioperative management and immunosuppressive strategies, advanced age itself is no longer a contraindication to renal transplantation. Based on a retrospective analysis of wait-listed patients >70 years old from the SRTR, 1990 to 2004, elderly transplant recipients had a 41% lower overall risk of death compared with wait-listed candidates.[13] These benefits also extend to selected patients over age 80.[14] Older patients may have better immunologic survival despite the higher mortality from cardiovascular disease. One explanation may be an age-related change in immunologic function that confers less alloreactivity with aging, as suggested by a registry analysis that demonstrated that acute rejection rates significantly fell with advancing recipient age.[15] Recipients older than 65 years demonstrated significantly elevated numbers of memory T cells, whereas counts for naive T cells were significantly reduced.[16] For this reason, many centers advocate the use of lower immunosuppression in elderly patients. In summary, kidney transplantation can now be safely and successfully performed in selected elderly patients but requires comprehensive screening of underlying cardiovascular disease and occult malignancy.



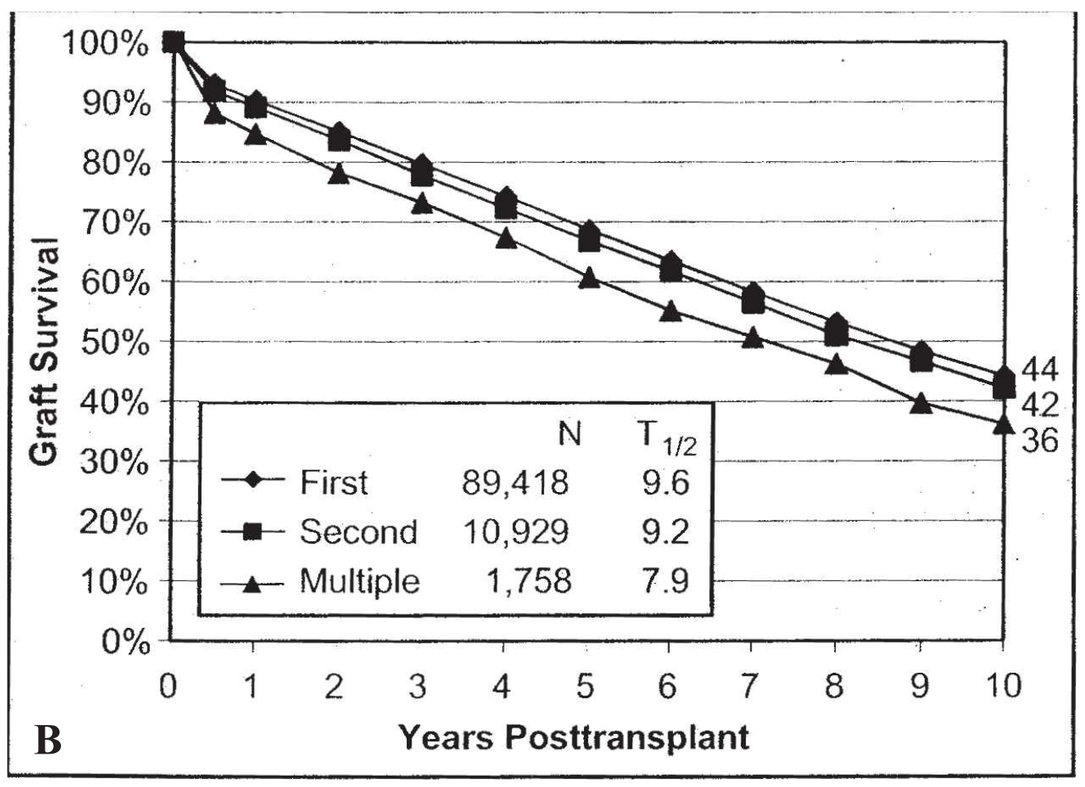


FIGURE 82.3 Graft survival related to immunologic factors. **A.** Effects of human leukocyte antigen (HLA) mismatches (MM) on the survival of first diseased donor transplants. Graft survival rates declined as the number of HLA-A, HLA-B, and HLA-DR MMs increased. The difference in graft half-life between the best and the worst matched grafts was 3 years (11.6 years vs. 8.6 years). **B.** Graft survival among first and repeat deceased donor transplant recipients. The differences between first and subsequent transplants have diminished, with no significant differences in graft survival. **C.** Graft survival related to HLA sensitization. HLA sensitization remains a significant risk factor for graft loss. Highly sensitized recipients (panel reactive antibody [PRA] >80%) have a lower long-term graft survival than patients with PRA <20%. Data are from the United Network for Organ Sharing Scientific Renal Transplant Registry, 1996–2005. (From: Cecka J, Terasaki P, eds. *Clinical Transplants 2008*. Los Angeles, CA: UCLA Tissue Typing Laboratory; 2008:1–18, with permission.)

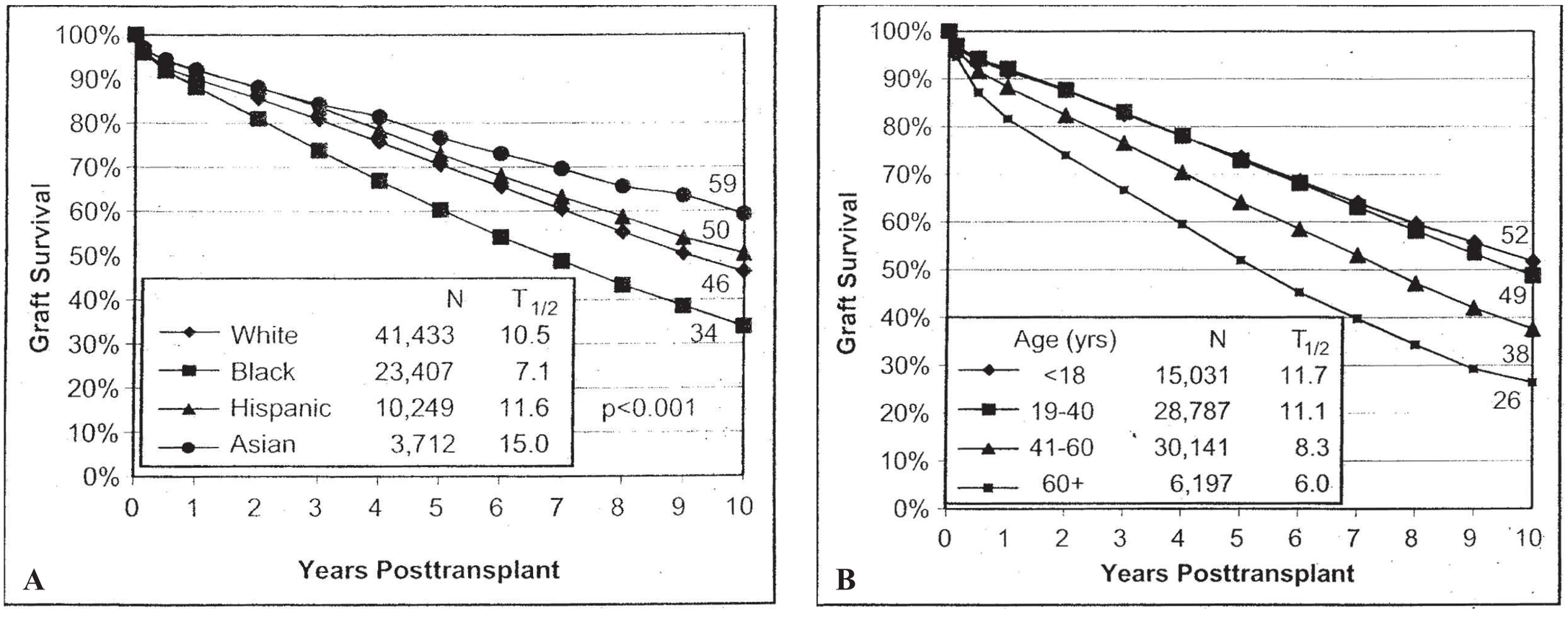


FIGURE 82.4 Graft survival rates of deceased donor kidney transplants are related to donor and recipient factors. **A.** The effect of recipient race on graft survival. The race of the recipients was a significant factor in the outcome of the first deceased donor transplants. Asian patients had the highest graft survival rates—59% at 10 years, respectively—whereas blacks had the poorest survival rates—34% at 10 years. **B.** The effect of donor age on graft survival. Donor age remains one of the most important factors in deceased donor kidney transplant graft survival. Data are from the United Network for Organ Sharing Scientific Renal Transplant Registry, 1996–2005. (From: Cecka J, Terasaki P, eds. *Clinical Transplants 2008*. Los Angeles, CA: UCLA Tissue Typing Laboratory; 2008:1–18, with permission.)

Obesity

Obesity alone is rarely an absolute contraindication to transplantation, yet it is a well-defined risk factor. Lower graft survival rates, higher postoperative mortalities, and complications have been demonstrated in patients with a body mass index (BMI) greater than 35 kg per square meter.[17,18] The large body size is also a risk factor for progression and subsequent premature failure due to the physiologic changes that have been linked to nephron hyperfiltration.[18] Although weight reduction is important for obese dialysis patients before proceeding to transplantation, often patients will regain weight following transplantation and mandatory weight loss pretransplant may not substantially improve longer term outcomes.[19]

82.2 Actual Transplant Half-Life for Transplants Performed in 1997, and Projected Transplant Half-Life for Transplants Performed in 2004[9]

Transplant Subgroup	Actual Graft Half-Life, 1997 Transplants	Actual Graft Half-Life, 1997 Transplants	Projected Graft Half-Life, 2004 Transplants	Projected Graft Half-Life, 2004 Transplants
	All recipients	African American recipients	All recipients	African American recipients
All deceased donor transplants	8.2 yr	6.3 yr	8.8 yr	7.1 yr
SCD	8.9 yr	6.8 yr	9.7 yr	7.7 yr
ECD (first transplant)	5.1 yr	4.4 yr	5.9 yr	5.4 yr
Living donor	12.0 yr	8.7 yr	14.2 yr	10.8 yr

SCD, Standard criteria donor; ECD, Expanded criteria donor.

82.3 Contraindications to Transplantation

Absolute	Relative
Active infection	Renal disease with high recurrence rate
Disseminated malignancy	Urologic abnormalities
Extensive vascular disease	Active systemic illness
High risk for perioperative mortality	Ongoing substance abuse
Persistent coagulation abnormality	Uncontrolled psychosis
Informed patient refusal of consent	Refractory nonadherence

Prior Kidney Transplantation

Renal allograft failure is now one of the most common causes of ESRD, accounting for about 30% of patients awaiting renal transplantation. Graft survival of a second transplant is decreased compared to that of the first, but outcomes have improved over time (Fig. 82.3).[7] Evaluation of a potential recipient for a repeat allograft requires careful attention to the reason for the graft failure, such as nonadherence with immunosuppressive medications, recurrent renal disease, or high alloreactivity with high panel reactive antibody (PRA) titers. These patients may also manifest complications of prior immunosuppressive therapy and, as such, should be screened for complications associated with these medications, such as infection and malignancy.[20] No controlled, prospective studies have been performed to determine the best method for tapering or withdrawal of immunosuppression following renal allograft failure, with some suggestion that nephrectomy after graft loss may improve patient survival and rates of retransplantation.[21] Most centers have adopted a policy of immediate withdrawal of immunosuppression combined with preemptive nephrectomy for patients with early allograft failure. However, this practice is less common for patients with late graft failure. A longer taper of immunosuppression may permit the maintenance of some residual renal function while on dialysis. Further studies are needed to determine the optimal means of immunosuppression withdrawal or nephrectomy in patients who return to dialysis.

Underlying Renal Diseases

It is most important to assess the cause of the potential recipient's renal failure. The primary pathologies leading to renal failure are expected to influence outcome depending on the etiologic mechanisms, propensity for recurrence, and status of the immune system.

Diabetes Mellitus

Although patients with diabetes are at a higher risk for posttransplant complications primarily related to their pretransplant comorbidities, kidney transplantation is the treatment of choice for otherwise eligible patients due to their high mortality rate while on dialysis.[22] In particular, patients with type 1 diabetes (T1DM) enjoy the highest net mortality benefit of transplantation compared to dialysis following receipt of a simultaneous pancreas kidney transplant (SPK) when compared to other kidney transplant recipients.[23] Patient survival and pancreas graft survival rates continue to improve, with data from U.S. centers demonstrating 95% and 86% 1-year patient and pancreas graft survival, and 85% and 70% 5-year patient and pancreas graft survival, respectively.[4]

With the increase in use of living donors for kidney transplantation, solitary pancreas transplant after kidney transplant (PAK) is often considered for patients with T1DM. Although this offers the benefit of timely kidney transplant, ideally prior to the need for hemodialysis, this strategy requires two separate survival procedures, two different HLA-mismatched organs, and the risks inherent to surgery. Pancreas allograft survival is worse as a PAK than SPK likely due to the additional immunologic factors of a second organ and the lack of use of renal function changes as a surrogate marker of pancreas function changes. Recommendations for patients with T1DM approaching kidney failure should be tailored to the individual's circumstance, and should include an assessment of the following: (1) can a living donor be identified; (2) is the patient (and transplant program) willing to accept a higher risk of early death and possibility of pancreas graft loss (~2% and ~15% in the first year, respectively) when considering SPK versus living donor kidney transplant; (3) how debilitating are the patient's diabetes-related quality-of-life issues and achieved level of glycemic control; and (4) what is the expected waiting time for an SPK in the patient's geographic region.[24] In general, SPK appears to offer advantages over kidney transplantation alone with respect to long-term survival if the waiting time for a deceased donor is not excessive and dialysis time can be minimized (perhaps to less than 6 months). For those patients who are unable to wait for SPK, a living donor kidney transplant followed by a later pancreas transplant appears to be associated with better kidney graft function with a risk of mortality that is similar to living donor kidney transplant alone.[25] One suggested algorithm for patients with T1DM and CKD considering their transplant options is provided in Figure 82.5.

Another treatment option in development for the patient with T1DM is pancreatic islet cell transplantation (ICT). In experienced centers, ICT can achieve insulin independence in 80% to 90% of recipients at 1 year; however, <30% have remained insulin free after 5 years.[26] At present, this therapy should still be considered experimental, because

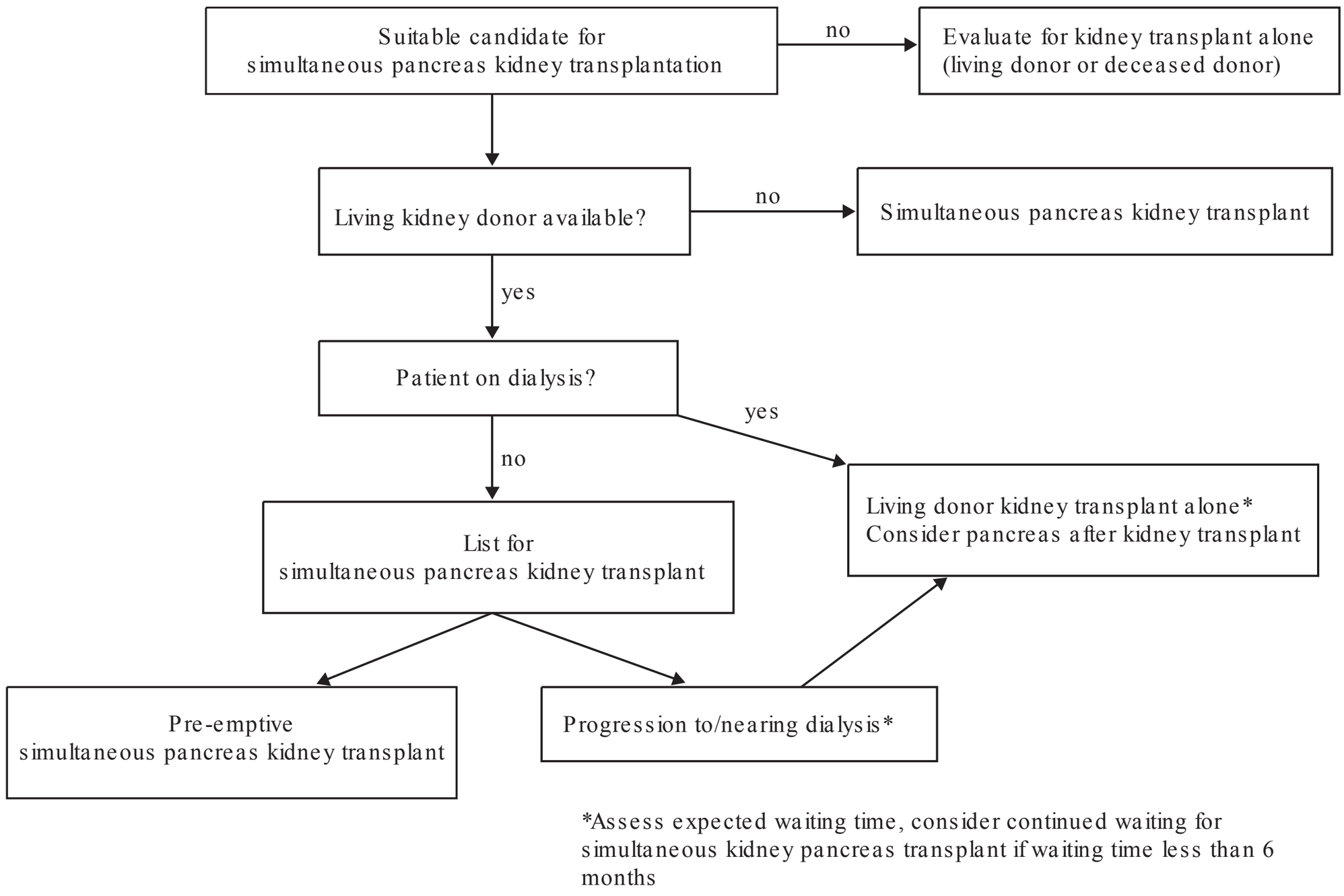


FIGURE 82.5 Proposed algorithm for type 1 diabetic patients requiring transplant. (Adapted from Wiseman AC. Simultaneous pancreas kidney transplantation: a critical appraisal of the risks and benefits compared with other treatment alternatives. *Adv Chronic Kidney Dis*. 2009;16(4):278–287, with permission.)

the long-term graft survival is unknown and the risks of immunosuppression and HLA sensitization must be weighed against the benefits of normalization of blood glucose.

Recurrence of the diabetic nephropathy in T1DM recipients is a late and slowly developing complication. An examination of biopsy specimens early after transplantation indicates that there are few glomerular pathologic abnormalities other than frequent afferent and efferent arteriosclerosis. Glomerular basement immunoglobulin G (IgG) deposition is seen <2 years after transplantation, but the onset and progression of glomerular basement membrane thickening and mesangial expansion only occurs after 2 years, and the typical nodular glomerular hyalinosis is rarely seen in these patients. Long-term follow-up has shown that recurrent nephropathy progresses to ESRD with the same time course as primary type I diabetic nephropathy. The mean time to recurrent ESRD is estimated to be 15 to 20 years. Therefore, recurrence of the lesion is not a barrier to long-term renal graft survival in diabetic recipients. The frequency and natural history of recurrence in type II diabetic recipients remain to be elucidated.

Metabolic and Congenital Disorders

Results of renal transplantation in the metabolic and congenital disorders causing end-stage renal failure such as Alport syndrome, amyloidosis, cystinosis, familial nephritis, gout, and cystic disease are similar to those of the more common causes of end-stage renal failure with the exception of primary hyperoxaluria, sickle cell, and Fabry disease, as discussed in detail in the following paragraphs.

Primary Hyperoxaluria

Although often presenting in childhood, inherited deficiencies in alanine:glyoxalate aminotransferase (AGT) levels or function may present in the young adult as calcium oxalate nephrolithiasis, nephrocalcinosis, renal failure, and systemic oxalate deposition. Registry analyses generally favor combined liver-kidney transplantation (to correct the AGT defect and promote long-term kidney graft survival), but occasionally, patients may have a functional AGT deficiency that is pyridoxine sensitive, and 5 to 10 mg/kg/day of pyridoxine may decrease oxalate levels to a level that is acceptable to consider kidney transplantation alone.[27,28] To reduce the chance of oxalate accumulation, dialysis treatment or kidney transplantation should be considered when the GFR approaches 20 mL per minute. Aggressive dialysis schedules should be implemented before transplantation to deplete the oxalate metabolic pool. Medical therapy with pyridoxine, neutral phosphate, and magnesium should be given after transplantation to reduce oxalate deposition and recurrence (Fig. 82.6).

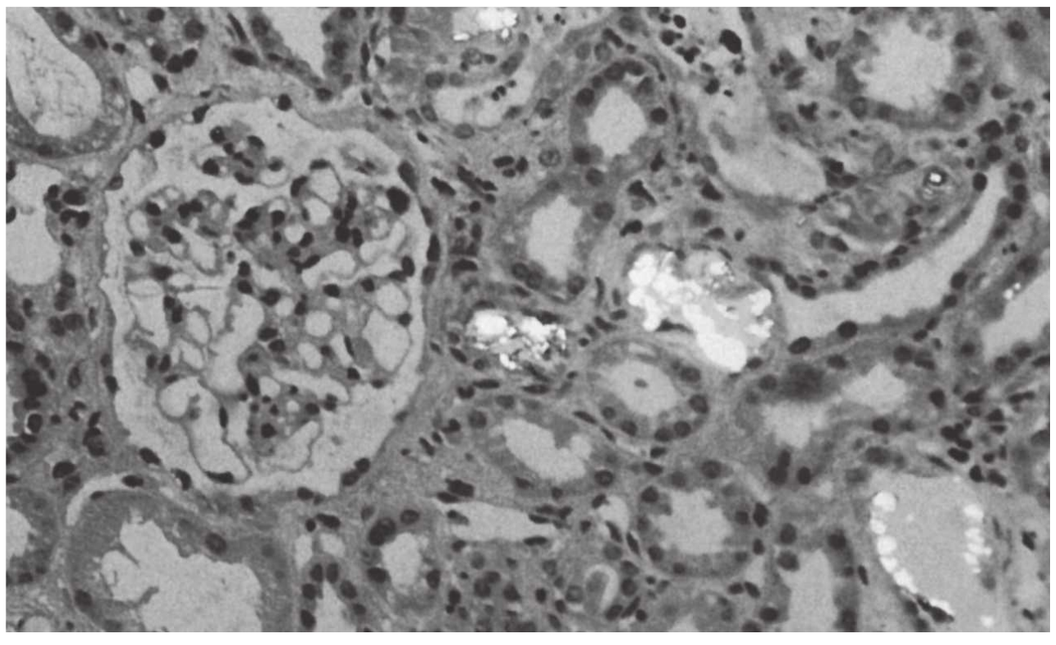


FIGURE 82.6 A renal biopsy specimen from a transplanted kidney showing calcium oxalate deposition in a patient with primary hyperoxaluria and a recurrence of oxalosis.

Unlike primary hyperoxaluria, secondary oxalosis is due to excessive intake or absorption of oxalates from the diet. Secondary oxalosis is seen primarily in fat malabsorption, short bowel syndromes after gastrointestinal surgery, and high-oxalate diets. For these patients, consideration should be given to reanastomosis of gastric bypass, hydration, and dietary restriction of oxalates. Good allograft function can be achieved when attention is paid to reduce the oxalate excretion load.[29]

Cystinosis

Cystine stones recur after transplantation, but have little effect on graft function.[30] Renal transplantation has been recommended as a preferred therapy in children with ESRD due to cystinosis. The systemic effects of cystine accumulation, including corneal crystallization and retinal degeneration, leading to blindness, progress after renal transplantation but can be reduced with chronic cysteamine therapy.[31]

Sickle Cell Disease

The autosomal recessive conditions of sickle cell disease and sickle cell trait may be complicated by a variety of renal abnormalities, which may eventually lead to ESRD.[32] The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) reports favorable outcomes in pediatric patients with patient survival of 89%, and graft survival at 12 and 24 months posttransplant of 89% and 71%, respectively.[33] A second registry analysis demonstrates comparable short-term but diminished long-term outcomes compared to other causes of ESRD.[34] The importance of recurrence after transplantation is difficult to determine because of the relatively nonspecific nature of sickle cell nephropathy.

Fabry Disease

Fabry disease is an X-linked disorder of glycosphingolipid metabolism due to a ceramide trihexosidase. Fabry nephropathy does not recur in the allograft, and transplantation provides superior outcomes to Fabry patients on dialysis.[35] Graft survival at 5 years is comparable to patients with other causes of ESRD, but with a higher risk of death.[36] Enzyme replacement therapy with agalsidase alfa is well tolerated in patients with Fabry disease following renal transplantation, but data regarding an impact on survival has yet to be determined.[37] Transplantation is considered the optimal mode of renal replacement therapy for otherwise eligible patients with Fabry disease.

Amyloidosis

Recurrent nephrotic syndrome and graft failure can occur in primary and secondary amyloidosis. Although transplantation is uncommonly performed for patients with primary amyloid light chain (AL) amyloidosis, in selected patients kidney transplantation has been shown to be successful.[38] Often, the treatment for this disorder requires chemotherapy and autologous stem cell transplantation. The decision to perform stem cell transplant before or after kidney transplant has been debated; reports of living donor kidney transplant followed by stem cell transplant have demonstrated favorable results.[39] Without definitive treatment, the recurrence of renal AL amyloidosis is common following kidney transplant.[40] Familial Mediterranean fever (FMF), rheumatoid arthritis, and osteomyelitis are the most common causes of secondary amyloidosis. FMF is an autosomal recessive disorder that occurs in Sephardic Jews, Armenians, Turks, and Arabs of the Levant. In Israel, amyloidosis constitutes 6% of all patients on dialysis, compared to 0.6% in Europe. Although there has been a higher early mortality rate in the transplanted patients in the past, the incidence of rejection episodes is lower than in patients without amyloidosis. Reduced immunosuppression has decreased postoperative mortality and morbidity. Colchicine at 1 to 2 mg per day dramatically relieves the symptoms and reduces the incidence of attacks in FMF, and interleukin (IL)-1 receptor antagonism is an increasingly attractive treatment alternative.[41]

Alport Syndrome

Dialysis and transplantation pose no particular problems for patients with Alport syndrome. Recurrent disease has not been well documented. Improvement or stabilization of deafness after renal transplantation has occasionally been reported. There is a 3% to 5% risk of developing de novo antiglomerular basement membrane (anti-GBM) nephritis after transplantation, typically occurring within the first year and resulting in graft loss.[42]

Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease is responsible for approximately 4% to 12% of ESRD cases in the United States and Europe. Native kidney removal is only required if the kidneys are massive due to polycystic disease or there is associated persistent infection or severe hypertension. Embolization of native kidneys prior to transplant may be a

less invasive treatment strategy in the future.[43] Occasionally, patients with severe liver cysts will require combined liver-kidney transplantation, primarily due to symptoms related to cyst volume and the impact on nutritional status.[44] Screening for cerebral aneurysms prior to transplant is generally directed toward those with a family history or with new onset headaches.[45]

Glomerulonephritis

Almost all types of glomerulonephritis have been reported to recur after transplantation. There is, however, much variation between the various types of glomerulonephritis with regard to the frequency of recurrence, the clinical course, and the prognosis. The overall incidence of recurrence is less than 10% to 20% and recurrent disease accounts for less than 2% to 4% of all graft failures (Table 82.4).[46]

Focal Segmental Glomerulosclerosis

Recurrent focal sclerosis may be seen early after transplantation, presenting with nephrotic-range proteinuria and a rapid decline in renal function. Histologically, the features on light microscopy that permit categorization are focal and segmental sclerosis, affecting a small number of glomeruli, often those in the deep juxtamedullary cortex. The development of foot-process fusion can be immediate after transplantation and precede glomerular segmental sclerosis by weeks to months (Fig. 82.7). The frequency of recurrence is about 20% in adults and may be as high as 40% in children. When stringent definitions of primary focal segmental glomerulosclerosis (FSGS) are applied (i.e., the nonfamilial inheritance pattern from patient history and documented biopsy-proven disease), the recurrence rate approaches 50%.[47] Patients presenting with rapid progression of renal disease from the time of diagnosis of nephrotic syndrome to ESRD have higher risk for recurrence. If a transplant patient suffers graft loss because of recurrent FSGS, there is ~50% risk of subsequent allograft failure within 5 years of a second transplantation. With increasing understanding of the genetic causes of FSGS (e.g., podocin and nephrin mutations) a more tailored approach to FSGS may be possible in the future, with avoidance of living donors with similar genetic risk.[48]

Treatment for recurrent FSG remains disappointing. Heavy proteinuria and nephrotic syndrome are usually resistant to steroids.[49] Cyclosporine (CsA) or other immunosuppressants do not seem to prevent recurrence. In many cases, the rapidity of recurrence immediately post-transplant strongly suggests the presence of a circulating factor in primary FSGS that is toxic to the glomerular epithelial cell/podocyte interface. It has been shown that sera from some patients with FSGS increases the permeability of isolated glomeruli to albumin.[50] Recently, this circulating factor has been suggested to be urokinase receptor (uPAR) potentially derived from circulating neutrophils.[51] Use of a regenerating protein adsorption

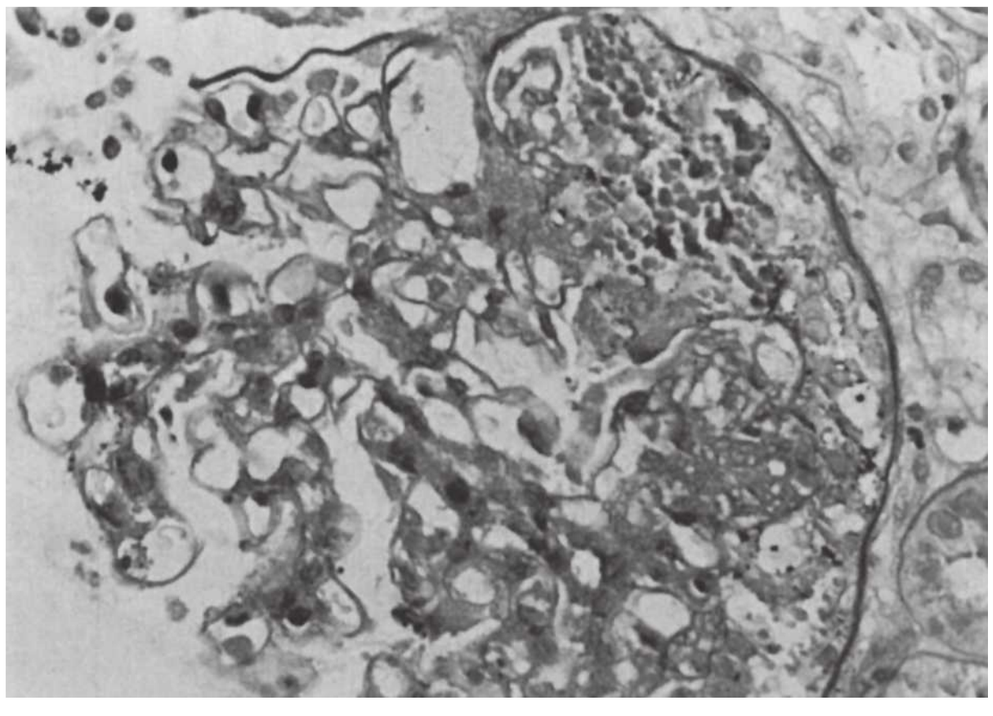


FIGURE 82.7 A renal biopsy specimen of a transplanted kidney showing recurrence of focal segmental glomerulosclerosis. (Periodic acid–Schiff stain, magnification ×250.)

82.4 Recurrent Disease in Renal Allografts

Disease	Approximate Recurrence Rate (%)	Graft Loss Due to Recurrence
Primary Glomerulonephritis		
Membranous	10%–30%	Uncommon
FSGS	30%–60%	Common
HUS	20%–50%	Common
Type I MPGN	20%–30%	Common
Type II MPGN	80%–100%	Common
HSP	15%–50%	Uncommon
IgA nephropathy	30%–50%	Uncommon
Anti-GBM	Rare	Uncommon
ANCA associated	20%	Common
Systemic Disease		
Hyperoxaluria	80%–100%	Common
Cystinosis	50%–100%	Uncommon
Fabry disease	Rare	Common
Sickle cell disease	Rare	Common
Diabetes type I	100%	Uncommon
SLE	<10%	Uncommon

FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; MPGN, membranoproliferative glomerulonephritis; HSP, Henoch-Schonlein Purpura; IgA, IgA nephropathy; GBM, anti-glomerular basement membrane disease; ANCA, antineutrophil cytoplasmic antibody associated vasculitis; SLE, systemic lupus erythematosis.

column or plasma exchange can reduce protein excretion in patients with recurrent FSGS in the transplant. More prolonged remissions have been achieved using plasma exchange that is initiated promptly after the onset of proteinuria or the combination of plasma exchange and cyclophosphamide. These prolonged beneficial results have also been reported in children treated with plasma exchange and cyclophosphamide.[52]

Antiglomerular Basement Membrane Disease

Based on histology and fluorescence studies, anti-GBM disease is associated with >50% recurrence rate in the allograft. However, only 25% of patients with biopsy-proved IgG staining along the capillary wall have evidence for clinical disease activity. Furthermore, graft failure due to recurrent disease is less common, estimated at <5%.[53] Although engraftment during the presence of anti-GBM antibodies has been reported to be successful, many transplant centers still prefer serologic quiescence of anti-GBM antibody production for 6 to 12 months before proceeding with transplantation to reduce the risk for recurrent anti-GBM disease. Despite delaying transplantation to allow anti-GBM antibody to fall, recurrence has been reported.[54]

Hemolytic Uremic Syndrome (HUS)

Typical (diarrhea-associated) hemolytic uremic syndrome (HUS) does not recur in the transplant, although atypical (nondiarrheal) aHUS has a high recurrence rate that usually leads to graft loss.[55] aHUS is the clinical manifestation of complement dysregulation, either via complement deficiencies or autoantibodies. Recurrence rates of 80% to 100% have been reported for factor H or I deficiencies, whereas membrane cofactor protein (MCP) deficiency does not usually recur. The recurrence rate may be higher in recipients of living-related transplants, those of an older age at the onset of HUS, those with a short duration between disease onset and ESRD or transplantation, who use living related donors, and, to a lesser degree, in those who had been administered calcineurin inhibitors (CsA or tacrolimus).[56] There is no treatment for recurrent HUS that has been proven to be consistently successful. Salicylates, dipyridamole, plasma infusion, and plasma exchange have been shown to be of limited benefit. However, case reports of successful treatment and prevention of recurrent HUS in kidney transplant with the anti-C5a antibody eculizumab have generated encouraging results.[57,58] In preparation for transplant, patients with suspected aHUS should be screened at a minimum for factor H, I, and MCP deficiencies to aid in prognosis and in potential peritransplant treatment with plasma exchange and/or eculizumab. CsA and tacrolimus have both been associated with altered coagulation mechanisms and the development of de novo HUS in renal transplant recipients, particularly in combination with sirolimus.[59] These agents should, therefore, be used with caution in patients whose original kidney disease was due to HUS.

IgA Nephropathy/Henoch-Schönlein Purpura

In many parts of the world, IgA nephropathy (IgAN) is the most common type of glomerulonephritis. Although histologic recurrence of IgAN is common (up to 75%), its presentation is often clinically mild, and graft loss specifically due to IgAN is uncommon (<5%).[46] Patients with IgAN have at least comparable if not better graft survival rates than those with other diseases.[60]

The closely related Henoch-Schönlein purpura (HSP) has been reported to recur with similar frequency and outcomes as IgAN.[61] Clinically, recurrent HSP or IgAN can be severe with crescentic glomerulonephritis, nephrotic syndrome, graft failure, and variable recurrence of purpura.[62] To reduce recurrence, the delay of engraftment is recommended for at least 6 to 12 months after the skin lesions of HSP have resolved.

Membranoproliferative Glomerulonephritis Type I and Type II

Type I and type II membranoproliferative glomerulonephritis (MPGN) can recur posttransplant and can negatively impact long-term graft survival.[63] Type II MPGN may recur at a higher frequency (60% to 100%) than type I MPGN (15% to 30%).[64,65] The early development of nephrotic syndrome and persistent microscopic hematuria from the time of transplantation are clinical markers suggesting recurrence rather than rejection. Levels of serum C3 do not accurately predict recurrences. Specific disease-targeted therapy is not well defined, except in the case of MPGN type II with known complement factor deficiency (factor H or I) in which plasma exchange is warranted.[66]

Membranous Nephropathy (MN)

Graft survival for patients with membranous nephropathy (MN) is similar to the general transplant population despite a recurrence rate of up to 40%.[67,68] MN can also present as a primary de novo condition in allograft recipients.[69] Recurrent MN with nephrotic syndrome generally occurs earlier, at an average of 10 months compared with de novo MN, which is usually seen about 18 to 20 months after transplantation (Fig. 82.8). Rituximab has been shown in initial reports to be of benefit in proteinuria regression and renal function stabilization.[68,70]

Systemic Lupus Erythematosus (SLE)

Recurrence of clinically significant systemic lupus erythematosus (SLE) is relatively rare following transplant.[71] Similarly, the reactivation of other nonrenal manifestations of SLE after transplantation is extremely infrequent and is often controlled by the immunosuppressive medications when it occurs.[72] Recurrence is not predictable with serologic monitoring. However, there should be no systemic disease activity prior to transplantation.[73] Recurrences can be successfully treated with steroids, mycophenolate mofetil, or chlorambucil.

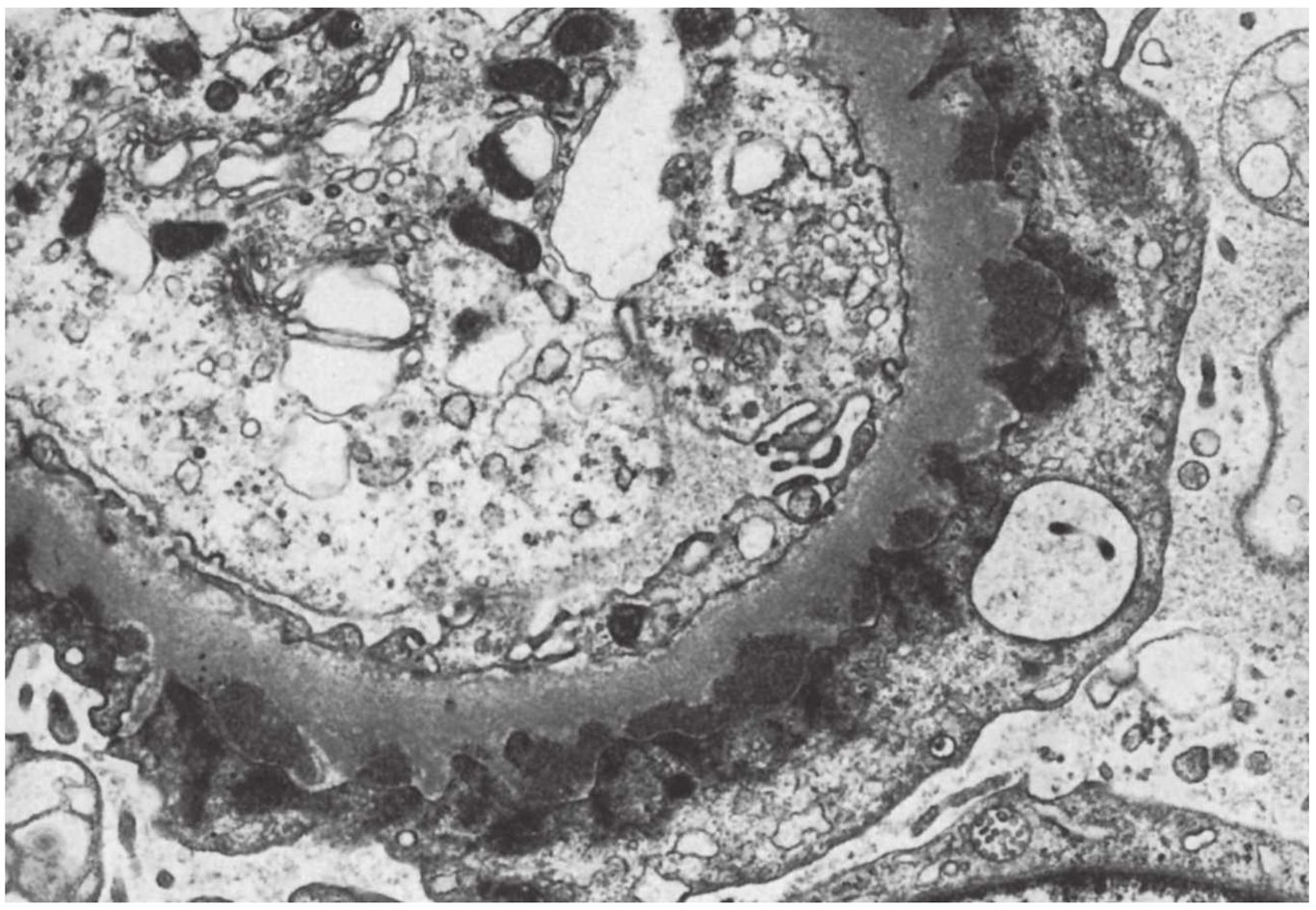


FIGURE 82.8 An electron micrograph of de novo membranous glomerulonephritis.

Antineutrophil Cytoplasmic Antibody–Associated Small Vessel Vasculitis

Patients with antineutrophil cytoplasmic antibody (ANCA)-related vasculitis have graft survival rates comparable to nondiabetic transplant populations.[74] As a relapsing and remitting disease, its recurrence rate following transplant is ~20%, which is slightly less than those remaining on dialysis.[75] ANCA titers do not appear to be predictive of recurrence posttransplant, thus transplantation can be reasonably pursued once clinical remission is achieved.[76] Recurrences are not prevented by baseline transplant immunosuppression, but can be treated successfully by adding cyclophosphamide and by increasing the steroid dose, together with decreasing or discontinuing some transplant medications.

Progressive Systemic Sclerosis (Scleroderma)

Transplant outcomes for patients with scleroderma are worse than in other diseases but are better than their wait-listed counterparts on dialysis.[77] Recurrence in the graft can occur within the first few months after transplantation. Recurrent scleroderma renal crisis in the allograft may be preceded by systemic features of scleroderma, such as the progression of diffuse skin thickening, new onset anemia, and cardiac complications.[78] The current recommendation for transplantation is that the patient should be clinically stable with an absence of visceral progressive systemic sclerosis activity prior to transplantation. Patients with early diffuse scleroderma should be closely monitored for new onset hypertension and should be treated continuously with angiotensin-converting enzyme (ACE) inhibitors. The majority of patients with scleroderma will improve generally after transplantation with a loss of Raynaud syndrome and improvement of the skin condition.[77] Therefore, transplantation is justified if the patient has not been severely debilitated by the systemic effects of scleroderma.

Interstitial Disease

Chronic Pyelonephritis

Chronic pyelonephritis is a diagnosis that has been frequently used for nonspecific interstitial nephritis, not necessarily caused by bacterial infection. The presence or history of significant urinary infection is important to identify. Because of the risk of residual foci of infection that may predispose a patient to bacteremia or may seed the urinary tract and transplant kidney, pretransplant nephrectomy may be indicated in these patients.

Analgesic Nephropathy

Patients with analgesic nephropathy need to be identified because cessation of the use of nephrotoxic analgesics is essential for these patients. Kidney function may improve after cessation of the use of analgesics, and damage to the allograft is a significant risk if this use persists. There is an increase in the incidence of transitional cell carcinoma of the urinary tract in patients with analgesic nephropathy.

GENERAL EVALUATION

This assessment should include not only a complete medical evaluation and a determination where possible of the underlying disease causing renal failure, but also a careful surveillance for problems that might arise following transplantation (Table 82.5).[79]

A careful physical examination should be performed to identify coexisting cardiovascular disease, infection, and malignancy. Additional examinations should assess pulmonary reserve, gastrointestinal (GI) disease, and genitourinary (GU) disease, as indicated by the patient's history. A psychosocial assessment should be performed to screen for potential barriers to successful transplantation.

82.5 Pretransplantation Recipient Medical Evaluation

1. History and physical examination
2. Social and psychiatric evaluation
3. Determine primary kidney disease activity and residual kidney function
4. Dental evaluation
5. Laboratory studies
   - Complete blood cell count and blood chemistry
   - HBsAg
   - HIV
   - Antibodies to cytomegalovirus and Epstein–Barr virus
   - HLA typing and antibodies screening
   - Urine analysis and urine culture
6. Chest X-ray
7. Electrocardiogram
8. Special procedures for selected patients
   - Abdominal ultrasound of gallbladder
   - Upper gastrointestinal study or endoscopy
   - Barium enema or colonoscopy
   - Purified protein derivative (PPD) skin test for tuberculosis
   - Cardiac stress testing
   - Angiogram: coronary
   - Cystourethrography
9. Consults (optional)
   - Psychiatric
   - Gynecology evaluation and mammography (for female >40 yr)
   - Urologic assessment (voiding cystourethrography, cystoscopy, or urodynamic studies in patients with vesicoureteric reflux, neurogenic bladder, bladder neck obstruction, or strictures)

HBsAg, hepatitis B surface antigen; HLA, human leukocyte antigen; PPD, purified protein derivative.

The laboratory evaluation should include routine hematologic tests to detect leukopenia or thrombocytopenia, liver function tests to identify patients in whom the metabolism of immunosuppressive agents may be abnormal, complete hepatitis and HIV profiles, viral titers, and urinalysis when possible.

In general, there are few absolute contraindications to transplantation (Table 82.2). Conditions excluding a patient from renal transplantation may include the presence of severe ischemic heart disease, the presence of persistent infection, or untreated cancer. When a patient has had previous curative therapy for cancer, it is generally thought appropriate to wait at least 2 years with proven freedom from recurrence before proceeding with transplantation, although individual tumor types and patient circumstances may shorten this waiting time.[80]

Cardiovascular Evaluation

Cardiovascular disease is a major cause of morbidity and mortality for the patient with CKD and ESRD, whether the patient remains on dialysis or chooses to have a kidney transplant.[81,82] Risk factor assessment and modification should be pursued. Patients considered at high risk for heart disease (for patients with CKD, men >45 years and women >55, those with an abnormal ECG, history of DM or of prior ischemic heart disease) should undergo further investigation with a stress test and/or coronary angiography.[83] Up to 50% of asymptomatic diabetic transplant candidates have significant coronary artery disease, which may be missed on stress testing.[84] Thus, some centers consider angiography as the initial screening test for this subgroup. Although most centers will intervene on identified asymptomatic coronary lesions either with stenting or coronary artery bypass grafting, no randomized trial has clarified the value of this preemptive strategy, and in the nontransplant scenario (major vascular surgery), intervention has not been shown to be of benefit.[85,86] Additional assessment of peripheral arterial disease should be considered in those with known atherosclerotic disease, diabetes, and poor femoral or peripheral pulses on exam.

Hepatitis Screening

Hepatitis B Virus

Patients should undergo routine screening for the hepatitis B surface antigen (HBsAg), surface antibody, and core antibody pretransplant. Because of the poor conversion rate in patients with ESRD, a hepatitis B vaccination of patients should be given early in the course of progressive renal failure.[87] Previously vaccinated patients who are HBsAg-negative should be tested annually for antihepatitis B virus (HBV) antibodies and should receive booster vaccinations when the titer decreases to <10 mIU per milliliter. No known loss of graft function has occurred as a result of active vaccination with the hepatitis B vaccine.[88] Given the success of antiviral therapy (lamivudine, entecavir, tenofovir, and adefovir) against hepatitis B, chronic HBV infection is not a contraindication to transplantation.[89] Pretransplant management should include a liver biopsy to determine the degree of underlying liver disease and risk of progressive liver failure after transplantation. Patients with decompensated cirrhosis and ESRD should be evaluated for a combined liver–kidney transplant rather than kidney or liver transplant alone because of the high mortality risk associated with cirrhosis in this population.[90] To minimize the risk of viral replication and progressive liver disease, HBsAg-seropositive kidney transplant recipients should be treated with antiviral therapy at the time of transplantation, irrespective of their HBV–DNA level.

Hepatitis C Virus (HCV)

The prevalence of antihepatitis C virus (HCV) antibody positivity in kidney transplant recipients is estimated to be between 6% and 46% depending on the transplant center and/or country.[91] Although HCV-related liver disease can worsen

after transplantation in the setting of chronic immunosuppression, the survival benefit of transplantation over dialysis outweighs this risk. Transplant candidates who are HCV+ with detectable RNA and no clinical stigmata of cirrhosis should undergo liver biopsy to determine histologically the degree of underlying liver disease. In those with cirrhosis, combined liver–kidney transplantation should be considered (Fig. 82.9). In those without cirrhosis, antiviral therapy should be considered to minimize the risk of developing post-transplant complications.[92] Goals of therapy are not only to avoid progressive liver disease, but also to avoid the extrahepatic complications such as the development of new onset diabetes after transplantation (NODAT) or glomerulonephritis that may occur in HCV infected renal transplant recipients.[93] A 48-week course of pegylated interferon (IFN)-α and ribavirin is often used in non-CKD populations. Unfortunately, in the setting of CKD, rapid accumulation of ribavirin can occur, which can lead to significant hemolysis. In the setting of CKD, pegylated IFN-α is associated with a high rate of adverse effects that lead to discontinuation of this therapy with no demonstrable benefit in sustained viral response (SVR) over nonpegylated IFN-α. Therefore, in patients on dialysis, monotherapy with nonpegylated IFN-α for 24 to 48 weeks is suggested as first-line therapy, with viral response rates as high as 70% to 80%, with the average SVR of 30% to 40%.

HIV Screening

All patients should be screened for HIV prior to transplantation. Successful transplantation in HIV individuals is now common.[94] Current disease-specific inclusion criteria for transplantation include an undetectable viral load, CD4 T-cell count >200 cells per milliliter, in addition to other features from the medical history including absence of multidrug-resistant fungal infection, history of malignancy, or progressive multifocal leukoencephalopathy. Unique considerations in the management of the patient with HIV following transplant include the potential for significant drug interactions between protease inhibitors, nonnucleoside reverse transcriptase inhibitors and calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, and the surprisingly high rate of acute rejection encountered in HIV+ transplant recipients.[95] For these reasons, management is often coordinated with infectious disease consultation at experienced transplant centers.

Malignancy Screening

Patients with no history of malignancy should be screened using age-appropriate guidelines developed for the general population. Additionally, screening for renal cell carcinoma via ultrasound is gaining attention given its increased prevalence in patients with end-stage kidney disease and following a transplant.[96,97] Patients with a history of malignancy should be disease free prior to transplantation. Generally, it is recommended that patients should have a disease-free interval of 2 to 5 years prior to transplantation, due to the increase in malignancy risk ascribed to immunosuppressive medications following the transplant. However, with advances in treatment options for patients with various forms of malignancy, it is often difficult to ascribe a specific waiting period following successful treatment. The Canadian Society of Transplantation

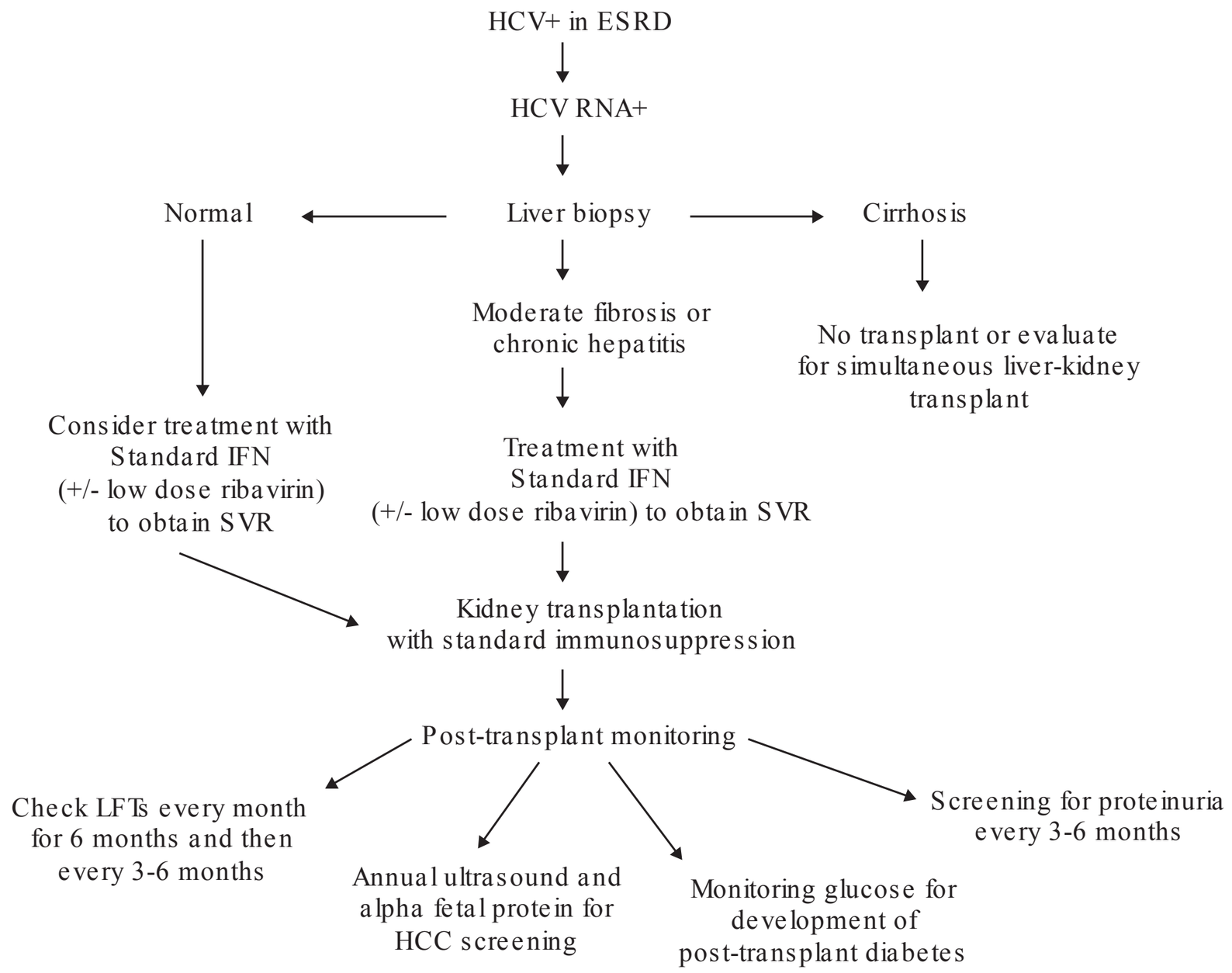


FIGURE 82.9 An algorithm for pre- and posttransplant management of HCV+ patients. *ESRD,* end-stage renal disease; *IFN,* interferon; *SVR,* sustained viral response; *HCC,* hepatocellular carcinoma. (Adapted from Huskey J, Wiseman AC. Chronic viral hepatitis in kidney transplantation. *Nat Rev Nephrol.* 7(3):156–165, with permission.)

has published consensus guidelines that attempt to take into consideration a number of more common clinical circumstances, but these must continue to be reviewed in the context of emerging data.[80] Oncology referral and discussion of expected disease-free survival is an important part of the evaluation process for those with a history of malignancy.

Infection

Patients should be free of active infection prior to transplantation. Appropriate immunizations against influenza, pneumococcus, hepatitis B, and, when appropriate, varicella, should be performed prior to transplant. Patients in areas with high prevalence rates of tuberculosis and those with an abnormal chest X-ray suggesting granulomatous disease should undergo purified protein derivative (PPD) testing. If the PPD is nonreactive (as is common in patients with renal failure) or if the patient has a history of BCG vaccination, IFN-γ release assay testing may be of benefit in the diagnosis of latent tuberculosis.[98]

Additional Pretransplant Evaluation Considerations

Gastrointestinal Evaluation

In patients with symptomatic cholelithiasis, a cholecystectomy should be performed to eliminate the risk of possible sepsis after transplantation. Patients with diabetes and asymptomatic gallstones seen with ultrasonography (~20% to 30% prevalence) may also benefit from pretransplant elective cholecystectomy.[99] A colonoscopy should be performed for patients >50 years of age to screen for colon cancer. Those with known colonic disease, especially those with diverticulitis, should be evaluated with a barium enema and a colonoscopy and, if appropriate, should be treated with surgical resection prior to transplantation.

Genitourinary Evaluation

An accurate evaluation of the lower urinary tract function prior to transplantation is important to minimize postoperative urologic complications. The original renal disease must be clearly defined. Any history of prior bladder surgery, repeated urinary infections, and current reports of urine cultures should be obtained. A voiding cystourethrogram should be performed if there is clinical or historical evidence of a bladder or ureteric abnormality. Cystoscopy and urodynamic studies should be performed in patients with evidence of bladder dysfunction. Urologic operations are necessary either to correct or improve obstructive lesions or sometimes to provide a conduit in the presence of a neurogenic bladder or a previous cystectomy.

Immunologic Evaluation

The human HLA system—encoded on the short arm of chromosome 6—encodes antigens that play a major role in host immune responses. The importance of these antigens in the practice of organ transplantation became evident when immunologic mechanisms were found to be responsible for immediate allograft destruction in early attempts at kidney transplant between non-HLA identical pairs.[100] Antibodies against HLA antigens are formed as a result of pregnancy, transfusions, and prior organ transplantation and have the potential to cause hyperacute, acute, or chronic antibody-mediated allograft rejection (AMR).[101] A landmark study by Drs. Patel and Terasaki in 1969 described a complement-dependent cytotoxicity assay (CDC) for anti-HLA antibodies that was highly predictive of hyperacute graft rejection.[102] The CDC assay screens for donor-directed complement fixing antibodies in the sera of recipients via in vitro mixing studies with donor lymphocytes, and became the first routinely used cross-match technique in organ transplantation.

Although CDC cross-matching revolutionized the pretransplant immunologic evaluation and has remained in use for 5 decades, it is associated with limited sensitivity and requires a subjective visual assessment of cell lysis. Flow cytometry (FCXM) was introduced in the 1980s as a method for screening recipient sera for donor-directed HLA antibodies with up to a threefold higher sensitivity compared to CDC. FCXM involves the incubation of donor T and B lymphocytes with recipient sera, allowing for the binding of any donor-directed HLA antibodies that may be present. After the addition of a fluorochrome-conjugated secondary (anti-IgG) antibody, anti-HLA antibody strength is measured by mean fluorescence intensity (MFI) or channel shift. Positive FCXM has been shown to be predictive of rejection and graft loss.[103] In addition to a more sensitive antibody detection, FCXM involves independent testing of B and T lymphocytes and thus allows for further characterization of HLA antibodies as specific to antigens belonging to either class I (present on all nucleated cells) or class II (present only on antigen-presenting cells such as B cells).

More recently, the practice of pretransplant antibody screening was again revolutionized by the introduction of solid phase testing using antigen-coated microbeads (SAB).[104] This assay, unlike the cell-based CDC and FCXM, uses microparticle "beads" coated with a single HLA antigen peptide incubated with recipient sera and a fluorochrome-conjugated secondary antibody. The strength of antibody binding is again determined by MFI; however, the identification of exact antigen specificities is now possible with anti-HLA antibodies further characterized as donor specific (DSA) or not. The presence of pretransplant DSA detected by single antigen beads (SAB) has been associated with an increased risk of antibody-mediated rejection (AMR) in multiple reports, however the antibody strength (MFI) that correlates with poor graft outcomes remains a matter of debate.

In addition to HLA and blood group ABO typing, most patients undergo a final cross-match prior to the kidney transplant in order to minimize the risk of hyperacute and acute AMR. There is considerable center-to-center variation in the cross-match technique and it includes CDC, FCXM, SAB, or any combination of the three. In general,

contraindications to transplant include a positive CDC cross-match or T-cell FCXM.[105] A number of transplant centers in the United States have forgone the CDC method in favor of FCXM and SAB analysis, tests that offer improved sensitivity at the likely expense of decreased specificity. For example, although a positive CDC cross-match has remained an absolute contraindication to transplant, the clinical implications of a weak FCXM or low level antibodies detected by SAB are less clear and are currently a matter of intense clinical research. Thus, the evolution of cross-match techniques has resulted in increasing protection against early AMR at the expense of potentially withholding the transplant in patients with clinically irrelevant antibodies detected by sensitive assays.

Although pretransplant cross-matching serves to minimize the risk of early AMR between a recipient and a particular donor, the overall level patient sensitization helps to estimate the likelihood of positive cross-match with the general population. Patients with high levels of circulating anti-HLA antibodies are regarded as sensitized and of higher immunologic risk. Sensitization is quantified by the degree of PRA, or more recently by calculated PRA (cPRA). Historically, PRA has been determined by complement-dependent cytotoxicity mixing studies of recipient sera with a panel of lymphocytes derived from the general population, where positive reactions in 50% of samples would correspond to a PRA of 50%. It should be noted that the degree of sensitization has no bearing on the outcome of a cross-match between recipient and an individual donor, serving instead to estimate the probability of a positive cross-match between recipient and any given potential donor in the general population. As increasing levels of PRA correspond to decreasing numbers of donors to which the recipient will have a negative cross-match, sensitized patients wait much longer for transplants and are transplanted at a lower rate per year. Strategies aimed at desensitizing patients with either high PRA or positive cross-matches to potential living donors using plasmapheresis, intravenous immunoglobulin (IVIG), and anti-B cell agents bortezomib and rituximab have been met with variable success and are associated with high rates of posttransplant AMR.[106,107]

In October 2009, the United Network for Organ Sharing (UNOS) implemented a strategy replacing conventional PRA measurements with cPRA, a measure of sensitization based on unacceptable antibody levels as determined by SAB analysis.[108] Potential transplant patients are screened for antibodies against HLA antigens by SAB assays at various intervals while on the waiting list, with antigens to which the patient has significant levels of antibody listed as "unacceptable" by the transplant center. The cPRA is determined by entering the patient's unacceptable antigens into a formula that calculates the relative frequency of these antigens in the general population. Using this strategy, patients are able to undergo a "virtual" cross-match with prospective donors, taking into account both the donor HLA profile and the previously listed unacceptable antigens for the recipient. Final cross-matching is then performed only if the virtual cross-match is negative. An initial analysis of virtual cross-matching shows improved organ allocation efficiency and improved access to transplantation for sensitized patients on the waiting list compared to prior eras.[109]

DONOR SELECTION

Live Kidney Donation

Living donor transplants comprise about 35% of all transplants performed in the United States (Fig. 82.2), whereas their proportion is much less (10% to 15%) in Europe and Australia, and much higher in the Middle East.[110] Outcomes of related versus unrelated donor kidney transplants are comparable, with the exception of the 2-haplotype HLA matched living related donor transplant, and are superior compared to kidney transplants from a deceased donor.[4] This is due to a number of factors that include the minimization of cold ischemia time and the risk of delayed graft function, as well as the benefits imparted by the opportunity to perform a detailed history and medical assessment of the donor.

The initial series of tests for a potential living donor include ABO blood group and HLA tissue typing, which can be completed at a brief outpatient visit. The living donor not only needs a thorough medical evaluation, with particular attention to renal function and the urinary tract, but also a renal angiography or magnetic resonance angiography to identify vascular or anatomic variation of the kidneys or the collecting systems (Table 82.6). It is important to ascertain that both kidneys are of normal size and configuration and that a donor kidney with a single renal artery can be obtained. Several long-term follow-up studies have not revealed any adverse problems for the living donor with a single kidney and support the judicious use of the live kidney donor.[111,112] The donor surgical mortality risk is 3.1 per 10,000 donors, and life expectancy in the donor remains unaffected.[112] Although compensatory hyperfiltration occurs in the remaining kidney, the achieved glomerular filtration rate is typically 70% of baseline after 2 to 4 weeks. Blood pressure appears to increase by ~5 mm 5 to 10 years from donation over pretransplant values, adjusted for blood pressure increases with aging.[113] Black donors appear to have a greater risk of hypertension than white donors, thus it may be reasonable to have more stringent blood pressure thresholds for the black potential kidney donor.[114] Women who may desire pregnancy following kidney donation should be counseled that current observational data suggest a similar rate of fetal loss, preeclampsia, gestational diabetes, and gestational hypertension compared to the general population, but higher rates of each of these parameters compared to pregnancies that had occurred in donors prior to donation.[115,116]

Efforts to increase transplantation rates have led to the consideration of living donors with mild medical conditions and from extended social relationships from the potential recipient (Table 82.7). The nondirected kidney donor, an individual who contacts transplant centers wishing to

82.6 Suggested Evaluation Process for Potential Living Donors

Donor screening
Educate patient regarding deceased and live donation
Take family and social history and screen for potential donors
Review ABO compatibilities of potential donors
Tissue type and cross-match ABO-compatible potential donors
Choose primary potential donor with patient and family
Educate donor regarding process of evaluation and donation
Donor evaluation
Complete history and physical examination
Comprehensive laboratory screening to include complete blood count, chemistry panel, HIV, very low-density lipoprotein, hepatitis B and C serology, cytomegalovirus, glucose tolerance test (for diabetic families)
Urinalysis, urine culture, pregnancy test
Protein, 24-hr urine collection
Creatinine, 24-hr urine collection
Chest radiograph, cardiac stress test for patients >50 years of age
Helical computed tomography urogram
Psychosocial evaluation
Repeat cross-match before transplantation

82.7 Exclusion Criteria for Living Kidney Donors

Age <18 or >65–70 yr
Significant medical illness (e.g., cardiovascular/pulmonary diseases, recent malignancy)
History of recurrent kidney stones
History of thrombosis or thromboembolism
Psychiatric contraindications
Obesity
Hypertension (>140/90 mm Hg or necessity for medication)
Proteinuria (>250 mg/24 hr)
Microscopic hematuria
Abnormal glomerular filtration rate (<80 mL/min)
Diabetes (abnormal glucose tolerance test or hemoglobulin A_{1c})
Urologic/vascular abnormalities in donor kidneys

donate a kidney for purely altruistic reasons, provides an opportunity to benefit individuals who may have an incompatible donor or individuals without a living donor option.[117] Paired exchange programs have been developed to identify two potential donors who wish to donate to a family or friend but are unable to due to blood group incompatibility or a positive cross-match. Two such donors and their prospective recipients are then paired, with donor A donating to recipient B and donor B donating to recipient A. When an altruistic donor is introduced to paired exchange programs, it may result in significant opportunity for transplantation of a number of incompatible pairs.[118,119] Another circumstance is the matched donor in which a prospective recipient pays a monthly fee to a coordinating site, which presumably has access to a list of potential parties interested in donating their kidney. In the United States, assurances required from these donor/recipient circumstances must include the lack of monetary benefit for the donor (altruism). The U.S. Organ Transplantation Act of 1984 (HR5580, Title II) makes it a federal crime to engage in organ sale and commerce. Other countries have eliminated the waiting list with the use of monetary incentives for living unrelated donation, a topic that continues to be debated worldwide.[120,121]

Deceased Kidney Donation

Deceased kidney donors can be classified as those donors who are deceased by brain death (DBD) or those who are deceased by cardiac death (DCD). The criteria for the diagnosis of brain death have been well defined in most Western countries, although the requirements vary little from country to country (Table 82.8). Protocols exist that vary from country to country regarding DCD donation, but generally involve a waiting period of 5 minutes following the declaration of death prior to organ procurement.

DBD donors have been subcategorized as standard criteria donors (SCD) or expanded criteria donors (ECD). ECD donors are defined based on the presence of variables

82.8 Medical Evaluation of the Potential Deceased Donor

I. Diagnosis of death
  A. Preconditions
    1. Positive diagnosis of brain death (irremediable structural brain damage)
    2. Planned withdrawal of cardiopulmonary support for irreversible conditions
  B. Exclusions
    1. Primary hypothermia (<33°C)
    2. Drugs
    3. Severe metabolic or endocrine disturbances
  C. Tests
    1. Absent brainstem reflexes
    2. Apnea (strictly define)
II. No preexisting renal disease
III. No active infection tests:
  A. HBsAg; five antibodies to cytomegalovirus and hepatitis C virus
  B. HIV antibodies
  C. HIV antigen in high-risk patients

HBsAg, hepatitis B surface antigen.

that increased the risk for graft failure by 70% compared with an SCD kidney and include donors over the age of 60, or donors between the ages of 50 to 59 with two of three additional criteria: (1) cerebrovascular accident as a cause of death, (2) prior diagnosis of hypertension, or (3) terminal serum creatinine greater than 1.5 mg per day. The rationale for making the distinction between SCD and ECD was to allocate kidneys efficiently to those in greatest need (those at greatest risk for mortality while on dialysis).[122] The survival benefit of ECD transplant over dialysis is present across all candidates, but in particular is of benefit to those with diabetes over the age of 40 or who are in regions with waiting times for a transplant of >1,350 days.[5]

DCD donors can be controlled (with a planned withdrawal of cardiopulmonary support following a consent for donation) or uncontrolled (a cardiopulmonary death in a medical setting with rapid perfusion of organs, prior to consent). The latter is practiced in countries in which there are national policies of presumed consent.[123] The additional warm ischemia time that occurs during the DCD procurement process results in higher rates of delayed graft function and primary nonfunction, but with comparable long-term graft survival to SCD kidney transplants.[124] Figure 82.10 summarizes the most recent graft survival data from the United States by type of organ.

For all organ donors, there should be no evidence of primary renal disease and no generalized viral or bacterial infection. Biopsies are often performed to determine glomerulosclerosis in cases in which there is a question of suitability for transplant, but this has not consistently demonstrated a predictive value for graft function or longevity.[125] Screening for hepatitis B, C, and HIV infection is performed to exclude donors, although in the case of hepatitis C reactivity, these donors may be used for selected recipients with chronic hepatitis C infection with good results.[126] Epstein–Barr virus (EBV) and cytomegalovirus (CMV) testing is performed to assess the risk of transmission and posttransplant complications for the recipient.

THE TRANSPLANT OPERATION–DONOR PROCUREMENT

Living Donor Nephrectomy

A living donor nephrectomy can be performed via either an open or a laparoscopic approach. The open approach entails a flank incision by an open nephrectomy. The approach to the kidney, typically the left kidney because this has the longer renal vein, may be either below or through the bed of the 12th rib using a retroperitoneal approach, or rarely via an anterior transperitoneal approach using a midline incision. Care

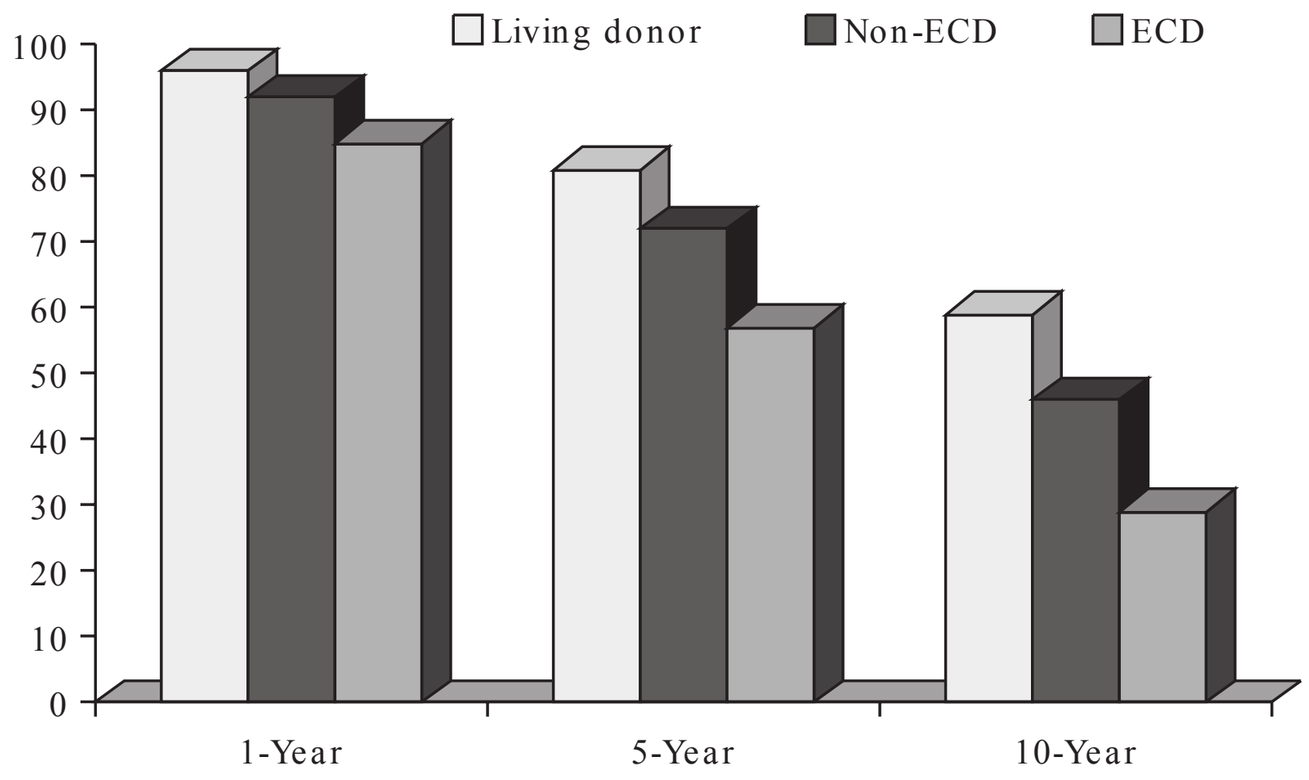


FIGURE 82.10 One, 5-, and 10-year kidney graft survival from living donors (LD), standard criteria donors (non-SCD), and expanded criteria donors (ECD). (Adapted with permission from 2009 OPTN/UNOS Annual Report, Tables 5.10a, b, d.)

82.9 Advantages and Disadvantages of Laparoscopic Nephrectomy

Advantages

- Less postoperative pain
- Minimal surgical scarring
- Rapid return to fill activities and work (approx. 4 weeks)
- Shorter hospital stay
- Magnified view of renal vessels

Disadvantages

- Longer operative time, impaired early graft function, graft loss or damage during "learning curve"
- Pneumoperitoneum may compromise renal blood flow
- Tendency to have shorter renal vessels and multiple arteries
- Added expense of specialized instrumentation

must be given to retraction of the kidney during its removal to avoid traction injury of the renal artery and dissection in the hilum of the kidney, particularly between the ureter and the renal artery, which should be avoided to prevent damage to the ureteric blood supply. Furthermore, in removing the ureter down to the brim of the pelvis, care should be taken to leave an adequate amount of periureteric tissue. A living donor nephrectomy for transplantation can also be performed by laparoscopic approach.[127] This approach results in less postoperative surgical pain, a shorter hospital stay, and a quicker recovery than the standard open donor nephrectomy (Table 82.9). The laparoscopic techniques have been rapidly adopted worldwide; an analysis from Australia/New Zealand transplant centers upon the introduction of the laparoscopic technique in 1997 through 2004 demonstrates comparable rates of technical failure, delayed graft function, and graft survival to an open nephrectomy, with a conversion rate to open procedures of 6%.[128] This conversion rate is much higher than that reported for experienced centers of 1%.[129]

Deceased Donor Nephrectomy

Currently, most kidneys will be removed as part of a multiple-organ procurement procedure in which not only the kidneys are removed, but also the liver and heart and, occasionally, the lungs and pancreas. There are two basic approaches to a deceased donor nephrectomy. In one, each kidney is removed individually with a patch of aorta via an anterior approach, whereas in the other, which is the more satisfactory technique, both kidneys are removed en bloc with the appropriate segment of the aorta and vena cava. The dissection of the vessels and the kidneys can then be completed after hypothermic perfusion and storage. In situ perfusion may be performed in both cases before and during removal.

Renal Preservation

The effective preservation of the kidney is an integral part of a kidney transplantation program and has evolved on the basis of known principles of preservation because of a need for longer storage of kidneys.[130] The ability to preserve kidneys provides time for tissue typing and cross-matching and the selection of the most appropriate recipients for a particular donor on the basis of matching, as well as the preparation of the patients selected, who often may need dialysis before transplantation, and, finally, the transport of the kidneys to a center where an appropriately matched recipient may be awaiting a transplant.

There are two methods of preservation: simple cold storage in ice after flushing with a hypothermic solution to give a renal core temperature of 0°C and a more complicated approach of continuous perfusion of the kidney with an oxygenated colloid solution. The simple cold storage approach is most commonly used, and provides adequate preservation for at least 24 to 30 hours. The kidneys are initially flushed free of blood with a cold solution via the aorta and renal artery while the kidney is in situ. Many different flushing solutions have been used; currently the most common preservation solutions in use in the United States are Viaspan (University of Wisconsin [UW] solution or Belzer solution) and Custodiol (histidine-tryptophan-ketoglutarate [HTK]) (Table 82.10).[131] Drugs, metabolites, and other agents have been used to enhance the effects of cold preservation. The aim of these maneuvers is to reduce the incidence of posttransplant acute tubular necrosis.

In the absence of any warm ischemia, which is generally the case with a brain-dead donor on a ventilator, the immediate function can be obtained in most kidneys with up to 24 hours of preservation and even after 48 hours of preservation in some patients. However, from 24 hours onward, most kidneys will have a significant period of delayed function ranging from 1 day to several weeks and there will be a significant incidence of primary nonfunction. Because 18 to 36 hours is an adequate time for most units and also allows time for transport of kidneys within a region or country, there has been widespread adoption of the simple cold storage (CS) technique for preservation.

Compared to the more traditional CS technique, machine perfusion (MP) involves placing kidneys from a deceased donor on a perfusion device that provides either continuous or pulsatile flow of a hypothermic solution through the renal vasculature.[132] In theory, by eliminating toxic metabolic byproducts and providing nutrients and oxygen, MP may protect deceased-donor kidneys from peritransplant ischemia/reperfusion injury that is responsible for the majority of clinically significant delayed graft function (DGF), an event independently associated with acute rejection and poor graft survival.[133] In recent years, the use

82.10 Contents of Commonly Used Cold Preservation Solutions

	Custodiol (HTK)	UW
Sodium (mM)	15	30
Potassium (mM)	10	120
Magnesium (mM)	4	5
Histidine (mM)	198	—
Tryptophan (mM)	2	—
Alpha-ketoglutarate	n/a	
Mannitol (mM)	30	—
Sulfate (mM)	—	5
Phosphate (mM)	—	25
Lactobionate (mM)	—	100
Raffinose (mM)	—	30
Adenosine (mM)	—	5
Allopurinol (mM)	—	1
Glutathione (mM)	—	3
Insulin (units/L)	—	100
Dexamethasone (mg/L)	—	8
Hydroxyethyl starch (g/L)	—	50

HTK, histidine-tryptophan-ketoglutarate; UW, University of Wisconsin.

of kidneys from less traditional donors has been on the rise, including ECD and DCD, both of which are associated with significantly higher rates of DGF.[134,135] As a result, a number of recent clinical trials have studied preservation methods in an attempt to demonstrate improved rates of DGF in deceased donor kidney transplants.

Most recent clinical trials have shown improved DGF rates with the use of MP compared to CS. For example, in the largest prospective randomized controlled trial to date, Moers et al.[136] studied the outcomes of 336 kidney pairs, where 1 kidney per pair underwent MP and the other CS, and reported both lower rates of DGF and improved 1-year allograft survival in the MP group. Subsequent prospective extensions of this trial demonstrate lower DGF rates for both ECD and DCD, improved 1-year graft survival for ECD, but comparable 1-year graft survival for DCD kidneys with MP versus CS transplants.[137,138] In contrast, a UK-based paired kidney analysis of DCD kidneys undergoing either MP or CS failed to show any difference in terms of DGF rates or 1-year graft survival.[139] Despite these mixed results, MP likely results in modestly less DGF for deceased donor kidney transplants of any type compared to CS. Whether the increased cost associated with MP can be offset by improved long-term graft outcomes has yet to be clarified.

THE TRANSPLANT OPERATION–RECIPIENT SURGERY

The surgical technique of renal transplantation is standardized.[140] In cadaver transplantation, the kidney must first be inspected to ensure that it is suitable for transplantation before undertaking the operation. This procedure should be carried out in the operating room on a sterile back table. The procedure is to remove the unnecessary fatty tissue and to prepare the donor vessels. In small pediatric donors, both kidneys can be used en bloc for transplantation in adults.

The transplanted kidney is implanted in the retroperitoneal space in either the right or left iliac fossa through an oblique incision extending from the suprapubic area to a point just above and medial to the anterior superior iliac crest. For transplantation, after failed transplants in both iliac fossae, a lower midline intraperitoneal approach should be used.

The iliac vessels should be carefully dissected[141] and the lymphatics ligated to prevent lymphocele formation. The donor renal vein is anastomosed end to side to the external iliac vein. The renal artery is anastomosed to the external or common iliac artery end to side using a cuff of aorta as a patch for the anastomosis, or it is anastomosed end to end to the internal iliac artery, which has been previously ligated and divided. The end-to-side anastomosis using a cuff of aorta is the simpler anastomosis; it is the most appropriate one to use in cadaver transplantation when the renal artery is provided with a cuff of aorta. The end-to-end anastomosis to the internal iliac artery is technically more demanding and should only be used in living donor kidney transplantation.

Implantation of the ureter in the bladder is performed in one of two ways.[142] The first is to anastomose the spatulated end of the ureter mucosa to the dome of the bladder drawing muscle over the anastomosis to provide a tunnel. The second technique is to bring the ureter through the lateral wall of the bladder and down through a 2- to 3-cm submucosal tunnel and out in the vicinity of the patient's own ureteric orifices at the trigone, where it is anastomosed mucosa to mucosa. The success of the first technique is greater than the second. Preventive antibiotics with appropriate broad-spectrum activity should be given with the premedication, in particular to protect against the possibility of infection being transmitted with the transplanted kidney.

General Postoperative Management and Follow-up

Routine postoperative observations should include the monitoring of vital signs, fluid intake, and urine output. A postoperative hematuria is usually transient. The Foley

catheter is generally left in these patients for 3 to 4 days because of high urine outflow rates that occur during this time in order to prevent overdistension of the bladder. This is particularly important in diabetic patients who frequently have neurogenic bladders and can have extremely large bladder volumes before they develop an urge to micturate. Catheters should also be carefully monitored for obstruction and irrigated under sterile conditions if occluded by a clot.

Immediate function of the transplanted kidney makes postoperative management of the patient in the first few days much simpler than if the kidney is not functioning. The patient, particularly in the case of a living related transplant, may have a massive diuresis in the first 48 hours, and, for this reason, hourly monitoring of the urine output and a central venous line are essential to balance the fluid requirements appropriately. A very basic regimen, at least for the first few hours, is to replace fluid at the rate of the last hour's output plus 50 mL per hour of IV fluid. This can then be modified according to the kidney function and the central venous pressure.

Within 48 hours, particularly with a functioning kidney, the patient's restored sense of well-being is quite remarkable and most patients can get out of bed on the second postoperative day. Provided that no complications ensue and that any early rejection episode can be dealt with satisfactorily with appropriate treatment, these patients are ready to leave the hospital by the 3rd to 5th or 6th postoperative day.

After discharge from the hospital, the follow-up interval will depend on the patient's general condition and the development of additional problems. Routine biochemistry, hematology, and urine analysis should be obtained at each clinic visit. General guidelines for the frequency and type of posttransplant monitoring have been proposed by the Kidney Disease Improving Global Outcomes (KDIGO) workgroup,[143] which for the stable patient, include suggestions for monitoring laboratory parameters and clinic visits as frequently as every 2 to 3 times per week in the immediate posttransplant period tapering to a weekly, biweekly, and monthly schedule over the first 6 months.

IMMUNOSUPPRESSIVE THERAPY

Immunosuppressive therapy in renal transplant recipient consists of: (1) continuous baseline therapy (maintenance immunosuppression) to prevent the development of rejection and (2) short courses of intensive therapy peritransplant (termed induction therapy), or in the setting of acute rejection (antirejection therapy) to more completely abrogate the immunologic antidonor rejection response. The agents used for induction and antirejection therapy are similar and include high-dose methylprednisolone, monoclonal antibodies or polyclonal antisera, such as antilymphocyte globulin (ALG) and antithymocyte globulin (ATG), and B-cell directed therapies when the antidonor antibody is identified. The use of induction therapy in the United States now approaches 80% of all transplants and is employed for varying goals, including (1) the minimization of maintenance immunosuppresion such as corticosteroid withdrawal or calcineurin inhibitor minimization, avoidance or withdrawal (see later sections), (2) the minimization of risk for acute rejection in patients considered at increased immunologic risk, and (3) the delayed introduction of maintenance immunosuppression such as calcineurin inhibitors in settings of increased risk of delayed graft function/acute tubular necrosis, to avoid the vasoconstrictive effects and the potential for prolongation or potentiation of graft injury. Baseline immunosuppression traditionally involves the use of multiple drugs, each directed at a discrete site in the T-cell activation cascade and each with distinct side effects. The use of multiple agents at lower doses may provide greater protection from immunologic injury with fewer side effects than single agent therapy, thus two- and three-drug immunosuppression regimens are commonly employed. The maintenance immunosuppressive agents can be classified on the basis of their primary site of action as inhibitors of transcription (the calcineurin inhibitors cyclosporine and tacrolimus), inhibitors of nucleotide synthesis (azathioprine and mycophenolate), inhibitors of growth factor signal transduction (the mTOR inhibitors sirolimus and everolimus), and an oral corticosteroid, a broad immunosuppressant with inhibitory activity against lymphocytes, macrophages, and neutrophils. Current standard practice for chronic immunosuppression includes a calcineurin inhibitor (CsA or tacrolimus), an antiproliferative agent (mycophenolate, mTORi or azathioprine), and steroids. Many corticosteroid tapering schedules have been employed and are typically based on the immunologic risk of the recipient as well as the induction and baseline immunosuppression used. A conservative corticosteroid taper would be prednisone starting with a 20 to 30 mg daily dose for the first month and tapered by 2.5 to 5 mg every 2 weeks to a maintenance dose of 5 to 10 mg per day. Most centers do not routinely discontinue or switch to alternate-day steroids unless the patient is having problems with side effects (including worsening glucose control, hypercholesterolemia, or difficulties in blood pressure control) and has had stable renal allograft function with no episodes of acute rejection within the preceding 6 to 12 months. However, steroid-withdrawal strategies continue to be of significant interest to both transplant centers and potential transplant recipients. Overall, cumulative high-dose immunosuppression leads to a myriad of complications, increased infections, malignancy, and cardiovascular morbidity and mortality. The goal of transplant immunosuppression is to reduce immunosuppression to a level that will prevent or suppress rejection, but minimize the risk of life-threatening infections and other problems related to the treatment.

Induction Agents

Common induction agents currently in use can be defined as T-cell depleting or non–T-cell depleting agents. Although historically, equine antithymocyte serum (ATGAM) and murine monoclonal anti-CD3 (OKT3, now no longer in

production) had been prominently used as T-cell depleting agents, these have largely been replaced in clinical use by rabbit antithymocyte globulin (rATG, Thymoglobulin) and monoclonal humanized anti-CD52 (alemtuzumab, Campath 1-H), which also acts as a B-cell–depleting agent. These agents primarily function to eliminate the T-cell alloimmune response, with T-cell depletion lasting weeks (for rATG) to months (for anti-CD52). Although ATGAM and rATG have similar general mechanisms of action (both are pooled polyclonal antibodies developed from the administration of T cells to animals (the horse in the case of ATGAM, and the rabbit in the case of rATG), the relative efficacy of the two have been compared in one clinical trial,[144] suggesting a therapeutic advantage to rATG. The nondepleting induction agents include the IL-2 receptor antagonists daclizumab (currently not in production) and basiliximab. These agents function to inhibit the proliferation of activated T cells.

Many centers use induction agents in the immediate posttransplant period. In 2008, the use of rATG, anti-CD52, and IL-2ra for induction in the United States was 45%, 11%, and 29%, respectively (SRTR Annual Report 2009). For higher risk patients such as those with prior sensitization (elevated PRA), prior transplant, or African American ethnicity, induction therapy is usually combined with standard doses of immunosuppression to prevent rejection. For those with a lower risk (living donor kidney recipients, primary kidney transplants), induction therapy is often employed in an effort to minimize exposure to maintenance immunosuppression.

In low-risk patients, the need for induction therapy remains controversial when using a standard three-drug maintenance immunosuppression. A meta-analysis of 24 studies examining IL-2ra versus placebo reported a reduction in risk of both graft loss of 25% and acute rejection within the first year of 28%.[145] However, only three studies were included in the analysis that used tacrolimus/mycophenolate (TAC/MMF) as maintenance immunosuppression, and the rejection rate in the placebo/no induction arm was 38%. This rate is much higher than present day reports with TAC/MMF-based immunosuppression. A recent analysis of 28,000 patients treated between 2000 and 2008 with tacrolimus, mycophenolate, prednisone, and either IL-2ra or no induction suggests a minimal reduction in acute rejection rates and no impact on graft survival.[146]

For patients at a higher risk of acute rejection, two trials have compared nondepleting agents (IL-2ra) versus the T-cell depleting agent rATG in the prevention of rejection. Although the trials differed in inclusion criteria, the dosing regimen of rATG, and the baseline calcineurin inhibitor, they demonstrated similar findings of reduced rates of acute rejection in the rATG group (15% to 16%) versus the IL-2ra group (26% to 27%).[147,148] On the basis of these experiences, depleting agents generally are favored in the transplant recipient at elevated risk for rejection. A comparison of alemtuzumab and rATG has not been performed in the setting of triple agent maintenance immunosuppression, thus statements of efficacy differences between these agents cannot be accurately made.

With regard to safety, all depleting agents carry concerns regarding long-term risk of infection and malignancy.[149] Registry analyses suggest that there is an increased risk of a future development of lymphoma with depleting agents compared to nondepleting agents or no induction therapy, an association that appears to be dose dependent.[150, 151] For this reason, repeated or prolonged courses of depleting antibody therapy must be considered with this risk balanced by the potential for graft recovery or prolongation. A review of the mechanisms of action, administration, and side effects of commonly used induction agents is provided in the following paragraphs.

T-Cell Depleting Agents

Polyclonal Antisera to Human T Cells: Thymoglobulin and Equine Antithymocyte Serum

As described previously, antithymocyte globulins (rATG-Thymoglobulin, and equine ATG-ATGAM) are polyclonal antisera derived from immunization of lymphocytes, lymphoblasts, or thymocytes into rabbits or horses. The immunosuppressive product contains cytotoxic antibodies directed against a variety of T-cell–surface markers including the major histocompatibility complex (MHC) antigens. The administration leads to the depletion of peripheral blood lymphocytes. The lymphocytes are either lysed or cleared by the reticuloendothelial system, and their surface antigen may be masked by the antibody.

Dosing of either agent has not been defined, with a number of reports of efficacy using rATG given as 1 to 2 mg per kilogram intravenously for 3 to 14 days, whereas alternate day dosing and T-cell count-monitored dosing has demonstrated efficacy. Equine ATG is typically given 15 mg/kg/day for 7 to 14 days. Data suggest that rATG is superior to equine ATG for the prevention and/or reversal of rejection.[144]

Potential side effects of rATG and equine ATG include fever, chills, erythema, thrombocytopenia, local phlebitis, serum sickness due to cytokine release, and anaphylaxis. The potential for development of host anti-antithymocyte antibodies has not been a significant problem because of the use of less immunogenic preparations and additionally because rATG and equine ATG suppress the immune response to the foreign protein itself. To avoid allergic reactions and symptoms related to cytokine release, the patients receive intravenous medications consisting of methylprednisolone (30 mg) and diphenhydramine hydrochloride (50 mg) 30 minutes before injection. Acetaminophen should be given before and 4 hours after the commencement of infusion for fever control. Thrombocytopenia and leukopenia may necessitate reduction or curtailment of drug dosage.

Muromonab-CD3 (OKT3) Monoclonal Antibodies

OKT3 is a mouse monoclonal antibody directed against the CD3 molecule, which is a subunit of the T-cell receptor of the T lymphocyte. Administration leads to the depletion of peripheral blood lymphocytes. As mentioned previously,

OKT3 is currently not produced, primarily due a decrease in use over the last decade due to side effects related to cytokine release, but is presented briefly within this chapter as a number of analogs remain in clinical development.

OKT3 was commonly given 5 mg per day once daily for 7 to 14 days and administered as an IV push over <1 minute at a final concentration of 1 mg per milliliter. Premedication with Solu-Medrol at 15 mg per kilogram IV is administered prior to the first dose to decrease the incidence of reactions, which include fever, rigors, diarrhea, myalgia, arthralgia, aseptic meningitis, dyspnea, and wheezing. The release of tumor necrosis factor (TNF), IL-2, and IFN-γ in the serum are found after an OKT3 injection. The acute pulmonary compromise due to a capillary-leak syndrome is more common in patients who are > 3% of dry weight before the initiation of OKT3 treatment.

The development of host anti-OKT3 antibodies complicates the reuse of this drug in previously treated patients. Approximately 33% to 100% of patients develop anti–mouse antibodies after the first exposure to OKT3, depending on concomitant immunosuppression.[152] Anti-OKT3 titers of 1:10,000 or more usually correlate with a lack of clinical response. If anti-OKT3 antibodies are of low titer, retreatment with OKT3 is typically successful. If retreatment is attempted with anti–mouse titers of 1:100 or more, the peripheral lymphocyte count, CD3 T cells, and trough-free circulating OKT3 should be monitored. If the absolute CD3 T-lymphocyte count is greater than 10/μL or the free-circulating trough OKT3 level is not detected, it may be indicative of an inadequate dose of OKT3. Under these circumstances, increasing the dose of OKT3 from 5 to 10 mg per day can overcome the anti–mouse antibody response.

Nondepleting T-Cell Agents

IL-2 Receptor Antagonists: Basiliximab and Daclizumab

Basiliximab (Simulect) is a chimeric (murine/human) immunosuppressant monoclonal antibody that binds and blocks the alpha chain of the IL-2 receptor complex expressed on activated T cells, leading to a reduction in T-cell proliferation. Daclizumab similarly is a chimeric (90% human, 10% murine) monoclonal IgG antibody produced by recombinant DNA technology with the same binding site and mechanism of action.

Both were approved for use in kidney transplantation as induction agents but, as mentioned previously, daclizumab is currently not produced due to planned discontinuation by the manufacturer. Basiliximab is given 20 mg intravenously as a bolus or infusion over 20 to 30 minutes on days 0 and day 4, whereas daclizumab is given 1 mg per kilogram within 24 hours before transplantation (day 0), then every 14 days for 4 additional doses (total of 5 doses).

Notably, and in direct contrast to the depleting agents, the administration of basiliximab or daclizumab did not increase the incidence or severity of adverse effects over placebo in clinical trials.

B- and T-Cell Depleting Agents

Anti-CD52 (Alemtuzumab, Campath 1-H)

Alemtuzumab is a humanized recombinant DNA-derived monoclonal antibody directed against the cell surface molecule CD52 present on both B and T cells. As described previously, it has been used as an efficient T-cell depleting agent but also leads to the depletion of B cells. This effect occurs within hours of infusion and its effects may last beyond 6 months. This prolonged lymphopenia raises concerns regarding the potential for delayed acute rejection episodes, because T- and B-cell reconstitution occurs much later in the posttransplant course during which time monitoring may not be as frequent. Concerns have been expressed regarding an increased risk of unusual infections, reports have noted a comparable safety profile to other depleting induction agents, and reduced incidence of posttransplant lymphoproliferative disease.

Although no formal dosing strategy has been extensively evaluated, experiences with 30 mg intravenously given perioperatively and followed by a second 30 mg dose on day 1 or 2 is frequently reported, with few infusion-related side effects reported.

B-Cell–Targeted Therapy

Greater attention has been focused in recent years on the role of B cells and donor-specific antibody production (HLA and non-HLA) and graft injury. At the outset of transplantation, B-cell/antibody reduction strategies (referred to as "desensitization") may permit transplantation under circumstances that would previously result in rapid rejection (often referred to as hyperacute rejection, or delayed hyperacute rejection, see the following). Acute antibody-mediated rejection can occur at any time following a transplant, either with or without a T-cell component, and these agents have been used in this setting as well. Finally, the pathologic entity of chronic antibody-mediated rejection has been increasingly described, with small case series reports of B-cell therapies in this setting. Although the presentation, pathology, and management of antibody-mediated rejection is provided in a later section, a review of the agents used for B-cell/antibody–directed therapy is provided in the following sections. These interventions include bortezomib, rituximab, intravenous immunoglobulin, and plasma exchange.

Bortezomib. Bortezomib is a proteasome inhibitor that causes apoptosis of plasma cells among other effects. It has been approved for use in the United States for patients with multiple myeloma to control B-cell production of immunoglobulins. It has been used in small studies to inhibit HLA antibody production in the setting of acute antibody-mediated rejection, and may prove to be of value in desensitization protocols perioperatively.

For the treatment of multiple myeloma, a treatment cycle of 1.3 mg per square meter intravenously twice weekly for 2 weeks is usually repeated for a total of six to nine cycles.

Modeling this experience, transplant centers have adopted the four-dose, 2-week cycle as initial therapy with additional cycles depending on clinical response and reduction in donor-specific antibody titer.

In patients with multiple myeloma treated with repeated cycles, the incidence of peripheral neuropathy increases (up to 28% to 64% in those receiving up to 8 biweekly cycles) but resolved in 85% within a median of 98 days.[153]

Rituximab. Rituximab (Rituxan) is a humanized anti-CD20 antibody that binds to CD20 on mature B cells, resulting in B-cell depletion. Unlike bortezomib, it is not effective against plasma cells, because plasma cells do not express CD20 on the cell surface. It is approved for use in the United States for the treatment of certain non-Hodgkin lymphomas, and has been used experimentally to reduce donor-specific antibodies pretransplant as well as for treatment of acute humoral rejection and forms of posttransplant lymphoproliferative disease (PTLD) following transplant.

A common dosing strategy is 375 to 500 mg per square meter intravenously for one to four doses.[154] Fifty percent of patients will experience infusion-related side effects within the first 2 hours of the first rituximab infusion, 90% of which are mild and may include nausea, skin rash and pruritus, headache, fever, chills, dyspnea, and angioedema. These symptoms generally resolve within 3 hours. Subsequent infusions are associated with a lower risk of reactions. More severe reactions including bronchospasm and severe hypotension/anaphylaxis are rare (5% to 10%) but have been reported. Although the risk of infections appears low when used as monotherapy, there may be an increased risk of later opportunistic infections when used in conjunction with other B-cell modulating therapies and in the background of intensified maintenance immunosuppression.

Intravenous Immunoglobulin

Infusion of IVIG may provide blocking or anti-idiotypic antibodies that can reduce the production of anti-HLA antibodies in the pretransplant period and also has a number of additional effects that may modulate the immune response, including the blockade of Fc receptors, the decrease of inflammation, and the regulation of T cells.[155] There is also limited experience in the use of IVIG in the treatment of allograft rejection. Successful prevention and the treatment of acute humoral rejection were reported in a series of kidney transplant patients with steroid and antilymphocyte-resistant rejection.[156]

When used in desensitization protocols in the absence of plasma exchange, a dose of 1 to 2 g per kilogram is commonly used for up to six doses.[107,157] When used with plasma exchange, 100 to 200 mg per kilogram IV after each exchange has been reported.[158] When used as a treatment for acute rejection, a similar dosing strategy is typically employed.[158]

Infusion-related side effects may include flushing, chills, and myalgia, and arthralgia may occur in ~5% of patients. Aseptic meningitis has been reported in up to 11%, and typically lasts for up to 72 hours after infusion. An increased risk for venous thrombotic events has been suggested; currently, a U.S. Food and Drug Administration (FDA) warning exists for this potential adverse event.

Maintenance Immunosuppressive Agents

Maintenance immunosuppression has evolved from an era in which azathioprine and oral corticosteroids were the sole agents used for kidney transplant immunosuppresion to the cyclosporine era in which acute rejection rates within the first year fell from ~70% to ~50%, to an era in which newer calcineurin inhibitors and antiproliferative agents were introduced. Together with induction agents, acute rejection rates are commonly less than 20% in the first year and are often nearer to 10% in lower risk patient populations. With the improvement in prevention of acute rejection come greater considerations for the safety profiles of these agents, not only in terms of graft outcomes but in terms of patient risk factors such as cardiovascular, infectious, and malignancy risks. Within this context, the agents used for maintenance immunosuppression will be reviewed with a discussion of clinical trials that support (or fail to support) one strategy over another.

Corticosteroids

Corticosteroids have been known for more than 40 years to have a suppressive effect on the immune system. Their first use in renal transplantation was in 1960, when cortisone was used to reverse a rejection episode in a living related donor transplant recipient who had been immunosuppressed by total-body irradiation. Since then, steroids have been used for the treatment of rejection episodes and as part of the standard immunosuppressive regimen for the prevention of rejection. The complications of steroid therapy are numerous and involve many organ systems. Acute side effects include fluid and salt retention, which may exacerbate hypertension; steroid-induced diabetes, which may result from impaired glucose tolerance; or preexisting diabetes, and rarely, central nervous system (CNS) changes, such as steroid psychosis or pseudotumor cerebri. These changes occur when high doses of prednisone or methylprednisolone are given during the initial posttransplant period or in the treatment of a rejection episode. Generally, these short-term effects lessen or disappear when the doses of steroids are tapered. The long-term side effects are more insidious in onset and are associated with Cushingnoid changes, poor wound healing, and increased frequency of infections. Other side effects include cataracts, proximal myopathy, osteoporosis, and osteonecrosis.

In an effort to reduce the incidence of metabolic and infectious complications, the current trend is to use lower doses of steroids for maintenance and IV pulses of methylprednisolone for the treatment of rejection. Because of the growth-suppressive effects of corticosteroids, alternate day steroid

therapy is often used in children. However, this regimen has not been evaluated in randomized controlled trials in adults.

Steroid Withdrawal. Given the number of cosmetic, metabolic, and cardiovascular side effects attributable to chronic prednisone use, the elimination of corticosteroids from maintenance immunosuppression regimens have been an active area of study. Early corticosteroid cessation (within 7 days following a transplant) has become increasingly popular in the United States. In 2006, over 30% of all patients were discharged following transplant without maintenance prednisone therapy. Typically, patients at lower immunologic risk (low panel reactive antibodies, first transplants) are selected, and immunosuppression includes induction therapy, a calcineurin inhibitor (CNI), and an antiproliferative agent. Acute rejection rates in single center studies range from 10% to 15%.[159] In the only prospective, double-blind, multicenter study of corticosteroid cessation to date, a rapid elimination of steroids at 7 days posttransplant was compared to a standard steroid taper to 5 mg at 6 months versus a background of induction therapy plus a TAC/MMF-based immunosuppression.[160] Corticosteroid withdrawal was associated with less bone disease, less cataract formation, and lower triglyceride levels with similar graft function at 5 years. However, other cardiovascular risk factors and weight gain were equivalent, and rejection rates were higher in the corticosteroid withdrawal arm (18% versus 11%, P = .04). Post hoc analysis suggested a higher rate of chronic allograft nephropathy in the corticosteroid withdrawal arm. Outcomes using a strategy of steroid avoidance have recently been reported in an open-label study in comparison with a steroid withdrawal strategy after 7 days, or standard chronic steroid use (all in the setting of induction with basiliximab and chronic immunosuppression with CsA and MMF).[161] Both the steroid avoidance cohort and the steroid withdrawal cohort experienced a significantly higher amount of biopsy-proven acute rejection (31.5% and 26.4%, respectively) compared to the chronic steroid arm (14.7%).

Similar to the early steroid withdrawal experience, single center studies and uncontrolled analyses demonstrate the potential for benefit in the withdrawal of steroids later after transplant (3 to 12 months).[162] When studied in a randomized controlled fashion, steroid withdrawal at 3 months following transplant has been shown to result in unacceptably high acute rejection rates, particularly in African Americans.[163] Thus, an element of caution is required before recommending the routine use of steroid withdrawal. Clinicians must weigh the increased risk of acute rejection and the potential for chronic allograft injury versus the patient's interest in avoiding the side effects of chronic steroid use when determining if steroid withdrawal is appropriate.

Calcineurin Inhibitors: Cyclosporine and Tacrolimus

The calcineurin inhibitor CsA was first introduced in renal transplantation by Calne and his colleagues[164] in 1978 and resulted in a dramatic reduction in acute rejection rates, quickly becoming the standard immunosuppressive agent in transplantation. Tacrolimus (FK506 or Prograf) is a macrolide immunosuppressant introduced in clinical trials in the mid-1990s and is similar to CsA in its mode of action. Although cyclosporine is a fungal peptide that binds to cyclophilin, TAC binds to an immunophilin, FKBP (FK506 binding protein). Both the block of calcineurin-mediated T-cell receptor signal transduction leading to the inhibition of several T-cell growth-promoting genes such as IL-2, and the inhibition of T-cell–dependent B-cell activation. The original formulation of cyclosporine (Sandimmune) has been replaced by microemulsion formulations (Neoral and the generic formulations, Gengraf and cyclosporine USP). These are available as 25 and 100 mg capsules. TAC is available in branded (Prograf) and generic formulations in 0.5-, 1-, and 5-mg capsules. A long-acting formulation of TAC given once daily (Advagraf) is available in Europe but not in the United States.

CsA and TAC are administered orally as two 12-hourly doses. The starting oral dosage for CsA is 4 to 6 mg/kg/day and for TAC is 0.1 to 0.2 mg/kg/day, and adjusted according to graft function and trough (C0) levels. Both TAC and CsA are available in intravenous forms but are rarely used due to excellent bioavailability. When necessary (patients with ileus or other gastrointestinal dysfunction) the IV dosage is one-third of the oral dose. CsA should be given in a slow infusion with 0.9% sodium chloride or 5% dextrose over 2 to 6 hours, whereas TAC should be given as a continuous infusion. African American patients often require a higher dose of TAC (mean 37% higher dose than Caucasian patients) to achieve comparable blood concentrations.

Therapeutic Drug Monitoring of Calcineurin Inhibitor. Therapeutic monitoring is important due to the inter- and intra-patient variation in metabolism. Similar goals should be applied for generic formulations, as no adverse events have yet been reported regarding their use. Some consider the 2-hour peak as more predictive of CsA toxicity than C0 levels, but this has not been widely implemented. Typical C0 goals for TAC and CsA as compared in a recent pivotal head-to-head trial are listed in Table 82.11. Although the results of this trial compared trough level goals that are currently in clinical practice and thus form the basis of current recommendations, dosing may require modification in the individual patient. For example, for those who may not be able to tolerate an antiproliferative agent, higher calcineurin inhibitor exposure and a higher trough level goal may be required, whereas for those who suffer complications of overimmunosuppression, such as posttransplant lymphoproliferative disorder or polyomavirus nephropathy, a lower calcineurin inhibitor exposure and lower trough level goal is required.

Side Effects. A number of side effects have been observed in patients receiving calcineurin inhibitors. CNI nephrotoxicity

82.11 Acute Rejection and Graft Survival Rates from a Clinical Trial Comparing CNI-based Immunosuppression to MTOR-based Immunosuppression

Regimen	Acute Rejection (%)	Graft Survival (%)	GFR (mL/min)
Cyclosporine "standard": C0 goal CsA150–300 ng/mL × 3 months, then 100–200 ng/mL	25.8	89.3	57.1
Cyclosporine "low dose": Daclizumab induction, C0 goal CSA 50–100 ng/mL	24.0	93.1	59.4
Tacrolimus "low dose": Daclizumab induction, C0 goal TAC 3–7 ng/mL	12.3*	94.2*	65.4*
Sirolimus "low dose": Daclizumab induction, C0 goal sirolimus 4–8 ng/mL	37.2	89.3	56.7

*P <.05

* P <.05. CNI, calcineurin inhibitor; MTOR, mammalian target of rapamycin; GFR, glomerular filtration rate.

is a concern particularly at higher dosing and C0 concentrations, and is discussed in a later section addressing the long-term management of the transplant recipient. Other side effects include hypertension, fluid retention, hyperkalemia, hypomagnesemia, hyperuricemia, and rarely, a microangiopathic hemolytic anemia in association with hemolytic uremic syndrome. Other side effects that are more common to CsA than TAC include hypertrichosis, gingival hypertrophy, hyperuricemia, and hyperlipidemia, whereas those that are more common to TAC include more prominent neurologic side effects such as tremor, headache, insomnia, and more prominent metabolic side effects such as posttransplant diabetes, more frequent alopecia, an increased incidence of polyoma virus infection, and a higher rate of posttransplant diabetes.[165] Hypertrophic cardiomyopathy has also been reported in children treated with TAC.

Drug Interactions. Cyclosporine is metabolized almost entirely in the liver through the cytochrome P450 system. Most of the drug is excreted in the bile and liver dysfunction causes it to accumulate and serum levels to rise. TAC is absorbed primarily by the small intestine and its oral bioavailability is about 25%. Impaired renal function does not affect plasma or whole blood levels because only about 0.1% of the native drug is detected in the urine and only 10% of the metabolites of the parent compound are excreted in the urine. Like CsA, it is primarily metabolized by hepatic cytochrome P450. Therefore, the calcineurin inhibitor exposure level will be influenced by the concomitant administration of medications that affect cytochrome P450. The well-known interactions are listed in Table 82.12. Drugs that induce hepatic enzymes, such as rifampicin, phenytoin, phenobarbital, norfloxacin, and nafcillin, will increase the rate of metabolism of the calcineurin inhibitor and lower blood levels of the parent compound. Drugs that increase calcineurin inhibitor levels include calcium channel blockers, such as diltiazem, verapamil and nicardipine, erythromycin, and ketoconazole. It is important to consider the possibility of drug–drug interactions with any medication that is added to the transplant recipient's regimen given the potential influence on calcineurin inhibitor exposure (both inhibitors and inducers of the P450 system). A number of drugs can enhance CNI nephrotoxicity irrespective of drug–drug interactions.

82.12 Cyclosporine or Tacrolimus Drug Interactions

Increase Level	Decrease Level	Additive Nephrotoxicity
Erythromycin	Barbiturate	Aminoglycosides
Diltiazem	Carbamazepine	Amphotericin B
Ketoconazole	Isoniazid	Cotrimoxazole
Metoclopramide	Phenytoin	Trimethoprim
Oral contraceptives	Rifampicin	Acyclovir
Nicardipine		

These include aminoglycosides, amphotericin B, trimethoprim, and cotrimoxazole.

Cyclosporine Versus Tacrolimus: Efficacy and Side Effects

Most randomized trials comparing TAC to CsA demonstrate lower rejection rates with TAC. In a large multicenter randomized controlled trial using lower doses of tacrolimus (3 to 7 ng per milliliter) and CsA (50 to 100 ng per milliliter) in conjunction with IL-2ra, MMF, and steroids, the acute rejection rate in the TAC arm was 12% at 1 year, whereas in the CsA arm the acute rejection rate was statistically and clinically significantly higher (24%).[166] However, accompanying these benefits come an increased risk of diabetes and neurologic and GI side effects. The relative differences in efficacy may be overcome with more potent induction therapy.[167] A meta-analysis of randomized controlled trials generally favors TAC over CsA for the prevention of acute rejection. Treating 100 patients with TAC instead of cyclosporine would prevent 12 patients from experiencing acute rejection, and would form graft loss in 2, but would cause an additional 5 patients to develop insulin-requiring diabetes.[168]

Mycophenolate Mofetil and Enteric-Coated Mycophenolate Sodium

MMF and enteric-coated mycophenolate sodium (EC-MPS) are converted in vivo to mycophenolic acid (MPA), a noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (Fig. 82.11). This enzyme is responsible for the conversion of inosine monophosphate to guanosine monophosphate (GMP), which is required for the production of nucleic acids and other critical steps in cellular activation. Lymphocytes require the de novo synthesis of GMP, so that MPA causes a profound inhibition of T- and B-cell function. Most other cells possess a salvage pathway that permits a resynthesis of guanine derivatives and are relatively resistant to MPA. EC-MPS is an enteric-coated formulation of mycophenolate sodium that releases the active moiety MPA in the small intestine instead of the stomach with the aim of improving MPA-related upper GI adverse events.

The recommended initial dosing of MMF is 1 g administered twice daily, whereas the recommended dose of EC-MPS is 720 mg administered twice daily 1 hour before or 2 hours after food intake. For African Americans, a higher dose (the equivalent of 1.5 g twice daily) is preferable when given with

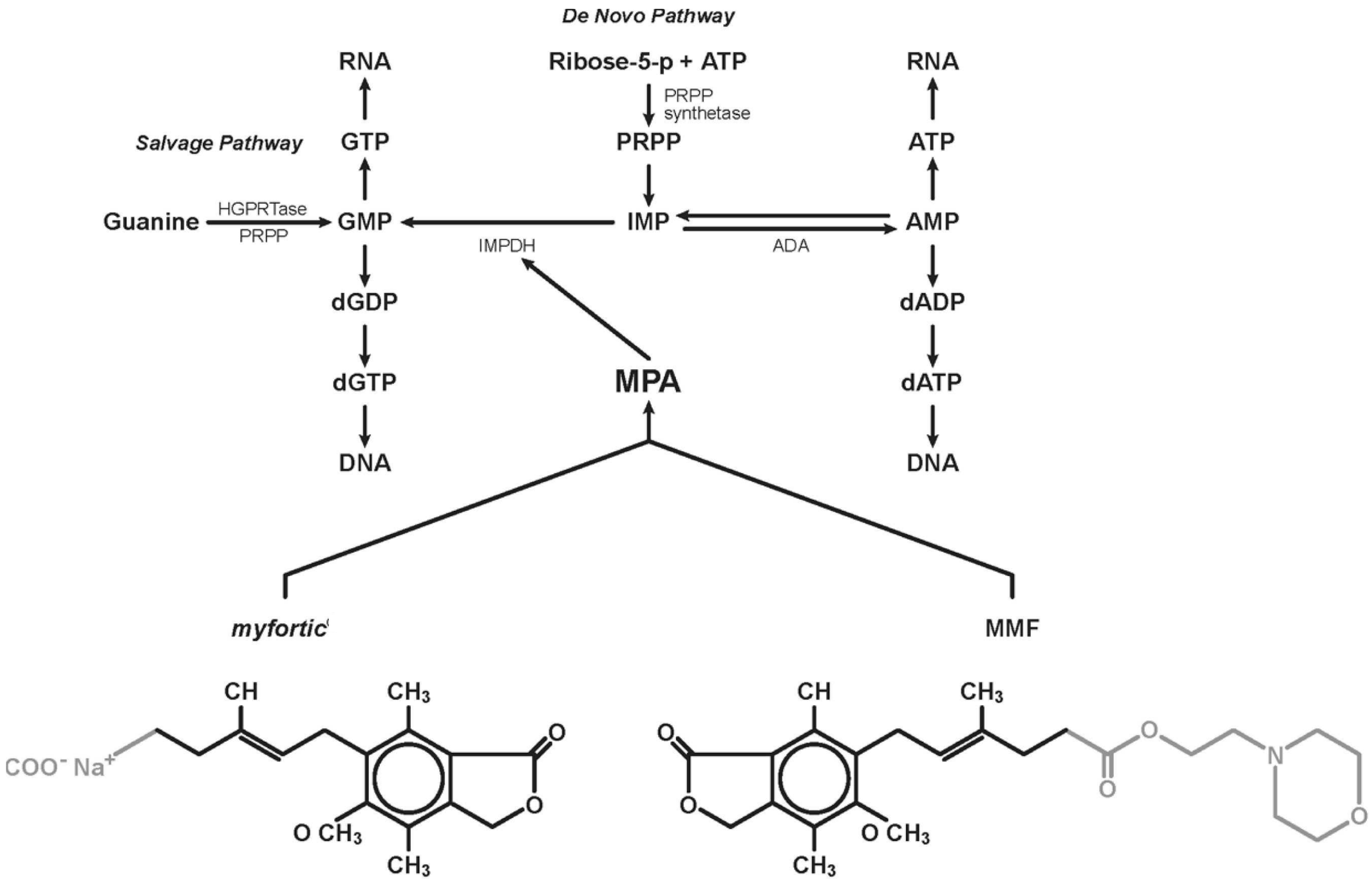


FIGURE 82.11 The site of inhibition by mycophenolic acid (MPA). MPA is the active moiety of myfortic (MMF). It is a potent, selective, and reversible inhibitor of inosine monophosphate dehydrogenase (*IMPDH*). The de novo pathway for the generation of guanosine monophosphate (*GMP*) is dependent on the conversion of inosine monophosphate (IMP) by IMPDH. *GTP,* guanasine triphosphate; *PRPP,* phosphoribosyl pyrophosphate; *AMP,* adenosine monophosphate; *dGDP,* deoxyguanosine diphosphate; *dGTP,* deoxyguanosine triphosphate. (From Allison AC, Eugui EM, Sollinger HW. Mycophenolate mofetil (RS-61443): mechanisms of action and effects in transplantation. *Transplantation Reviews* 1993;7:129–139.)

CsA. Efficacy is similar between EC-MPS and MMF in both de novo and maintenance patients. In the de novo setting, the incidence of GI adverse events was comparable between the two treatment groups throughout the 12-month study period, but the incidence of dose changes due to GI side effects was lower in the EC-MPS group, suggesting potentially less severe GI adverse events.[169]

Therapeutic drug monitoring of mycophenolate has not consistently correlated with outcomes, and in particular has not been formally tested in the case of EC-MPS.[170] high performance liquid chromatography (HPLC) methods have been established for the measurement of MMF, MPA, and mycophenolic acid glucuronide (MPAG), the principal metabolite that is pharmacologically inactive. Orally administered MMF is rapidly absorbed and hydrolyzed to MPA in the liver and is then glucuronidated to an inactive form of MPAG. The bioavailability of MMF is 90% with a half-life of 12 hours. There is no accumulation of MPA in hepatic or renal impairment. The maximum concentration of MPA and the area under the curve (AUC) value determined immediately after transplantation were only 30% to 50% of those measured for patients 3 months after transplantation, suggesting a need to increase dosing in the immediate posttransplant period. There is evidence of pharmacologic interaction between MMF and TAC, in that MPA exposure increases when MMF is used with TAC compared to cyclosporine.

The major side effects of MMF and EC-MPA include mild neutropenia and GI intolerance, such as diarrhea, esophagitis, and gastritis at high doses. The reason for leukopenia in transplant patients treated with MMF remains to be determined, because leukopenia was not predicted based on the mechanism of action of MMF and was not noted in patients with psoriasis or rheumatoid arthritis who were treated with this drug. The incidence of infection is not increased overall, although there may be a slight increase in tissue-invasive cytomegalovirus infection of the GI tract and liver.[171]

The mTOR Inhibitors: Sirolimus and Everolimus

mTOR is a regulatory kinase in the process of cell division. The term mTOR inhibitor refers to two similar immunosuppressant drugs, the mode of action of which is closely linked to the inhibition of this kinase. Sirolimus (SRL), also known as rapamycin, is a macrolide antibiotic compound that is structurally related to TAC and was approved in 1999 in the United States for the prophylaxis of organ rejection in patients receiving renal transplants. Everolimus (EVL, Zortress or Certican) is a structural analog of sirolimus with greater bioavailability (18% versus 10%) and a shorter half-life (18 to 35 hours versus 62 hours) than sirolimus. Everolimus was approved for use in kidney transplant recipients in Europe in 2005 and in the United States for low-to-moderate risk recipients in 2010.

The immunosuppressive function of the mTORi SRL and EVL ultimately results from the inhibition of cytokine and growth-factor activity upon T, B, and nonimmune cells. mTORi bind to the immunophilin FK506-binding protein 12 (FKBP12), a property shared with TAC. However, instead of inhibiting calcineurin like the TAC-FKBP12 complex, the EVL-FKBP12 complex inhibits the protein kinase mTOR, which causes an arrest in the G1 cell cycle.[172] mTOR belongs to the phosphoinositide 3-kinase (PI3K)-related protein kinases (PIKK) family and its signaling pathway couples energy and nutrient abundance to the execution of cell growth and division. mTOR complex 1 (mTORC1) and mTORC2 exert their actions by regulating other important kinases, such as S6 kinase (S6K) and Akt. At therapeutically relevant concentrations, the mTORi-FKBP12 complex mainly inhibits mTORC1 and thus inactivates the p70 S6 kinase in lymphocytes, resulting in the selective inhibition of the synthesis of ribosomal proteins and thus immunosuppression.

SRL is given at a dose of 2 to 6 mg orally once daily 4 hours after the morning dose of either CsA or concomitantly with TAC. A loading dose of 6 to 12 mg is often given on the first day of treatment due to its long half-life. The concomitant administration of SRL and Neoral formulation of CsA increased the AUC for SRL by 230% compared with the administration of SRL alone, whereas the administration 4 hours after the CsA dose increased the AUC by 80%. For this reason, it is recommended that SRL be administered 4 hours after the morning CsA dose. The pharmacologic interaction between SRL and TAC has not been rigorously explored. The recommended target trough levels vary between 5 to 15 ng per deciliter. Blood levels of SRL can be determined by HPLC with ultraviolet (UV) light detection or HPLC–mass spectrometry.

EVL can be started at 0.75 to 1.5 mg orally twice daily without a loading dose and can be given concomitantly with either CsA or TAC. The recommended therapeutic range for trough blood concentrations is 3 to 8 ng per milliliter in combination with CNIs. Potential benefits of the shorter half-life of EVL include the lack of necessity for a loading dose, the fact that the steady state is reached more quickly, and the fact that the drug is eliminated more quickly, which may permit a more rapid clinical response to changes in dose (e.g., in response to a drug–drug interaction or side effect).

The primary systemic side effects of mTORi are dyslipidemia, thrombocytopenia, and delayed wound healing. Side effects specific to kidney transplantation include increased lymphocele formation, proteinuria, the potential for prolongation of delayed graft function, and an enhancement of CNI-related nephrotoxicity. Although the drug is minimally nephrotoxic when used alone, the combination of SRL and CsA has caused synergistic toxicity in animals.[173] The mechanisms for the increased association of proteinuria with mTORi may include a loss of tubular reabsorption of protein, an inhibitory action of SRL on vascular endothelial growth factor, and a loss of nephrin in glomeruli.[174,175]

Azathioprine

Azathioprine (AZA) is an antimetabolite, a purine analog that incorporates into cellular DNA and inhibits the synthesis and metabolism of RNA. AZA was first used as

an immunosuppressive agent for kidney transplantation in 1962,[176] and for many years AZA at a dose of 1.75 to 2.5 mg/kg/day was used with high-dose steroids. Prior to the introduction of CsA in the 1980s, AZA and steroids were the mainstays of maintenance immunosuppression. Although largely replaced by mycophenolate and mTORi, due to better antirejection efficacy with the latter agents, its use is still of value in reducing medication costs and as a safe alternative in pregnancy.

When used as a secondary agent in combination with a CNI or mTORi, 1 to 2 mg/kg/day in a single oral dose is recommended. When used as the primary immunosuppressant, the dose should be increased to 2 to 3 mg/kg/day.

AZA can cause bone marrow depression with granulocytopenia, hepatic dysfunction, pancreatitis, and an increased risk of infection and neoplasia. Macrocytic anemia with megaloblastic erythrocytosis, pure red cell aplasia, thrombocytopenia, and suppression of all marrow cell lines have been reported. Trimethoprim–sulfamethoxazole, when administered with AZA, may lead to neutropenia and thrombocytopenia, possibly because of the antibiotic's antifolate effect, resulting in enhanced 6-MP marrow toxicity. Similarly, allopurinol inhibits the breakdown of AZA and thus acts to enhance drug exposure; concomitant allopurinol and AZA use is therefore discouraged. If necessary, AZA should be reduced by 25% to 50% when starting allopurinol, with frequent white blood cell and platelet count monitoring.

Selection of Antimetabolite

Clinical decision making as to whether a mycophenolate agent, an mTORi, or AZA should be used for a given patient is usually determined by efficacy (the prevention of acute rejection) and the side effect profile. When used in conjunction with CNI (without depleting induction therapy), AZA is considered to be inferior to MPA in preventing acute rejection based on MMF registration trials, and mTORi is considered to be at least equally effective in preventing acute rejection.[177–179] The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group compared the effectiveness of MMF at two doses: 3 g per day (164 patients) and 2 g per day (173 patients), to AZA (100 to 150 mg per day, 166 patients). Patients were treated with equivalent doses of corticosteroids and CsA. The MMF groups have a lower incidence of rejection—16% and 20% versus 36% with AZA; decreased use of antilymphocyte antibody for severe or steroid-resistant rejection episodes (4.9% and 8.8% versus 15.4%); and a nonsignificant trend toward improved graft survival at 1 year. At 3 years, both MMF groups continued to show a nonsignificant trend toward better graft survival and a lower rate of graft loss from rejection as compared to the AZA group.

When comparing acute rejection rates and short-term graft outcomes with MPA versus mTORi-containing, CNI-based regimens, acute rejection rates generally are comparable.[180] However, GFR on >1 year follow-up in most studies tends to be lower with mTORi, and registry analyses suggest a slight decrease in 5-year graft survival using TORi versus MPA as the antiproliferative agent.[181,182] This is likely due to enhanced CNI toxicity, which is noted with mTORi versus MPA. A reduction in CNI exposure with mTORi use may lead to similar kidney function without increasing acute rejection rates.[179]

With regard to differences in side effect profiles between antiproliferative agents, AZA is associated with the fewest side effects necessitating discontinuation, whereas mTORi tends to have the highest rates of discontinuation. Common side effects that prompt a transition from one agent to another include skin cancer/other malignancy (transition from AZA or MPA to mTORi), GI side effects (MPA to AZA or mTORi), and proteinuria (mTORi to MPA or AZA).

Calcineurin Inhibitor Avoidance and Minimization Strategies

Given the nephrotoxicity as well as metabolic and cosmetic side effects common with CNI use, the elimination or withdrawal of CNI from maintenance immunosuppression has been an area of active study. CNI minimization strategies can be segregated to (1) CNI avoidance, and (2) CNI withdrawal/conversion at time points following early CNI use (either "early" withdrawal/conversion, typically 3 to 6 months posttransplant, or "late" withdrawal/conversion, following the identification of graft dysfunction).

Calcineurin Inhibitor Avoidance. Most trials suggest that MMF/prednisone is inadequate for initial immunosuppression due to unacceptably high acute rejection rates of 50% to 70%. De novo SRL/MMF/prednisone maintenance immunosuppression has met with mixed results, with most randomized trials suggesting an increased acute rejection rate compared to CNI/MMF/prednisone-based control groups. A retrospective analysis from registry data also supports the findings of inferior graft survival and higher discontinuation rates in patients maintained on SRL/MMF compared to CNI/MMF combinations. In the largest comparison of SRL-based immunosuppression versus TAC or CsA-based immunosuppression (the ELITE-Symphony study), acute rejection rate at 1 year within the SRL cohort (goal trough 4 to 8 ng per milliliter) was 37% with 1-year graft survival of 89%, whereas in the low dose CsA cohort (trough 50 to 100 ng per milliliter) acute rejection at 1 year was 24%, and in the low dose tacrolimus (trough 3 to 7 ng per milliliter) cohort, acute rejection rate was 12%.[166] These findings have generally dampened enthusiasm for de novo CNI avoidance with medications currently available for use in transplantation.

Calcineurin Inhibitor Withdrawal (Early: 1 to 6 Months Posttransplant). Given the acute rejection rates noted previously with CNI avoidance and the perioperative complications that may result from mTORi such as an increased rate of lymphocele formation and delayed wound healing, an alternative strategy to de novo CNI avoidance is a brief

period of CNI followed by CNI withdrawal, with or without addition of another agent. In the large, prospective, multicenter CEASAR study, 536 patients on CsA, MMF, and prednisone maintenance were randomized to either undergo CsA withdrawal at 4 months, continue standard dose CsA (trough 150 to 300 ng per milliliter), or taper to low dose CsA (trough 50 to 100 ng per milliliter).[183] Although no difference was seen in the primary end point of GFR at 12 months, significantly higher rejection rates were noted in the CsA withdrawal group (38%) compared to either of the CsA continuation groups (25% to 27%). With SRL as the antiproliferative agent, 430 patients in the multicenter Rapamune Maintenance Regimen Trial on CsA, SRL, and prednisone were randomized to CsA withdrawal and increased SRL target trough levels 3 months after transplant, or remained on triple therapy. At 1 and 4 years, GFR was significantly better in the CsA withdrawal arm, despite a nominally higher acute rejection rate.[184] Although SRL may be more effective than MMF in CNI withdrawal strategies in combination with prednisone, issues of tolerability may limit this approach. To address this, the Spare the Nephron trial studied the efficacy and tolerability of the combination of both lower dose SRL and MMF in patients who undergo CNI discontinuation 1 to 6 months posttransplantation. Although this regimen was better tolerated and did not lead to an increase in acute rejection rates, differences in GFR using the CNI withdrawal strategy were small and not statistically significant after 24 months.[185]

Later Calcineurin Inhibitor Withdrawal/Conversion. When GFR is noted to steadily deteriorate or when biopsy findings suggest chronic nephrotoxicity and/or fibrosis, it is unclear if CNI withdrawal is safe or beneficial in slowing the rate of graft loss. A suggestion of benefit was noted in the Creeping Creatinine study,[186] in which the effect of removing CsA with MMF maintenance was compared to CsA maintenance (either alone or in combination with AZA or steroids). GFR stabilized without episodes of acute rejection in patients who underwent CsA discontinuation.[186] Another common CNI withdrawal strategy is conversion from CNI to SRL in patients on a CNI/MMF/prednisone regimen. Data from the multicenter randomized CONVERT trial, in which 830 patients 6 to 60 months post–kidney transplant were randomized 2:1 to SRL conversion versus CNI maintenance, suggests that subjects with GFR >40 mL per minute and minimal proteinuria (urine protein/creatinine ratio <0.11) at baseline experienced improved renal function at 24 months following CNI conversion to SRL without increased acute rejection rates, whereas those with proteinuria or GFR <40 mL per minute did not derive benefit from the transition.[187] As with single center experiences, improvements in renal function are noted, but issues of increased proteinuria and high rates of discontinuation of SRL due to adverse events remain common themes.[188] Taken together, CNI withdrawal appears most promising after a period of stability but prior to significant graft dysfunction. Novel agents currently are under investigation and may prove to be more effective than our current immunosuppressive agents in achieving CNI-free immunosuppression.

New Immunosuppressive Agents

New agents such as janus kinase (JAK) inhibitors, costimulatory blockade (primarily cytotoxic T-lymphocyte-associated protein 4-immunoglobulin [CTLA4-Ig] and anti-CD154 mAb), and PKC inhibitors are currently under experimental and clinical studies for maintenance immunosuppression as well as for the treatment of acute rejection.[189] Of these, the CTLA4-Ig Belatacept has completed phase II/III clinical trials.[190] In a CNI-free regimen, belatacept in combination with MMF and prednisone demonstrated improved GFR, less findings of interstitial fibrosis on biopsy, and less formation of donor-specific antibodies at 1 year compared to CsA-based immunosuppresion, but was also paradoxically associated with higher acute rejection rates and a higher incidence of posttransplant lymphoproliferative disease.[191] Longer-term follow-up of these findings will determine whether this agent becomes available for use in kidney transplantation.

COMMON POSTTRANSPLANT COMPLICATIONS

Surgical Complications of Renal Transplantation

The surgical technique of renal transplantation is reasonably standardized and overall direct surgical complication rates are low, accounting for only a small percentage of graft losses. Nevertheless, the transplant physician must be familiar with the diagnosis and treatment of surgically related complications to minimize recipient morbidity and mortality. The allograft is placed extraperitoneally into the iliac fossa in most cases. Thus, intraperitoneal bleeding, or bowel obstruction from adhesions or internal herniation, should not occur as a direct result of the surgery. In small children or in some recipients with a supravesical urinary diversion, the transplant is placed intraperitoneally and the potential surgical complications listed previously must be considered.

Wound Complications

The most important causes of wound infections stem from the operative complications of hematomas, urine leaks, and lymphoceles. Transplant recipients are vulnerable to wound infections because of postoperative immunosuppressive medications and poorly controlled uremia. Wound infections following transplantation are extremely bothersome, because if they are deep-seated infections around the arterial anastomosis, a secondary hemorrhage may occur. On presentation of a wound infection, adequate drainage should be provided immediately and appropriate antibiotic therapy should be introduced. However, the prevention of contamination during a donor nephrectomy and the use of preventive antibiotics before transplantation should ensure that

the incidence of wound infection after transplantation is no more than 3% or 4%.

Patients with high fever but benign-appearing incision sites can harbor large purulent abscesses, emphasizing the effect of steroids on masking signs of inflammation. If unexplained fevers persist, ultrasonography or computed tomography (CT) scanning of the wound may localize a fluid collection; needle aspiration of a fluid collection is indicated. Prophylaxis with the administration of intraoperative intravenous antibiotics has reduced both wound infections and sepsis.

Bleeding

A secondary hemorrhage following a renal transplant is, fortunately, an unusual event and is always secondary to infection, which usually has been introduced at the time of operation. During a fulminant rejection episode, acute swelling of the kidney may lead to rupture through its cortex, often originating at a previous biopsy site. Urgent surgical exploration is necessary in most cases of hemorrhage. The kidney and its surroundings should be examined, the source of bleeding should be identified if possible, and the wound should be evacuated to eliminate a potential nidus of infection. If a small cortical rupture is present without a venous obstruction, it may be repaired by packing it with autologous muscle or microfibrillar collagen. If the rupture is large or venous compromise is present, transplant nephrectomy is almost invariably indicated.

Vascular Complications

Arterial Thrombosis. A thrombosis of the renal artery is a rare complication in the early days after transplantation, probably due both to the high flow through the kidney and also to the associated anemia and coagulation defects present in most patients with end-stage renal failure. It occurs in less than 1% of renal transplants. Factors that may predispose one to thrombosis include a preexisting hypercoagulable state, technical difficulties with the anastomosis, heavy arteriosclerotic involvement of recipient or donor vessels, kidneys with multiple renal arteries, and hypotension. Thrombosis may also occur owing to CsA-associated arteriopathy or because of hyperacute humoral rejection. CsA has been associated with increased thromboembolic complications, possibly because of the enhancement of platelet aggregation. Thrombosis due to an error in suture technique may occur in any case, but would be extraordinarily rare in an end-to-side anastomosis performed between a patch of donor aorta to an arteriotomy in the common or external iliac artery. In the later weeks after transplantation, renal artery thrombosis may be seen secondarily to arteriolar thrombosis in an acutely rejecting kidney, but the major vessel thrombosis is not the primary event. A renogram will quickly establish the presence of an arterial blood supply to the kidney if this is in doubt.

A sudden cessation of urine flow in the setting of a previously working allograft and a patent urinary catheter should suggest the possibility of renal artery thrombosis. An emergency renal ultrasound study or radionuclide renal scan will confirm the presence or absence of parenchymal blood flow. A digital subtraction angiogram is reserved for the very few cases with a no flow renal scan. Attempts to remove the thrombus are usually unsuccessful because of extensive intrarenal clotting beyond the main arterial branches.

Venous Thrombosis. Thrombosis of the renal vein as an acute event in the transplanted kidney is unusual and is usually due to a technical mishap at the time of operation. Thrombosis of the renal vein at some later period after transplantation is probably more common than is realized. It may occur secondarily to thrombosis of the common iliac vein or may occur occasionally as the primary event. Venous thrombosis may be related to CsA use, but it may also occur after placement of the allograft into a tight scarred, retroperitoneal pocket after removal of a previous graft.

In the absence of the clinical features of thrombosis of the common iliac vein, thrombosis of the renal vein itself may present with proteinuria and a marked increase in the size of the kidney, but may also occur without any notable features. A partial obstruction of the iliac vein by the pressure of the allograft can produce unilateral leg swelling on the side of the graft and rarely may lead to deep venous thrombosis. If the diagnosis of deep venous thrombosis is confirmed by Doppler plethysmography or venography, anticoagulation therapy should be initiated unless there are absolute contraindications. A venography is the best test to confirm the diagnosis.

Treatment for a well-localized thrombosis involves a thrombectomy and revascularization. Alternatively, it can be treated with systemic anticoagulation. Treatment often is successful if the condition was due to a transient hypercoagulable state, but rarely succeeds if the process was one manifestation of severe rejection and high renal vascular resistance with low flow. In practical terms, however, by the time the diagnosis is confirmed by angiography or radionuclide scanning, salvage of the kidney is unlikely and transplant nephrectomy is the usual outcome. Deep vein thrombosis occurs with a frequency of around 10% of transplant patients. Anticoagulation of these patients for several months is required because a pulmonary embolism is not an uncommon cause of death in renal transplant patients.

Other Vascular Problems. In kidneys with multiple renal arteries, the thrombosis of a polar branch can lead to ureteral necrosis or segmental parenchymal infarction with the potential development of a calyceal cutaneous fistula. Careful attention to these tenuous, small-caliber polar branches has decreased the incidence of these complications. In cadaveric kidneys harvested en bloc, a small aortic cuff (Carrel patch) can be made surrounding the orifices of the renal arteries. The cuff can then be anastomosed end to side to the external iliac artery, thus preventing any possibility of anastomotic compromise. If no cuff is available, the polar branches can

be anastomosed end to side to the main renal artery, followed by anastomosis of the main artery to the recipient.

Many male patients with ESRD have erectile dysfunction because of decreased penile arterial flow, neuropathy, or both. Repeat transplant recipients should have an end-to-side reno-iliac arterial anastomosis if the contralateral hypogastric artery was used in the first transplant.

Urologic Complications

An accurate evaluation of lower urinary tract function prior to transplantation is important to minimize postoperative urologic complications. There are many approaches to the correction of these urologic complications, but, as a general rule, the approach should be early and aggressive rather than conservative. Many of the complications are preventable with careful attention to the technique of donor nephrectomy.

Urine Leak. Urine leak is an infrequent but serious problem and occurs in approximately 2% of renal transplant patients. It is seen early after transplantation and is usually secondary to necrosis of the entire or distal portion of the ureter or to infarction of the renal pelvis. This usually is due to the interruption or thrombosis of the ureteral artery, which is the main arterial supply to the donor ureter.

The source of the leak may be from the ureter, calyces, or the bladder. Upper urinary tract leakage is due to ischemia resulting from the loss of vascular supply during organ procurement. The preservation of hilar vessels and periurethral fat and adventitia is the key to prevention of this problem. A bladder urine leak may occur at the site of the ureteral reimplant or along the cystotomy closure.

The clinical presentation of a urine leak may be subtle unless a wound drain is in place. The leakage of urine from the lower end of the ureter is not usually evident until at least 1 week after transplantation and often much later. It may be associated with a decrease in urine output, fever, local tenderness, and swelling due to the localized collection of urine known as urinoma. Other clinical signs include unexplained fever and edema of the scrotum, labia, or thigh ipsilateral to the graft.

An ultrasonography is the preferred study for diagnosis of a suspected urine leak. Aspiration of the fluid mass and comparison of the fluid creatinine or urea content to serum values confirms the diagnosis of a urine leak. The dynamic phase of a renal scan also may demonstrate urinary extravasation. A cystography with oblique and drainage films will confirm whether the leak is from the bladder. Confirmation of an upper urinary tract leakage is more difficult, because attempts at retrograde pyelography in the early postoperative period often are unsuccessful.

Urine is a strong chemical irritant to tissues and predisposes the fresh vascular anastomoses to infection. Prolonged catheter drainage may be adequate treatment for a small bladder leak. Insertion of a percutaneous nephrostomy or ureteral stent can also be used to provide initial urinary drainage and stabilization of the patient. After function returns to baseline, surgical reexploration and repair is usually attempted. If the distal ureter is necrotic or stenotic, the necrotic portion can be removed and the vascularized proximal ureter can be reimplanted into the bladder. If the ureter is too short or the renal pelvis is necrotic, the ipsilateral native ureter can be detached from the native kidney near the pelvis and connected to the renal transplant by means of a ureteropyeloplasty. The anastomosis is protected by a temporary nephrostomy and ureteral stent. If a native ureter is not available or adequate, then the bladder can be mobilized and a Boari flap ureteronephrostomy can be constructed, or the bladder is anastomosed directly to the kidney pelvis, and a nephrostomy tube is left in place for several weeks.

Ureteral Obstruction. Acute ureteral obstruction in the early postoperative period may be due to distal ischemia, infarction, or rejection. Transient obstruction by a clot in the ureter or bladder immediately postoperatively may cause erratic urine output and can usually be taken care of by bladder catheter irrigation. Technical error as an early cause of obstruction of the ureterovesical junction is rare. Oliguria or anuria in the immediate posttransplant period should make one suspect the diagnosis. A cystogram is usually performed first to rule out a bladder leak. The diagnosis is confirmed by the presence of hydronephrosis by ultrasonography (Fig. 82.12) or by decreased flow from ureter to bladder or evidence of extravasation on percutaneous nephrostogram (Fig. 82.13). The site of obstruction can be identified by an antegrade pyelogram. Occasionally, obstruction of the ureter may be secondary to a hydrocele or hematoma, which can occur after a percutaneous needle biopsy.

Obstruction of the ureter may occur at some time remote from transplantation, often due to the development of a stricture, presumably as a result of previous ischemia. Progressive stenosis of the distal transplant ureter secondary

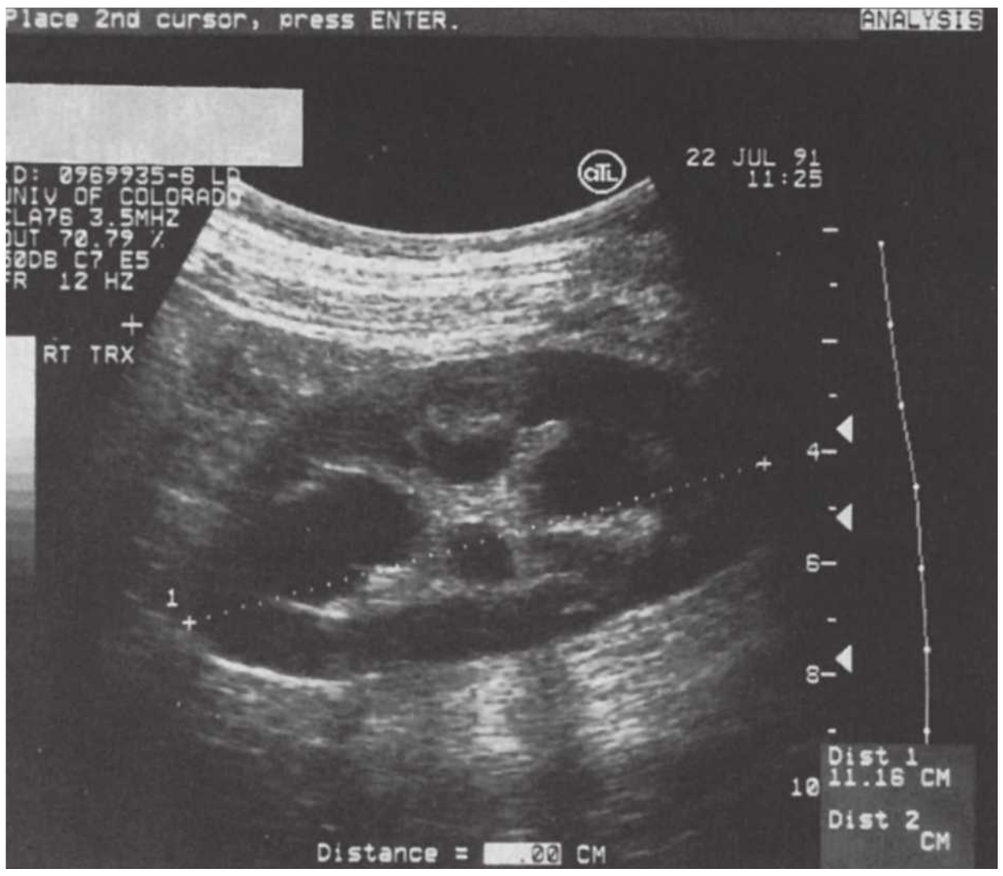


FIGURE 82.12 An ultrasound scan of a renal transplant showing hydronephrosis due to ureteric obstruction.

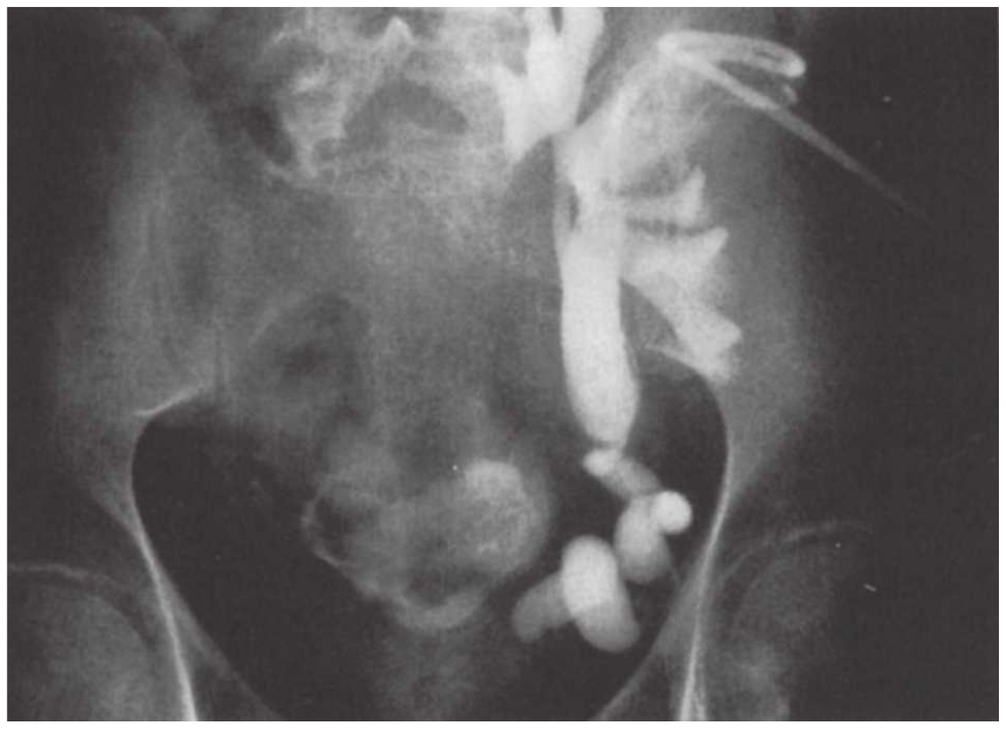


FIGURE 82.13 A percutaneous nephrostogram of a renal transplant. A nephrostomy tube placement with antegrade pyelogram to identify the site of obstruction.

to fibrosis or chronic ischemia may present as progressive azotemia over several months. An ultrasonography and an intravenous pyelogram or an antegrade pyelogram should confirm the diagnoses. A ureteric obstruction should always be considered in the patient with a gradual deterioration of renal function. Options for treatment include cystoscopic or percutaneous radiologic placement of an indwelling double-J ureteral stent, use of percutaneous nephrostomy, balloon dilatation, and surgical repair.

Reflux. Vesicoureteral reflux into the transplanted ureter has a reported incidence of 4% to 65%, depending on the technique of ureteral anastomosis; the creation of a distinct submucosal tunnel through the bladder wall has resulted in a lower incidence. The presence of vesicoureteral reflux in the transplanted allograft has not been found to increase the rate of urinary tract infections compared with nonrefluxing grafts.[192] Mathew and coworkers[193] found an increased incidence of proteinuria, microhematuria, hypertension, and graft failure in the refluxing group, a finding that has not been confirmed in additional studies.

Lymphocele. The major complication associated with lymphatics is the occurrence of a lymphocele, which usually presents in the first 2 or 3 months after transplantation as a large cystic mass in the vicinity of the kidney.[194] It is usually asymptomatic. Its presenting features are due to pressure on surrounding structures; it may cause deterioration in renal function due to pressure on the ureter, swelling of the leg due to pressure on the iliac vein, urgency due to pressure on the bladder, and diarrhea and tenesmus due to pressure on the rectum. An ultrasonography can confirm the presence of a perinephric (lymph) collection. Studies with radiolabeled lymph reveal that the major source of fluid in lymphoceles is from the lymphatics along the recipient iliac vessels and not from the renal hilum. Therefore, the meticulous ligation of the lymphatics during exposure of the vessels is the best prevention. Aspiration of the mass and measurement of fluid creatinine and potassium levels compared with the values in serum establishes the diagnosis of lymphocele and excludes urine leak, hematoma, or abscess. Sometimes, the lymphocele will not recur after two or three aspirations. However, if the lymphocele continues to recur, then it should be marsupialized into the peritoneal cavity after checking the aspirate for urine products and bacterial growth.

Assessing Renal Dysfunction in the Transplanted Kidney

An assessment of the cause of renal dysfunction is warranted in any patient with a sustained increase in serum creatinine >0.3 mg per deciliter or decrease in renal function of >20%. The differential diagnosis immediately following transplant (Table 82.13) and its assessment (Table 82.14) typically involves ruling out structural abnormalities with noninvasive testing, verifying drug level monitoring, and assessing for acute rejection. Noninvasive imaging of the transplanted kidney can be quite useful in differentiating the different causes of acute allograft dysfunction, particularly in the early posttransplant period.

Radionuclide Imaging. Renal perfusion can be assessed by technetium diethylene triamine pentaacetic acid (DTPA) or technetium-99m mercaptoacetyltriglycine (MAG3) and tubular function by iodohippurate (Hippuran) I^{131} uptake. A decline in initial renal blood flow and a decrease in tubular function often occur during acute rejection. Occasionally, scans can help diagnose uncommon posttransplant complications, such as venous thrombosis or urinary leak.

Ultrasound. Real-time and duplex Doppler sonography of the renal allograft is useful for evaluating recipients

82.13 Causes of Acute Renal Failure Associated with Renal Transplantation

Prerenal	Hypovolemia Arterial stenosis or thrombosis Venous thrombosis
Renal	Acute tubular necrosis Hyperacute/accelerated rejection Acute rejection Nephrotoxicity
Postrenal	Ureteral obstruction Urinary leak Lymphocele Hematoma

82.14 Approach to the Patient with Acute Renal Failure Following Transplantation

Immediate Acute Renal Failure (48 hr)
- Rule out catheter obstruction
- Rule out hypovolemia
- Radioisotope scan to rule out vascular catastrophe
- Ultrasound to rule out urinary extravasation or obstruction
- Radiocontrast studies (if indicated by previous)

Early or Late Acute Renal Failure (After 48 hr)
- History and physical examination to detect oliguria, tender swelling graft, fever
- Urine sodium, FENa (especially if baseline available)
- CsA or tacrolimus levels
- Radioisotope scan
- Ultrasound
- Therapeutic trial of steroids/lowering cyclosporine dose
- Renal biopsy

FENa, fractional excretion of sodium; CsA, cyclosporine.

with surgical complications, including perinephric fluid collections, hydronephrosis, and vascular complications (Fig. 82.14). The sonography reveals variable findings in acute rejection, such as graft enlargement, enhanced echogenicity of the parenchyma, and increased resistive index (>70%) of the vessels. The studies will not confirm the diagnosis of rejection, but will serve to exclude allograft thrombosis and urinary obstruction, and will indicate that a percutaneous transplant kidney biopsy with pathologic examination should be performed.

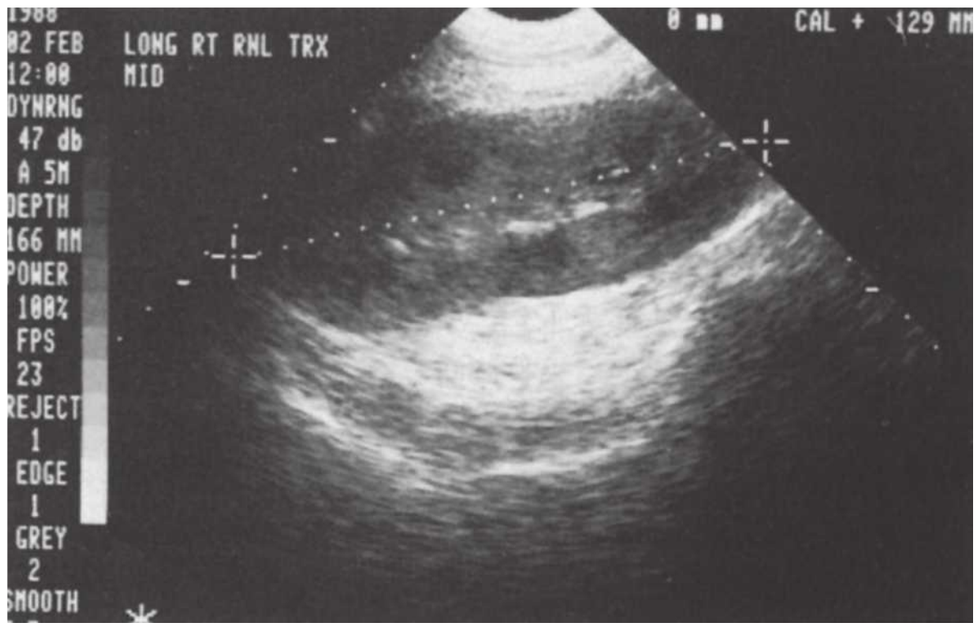


FIGURE 82.14 A normal renal ultrasound of a transplanted kidney.

Renal Transplant Biopsy. A biopsy will help to confirm the diagnosis of acute tubular necrosis (ATN) by the exclusion of a histologic picture of severe rejection (Table 82.15). A needle biopsy of the donor kidney just prior to or after implantation is helpful to detect renal disease or preservation injury that might confound the interpretation of delayed renal allograft function. However, a poor understanding of the natural history of transplant histology makes it an imperfect gold standard.

Technique of Renal Transplant Kidney Biopsy. The use of a percutaneous biopsy of the transplant kidney to diagnose rejection was first performed in 1967.[195] Since then, the technique has been well established as a useful tool in the differential diagnosis of allograft dysfunction. The position and alignment of the transplant kidney can vary from patient to patient (Fig. 82.15). In most instances, the transplant kidney is palpable and the orientation of the kidney can be estimated by reviewing an isotope scan of the transplant kidney (Fig. 82.16).

A biopsy can be obtained with a Vim–Silverman needle, a 14G to 16G disposable Tru-Cut biopsy needle, or an 18G

82.15 Histopathology of Renal Allograft Using Needle Biopsy

Changes Associated with Rejection
- Glomerular
  - Swelling of endothelium
  - Endothelial/mesangial proliferation
  - Exudation of polymorphs, mononuclear cells
- Interstitial
  - Edema
  - Infiltration of mononuclear cells
  - Macrophages
  - Eosinophils
- Vascular
  - Endothelial edema
  - Mural infiltration
  - Necrosis, hemorrhage
  - Severe vasculitis (especially interstitial hemorrhage) predicts eventual graft failure

Changes Associated with Cyclosporine
- Tubular changes
  - Giant mitochondria
  - Vacuolization
  - Microcalcification
- Interstitium
  - Mononuclear infiltration
- Vascular changes
  - Arteriolar necrosis

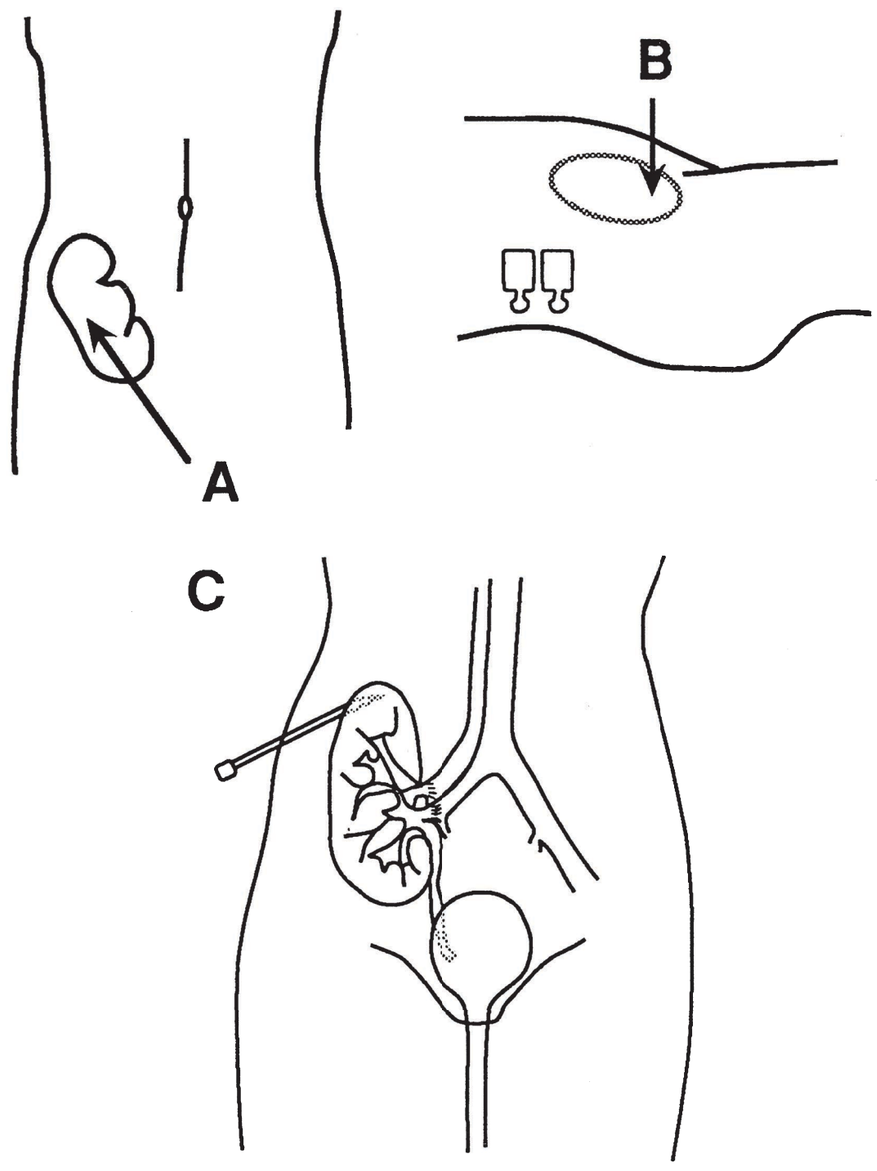


FIGURE 82.15 The site of biopsy for the transplanted kidney. The orientation of the transplanted kidney is localized by palpation and a review of the operative record and renal scan. The kidney is approached either tangentially or vertically **(A),** in a plane tangential to the lateral curvature of the allograft or **(B)** in a plane perpendicular to the kidney directed to the lower pole. **C:** Tangential across the upper pole of the transplanted kidney.

automatic Biopty or Monopty needle (Fig. 82.17). It is best performed under sonographic guidance. Relative contraindications to biopsy include abnormal coagulation studies or a low platelet count, an active urinary tract infection, and significant renal allograft hydronephrosis. Hydronephrosis, indicative of a urinary tract obstruction, should be further investigated. In patients with prolonged bleeding time due to uremia, intravenous desamino-D-arginine vasopressin (dDAVP) (0.3 μg per kilogram) can be used to correct the coagulation defect prior to a biopsy procedure. If the kidney has been transplanted via an intra-abdominal approach or is difficult to localize, then consideration should be given to a CT-guided direction, or occasionally, via a limited open surgical approach in the operating room. A biopsy considered adequate for analysis involves a sampling of at least 10 glomeruli and two small arteries, stained for hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) or silver, and trichrome stains, whereas a biopsy with 7 to 9 glomeruli and one artery is considered of marginal adequacy. When performed for clinical indications (renal dysfunction), two separate cores should be obtained because the findings of rejection are often patchy in distribution.[196]

Novel Diagnostic Techniques. Although a percutaneous needle biopsy is currently the gold standard for the diagnosis of renal allograft dysfunction, it is a time- and resource-intensive invasive procedure that is subject to sampling error as well as potential procedure-related complications. The noninvasive diagnosis of allograft dysfunction using biomarker profiles is an attractive alternative to invasive methods, and numerous reports have described targets identified in either blood or urine samples that are predictive and/or diagnostic of events such as acute rejection (AR) and DGF.

Because cytotoxic T lymphocytes play a dominant role in cell-mediated rejection, their effector molecules perforin, granzyme B, and FasL have been assessed noninvasively in transplant recipients for correlation with clinical sequelae. These effector molecules have been shown to be upregulated in both the blood and urine of patients with AR in some[197] but not all[198] reports. Moreover, elevated levels of urine perforin, granzyme B, and FasL mRNA have been described in conditions of nonimmune-mediated graft injury, including

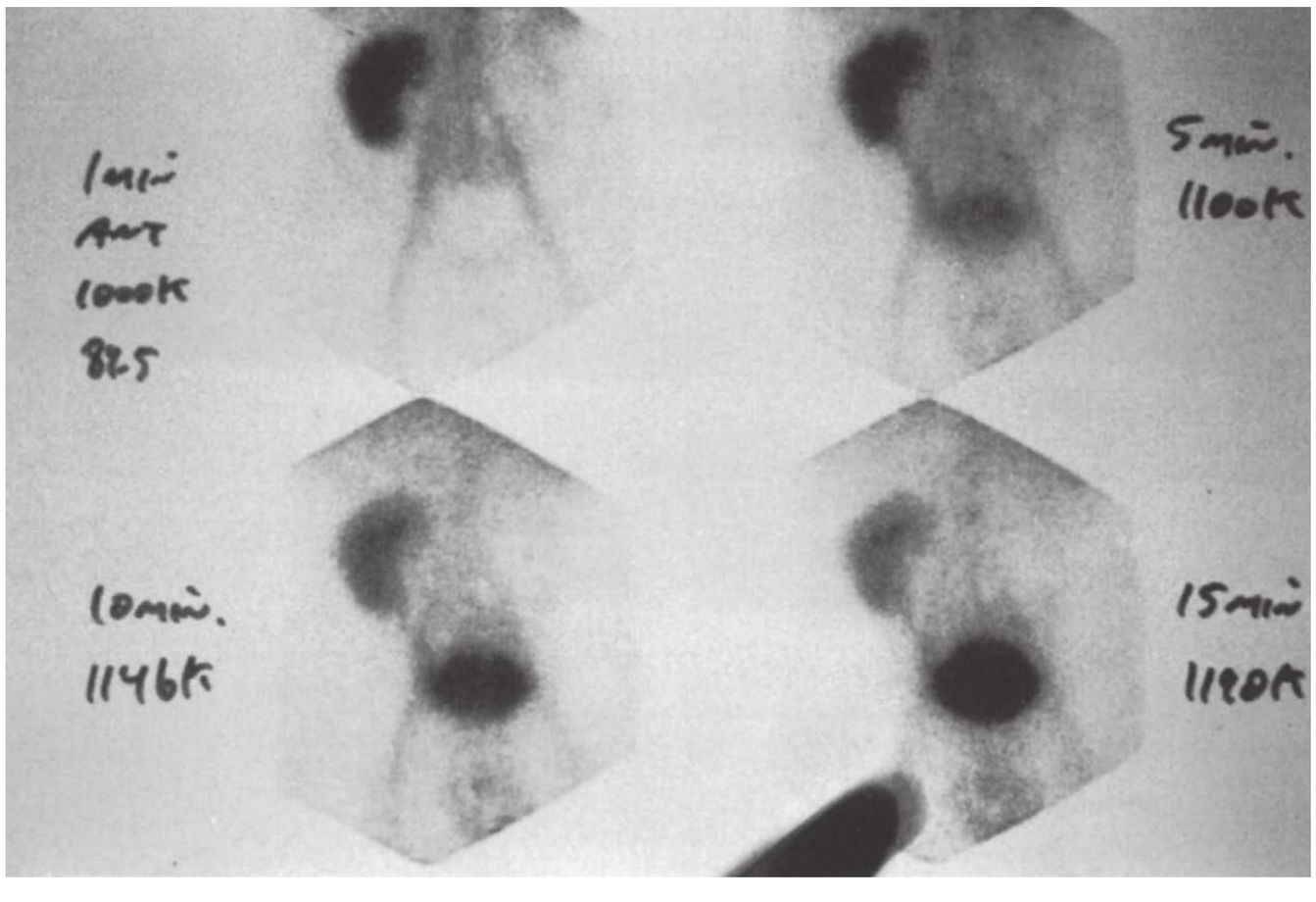
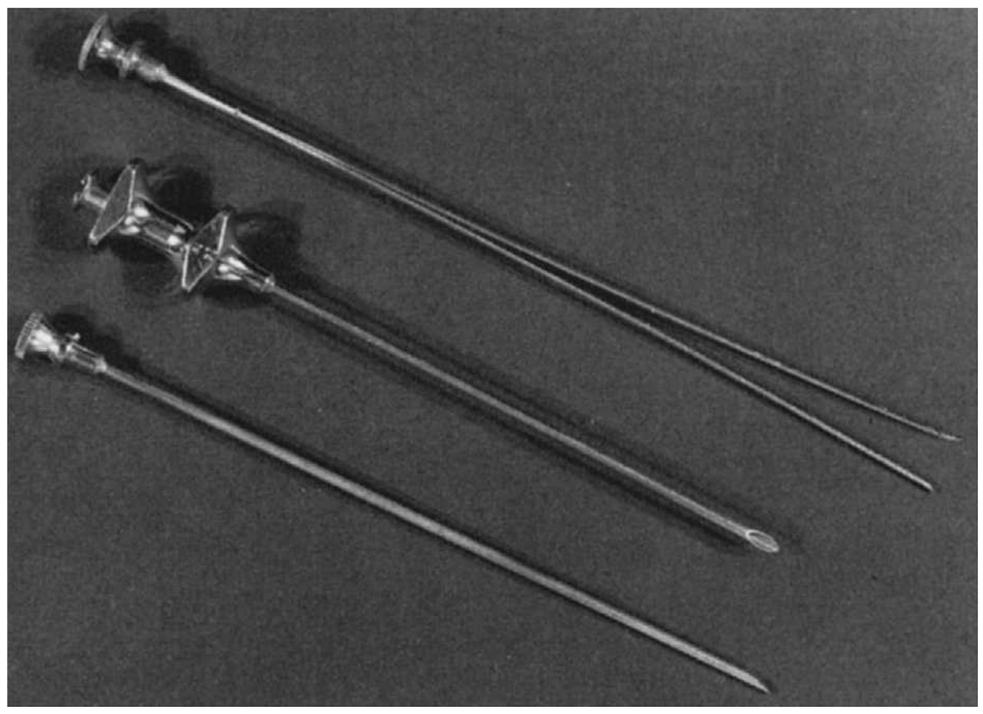
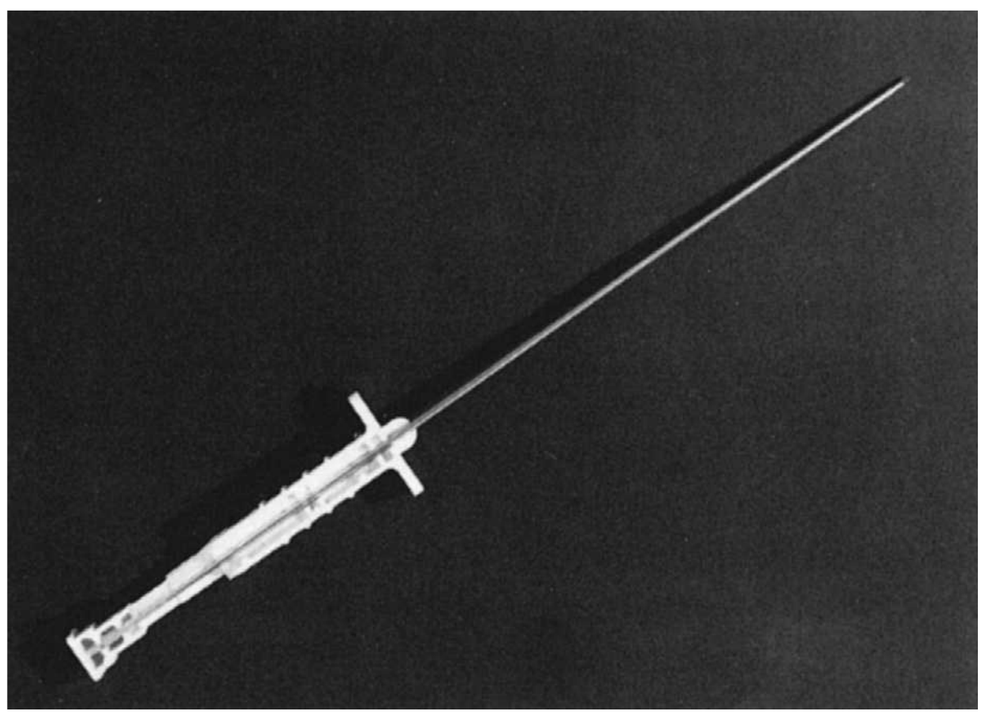


FIGURE 82.16 A diethylenetriamine pentaacetic acid scan showing good renal perfusion in a transplanted kidney.



A



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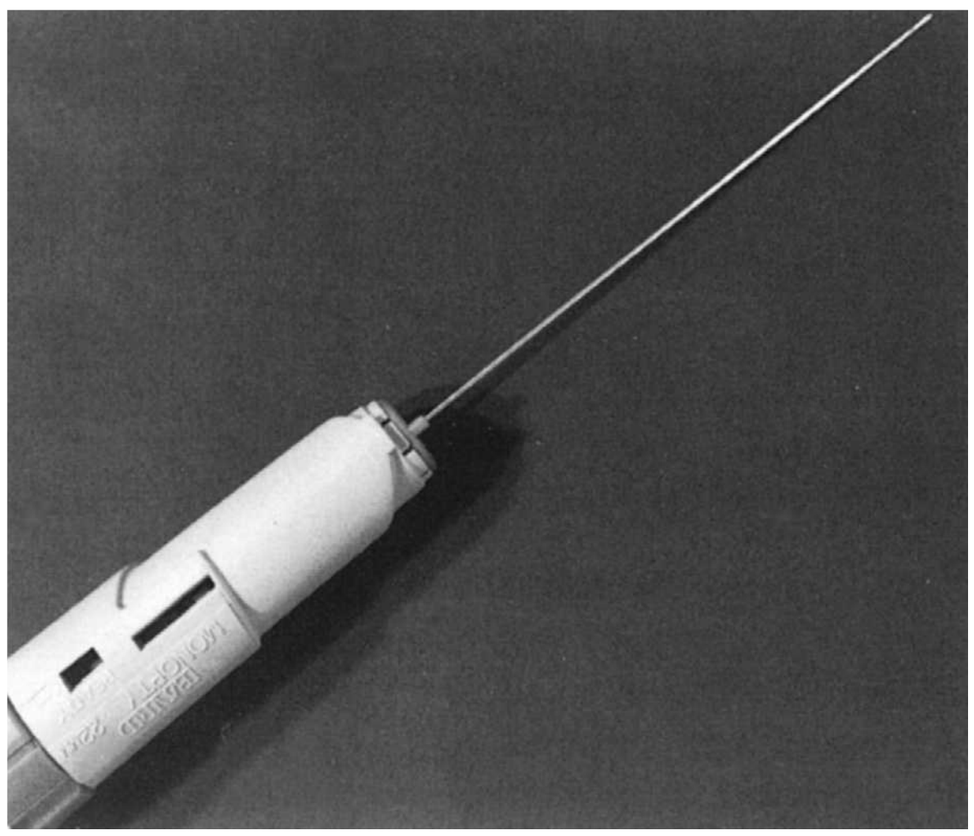

C

FIGURE 82.17 Different types of biopsy needles. **A:** Vim-Silverman. **B:** Tru-Cut 14 G (disposable needle). **C:** Biopty gun 18 G (disposable needle).

bacterial urinary tract infection, CMV infection, and DGF, potentially limiting their diagnostic use. Urinary levels of FOXP3 mRNA from T-regulatory cells has been shown to be increased in episodes of AR, and mRNA levels correlate with serum creatinine at the time of allograft biopsy.[199] TIM-3, a protein expressed on the surface of T-helper 1 cells, was also shown to be helpful in differentiating ATN from AR in 50 patients with DGF, where blood and urine mRNA levels were significantly higher in patients with AR with a sensitivity and specificity of 100%.[200] Finally, of interest in the setting of AMR is the Affymetrix microarray assay (Affymetrix Inc., Santa Clara, CA), which has shown higher intragraft expression of endothelial-associated transcripts in patients with AR compared to those without, and even higher levels in those with AMR versus cell-mediated rejection.[201] Despite the appeal of noninvasive diagnostic techniques and the encouraging data described previously, large clinical trials validating biomarkers as reliable alternatives to percutaneous biopsy have yet to be performed and their use remains experimental.

Medical Causes of Acute Allograft Injury

The transplanted kidney is susceptible to postsurgical, infectious, and immunologic insults, which are exacerbated by the lack of autoregulation that exists as a result of denervation following a kidney transplantation. In the immediate posttransplant period, there may be DGF or cessation of function after the initial good function. The most likely cause of renal failure during this period is ischemic tubular damage, but a vascular accident, ureteric obstruction, a urine leak, acute CNI nephrotoxicity, or rejection are all possible etiologies, and more than one cause of dysfunction can occur together (Table 82.13). Knowledge of the natural history of several clinical entities is extremely helpful in limiting the differential diagnosis.

Acute Tubular Necrosis

The pathogenesis of acute tubular necrosis (ATN) may arise from ischemic damage secondary to hypovolemia and hypotension in the donor and prolonged warm ischemia and cold ischemia during preservation. In the transplant setting, ATN is often interchangeable with DGF, although a complete diagnostic assessment should rule out all other causes prior to reaching this diagnosis. The most common definition of DGF is the need for dialysis within the first week following transplant. Using this definition, DGF is strongly associated with 1-year graft loss.[202]

Allograft Rejection

Rejection is a major cause of graft failure. It is important to diagnose acute rejection as soon as possible in order to promptly institute antirejection therapy. The classification can be made based on pathologic criteria with therapy directed at the specific pathogenic process (Table 82.16).

Hyperacute Antibody-Mediated Rejection. This form of rejection is caused by preformed antibodies against alloantigens that are present in response to previous exposure to antigens through prior transplantations, blood transfusions, or multiple pregnancies. When present at the time of surgery, alloantibody leads to the clinical manifestation of hyperacute rejection, a failure of the kidney to perfuse properly on

82.16 Banff 2007 Diagnostic Categories for Renal Allograft Biopsies

1. Normal
   The presence of patchy mononuclear cell infiltrates without tubulitis is not uncommon in normally functioning renal allografts and, when considered alone, does not warrant the diagnosis of acute rejection.
2. Antibody-mediated rejection (Rejection demonstrated to be due, at least in part, to antidonor antibody)
   Acute:
   I. ATN-like: C4d+, minimal inflammation
   II. Capillary: margination and/or thromboses, C4d+
   III. Arterial: v3, C4d+
   Chronic: active antibody-mediated rejection (Glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries, C4d+)
3. Borderline changes: "Suspicious" for acute rejection, foci of tubulitis and no arteritis, not reaching threshold of IA that follows
   This category is used when no intimal arteritis is present, but there are foci of mild tubulitis (1 to 4 mononuclear cells/tubular cross-section)
4. T-cell–mediated rejection

Acute T-Cell–Mediated Rejection

Type (Grade)	Histopathologic Findings
IA	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of moderate tubulitis (>4 mononuclear cells/tubular cross-section or group of 10 tubular cells)
IB	Cases with significant interstitial infiltration (>25% of parenchyma affected) and foci of severe tubulitis (>10 mononuclear cells/tubular cross-section or group of 10 tubular cells)
IIA	Cases with mild-to-moderate intimal arteritis
IIB	Cases with severe intimal arteritis comprising >25% of luminal area
III	Cases with "transmural" arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells

Chronic active T-cell–mediated rejection
(Chronic allograft arteriopathy: arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology

Grade	Histopathologic Findings
I (mild)	Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
II (moderate)	Moderate interstitial fibrosis and tubular atrophy (26-50% of cortical area)
III (severe)	Severe interstitial fibrosis and tubular atrophy (>50% of cortical area)

6. Other changes not considered to be due to rejection
   Posttransplant lymphoproliferative disorder
   Polyomavirus-associated interstitial nephritis
   Acute tubular necrosis
   Acute interstitial nephritis
   Cyclosporine or FK506-associated change

release of the vascular clamps just after vascular anastomosis is completed. The kidney initially becomes firm and then rapidly becomes blue, spotted, and flabby. The presence of neutrophils in the glomeruli and peritubular capillaries in the kidney biopsy confirms the diagnosis, and is supported by the finding of markers of complement deposition (C4d) in peritubular capillaries.[203] It can be prevented by careful testing of recipients for the presence of the preformed cytotoxic antibodies. Although hyperacute rejection is rare due to effective pretransplant HLA typing and cross-matching, delayed

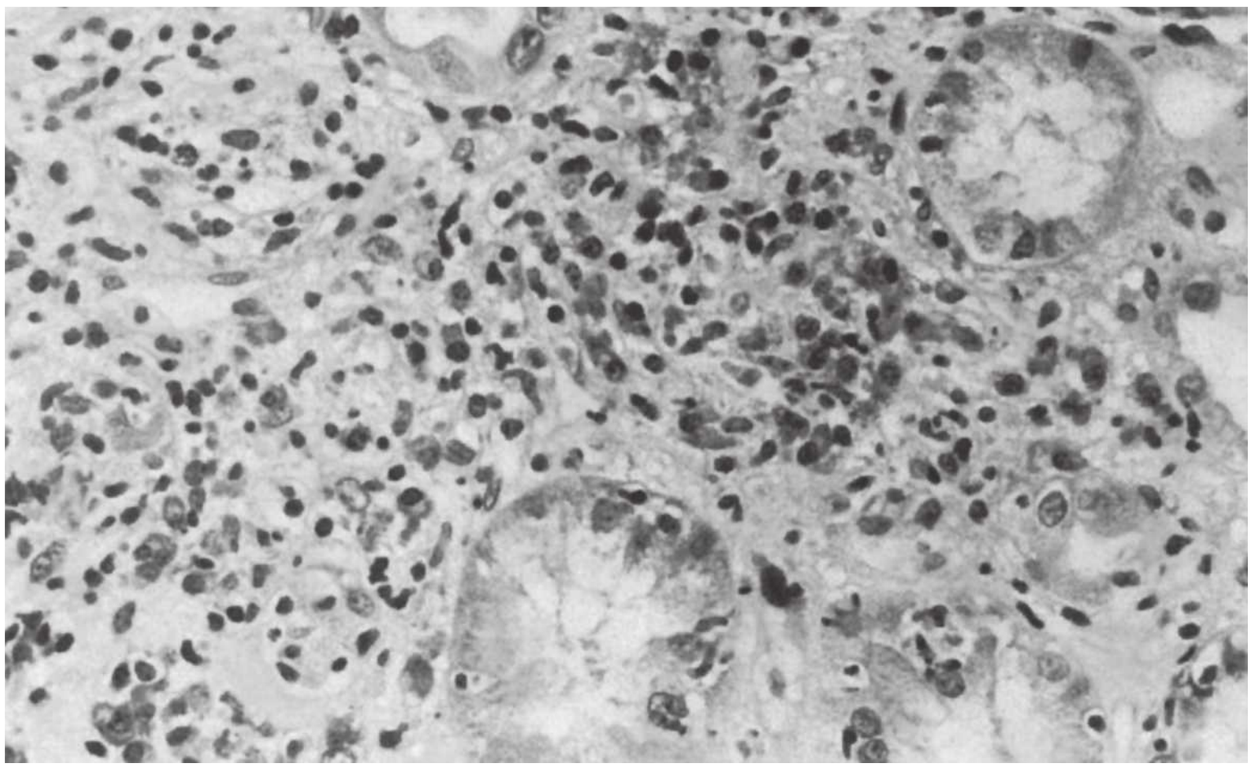

FIGURE 82.18 Acute cellular rejection, Banff 1b. A percutaneous renal transplant biopsy specimen showing tubulitis with tubular epithelial infiltrates of lymphocytes and plasma cells.

hyperacute rejection has become more common as centers attempt to transplant across incompatible HLA and ABO types with desensitization strategies. In the previously sensitized patient in whom preformed anti-HLA antibodies are present, the memory B-cell response is upregulated in the week following transplant and donor-specific antibodies are formed, which lead to rapid decline in renal function and a similar clinical picture to that mentioned for hyperacute rejection.

Acute antibody-mediated rejection can occur at any time following transplantation either in combination with a T-cell–mediated process, or in isolation with the development of donor specific antibodies (Table 82.16). Diagnosis is made by a triad of findings comprised of tissue injury (classically, peritubular capillaritis composed primarily of neutrophils), the presence of circulating antidonor antibodies (donor-specific antibodies), and evidence of complement activation via staining for C4d. Although the presence of all three findings is specific for acute antibody-mediated rejection, all three findings are not required to make this diagnosis and initiate therapy in the setting of rapid graft dysfunction.

Acute T-Cell–Mediated (Cellular) Rejection (ACR). Acute T-cell–mediated rejection (ACR) episodes may occur as early as 5 to 7 days, but are generally seen between 1 and 4 weeks after transplantation. The classic acute rejection episode of the earlier era in a patient treated with AZA/prednisone was accompanied by swelling and tenderness of the kidney and the onset of oliguria with an associated rise in serum creatinine, and was usually accompanied by a significant fever. However, in patients who have been treated with higher degrees of immunosuppression, the clinical features of an acute rejection can be minimal in that there is perhaps some swelling of the kidney, usually no tenderness, and there commonly is an absence of fever. Because such an acute rejection may occur at a time when there is a distinct possibility of acute CsA or TAC toxicity, the differentiation between the two entities may be extremely difficult and requires a biopsy for an accurate diagnosis.

Pathologic changes of acute cellular rejection include interstitial infiltration with mononuclear cells and disruption of the tubular basement membranes (tubulitis) by the infiltrating cells (Fig. 82.18).[196] The presence of patchy mononuclear cell infiltrates without tubulitis is not uncommon in normal functioning renal allografts and is not sufficient to make the diagnosis of acute rejection. The finding of interstitial infiltrates and tubulitis in a kidney transplant biopsy is not specific to acute cellular rejection and other etiologies such as viral nephropathy (BK virus, less commonly cytomegalovirus [CMV]), pyelonephritis, or posttransplant lymphoproliferative disease should be considered based on the clinical presentation. In contrast, the histologic finding of endothelialitis is pathognomonic of acute cellular rejection. The intrarenal arteries and arterioles show characteristic changes of intimal thickening and the presence of inflammatory cells within and adherent to the endothelium (Fig. 82.19). The glomerular changes are usually unremarkable in rejection. However, glomerular capillary and vascular intimal infiltrates can occur in the setting of mixed humoral and cellular rejection (Fig. 82.20). A periodic examination of histologic features in the absence of changes in renal function (protocol biopsies) may reveal silent allograft rejection (subclinical rejection). Although potentially predictive of chronic graft dysfunction, treatment of subclinical rejection is of unclear benefit.[204]

Treatment of acute rejection. Treatment of T-cell–mediated acute rejection is often directed by the findings on biopsy and the clinical response to pulse corticosteroids. For the patient with graft dysfunction and biopsy-proven rejection, treatment with intravenous methylprednisolone 3 to 5 mg per kilogram (250 to 500 mg per day) for 3 to 5 days is often effective if the histologic injury is tubulointerstitial (Banff class IA or IB) (see Fig. 82.18). If there is an inadequate response following corticosteroid pulse therapy or if there is vascular involvement (Banff class IIA, IIB) (Fig. 82.19), corticosteroids often must be supplemented with T-cell–depleting antibody therapies in a similar dosing strategy, but a longer treatment course when compared to their use for induction. Most studies have

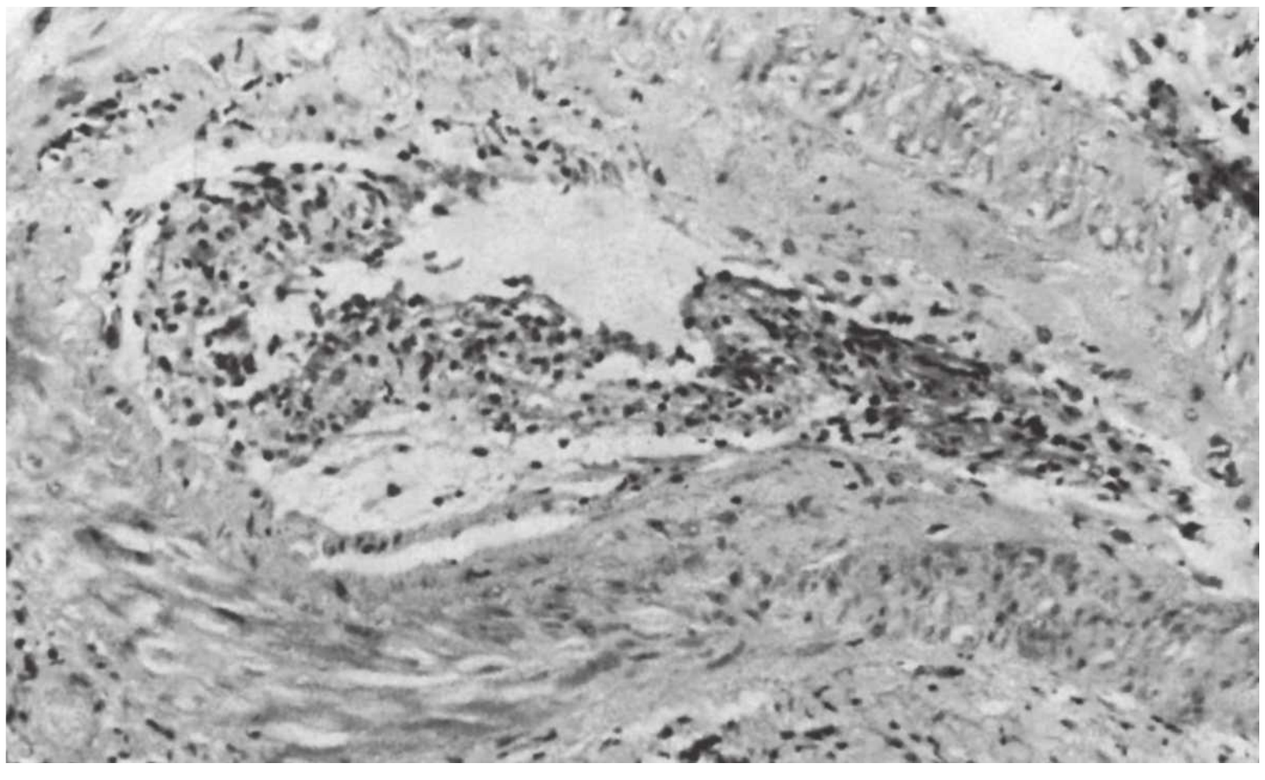

FIGURE 82.19 Acute cellular rejection, Banff IIb. A renal transplant biopsy specimen showing marked endovasculitis and acute inflammatory endothelial infiltrates.

used these agents in 7- to 14-day treatment courses, with no clinical trials investigating the efficacy of shorter courses versus longer courses. For patients who are on a maintenance regimen that is not TAC based, TAC conversion may also be considered in the setting of rejection with an inadequate response to corticosteroids. For patients on a corticosteroid-free regimen, the reinstitution of maintenance prednisone may be warranted. The treatment of acute antibody-mediated rejection is indicated when the triad of graft injury, C4d+ staining in peritubular capillaries on biopsy, and circulating donor-specific antibody is present, but should also be considered in high-risk circumstances (prior desensitization or known donor-specific antibody) even if all three criteria are not met. Treatment entails the removal of the pathogenic immunoglobulin(s) with plasma exchange and inhibition/suppression of antibody production with IVIG. In general at least 5 plasma exchange treatments should be administered with 1 to 2 g per kilogram total dose IVIG. Because IVIG is removed by plasma exchange, a common strategy employed is to administer IVIG 100 to 200 mg per kilogram after each exchange. For refractory acute humoral rejection, rituximab or bortezomib may be considered. Finally, there are case reports of splenectomy for refractory acute antibody-mediated rejection.[205] These therapies are typically coupled with targeted T-cell therapy such as high dose steroids and/or depleting antibody therapy, because helper T-cell function may contribute to an enhanced B-cell response.

Acute Calcineurin Inhibitor Nephrotoxicity. Nephrotoxicity is the most frequently encountered and the most important side effect of CNI therapy. Acute CNI nephrotoxicity can occur within days or weeks after renal transplantation. The pathogenesis of acute nephrotoxicity is due to a dose-dependent CNI-induced renal arteriolar vasoconstriction leading to a decline in renal blood flow with a consequent fall in GFR.[206] A small increment in serum creatinine occurs, which is frequently correlated with high serum CNI trough levels. Serum creatinine returns to baseline within 24 hours of reduction of CNI dosage. In the early posttransplant period, functional CNI nephrotoxicity has clinical features similar to those of acute renal allograft rejection, and an allograft biopsy specimen should be obtained if the diagnosis is uncertain. Histologically, acute CNI nephrotoxicity can be distinguished from acute rejection chiefly by the absence

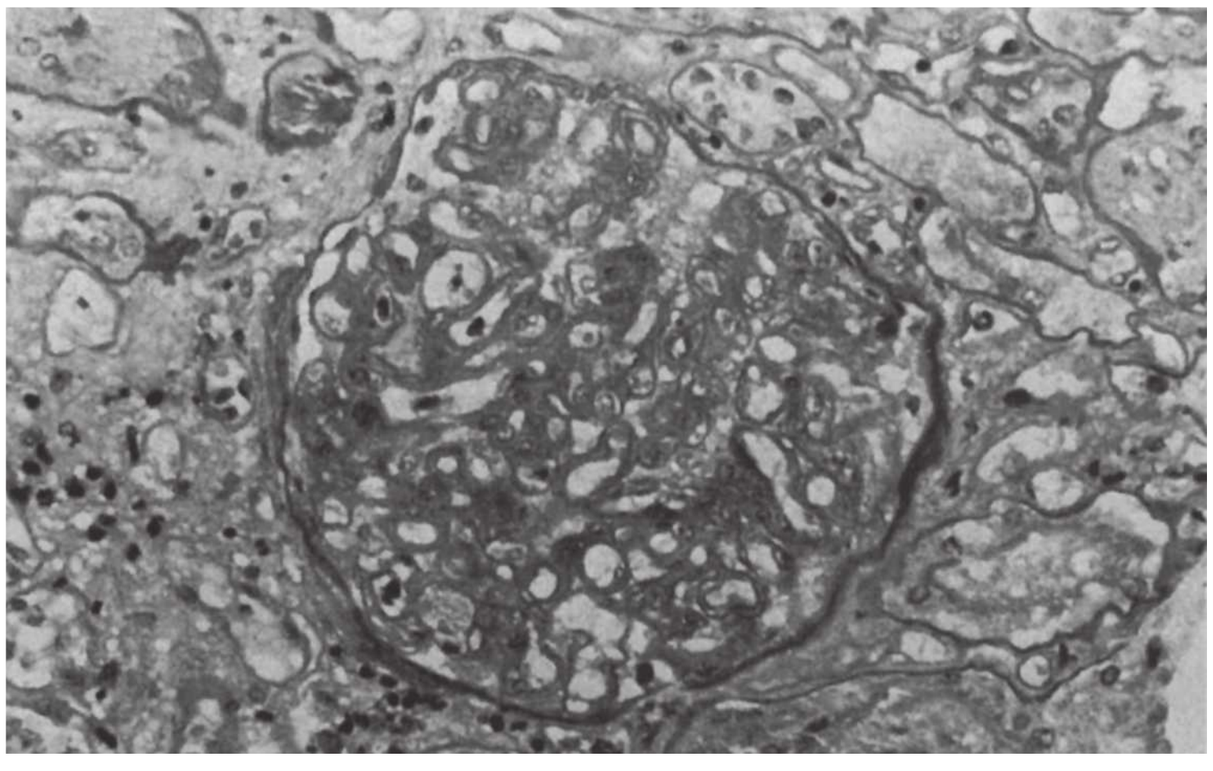

FIGURE 82.20 Acute cellular and humoral rejection. Glomerular and vascular endothelial infiltrates and swelling.

of an extensive inflammatory infiltrate. Rarely, a thrombotic microangiopathic vascular lesion can be seen, presumably due to endothelial injury. This appears to be more common with CsA than TAC and is more prevalent when mTORi is used rather than MPA as concurrent therapy.[59]

Causes of Subacute/Chronic Allograft Injury

Although early after transplant the differential diagnosis of graft dysfunction primarily involves surgical complications and acute rejection, after a period of stability, the progressive loss of graft function is common and is often due to both immunologic and nonimmunologic factors. Recently, a series of 1,317 patients who were on standard CNI-based immunosuppression were assessed by biopsy for etiologies for graft loss.[207] They reported that following the acute transplant period, the most common causes of graft loss were glomerular disease (37%), interstitial fibrosis/tubular atrophy (IF/TA) (31%), followed by acute rejection (12%) and other medical/surgical etiologies (16%). Graft losses due to glomerular injury were equally divided into recurrent glomerulonephritis, de novo glomerulonephritis, and glomerular disease associated with anti-HLA antibodies, whereas those due to IF/TA were comprised primarily of patients with prior acute rejection episodes, BK virus infections, and recurrent pyelonephritis episodes, which could explain the IF/TA lesion. Thus, the differential of subacute and chronic graft dysfunction must focus on glomerular etiologies and a determination of potential clinical clues that may lead to IF/TA.

Polyomavirus. Both the BK virus (Polyomavirus hominis) and the JC virus (Polyomavirus hominis) belong to the human Papovavirus family. About 60% to 80% of adults are seropositive for the BK virus. In immunocompetent individuals, the virus has little clinical significance, residing in a latent state in the kidney. However, in immunocompromised/suppressed patients, the BK virus can undergo replication, which leads to an immune response that causes an interstitial nephritis. In addition, renal allograft recipients were reported to have BK virus associated with ureteral stenosis and bone marrow transplant recipients from hemorrhagic cystitis. Histologically, it can be difficult to distinguish from the tubulitis and interstitial inflammation of acute cellular rejection. The presence of BKV-associated interstitial nephritis is suggested by the finding of large basophilic intranuclear viral inclusion bodies in tubular epithelial cells along the entire nephron and also the transitional cell layer and confirmed by special staining with SV40 (simian virus, related to BKV) immunohistochemical staining. Graft loss is common when identified late in its presentation, thus screening protocols have been recommended to detect early BKV reactivation in order to intervene at an earlier stage.[208] Screening can be from urine (via Papanicolaou staining for decoy cells or urine polymerase chain reaction [PCR]) or blood by PCR (Fig. 82.21). The primary risk factor for BK virus disease is high-dose immunosuppression. No established therapy for a polyomavirus infection is available and the reduction of immunosuppression offers the best therapeutic option. Leflunomide, cidofovir, IVIG, and corticosteroids have been used as potential therapeutic options but have not been studied in controlled trials.

Chronic Calcineurin Inhibitor Nephrotoxicity. The debate about long-term nephrotoxicity of CNI remains unresolved. Prospective biopsy series using CsA report a high incidence of lesions consistent with chronic CNI nephrotoxicity increasing to near universal presence over 10 years but without functional consequence, whereas a more recent series using TAC suggest that CNI-related fibrosis is uncommon and not uniformly progressive.[209,210] CNI-based immunosuppression can provide stable, long-term allograft function.[211] Support for the role of CNI in CKD derives primarily from nonrenal transplants in whom the cumulative incidence of CKD $<$30 mL per minute at 5 years ranged from 7% (recipients of heart–lung transplants) to 21% (recipients of intestine transplants).[212] While the classic renal biopsy findings of obliterative arteriopathy (suggesting primary endothelial damage), ischemic collapse or scarring of the glomeruli, vacuolization of the tubules, global and focal segmental glomerulosclerosis, and focal areas of tubular atrophy and interstitial fibrosis (producing a picture of striped fibrosis) may be present, unfortunately many of these lesions may overlap with lesions due to hypertension, vascular disease, or chronic T-cell–mediated rejection. Therefore, the diagnosis of isolated CNI nephrotoxicity may be an unusual occurrence.[207]

The treatment of chronic CNI nephrotoxicity is nonspecific, with immunosuppression manipulation (CNI dose reduction, withdrawal, or substitution with another agent) all meeting with modest and sporadic improvements, likely due to the significant overlap with other etiologies of renal injury that occur.

Chronic T-Cell–Mediated Rejection and Chronic Antibody-Mediated Rejection. Chronic antibody-mediated rejection is likely the result of an indolent alloimmune response that results in transplant glomerulopathy and arteriopathy. Although transplant glomerulopathy is often associated with circulating donor-specific antibodies and with C4d deposition, 30% to 50% of cases will be identified in the absence of these diagnostic markers.[213] This suggests that these lesions are not solely due to a humoral immune response, or that the lack of a temporal relationship of donor-specific antibodies or C4d deposition to biopsy findings is related to the waxing/waning nature of the humoral immune response. The diagnosis of chronic antibody-mediated rejection is suggested by (1) evidence of donor-specific antibodies, (2) C4d deposition in peritubular capillaries, and (3) evidence of chronic tissue injury. The forms of chronic tissue injury may include duplication of the glomerular basement membrane, multilamination of the peritubular capillary basement membrane, arterial intimal fibrosis without elastosis, and/or interstitial fibrosis with tubular atrophy.

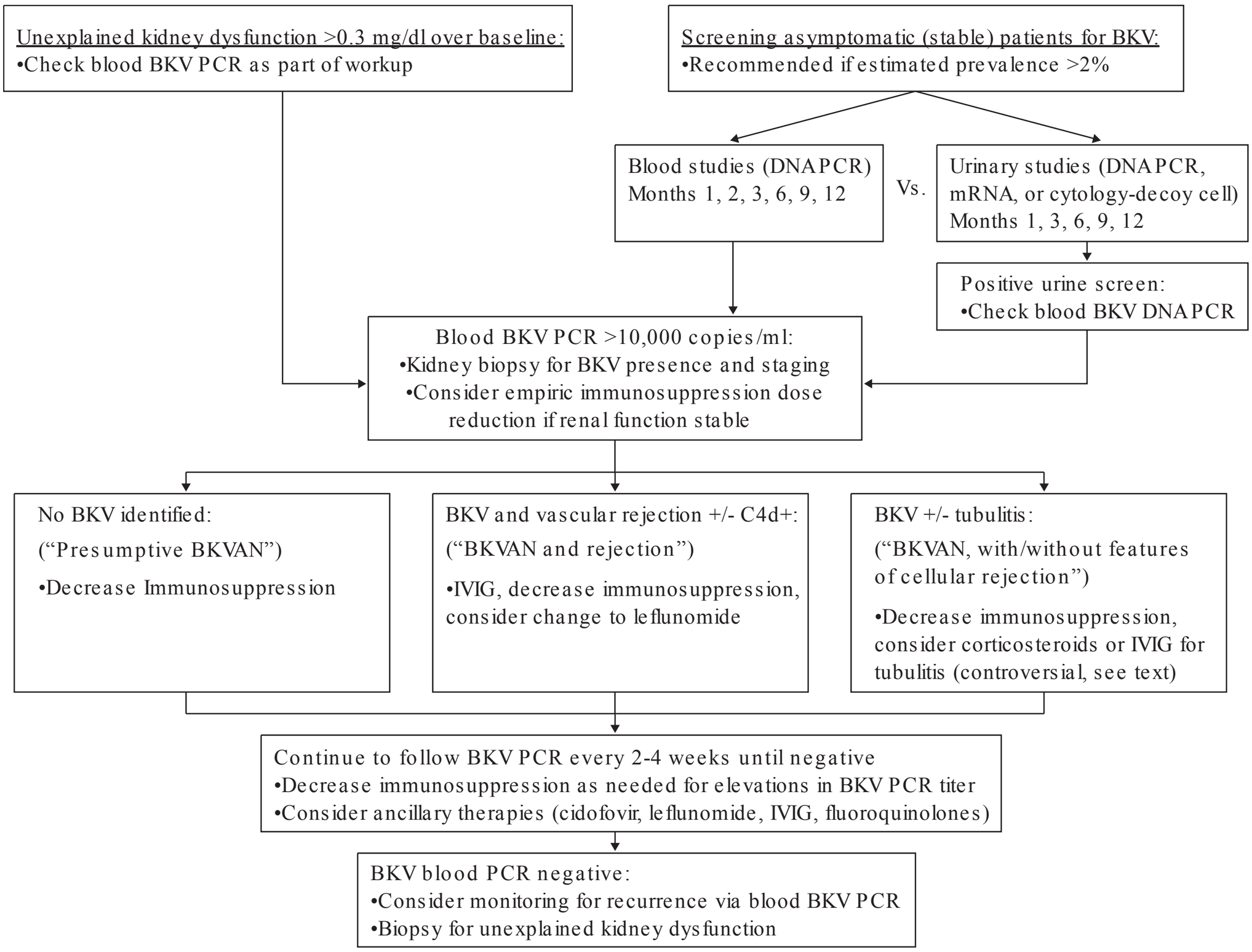

FIGURE 82.21 The screening algorithm for the detection of BKV infection and nephropathy following a kidney transplantation. *PCR,* polymerase chain reaction; *BKVAN,* BKV associated nephropathy; *IVIG,* intravenous immunoglobulin. (From Wiseman AC. Polyomavirus nephropathy: a current perspective and clinical considerations. *Am J Kidney Dis.* 2009;54(1):131–142, with permission.)

Chronic active T-cell–mediated rejection is a histologic diagnosis that refers to arterial intimal fibrosis, specifically with evidence of mononuclear cell infiltration and the formation of neointima. This is distinguished from chronic antibody-mediated rejection by the location of vascular injury and a lack of evidence of the pathogenic antibody, and is distinguished from other nonimmunologic processes that may lead to vascular and interstitial fibrosis (such as CNI nephrotoxicity) by the presence of persistent infiltrating cells within vessels (Fig. 82.22).

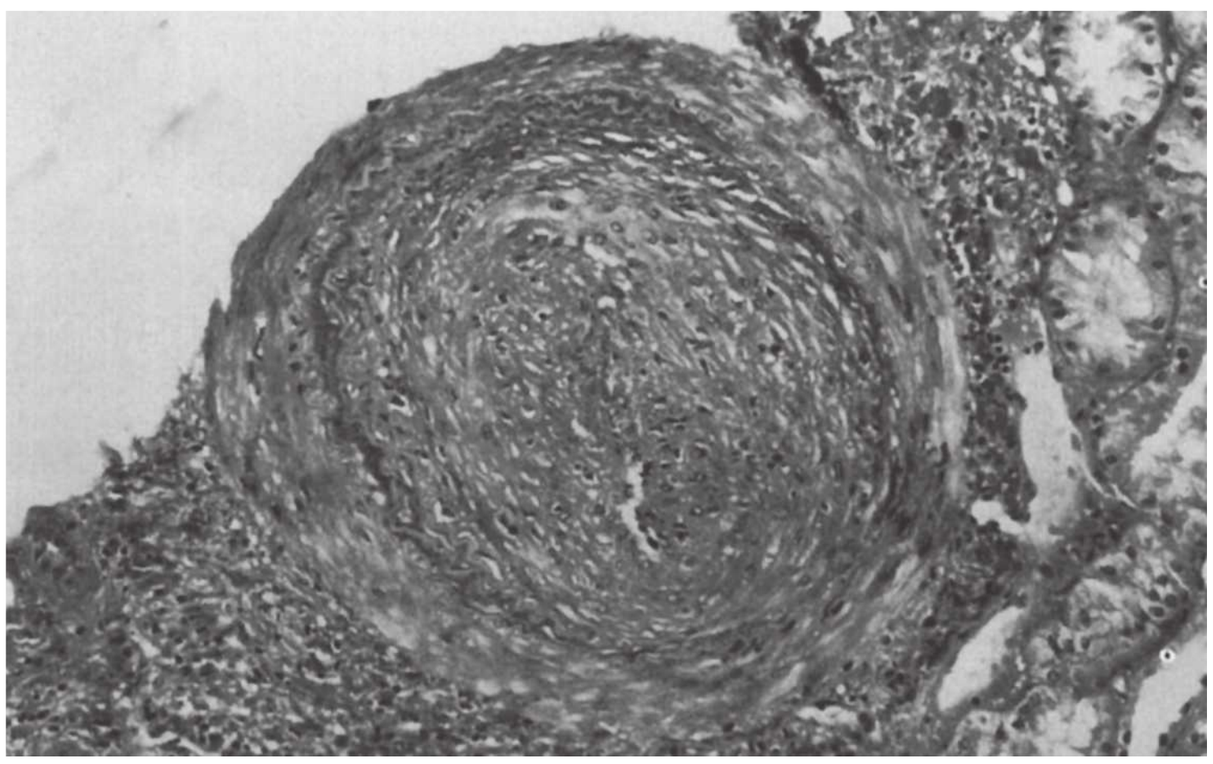

FIGURE 82.22 Chronic T-cell mediated rejection. A renal transplant biopsy specimen showing obliterative arteriopathy and fibrointimal vascular narrowing.

Glomerular Injury in Allografts

Four main etiologies of glomerular injury may occur in allografts: (1) the donor kidney may be the seat of glomerular disease before grafting; (2) recurrent glomerular disease may develop due to the persistence of the original stimulus and recurrence of the original disease in the recipient; (3) transplant glomerulopathy may occur as a result of host response to the graft; and (4) de novo glomerulopathies may arise in a previously normal allograft.

Nephritis of Donor Origin. Diseased donor kidneys may have unsuspected glomerulonephritis. Interestingly, donor glomerulonephritis may resolve following transplant.[214] When possible, pretransplant donor biopsies can provide a good understanding of the nature of preexisting glomerulopathies. Proteinuria immediately posttransplant cannot be used as a guide for recipients versus a donor-related source of glomerular disease, because proteinuria posttransplant may still arise from the recipient's native renal residual function for the first 2 to 6 weeks.[215]

Recurrence of Primary Renal Disease. Essentially all glomerulopathies have been described to recur in renal allografts (see Patient Selection, previously).[216] However, there is much variation between the various types of glomerulonephritis with regard to the frequency of recurrence, the clinical pattern, and the prognosis (Table 82.4). The clinical manifestations of recurrent glomerulonephritis include microscopic hematuria and proteinuria, which may progress to nephrotic syndrome. Recurrent glomerulonephritis is the most common cause of nephrotic syndrome following transplantation. Proteinuria may also be a manifestation of de novo glomerular disease or chronic rejection. Although the documented overall incidence of graft failure from recurrent disease is less than 2%, this is an underestimate due to difficulty in firmly establishing this diagnosis and in defining the cause of primary ESRD and graft dysfunction or whether loss occurred because of the same pathologic process.

Transplant Glomerulopathy. Transplant glomerulopathy is an entity that may be considered a special form of chronic alloimmune injury. It is believed to be related to alloantibody because the frequency of glomerular lesions was found to be inversely related to HLA compatibility and is often found in conjunction with circulating donor-specific HLA antibodies (see Chronic T-Cell–Mediated Rejection and Chronic Antibody-Mediated Rejection, previously). Histologically, it may resemble membrano-proliferative glomerulonephritis (type I MPGN) with mesangial proliferation and thickening or reduplication of the glomerular basement membrane. It is the most common cause of nephrotic syndrome in renal transplant patients. Along with proteinuria, the clinical presentations include microscopic hematuria and progressive graft dysfunction.

De Novo Glomerulopathy. The development of glomerular lesions in patients with no history of glomerulonephritis suggests the presence of a de novo process in the allograft. For example, de novo membranous nephropathy (Fig. 82.8) is reported to occur with an incidence of less than 1%. Nephrotic range proteinuria occurred at a mean time of 1 to 2 years after transplantation. In contrast to the indolent course of idiopathic membranous glomerulonephritis in nontransplant patients, de novo membranous nephropathy can lead to graft loss. This may be due to superimposed glomerular and interstitial lesions associated with chronic rejection.

Focal segmental glomerulosclerosis is not uncommon among transplant recipients whose original disease was not FSGS. The mechanisms underlying de novo glomerulosclerosis are not clear. It may represent a nonspecific response to chronic rejection, glomerular ischemia, vesicoureteral reflux, or infections such as hepatitis B and HIV. Circulating anti-GBM antibodies and anti-GBM disease can develop in some patients with Alport disease after renal transplantation. Patients with Alport disease lack a component of the GBM and do not bind anti-GBM antibodies isolated from patients with Goodpasture syndrome. When the allograft, which contains these GBM proteins, is transplanted, the recipient may mount a humoral response against these proteins, which may lead to anti-GBM disease.

Other Causes of Chronic Graft Injury. Nonimmunologic causes can also contribute to the decline in renal function. Atheromatous renovascular disease of the transplant kidney can be responsible for a significant number of cases of progressive graft failure (Fig. 82.23). The reduction in nephron mass as a result of earlier immunologic injury, donor-recipient size mismatching, or donor renal disease (in the case of expanded criteria or older donors), likely contributes to a further decline in function. Retrospective analyses suggest that control of hypertension preserves graft function, but a specific agent has not been shown to be superior to another.[217,218]

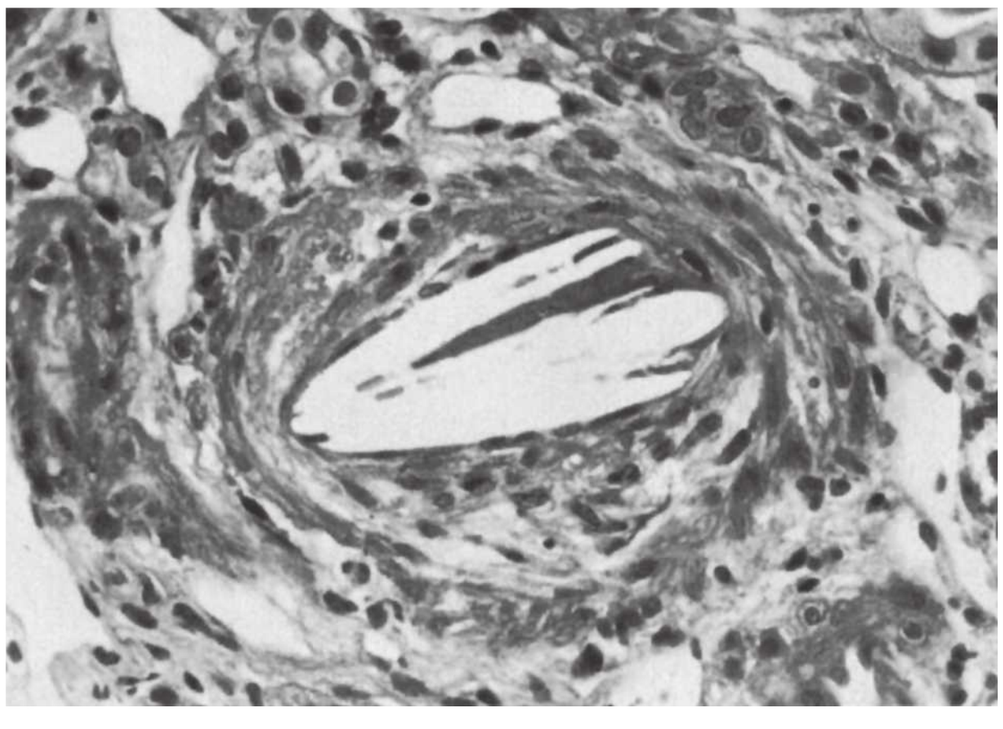

FIGURE 82.23 A percutaneous needle biopsy of a kidney 20 years posttransplantation showing an atheroembolus in a small artery. (Trichrome stain, magnification ×400.)

SYSTEMIC COMPLICATIONS

Infectious complications of immunosuppressive therapy, cardiovascular diseases, and malignancy are the most important causes of death following a kidney transplantation.[11,219,220] Additional concerns following transplantation include but are not limited to bone disease, nutritional status, growth and development in children, and pregnancy in women.

Infection

The occurrence of infection is due primarily to the interplay between two factors: the degree of immunosuppression in the patient and the epidemiologic exposures that the patient encounters. The most common presentation of an infection in a transplant patient is fever; some guidelines to the approach to the patient with fever are given in Table 82.17. The prevalence of particular infections vary according to the degree of immunosuppression; thus, it is helpful to consider the time posttransplant in the diagnostic approach to a patient with a possible infection. During the first posttransplantation month, opportunistic infections are rare and the major infectious disease hazards are similar to those for patients undergoing major urologic surgery. The period between 1 and 6 months after transplantation is when most serious infections occur. This is because of the maximal effect of the immunosuppressive drugs on the host's defense system, as well as it coinciding with the period when attempts are made to reverse rejection episodes with potent antirejection therapy. As in other states of immune deficiencies, opportunistic infections derived from endogenous flora including Cryptococcus, Candida, Aspergillus, Pneumocystis carinii, CMV, and herpes zoster are seen after transplantation. Candida albicans, a normal inhabitant in healthy individuals of the oropharynx, intestine, and vagina, may cause severe pharyngitis, esophagitis, vaginitis, and systemic infections in immunosuppressed patients. Wound infections and urinary infections are commonly due to bacterial infections. Septicemia is not uncommon after transplantation and is usually due to a gram-negative organism with the primary focus in the urinary tract. However, Staphylococcus aureus, Listeria, and Candida may also cause septicemia. Although awaiting the results of blood culture, appropriate broad-spectrum antimicrobial treatment should be commenced. A vigorous search for the focus of infection must be made and dealt with as appropriate.

82.17 The Diagnostic Approach to the Transplant Patient with an Unexplained Fever

Possible sites of infection
- Chest: pulmonary infection, pericarditis, endocarditis
- Mouth: Candida
- Lower limb: deep venous thrombosis
- Soft tissues: skin (e.g., fungi, Nocardia, mycobacteria), joints
- Transplant wound: rejection, abscess, urine leak, hematoma
- Peritoneal cavity: pancreas, colon, dialysis catheter
- Urinary tract: bladder, prostate, native kidneys
- Central nervous system (CNS): Listeria, Cryptococcus, Aspergillus, tuberculosis, Nocardia
- Systemic: viral infection, tuberculosis

Investigations
- Chest X-rays
- Ultrasound of transplanted kidney
- Cultures: mouth, sputum, urine, blood, stool, access sites
- Serology: viral antibodies, especially cytomegalovirus
- Lumbar puncture and computed tomography of head if CNS infection suspected

Viral Infections

Cytomegalovirus. CMV is one of the most important viral infections that occur in transplant recipients. The incidence and severity of CMV infection depend on the presence of latent infection in the donor, the immune status of the recipient, and the degree of immunosuppression.[221] CMV infection (defined as evidence of CMV viremia either via culture techniques, or more commonly, detection by blood PCR) occurs in 20% to 70% of patients depending on the serostatus of donor and recipient. CMV infection takes two forms: namely, that of a primary infection, which occurs in patients who are seronegative at the time of transplantation and received a kidney from a seropositive donor, and that of a secondary (or reactivated) infection. Use of DNA-restriction enzyme analytic methods to detect different CMV serotypes indicates that many of the clinical CMV infections in individuals seropositive for CMV before transplantation are due to superinfection with the donor virus strain. Patients with a secondary infection or reactivation of latent CMV often are not symptomatic, whereas those with superinfection of a new viral strain may demonstrate the acute symptoms of active CMV. CMV infection has been associated with decreased survival and decreased allograft survival rates.[221,222]

CMV infection can progress to clinical symptoms and tissue invasion, which is referred to as CMV disease. A common presentation is that of a fever that may be spiking or constant and usually occurs between 4 and 10 weeks after transplantation or after discontinuation of antiviral prophylaxis. It may be associated with neutropenia, liver function abnormalities, or GI symptoms, and atypical lymphocytes may be identified in the blood smear. CMV pneumonia is a serious complication of CMV infection and should be ruled out in any seronegative transplant recipient who received a kidney from a seropositive donor and presents with a fever

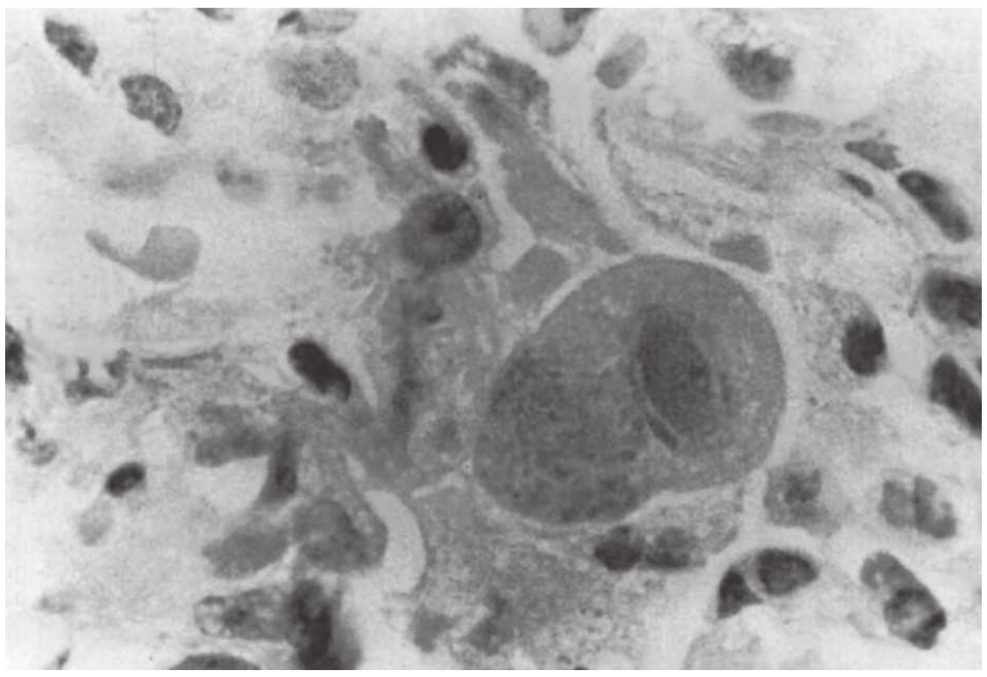

FIGURE 82.24 A typical cytomegalovirus-infected lung cell showing cytomegaly, large intracellular inclusions with peripheral chromatin clumping, and abundant intracytoplasmic inclusions. (Hematoxylin and eosin stain, magnification ×1,000.)

and radiologic pulmonary infiltrates (Fig. 82.24). Less commonly, hepatitis, arthralgia, splenomegaly, myalgia, and GI ulceration may be presenting features. In rare instances, chorioretinitis can occur, occasionally without prior evidence of CMV activity. CMV encephalitis, transverse myelitis, and cutaneous vasculitis also have been reported.[223]

The impact of CMV on graft function has been debated. A deterioration in renal transplant function may be seen during the early stages of CMV infection, and a frank glomerulopathy has been reported to occur.[224] It has been proposed that CMV infection, through the elaboration of lymphokines and IFNs, may cause upregulation of histocompatibility antigens on the allograft. This change results in the induction of immune responses that histologically lead to glomerular endothelial changes and possibly increase the risk for acute rejection[225] and contribute to allograft dysfunction.

Management of CMV after transplant should take into account a patient's risk for CMV infection and disease, with consideration of monitoring and/or prophylactic therapy and aggressive treatment in established disease. The prophylactic administration of oral ganciclovir (ganciclovir or valganciclovir) and valacyclovir to renal allograft recipients for 12 weeks after transplantation has been shown to reduce symptomatic active CMV infections. Valganciclovir is the L-valine ester of ganciclovir and is administered orally at 450 to 900 mg per day for CMV prophylaxis. This dose produces similar AUC values to IV ganciclovir (5 mg/kg/day) and much higher values than oral ganciclovir (3 g per day). The major side effects of ganciclovir and valganciclovir are bone marrow suppression, sterility, and potential nephrotoxicity. Dose adjustment is necessary for patients with renal impairment (Table 82.18).

Trials investigating two approaches to the management of CMV prevention following transplant, a prophylaxis approach (prophylaxis) versus a monitoring and preemptive therapeutic approach (preemptive), have generally been found to be similarly effective in preventing CMV disease. For high-risk recipients (seronegative recipients of kidneys from seropositive donors), late CMV disease that occurs after stopping prophylaxis has been problematic. In this patient population, extending the time of prophylactic therapy from 3 to 6 months after transplant may be considered.[226]

Treatment of overt CMV disease requires high-dose ganciclovir therapy (either IV ganciclovir 5 mg/kg/day or oral valganciclovir 900 mg twice per day (bid), adjusted for renal function) and reduction in immunosuppressive therapy. High-dose therapy should be given for 21 days or until clinical CMV disease is absent and CMV viremia is no longer present. Prophylaxis should be reinitiated and continued until stable on reduced dose immunosuppression for 3 to 6 months.

82.18 Dosage Adjustment for Intravenous Ganciclovir and Valganciclovir in the Initial Treatment of CMV Infection

Estimated GFR	Ganciclovir (IV)	Valganciclovir (PO)
>60 mL/min	5 mg/kg q12hr	900 mg q12hr
40–59 mL/min	2.5 mg/kg q12hr	450 mg q12hr
25–39 mL/min	2.5 mg/kg q24hr	450 mg q24h
10–24 mL/min	1.25 mg/kg q24hr	450 mg q48h
Dialysis	1.25 mg/kg 3×/week after dialysis	Not recommended

GFR, glomerular filtration rate; IV, intravenous; PO, by mouth.

Herpes Simplex Virus. Reactivation of latent herpes simplex virus (HSV) infections is extremely common in transplant patients. The most common lesion is the orolabial HSV type 1 infection. Occasionally, an anogenital lesion due to an HSV type 2 infection may occur. Rarely, a Kaposi varicelliform eruption, due to a disseminated HSV infection in the skin, may develop in transplant patients. Therapy of acute HSV infection with acyclovir or valacyclovir will lead to clinical improvement.

Varicella Zoster. Varicella zoster is frequently seen in transplant patients and can occur at any time after transplantation. It is commonly presented as a localized zoster due to the reactivation of the latent virus present in the dorsal root ganglion since childhood chickenpox. For localized dermatomes, oral acyclovir can be used, but with multidermatomal involvement or optic nerve involvement, intravenous acyclovir is the treatment of choice. Chickenpox is a rare but often extremely virulent infection. Should a patient without humoral immunity to varicella zoster be exposed to chickenpox, varicella zoster immune globulin should be given within 72 hours of the exposure. If chickenpox develops, intravenous acyclovir needs to be instituted without delay.

Epstein–Barr Virus. In general, EBV is not a common problem in transplant patients, although occasionally EBV may be the cause of a glandular febrile illness. However, infection or reactivation of latent EBV can cause an acute lymphoproliferative syndrome or even a polyclonal lymphoma. Using the DNA hybridization technique, EBV has been identified in lymphoma and lymphoproliferative lesions of renal transplant patients, described under "Cancer in Transplant Patients," which follows.

HIV. The impact of HIV infection and AIDS on recipients of organ transplantation has not yet been fully realized. In patients who have clinically quiescent disease and are on stable antiretroviral therapy, there does not seem to be an increase in the progression of HIV or deterioration in CD4 counts with standard immunosuppression, although depleting antibody induction therapy may indeed lead to prolonged depression of CD4 counts.[94] Close monitoring of CD4 count and viral load is appropriate following transplant.

Hepatitis

Chronic liver function impairment is not rare after renal transplantation. Viral hepatitis and drug-related hepatitis are the most common causes. Drugs that may cause hepatic dysfunction include CsA, AZA, antihypertensives, and lipid-lowering agents. CsA- and AZA-induced liver enzyme elevation usually resolves on dosage reduction. For the patient with elevated liver enzymes following transplant, a careful review of medications should be followed by retesting for hepatitis viral infections.

Hepatitis B Virus. HBV is a relatively uncommon viral infection after transplantation, but the main cause for concern is the outcome of transplantation in a patient who is a carrier of the hepatitis B antigen. There is considerable concern about the possible progression of liver disease leading to liver failure. Additionally, the incidence of hepatoma in those chronic carriers of hepatitis B is 15%, much higher than in the general population who contract hepatitis. Immunosuppression enables persistent viral replication, leading to a greater frequency of hepatitis e-antigen, viral DNA, and viral DNA polymerase in the sera of transplanted individuals.

The natural history of liver disease due to chronic hepatitis B in transplant patients differs from that in both the general population and hemodialysis patients. Transplant recipients who have hepatitis B typically remain surface antigen–positive for longer than 6 months and do not revert to seronegativity. Most episodes of hepatitis in the early posttransplantation period are relatively mild, but an unusually high rate of transformation from chronic persistent to chronic active hepatitis occurs in this patient population. Patients who have persistent hepatitis e-antigenemia or concomitant delta virus infection are at higher risk for chronic active hepatitis and more rapid deterioration.

For kidney transplant recipients with chronic HBV infection, the use of antiviral therapy has provided a major advancement in pretransplant and posttransplant management and patient outcome. Lamivudine is an oral nucleoside analog that effectively inhibits viral replication. However, the development of antiviral resistance is common, which increases progressively with treatment duration and has been reported to be >70% after 8 years of continuous treatment. Other treatment alternatives include initial prophylactic treatment with tenofovir or entecavir. Therapy should be continued indefinitely.[92]

Hepatitis C Virus. The prevalence of anti-HCV positivity in renal transplant recipients is estimated to be between 6% to 46% depending on the center and/or country.[91] Patients with hepatitis C are at increased risk of liver disease, cardiovascular disease, infection, sepsis, proteinuria, and a significantly higher rate of NODAT. In the setting of posttransplant immunosuppression, HCV loads can increase, but these do not reliably predict progressive liver disease.[227] Antiviral therapy posttransplant is less effective than pretransplant treatment and is associated with an increased risk of acute rejection. Because posttransplant noninvasive monitoring is unreliable and pretransplant cirrhosis is associated with increased posttransplant mortality, liver ultrasound should be performed every 1 to 2 years in patients with active hepatitis C following a transplant to monitor for hepatoma, and attention to the biochemical and the clinical stigmata of ongoing liver injury should be continuously monitored.

Pneumocystis carinii Pneumonia. This is a relatively common pathogen that can cause pulmonary infection in states of significant immunosuppression. In the transplant setting, this risk is highest in the first 1 to 6 months following

transplant, thus antibiotic prophylaxis is often used during this period. The preferred therapy is trimethoprim/sulfamethoxazole (TMP/SMZ), but in the case of sulfa allergy, aerosolized pentamidine or oral dapsone therapy may be considered. Patients with suspected pneumocystis pneumonia typically present with a fever and are often associated with some dyspnea, but with very few physical signs on examination. A chest X-ray shows diffuse shadowing that tends to be linear in distribution but can be normal. TMP/SMZ in high doses is the antimicrobial of choice.

Mycobacterial Infections

The incidence of tuberculosis in transplant recipients varies from region to region, but certainly is more common in transplant recipients than in the general population.[228] The symptoms are frequently nonspecific and the site of infection is often in organs other than the lungs. Treatment of the established case should be the routine antituberculous therapy (e.g., rifampicin and isoniazid). It should be remembered that these drugs are metabolized in the liver. Rifampicin induces hepatic enzymes; therefore, CNI or mTOR levels must be closely monitored. Chemoprophylaxis should be considered in patients with calcification on a chest roentgenogram and in the presence of a positive tuberculin skin test. Therapy for 6 to 9 months with isoniazid should be given to patients who have never received adequate treatment and who are PPD positive.[229]

Fungal Infections

Fungal infections are relatively common in transplant patients and must always be considered as a possible cause of fever and pneumonia, especially in the presence of excessive immunosuppressive therapy. Pulmonary infiltrates due to fungal infection include Aspergillus, Cryptococcus, Coccidioides, Candida, and Histoplasma capsulatum. Aspergillus is a hyphal saprophytic fungus in which infection is started by the inhalation of spores; the lungs are, therefore, the primary site of infection. In the lung, Aspergillus causes a patchy infiltration followed by a consolidation and abscess formation (Fig. 82.25). Histoplasmosis is another fungal pneumonia, caused by H. capsulatum, which can occur in renal transplant recipients. This may also be acquired or result from reactivation and usually presents with fever, pulmonary infiltrates, and skin lesions at any time after transplantation. These infections require aggressive therapy with conventional amphotericin B, a lipid-based amphotericin B preparation (Abelcet, AmBisome, or Amphotec), or an appropriate azole antifungal agent. Ketoconazole, fluconazole, and itraconazole are useful for treating mucocutaneous fungal infections and infections of the GU tract and GI system, lungs, and under specific conditions, the central nervous system. All of the triazole antifungals impair calcineurin inhibitor metabolism and increase blood levels of CsA and TAC. CsA or TAC dose reduction, therefore, may be necessary while patients are on triazole treatment.[230]

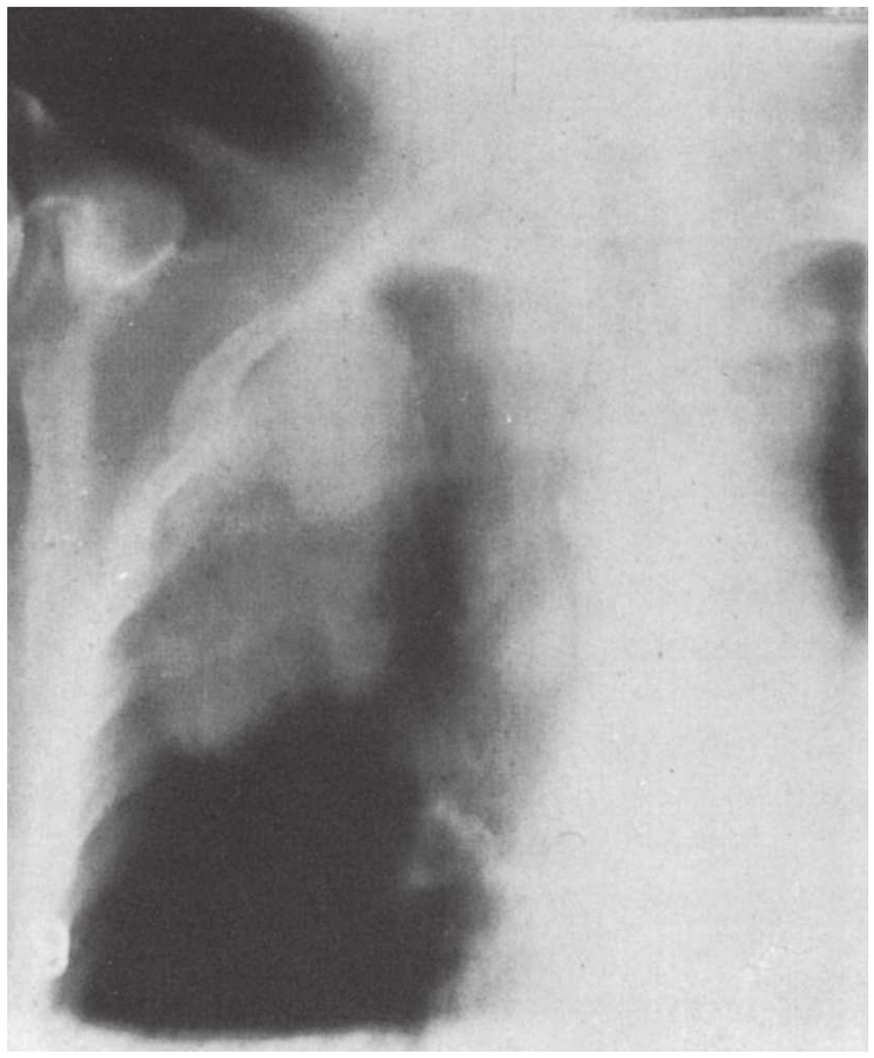

FIGURE 82.25 An *Aspergillus* infection of the lung in a patient who underwent renal transplantation after several courses of antirejection therapy with high-dose intravenous methylprednisolone. (From Morris PJ. *Kidney Transplantation: Principles and Practice*. 2nd ed. New York: Grune & Stratton; 1984, with permission.)

Central Nervous System Infection

Infections of the CNS after renal transplantation typically present between 1 and 12 months posttransplant and are characterized by a subacute onset and the frequent lack of systemic signs. Organisms commonly associated with a CNS infection in renal transplant recipients include Listeria, Cryptococcus, Mycobacterium, Nocardia, Aspergillus, fungi of the Mucorales order, Toxoplasma, Candida, and Strongyloides. Listeria may cause an acute or focal brain infection. Cryptococcus and, less often, Mycobacterium and Coccidioides are important causes of subacute meningitis. Focal lesions are most common with Aspergillus, Toxoplasma, and Nocardia. HIV can cause a variety of CNS syndromes, most predominantly, a global-dementing illness. JC virus infection can also cause dementia with progressive multifocal leukoencephalopathy.

In acute meningoencephalitis, nuchal rigidity may be absent. The development of fever and mild headache should be sufficient to alert the physician to the possibility of CNS infection. The aseptic meningitis that occurs during OKT3 or IVIG administration is self-limited, but if severe or persistent, may require diagnostic workup to rule out infection. Focal findings on neurologic examination are not common except with well-developed focal brain infections. Because the early findings in these infections are often nonspecific, lumbar puncture and cranial CT scanning or magnetic resonance imaging (MRI) should not be delayed.

Aspergillus. Aspergillus may cause pneumonia in the immunocompromised host and may disseminate to the brain, skin, kidney, and gut. Aspergillus, which infiltrates the vasculature, is not found free in the cerebrospinal fluid (CSF) and is often impossible to diagnose before death. The organism may be suspected in patients with clinical evidence for meningitis and CSF cytology and chemistry determinations consistent with meningitis, especially in the absence of a positive culture, inflammatory foci, and culture or serologic findings consistent with cryptococcal infection. The treatment of choice is amphotericin B.

Cryptococcus. Although rare, Cryptococcus is another cause of meningitis in the transplant patient. It tends to be seen relatively late in the transplantation course and has a rather nonspecific presentation, and hence, the diagnosis is often delayed. Lung involvement is also common when this infection is present. Amphotericin B is again the indicated treatment.

Coccidioides. Coccidioides is quite rare in Europe but does occur commonly in parts of the United States. It may cause destructive lesions of the lungs, liver, brain, and spleen and is sometimes due to reactivation of an existing latent infection. Amphotericin B is the appropriate treatment.

Listeria monocytogenes. Listeria monocytogenes may present as meningitis, brain abscess, or as meningoencephalitis. It may occur at any time after transplantation, but is usually associated with increased or excessive immunosuppressive therapy for rejection. Listeria should be the primary suspect in a patient with meningoencephalitis because other causes of meningitis are rare in transplant recipients. CSF findings may not be striking. Treatment with ampicillin should be commenced as soon as CSF and other specimens for culture have been taken.

Nocardia. Nocardia usually presents as respiratory illness with an unproductive cough, fever, malaise, and a nodular infiltrate on the chest X-ray. Occasionally, the infection may spread to the brain, presenting as a space-occupying lesion, but it may also be seen as skin abscesses or joint infections. The treatment of choice is probably sulfonamide, which is given for at least 2 months, although some would advocate treatment for 12 months.

Urinary Tract Infection

A urinary tract infection is the most common bacterial infection following transplantation. Urinary tract infections appearing within the first 3 or 4 months after transplantation are often associated with transplant pyelonephritis, septicemia, and relapse after standard antibiotic therapy. Patients with an anatomic abnormality requiring urinary diversion or stent placement and those with pyelonephritis should receive chronic suppressive antibiotics in addition to the 4- to 6-week course of primary treatment. Uncomplicated urinary tract infections that occur later after transplantation can be treated with a standard 1- or 2-week course of oral antibiotics.

Cancer in Transplant Patients

The incidence of cancer in transplant recipients varies considerably from region to region, ranging from a low incidence of 1.6% of patients developing cancer after transplantation in Europe to as high as 24% of patients in Australia.[231,232] Much of this variation is due to the high incidence of skin cancer in those areas at risk for these cancers. In regions with limited exposure to the risk, there is a four- to sevenfold increase, but in areas with copious sunshine there is an almost 29-fold increase in incidence as compared with the control population. There is also a well-recognized and highly significant increase in the risk of developing a malignant (non-Hodgkin) lymphoma. Even with skin cancers and malignant lymphomas excluded from the analysis, there is an increased incidence in all forms of cancer in patients after transplantation (Table 82.19).

TABLE 82.19 **Common Malignancies Encountered in Renal Transplant Recipients**

Cancer	Increased Risk Compared to General Population
Cancers of the Skin and Lips	**>20×**
Squamous cell carcinomas	
Basal cell carcinomas	
Malignant melanoma	
Malignant Lymphomas	**>20×**
Non-Hodgkin lymphoma	
Reticulum cell sarcoma	
B-cell lymphoproliferative syndrome (Epstein–Barr virus)	
Kaposi Sarcoma	**>20×**
Cutaneous form	
Visceral and cutaneous form	
Genitourinary Cancer	**>15×**
Carcinoma of native kidney (acquired cystic disease)	
Carcinoma of transplanted kidney (hypernephroma)	
Carcinoma of the urinary bladder (cyclophosphamide associated)	
Uroepithelial tumors (associated with analgesic nephropathy)	
Gynecologic Cancer	**5×**
Carcinoma of cervix	
Ovarian cancer	

Careful physical examination to detect the common malignancies is essential in the long-term follow-up of renal transplant patients. The increased incidence of cervical cancer in females after transplantation implies that all female transplant patients should have an annual cervical smear, and although the cost-effectiveness of screening for breast, colorectal, and prostate disease remains an unresolved issue, it appears that the benefits of screening may outweigh harm.[233]

A number of factors contribute to the increased risk of cancers in immunosuppressed recipients of a kidney transplant. These include depression of immune surveillance, chronic antigenic stimulation in the presence of immunosuppression, a directly neoplastic action of the immunosuppressive drugs themselves, and increased susceptibility to oncogenic viral infection. First, alterations in the immune surveillance due to immunosuppressive therapy may allow potentially malignant cell mutants to become established in the host because they cannot be detected and killed in the usual fashion. The allograft with its foreign HLA may also stimulate the host lymphoreticular system, resulting in the development of lymphoid malignancies. Depleting T-cell induction therapy has been associated with an increased risk of lymphomas.[151] Finally, latent oncogenic viruses may be activated in immunosuppressed hosts who are simultaneously experiencing stimulation immunologically by an antigen. An association exists between the papilloma virus and the development of squamous skin cancer, as well as condyloma acuminatum with cervical carcinoma. EBV has also been implicated in polyclonal B cell lymphoproliferative disease. In addition to primary cancer developed de novo in patients after transplantation, cancer may be transferred in the transplanted kidney from a donor with cancer undetected at the time of donor nephrectomy.

Skin cancer is the most common neoplasia in transplant patients, with an incidence 4 to 21 times the population average.[234] Squamous cell carcinoma predominates over basal cell skin cancer. Patients who live in warm climates should be carefully advised after transplantation to use sun-blocking creams and to wear appropriate clothing while in the sun. The appearance of neoplasia can be atypical, and an early biopsy of any suspicious lesion is indicated. The prognosis after the resection of skin cancer is excellent, provided strict avoidance of sun exposure is followed. A reduction in immunosuppression may be considered if the malignancy is extensive or rapidly progressive.

Lymphoma occurs earlier than other tumors and accounts for 20% to 30% of posttransplant neoplasms. The incidence of this neoplasm is relatively higher in the last decade, which is probably related to the use of monoclonal or polyclonal globulin and other immunosuppression. Two types of lymphoproliferative disease are seen in patients after transplantation.[235] The first presents with an infectious mononucleosislike illness within the first year of transplantation with fever, sore throat, and lymphadenopathy. The clinical course is often short and can be fatal. Cessation of the immunosuppression will lead to regression in some patients. This type of lymphoproliferative disease is due to infection with EBV. With acyclovir treatment, remission can occasionally be achieved without the cessation of immunosuppression. The second group of lymphoproliferative diseases presents as localized solid tumor masses and can be localized to the graft or to the CNS in a high percentage of patients. Lymphoma, therefore, should be considered in the differential diagnosis of any CNS abnormality. These lymphomas are often more rapidly progressive than those seen in the normal population and, although responsive to conventional therapy for non-Hodgkin lymphoma, carry a high mortality rate. In addition to the standard established treatment for each malignancy, consideration must be given to reduce or cease immunosuppressive medications. Many of the therapeutic agents are cytotoxic and additive suppression of the bone marrow can occur. An initial course of rituximab can be considered, with or without additional cytotoxic therapy.[236] In most cases, regression does not appear to occur with the cessation of immunosuppression, and the patients do not respond to acyclovir.

The incidence of Kaposi sarcoma is 300 to 400 times that of the normal population and accounts for 5% to 10% of posttransplant neoplasms. Those with Kaposi sarcoma involving only the skin do better than those with visceral disease, with complete remission in 50% compared with 14%, respectively, after chemotherapy or the cessation of immunosuppression. Remissions in Kaposi sarcoma confined to the skin may occur with the discontinuation of immunosuppression as the sole therapy. mTOR inhibitors have been shown to be effective in achieving remission while preserving graft function.[237]

Cardiovascular Complications

Cardiovascular Disease

Cardiovascular disease is a major cause of morbidity and death after renal transplantation. This risk can be attributed to the cause of the underlying disease for renal failure (e.g., diabetes), and to chronic kidney disease as an independent cardiovascular risk factor.[238] Independent predictors of cardiovascular disease include tobacco use, diabetes, obesity, hypertension, and dyslipidemia. Once the patient has been transplanted, it is essential that rigorous advice be given to the management of these risk factors.

Hyperlipidemia

It has been known for some time that uremic patients frequently have type IV hyperlipidemia with marked hypertriglyceridemia. Total cholesterol is usually normal or low. In particular, high-density lipoprotein (HDL) levels are abnormally low. After transplantation, the hypertriglyceridemia of uremia shifts toward hypercholesterolemia. Very low-density lipoprotein and low-density lipoprotein cholesterol levels are elevated in transplant patients. Hypertriglyceridemia

may persist, but triglyceride levels often decrease. Overall, the incidence of hyperlipidemia following transplantation is about 50%.

Immunosuppressive agents contribute to hyperlipidemia following transplant, in particular mTOR inhibitors and corticosteroids. Hypertriglyceridemia is a common side effect of mTOR inhibitor therapy.[239] High dose prednisone contributes to the development of mixed hyperlipidemia, but improves after the reduction of the initial steroid dose, HDL levels increase and become normal, with normal proportions of HDL3 and HDL2, but hypertriglyceridemia may persist.[160] Dietary therapy should be initiated during the first 6 months after transplantation when hypercholesterolemia is most often marked. Patients should be advised to avoid high-calorie, high-carbohydrate, and high-fat diets. Supplementation of the diet with omega-3 fatty acids may reduce triglyceride and cholesterol levels, and may increase HDL levels. If hypercholesterolemia persists beyond 6 months on diet therapy and on maintenance steroid dose, drug therapy should be considered. Potential pharmacologic agents include niacin, bile-binding resins, fibrates, and statins. Niacin lowers triglyceride and cholesterol levels. A slow-release preparation of niacin may reduce the side effects of flushing and GI distress. Bile-binding resins are rarely used because they may interfere with immunosuppressive drug absorption. Fibrates (gemfibrozil) primarily reduce triglyceride levels, but they can lower cholesterol when triglyceride levels are normal. Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis, and are effective at reducing cholesterol levels. Liver enzymes should be monitored in all patients receiving niacin, gemfibrozil, and statins because hepatitis is a major adverse effect. Reports have been made of myositis and myalgia occurring at low frequency secondary to gemfibrozil and statins. An increased risk of myositis has been described in those patients receiving CsA who also were treated with lovastatin.

The cardiovascular benefits of LDL reduction with statin therapy are well known in the general population. In the kidney transplant setting, one randomized, double-blind controlled trial of fluvastatin (n = 1,050) or placebo (n = 1,052) lowered LDL cholesterol concentrations by 32% and was associated with a 35% reduction in risk for cardiac deaths or non-fatal myocardial infarction.[240] In a 2-year extension study, patients randomized to fluvastatin had a 29% reduction in cardiac death or non-fatal MI, supporting the use of aggressive LDL cholesterol management to LDL <100 mg per deciliter.[241]

Hypertension

Hypertension is extremely common after renal transplantation. Hypertension after transplant is associated with reduced graft function and patient survival after transplant.[217] Hypertension in the transplant recipient may be due to the native kidney disease, chronic allograft injury/CKD of the transplanted kidney, renal artery stenosis in the transplanted kidney, and medication side effects of corticosteroids, and calcineurin inhibitors. The relationship between hypertension and activity of the renin–angiotensin system in patients with a renal transplant is unclear. It is apparent that the patient's native kidneys may contribute to hyperreninemia, but conflicting reports exist concerning the role of the renin–angiotensin system in the transplanted kidney as a cause of hypertension.

Although steroid therapy certainly contributes to hypertension, this is less common now that low-dose steroid protocols are used by most centers. The incidence of hypertension in patients treated with CNIs, either with or without steroids, is greater than that seen in patients treated with CNI-free regimens.[184] The degree to which CsA might increase blood pressure is dose dependent, as demonstrated by the fact that there is a general decrease in blood pressure following the reduction of the CsA dose to a maintenance therapy level of 4 mg/kg/day.

The initial management of hypertension in patients with stable graft function includes salt restriction, weight reduction, elimination or reduction of medications that may contribute to hypertension, and the use of antihypertensive agents.

Most standard therapies have been demonstrated to be safe and effective after renal transplantation. There are, however, a number of management issues that are unique to transplant recipients. Transplant patients may be more prone to decreased renal function resulting from diuretic use than are hypertensive patients in the general population. Patients may occasionally develop decreased renal function after ACE inhibitor therapy, especially if patients exhibit renal artery stenosis or chronic allograft nephropathy. Anemia and hyperkalemia may also be associated with the use of ACE inhibitors and angiotensin II (Ang II) receptor antagonists. Several studies have shown, however, that these drugs are generally safe, effective, and well tolerated. They may reduce proteinuria and may stabilize the deterioration in renal function in chronic allograft failure, possibly by reducing TGF-β. They may also have additional benefits in reducing the incidence of cardiovascular events in high-risk patients.

ACE inhibitors are useful in treating posttransplantation hypertension in patients who do not have transplant artery stenosis. Calcium channel blockers are often used in the treatment of hypertension, because there is evidence that these agents may counteract the decreased effective renal plasma flow and increased renovascular resistance of calcineurin inhibitors. Patients with hypertension associated with renal dysfunction should be evaluated to determine the cause of the dysfunction. Possibilities might include chronic immunologic injury, CNI nephrotoxicity, or a recurrence of the original disease. A renal biopsy may be appropriate to rule out rejection. If hypertension is severe or associated with worsening renal function, with no evidence for rejection, transplant artery stenosis may be pursued by arteriography.

Renal Artery Stenosis

When hypertension cannot be controlled, particularly if attempts to reduce blood pressure results in decreased renal function, the possibility of renal allograft artery stenosis should be considered. Transplant renal artery stenosis (RAS) currently is diagnosed in <2% of cases. Occasionally, RAS may occur in the early months after transplantation; at this time it is always due to a technical defect at the anastomosis. For deceased donor kidney transplants, the use of end-to-side anastomosis of an aortic patch containing the renal artery origin onto the recipient external iliac artery has resulted in much lower rates of transplant RAS. RAS may present 1 to several years after transplantation with poorly controlled hypertension and a deterioration of renal function. Other causes of arterial stenosis include arteriosclerosis, the development of a fibrous plaque in the artery at the anastomotic site or constriction beyond it, technical narrowing of the anastomosis, perfusion injury, kinking of the vessels, and chronic microvascular rejection. A sudden occurrence or increase in severity of hypertension, the presence of a new bruit over the allograft, or a decline in renal function in the absence of rejection all suggest the possibility of RAS. A rise in the serum creatinine level after treatment with an ACE inhibitor for hypertension is very suggestive of renal allograft arterial stenosis. On occasion, renal vein and peripheral renin levels may be of value. Angiographic evidence of RAS is relatively common in the transplanted kidney, but this does not necessarily mean that it is the cause of hypertension. Making the diagnosis of a functional RAS is difficult. In the presence of poorly controlled hypertension and deteriorating renal function, a magnetic resonance angiography of the kidney or renal arteriography as well as a renal biopsy should be considered. If the biopsy shows evidence of moderate-to-severe chronic allograft injury with intimal fibrosis of the arteries and arterioles, correction of the RAS is unlikely to be very successful. Another more diagnostic sign of a functional stenosis is a loss of renal function following treatment with an ACE inhibitor, such as captopril or enalapril. This does imply a prominent role for the renin–angiotensin system in the etiology of the hypertension. A radionuclide scan may show a delay and a decrease in allograft blood flow but is a relatively insensitive tool for the diagnosis of RAS. Doppler ultrasonography is a moderately sensitive and noninvasive means of establishing the diagnosis; however, many false negative studies occur. If a significant chronic allograft injury can be excluded, surgical correction of the stenosis can be considered, but because of the difficulty of the surgery, a percutaneous transluminal angioplasty is considered the treatment of choice for renal artery stenoses.[242]

Erythrocytosis

Erythrocytosis, defined as a hematocrit value greater than 52%, occurs with a frequency of up to 15% in kidney transplant recipients, typically within the first year after transplantation. It can present in settings of good allograft function, chronic allograft injury, transplant RAS, and hydronephrosis, and may be caused by native kidney and hepatic erythropoietin production and the use of androgenic steroids. In patients with good allograft function, it is postulated that correction of the uremic milieu allows overzealous red blood cell production because of a reset marrow response to erythropoietin (EPO).[243] In patients with RAS or hydronephrosis, intrarenal hypoxemia may stimulate EPO production. In most cases, the precise etiology is uncertain, but studies of EPO levels after transplantation indicate that graft function restores the hematopoietic response to normal. The phenomenon usually is self-limited, lasting 3 to 12 months. Low-dose ACE inhibition can be used to reduce the hematocrit because Ang II appears to promote EPO in bone marrow precursors, and ACE inhibitors can induce anemia in some renal transplant recipients without erythrocytosis. The effect begins within 6 weeks and is complete in 3 to 6 months. Compatible with the role of an EPO-independent mechanism is the observation that withdrawal of the ACE inhibitor results in a gradual rise in hematocrit without a concurrent elevation in EPO levels. An alternative to ACE inhibition is theophylline. Theophylline appears to act as an adenosine antagonist in this setting, suggesting that adenosine facilitates both the release and perhaps the bone marrow response to EPO. In severe cases (hematocrit >52%), a phlebotomy should be considered to prevent thromboembolic complications.

Bone Complications

The main types of renal osteodystrophy are secondary hyperparathyroidism and osteomalacia. After a successful transplantation, the metabolic milieu of bone changes, with correction of acidosis, cessation of aluminum hydroxide gel therapy, and improved vitamin D metabolism, whereas immunosuppressive agents such as corticosteroids and CNIs contribute to osteoporosis. This leads to varying degrees of resolution of preexisting renal osteodystrophy and osteomalacia. A progressive resolution of hyperparathyroidism occurs as early as 3 months after transplantation, but many patients have sustained hyperparathyroidism lasting more than 1 year. Indications for a parathyroidectomy include the progressive elevation of parathyroid hormone (PTH) and alkaline phosphatase levels, progressive or new metabolic bone disease, osteonecrosis, metastatic calcification, and severe symptoms of pruritus and proximal myopathy. Osteoporosis is primarily related to steroid therapy. Vertebral bone loss occurs at a more rapid rate in the first 6 months posttransplant, and decreases at a slower rate as corticosteroids are tapered.[244] The development of osteopenia places the patient at increased risk for pathologic fractures. The prevalence of atraumatic fractures in the renal transplant recipient may be as high as 22%; these fractures occur primarily at sites of high cancellous bone, such as the vertebrae and ribs. Glucocorticoid suppression of bone formation is the most important factor in the genesis of early bone loss. Steroids are directly toxic to osteoblasts and lead to increased osteoclast activity. They also have

other effects that promote calcium loss and the development of osteopenia. These include decreased calcium absorption, reduced gonadal hormone production, diminished insulin-like growth factor-1 production, and decreased sensitivity to PTH. Cyclosporine, which induces a high turnover osteopenia in rodents, also may contribute to bone loss, especially in long-term survivors and in subjects treated only with cyclosporine. A higher rate of bone disease-related complications is reported with doses of prednisone as low as 5 mg per day compared to corticosteroid-free regimens.[160]

The main bone disorder that can be directly attributed to high-dose corticosteroids is avascular necrosis or osteonecrosis, which most commonly affects the hips (Fig. 82.26) and tends to be bilateral, but may affect other joints, including the wrists, elbows, knees, ankles, and shoulders. Pain may be severe and is the most common presenting symptom, usually occurring between 1 and 3 years after transplantation. The mean time to onset was 12 months after transplantation (range, 6 to 21 months). The incidence of avascular necrosis is ~2% using current immunosuppressive protocols.[160,166] Pain usually precedes any radiologic changes by several months. In well-established cases, the diagnosis can be made on plain radiographs, whereas CT scanning, MRI, and nuclear bone scanning may detect earlier changes. If performed early, core decompression to relieve the intramedullary venous outflow obstruction can prevent osteonecrosis. With more severe disease, prosthetic total hip replacement has been used with excellent functional recovery. In general, surgery should be performed early in order to facilitate rehabilitation.

The management of bone disease posttransplant is challenging, given the many different factors that contribute to bone disease in the renal transplant recipient. It is important to monitor bone mineral density in the renal transplant recipient using dual-energy X-ray absorptiometry (DEXA). It is recommended that lumbar spine and hip-bone mineral densities should be measured at the time of transplant, after 6 months, and then every 12 months if results are abnormal. Those subjects displaying rapid bone loss and/or a low initial bone density should be considered for treatment. Calcium supplementation (1 g per day) should be considered in nonhypercalcemic patients. The administration of vitamin D analogs (such as calcitriol) can further improve calcium absorption. Vitamin D levels should be measured and corrected. If bone loss is severe and/or rapid, consideration should be given to the administration of calcitonin or other antiresorptive agents, such as the bisphosphonates. Although not approved for use in kidney transplant recipients, cinacalcet may be considered in the patient with persistently elevated PTH after transplant provided hypocalcemia is not a concern.

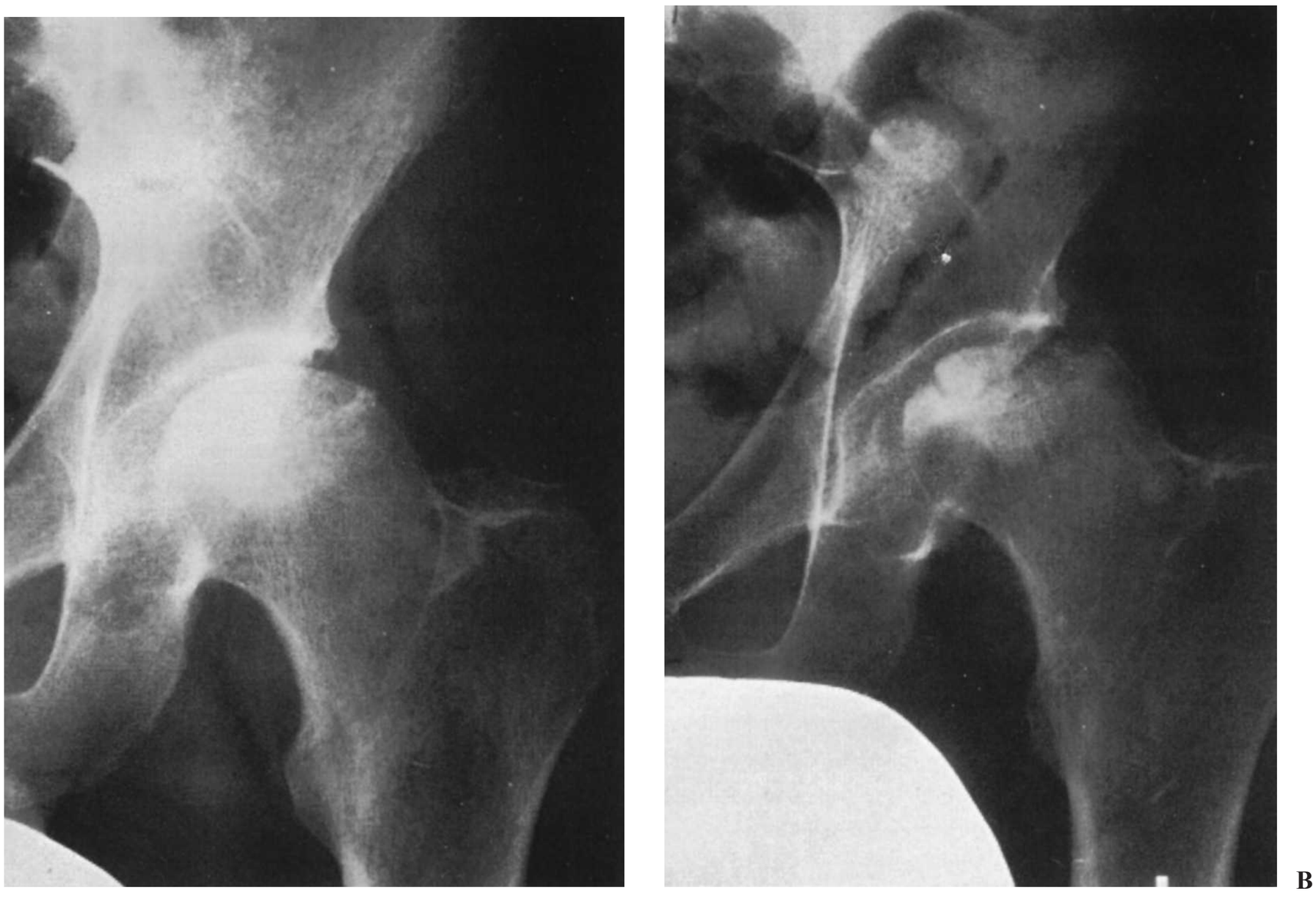

FIGURE 82.26 An avascular necrosis of the head of the femur after transplantation. **A.** A normal radiograph of the hip 10 months after transplantation, at which time the patient was complaining of pain. **B.** The same hip 8 months later. This patient had received azathioprine and high-dose steroids and subsequently had a successful hip replacement. (From Morris PJ. *Kidney Transplantation: Principles and Practice*. 2nd ed. New York: Grune & Stratton; 1984, with permission.)

Gastrointestinal Complications

GI complications include peptic ulceration, esophagitis, intestinal or colonic perforation and hemorrhage, pseudomembranous colitis, necrotizing enterocolitis, and diverticulitis.

Complications of a peptic ulcer, either hemorrhage or perforation, are associated with a high mortality in transplant patients. Whereas about 8% of patients with negative peptic ulcer histories before engraftment later develop gastroduodenal complications, 19% of those with previous episodes of uremic gastritis develop further complications after transplantation. Most transplant centers now prescribe proton pump inhibitors or histamine antagonists prophylactically during the first few months after transplantation to prevent these complications. Both hemorrhage and perforation from a peptic ulcer after transplantation should be treated promptly and aggressively by surgery.

Infection of the gastrointestinal tract presents commonly as Candida stomatitis or esophagitis. This is particularly common in transplant patients who are debilitated from other complications or infections or who have the presence of leukopenia or excess immunosuppressive therapy. Esophageal candidiasis is probably the most severe form of local infection due to this pathogen, but occasionally a septicemia may ensue. The epiglottitis and esophagitis respond to local nystatin, but more severe infections should be treated with amphotericin B or fluconazole. Classic enteric pathogens are not notably common after transplantation.

Spontaneous perforation of the small intestine is rare and the etiology is often not understood, although CMV infection, obstruction, intestinal ischemia, and the use of steroids have been implicated. Hemorrhage of the large bowel with ulceration and perforation occurs in 0.9% of such patients. Possible causes include uremia, the effects of immunosuppressive therapy, the use of antibiotics, atherosclerosis, and the sequelae of irradiation. The administration of sodium polystyrene resin in sorbitol to treat patients with hyperkalemia can also be complicated by colonic perforation.

Pseudomembranous colitis is an antibiotic-associated diarrhea and thus may occur in transplant patients who are receiving broad-spectrum antibiotic therapy for a concomitant bacterial infection. However, it may also occur in transplant units where Clostridium difficile infection is endemic. This condition is highly infectious and should be treated as such to avoid spread within a transplant unit. Occasionally, a necrotizing enterocolitis with gangrene of part or all of the colon, and even occasionally involving only the small bowel, is seen. This is inevitably fatal and the cause is uncertain, although it has been associated with CMV infection. Solitary ulcers, which may bleed or perforate, may also be encountered, especially in the cecum. A colonoscopy is a useful diagnostic tool in some of these colonic complications.

Diverticulitis is no more common in the transplant patient than the normal population except perhaps in patients with polycystic kidneys, but again, complicated diverticulitis does present a very serious problem with a high mortality. For this reason, some surgeons believe that the presence of diverticulosis in patients before transplantation is an indication for colectomy in order to avoid complications arising after transplantation.

Pancreatitis

Although mild hyperamylasemia without pancreatitis is common in patients with poor graft function, due to decreased clearance of the enzyme, high serum amylase and lipase levels suggest active pancreatitis. Acute pancreatitis has been reported to occur in 2% to 12% of transplant recipients. Several causes have been considered. Inflammatory changes, possibly due to secondary hyperparathyroidism, may be seen in the glands of uremic patients. Microscopic examinations occasionally have revealed changes consistent with the presence of CMV, but the role of this organism is unknown. Corticosteroids may produce pancreatitis both experimentally and clinically, and AZA and CsA can be rare causes of pancreatitis. Acute pancreatitis in renal transplant patients often follows a fulminating course with an acute abdomen, electrolyte disturbances, tetany, jaundice, and hypotension.

Renal Electrolyte and Tubular Disorders

Proximal bicarbonate wasting occurs most often in the early transplantation course and resolves gradually. Proximal renal tubular acidosis may be related to ischemic preservation injury, secondary hyperparathyroidism, malnutrition, acute tubular necrosis, and acute rejection. Distal renal tubular acidosis sometimes occurs either as a consequence of acute rejection or as a result of the interstitial nephropathy caused by chronic allograft injury. Hyperkalemia is common in patients on CNIs and is readily reversible by lowering of the dose. The mechanism is unclear but the decreased potassium excretion may be due to diminished serum aldosterone levels or to a primary tubular defect.

Hypercalcemia

Acute hypercalcemia usually occurs in the setting of severe secondary hyperparathyroidism. Because of the improved management of secondary hyperparathyroidism preoperatively, this is less frequently seen with oral phosphate binders, calcium supplementation, and vitamin D administration. Most hypercalcemic patients have transient elevations in serum calcium levels, in the range of 11 to 12 mg per deciliter. The treatment of hypercalcemia includes a dietary reduction of calcium and the cessation of thiazide diuretics and vitamin D supplements, which may exacerbate hypercalcemia. Persistent mild hypercalcemia is generally managed conservatively with serial serum calcium determinations, unless there are indications for a more aggressive intervention with a parathyroidectomy. Serum-intact PTH should be measured at 6 and 12 months and then annually posttransplantation.[143]

Indications for a parathyroidectomy in these patients include severe symptomatic hypercalcemia and persistent hypercalcemia in association with elevated PTH for longer

than 6 to 12 months. Approximately 4% to 10% of patients remain hypercalcemic after 1 year. An elective parathyroidectomy should be considered if the plasma calcium concentration remains above 12.5 mg per deciliter (3.1 mmol per liter) for more than 1 year, particularly if associated with a radiologic evidence of increased bone resorption.

Hypophosphatemia

Hypophosphatemia (serum phosphorus levels <2.6 mg per deciliter) is very common in the early weeks after transplantation. The newly transplanted kidney may waste phosphate due to PTH-dependent and -independent mechanisms.[245] Hypophosphatemia is usually not symptomatic and typically resolves over 6 to 12 months. Hypophosphatemia is observed in 60% to 70% of patients within 1 year after transplantation. Hypophosphatemia may persist for more than 1 year in 20% to 25% of cases, even in the absence of hyperparathyroidism, a phenomenon that may be related to persistent elevations of the phosphaturic hormone FGF-23.[246] Plasma phosphate levels below 1.0 to 1.5 mg per deciliter (0.32 to 0.48 mmol per liter) can cause muscle weakness. Severe and prolonged hypophosphatemia can lead to osteomalacia and fractures. Oral phosphate replacements are required if hypophosphatemia persists. One important exception is the patient with significant persistent hyperparathyroidism, as detected by elevated plasma-intact PTH levels. In this setting, the administration of phosphate can exacerbate the hyperparathyroidism in part by complexing with calcium and lowering intestinal calcium absorption.

Hypomagnesemia

Hypomagnesemia (serum total magnesium levels <1.5 mg per deciliter) is common in the early weeks after transplantation. It can result from CsA- or tacrolimus-induced renal magnesium wasting via the downregulation of calcium and magnesium transport proteins,[247] and may be present in up to 25% of long-term CNI-treated patients. The prevalence decreases with time after transplantation, possibly because of decreasing CNI blood levels. Muscle weakness, hypokalemia, hypocalcemia, and rarely, seizures may result from severe hypomagnesemia. Treatment for asymptomatic hypomagnesemia with oral agents such as magnesium oxide are effective, but if symptoms potentially related to hypomagnesemia are present, consideration for the intravenous administration of magnesium sulfate is warranted.

Hyperuricemia

Renal handling of uric acid is reduced by the use of CNI agents, particularly CsA, and leads to an increase in gout attacks following transplantation.[248] Asymptomatic hyperuricemia occurs in 55% of patients receiving CsA and in 25% of those taking AZA. There is no report of graft failure due to urate nephropathy in the transplanted kidney. Crystal-induced erosive arthritis can occur in these patients. The optimal therapy for acute attacks remains colchicine with or without a brief corticosteroid pulse (20 to 30 mg for 2 to 3 days) and tapering. Nonsteroidal anti-inflammatory agents should be avoided because of the potential negative influence on renal hemodynamics and the development of interstitial nephritis. For patients with hyperuricemia and recurrent gout attacks, allopurinol, a xanthine oxidase inhibitor, can be used with attention to renal-adjusted dosing. However, allopurinol should be avoided in patients taking AZA because the concomitant administration of allopurinol and AZA results in marrow suppression and a fourfold increase in immunosuppression.

New Onset Diabetes after Transplant

Rates of NODAT have been reported at a rate of 4% to 18%, depending on the clinical trial and the immunosuppressive agents used. Both mTOR inhibitors and CNIs may cause pancreatic toxicity, with hyperglycemia occurring in a dose-dependent fashion and exacerbated by prednisone administration.[160,166] TAC appears to have a greater diabetogenic effect than CsA, and patients treated with TAC and sirolimus have the highest rate of NODAT, compared to CsA and MMF.[249] Older individuals, patients with hepatitis C, and African American and Hispanic patients are most susceptible. Transplant recipients who develop diabetes are at a greater risk of death, and support the concept of individualized immunosuppressive agent selection based on the risk for rejection versus risk for NODAT.[250]

Obesity

Lower graft survival rates, higher postoperative mortalities, and complications have been demonstrated in patients with a body mass index (BMI) >35 kg per square meter.[17,18] However, approximately 40% of renal transplant recipients are obese, defined as a BMI >30 kg per square meter or more than 130% of the ideal body weight, 1 year after transplantation. Increased calorie intake may occur after transplantation primarily because of enhanced appetite associated with corticosteroid use. If obesity ensues, it may contribute to the development or exacerbation of hypertension, hyperlipidemia, cardiovascular disease, and steroid-induced diabetes. Weight loss is recommended to improve the lipid profile, to lower blood pressure, and to improve glycemic control for patients with T2DM. In addition to limiting calorie intake, the management of posttransplantation obesity includes behavior modification, an exercise program, and early nutritional counseling. Although corticosteroid use is often implicated in posttransplant weight gain, 5 mg per day did not result in a greater weight gain compared to a steroid withdrawal strategy.[160]

Cataracts

Posterior lenticular cataracts appear in up to 10% of transplant patients receiving high-dose steroids. Usually the cataracts are small and do not present a severe handicap to the patient, although in some instances, cataracts are large and require the removal of the lens.

82.20 Criteria for Renal Transplantation Desiring Pregnancy

1. Preferably 1 yr after transplantation
2. Stable graft function with minimal immunosuppression, serum creatinine <1.5–2.0 mg/dL
3. No evidence of graft rejection
4. No significant proteinuria
5. Good blood pressure control
6. No evidence of pelvicalyceal distortion

Parenthood after Renal Transplant

Chronic renal failure is associated with a loss of libido, amenorrhea in women, and impotence in men. After a successful transplantation, menstruation returns in young women, and men usually redevelop their libido and potency. Women have had successful pregnancies and men have fathered children. Spontaneous abortions and ectopic pregnancies do not appear to be more frequent in posttransplant pregnancies compared to the general population, but there is a higher rate of preeclampsia, hypertension, proteinuria, preterm delivery, and intrauterine growth retardation.[251] Given these potential complications, it is generally recommended that women have stable graft function (creatinine [Cr] <2.0 mg per deciliter, ideally <1.5 mg per deciliter and < 1 g proteinuria) for 1 year prior to conception (Table 82.20).[143] Medications should be reviewed for potential teratogenicity. Mycophenolate has been associated with congenital fetal abnormalities and should be discontinued in patients considering pregnancy.[252] Little data exist for the use of mTOR inhibitors during pregnancy; however, in men there has been an association with impaired spermatogenesis.[253]

There are no reported adverse effects of CsA or TAC on human fetuses. Although rare, steroids may cause adrenal insufficiency in the neonate. Steroids and low concentrations of AZA and CsA are found in breast milk. Because there are few data on the effect of continued exposure to low doses of immunosuppressive agents to the infant, no definitive recommendations can be offered regarding the safety of breastfeeding. With the established safety of TAC, cyclosporine, AZA, and prednisone in pregnancy, a common strategy is to use these agents whenever possible.

CURRENT SUCCESSES AND FUTURE CHALLENGES

Dramatic improvements have occurred in the outcome of renal transplantation over the past 50 years. Immunosuppressive drug regimens have become more sophisticated with better graft survival and less morbidity and mortality. Currently, the 1-year graft and patient survival rates are over 90% and 95% in most transplant centers, despite the fact that an increasing number of high risk patients are undergoing transplantation as a replacement therapy for ESRD. The long-term issues confronting the patient and physician are both the relentless decline in allograft function resulting in poor graft survival beyond 5 years and the medical complications, particularly those resulting from the use of chronic immunosuppression. Renal allograft failure is now one of the most common causes of ESRD, accounting for 20% to 30% of patients awaiting renal transplantation. Future efforts will continue to be directed toward increasing the supply of donor organs and increasing the safety of the immunosuppressive regimen.

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