INTRODUCTION

Because of advances in critical care and medical treatment, more patients are living with end-stage renal disease (ESRD). By the end of 2009, more than 398,000 patients in the United States received some form of renal replacement therapy for ESRD. The economic burden of ESRD is staggering, with $42.5 billion spent in the United States in public and private funds in 2009. The annual cost for treating a patient on hemodialysis is approximately $70,000 which is about three times the cost of caring for a transplant patient (1). Renal transplantation is clearly the most cost-effective treatment option for ESRD when compared to all other forms of renal replacement therapy (2,3). The improvement in outcome after renal transplantation has resulted in a more liberal selection of patients. Unfortunately, the demand for kidney transplants far exceeds the supply of available organs. Although nearly 110,000 patients currently await renal transplantation in the United States, only 17,106 renal transplant procedures were performed in 2014 (4). As a result, patients on the deceased donor organ transplant waiting list wait prolonged periods and suffer the consequences of chronic disease and associated comorbidities before finally undergoing transplantation. This serious shortage of donor kidneys has prompted many institutions to expand their donor criteria. In an attempt to increase the utilization of suboptimal kidneys, transplantation of both kidneys (dual transplant) with intent to increase the nephronmass into a single recipient has been performed at some centers with good short-term results (5). There has been increase in the use of organs from donors after cardiac death (non-heart-beating donors) also with good results (6,7). Another innovative strategy to increase living-donor transplantation includes “kidney paired exchange programs” in which incompatible living-donor/recipient pairs are enrolled in a registry in hopes of finding a compatible pair by exchange. This can sometimes result in complicated chains of exchange and these kidneys now travel to distant centers. Although this can potentially increase the opportunity for kidney transplant, it can also increase the ischemic times of living-donor kidneys, which traditionally had little, if any, cold ischemia time, as the procurement and transplant procedures were previously done within the same institutions. For these reasons, the result of which may lead to an increase in the incidence of delayed or slow graft function, the critical care management of these patients has become increasingly important. Furthermore, advances in transplant management now allows for long-term survival after transplantation. There are now over 140,000 patients living on chronic immunosuppression after renal transplant in the United States, some of whom may present to the critical care unit for unique problems and complications long after they have undergone transplant surgery (8).

EVALUATION OF POTENTIAL TRANSPLANT CANDIDATE

Before undergoing renal transplantation, each patient must undergo thorough evaluation, as not all ESRD patients are appropriate candidates for transplantation. Although each center has a specific protocol for candidate evaluation, the main purpose of any evaluation is to identify major contraindications to transplantation including active malignancy, advanced cardiopulmonary disease, active infection, substance abuse, and noncompliance with medical therapy. With most malignancies, a waiting period before transplantation is recommended (time period varies with the type of malignancy) and patients should be thoroughly evaluated for any recurrence or metastasis, which would contraindicate transplantation. There is no completely reliable algorithm for evaluating patients for cardiac disease for renal transplant surgery. General recommendations include noninvasive cardiac stress testing for the following population: diabetics, males older than 45 years, females older than 55 years, a family history of premature cardiac disease (myocardial infarction [MI] or sudden death in first-degree male relative younger than 55 years or first-degree female relative younger than 65 years), current cigarette smoking, hypertension, total cholesterol above 200 mg/dL, and high-density-lipoprotein cholesterol below 35 mg/dL. For those with positive stress testing, coronary angiography may be indicated. Some centers routinely advocate coronary angiography for all diabetics, as the incidence of ischemic heart disease is high in this population (9).

Patients undergoing evaluation should be screened for hepatitis B and C viruses, and HIV; any active infection should be treated. Although hepatitis B and C viruses and HIV positivity are not absolute contraindications, patients with advanced forms of these infections are generally not candidates for transplantation.

Other potential relative contraindications to transplantation include obesity, severe peripheral vascular/cerebrovascular disease, and advanced age. Although obesity is not an absolute contraindication, U.S. data on over 27,000 patients have indicated that those with morbid obesity (body mass index [BMI] >35) have a higher rate of delayed graft function, acute rejection, and worse overall survival, as well as longer hospitalizations (10). Thrombophilia, prostatic disease, high immunologic sensitization, psychosocial problems, and renal diseases with a high recurrence rate such as focal and segmental glomerulosclerosis should be identified during this transplant evaluation. Potential anatomic abnormalities such as severe iliac arterial disease and genitourinary anomalies should also be delineated before transplantation.

Candidates on the deceased donor waiting list should be reassessed periodically for any changes in the status of their
medical and psychosocial problems. Potential recipients with diabetes mellitus should be evaluated annually as they often have associated ischemic heart disease. As patients wait longer for deceased organ donors, they will need to be monitored carefully as significant changes in their medical status may occur during the waiting period.

**TYPES OF DONORS**

Kidneys are transplanted from deceased donors after brain death or cardiac death, and from living donors. Brain death is defined by the Uniform Determination of Death Act of 1981 as follows: “an individual is dead if there is irreversible cessation of circulatory and respiratory functions or if there is irreversible cessation of all brain functions of the entire brain, including the brainstem.” A brain-dead donor has suffered head trauma, cerebrovascular accident, cerebral anoxia, or a nonmetastasizing brain tumor. Physicians caring for the patient can diagnose brain death with the assistance of physical examination findings and a confirmatory study: an apnea test, a nuclear brain flow scan, or—less commonly—an electroencephalogram, though none of these tests is specifically required. It is the responsibility of all health professionals, and especially critical care medicine physicians, to report all patients with brain death and impending brain death to the local organ procurement organization (OPO). Once family members have accepted that their relative is brain dead, the trained donation coordinator may approach the family to discuss organ donation.

Because of the disparity between organ demand and supply, kidneys that traditionally would not have been used are now being considered. These deceased donors were previously defined by the United Network for Organ Sharing (UNOS), the national organization that coordinates organ allocation, as “expanded donors.” Expanded criteria donors (ECDs) included all kidneys procured from donors of age older than 60, or aged between 50 and 59 years with at least two of the following: hypertension, serum creatinine over 1.5 mg/dL, or death due to a cerebrovascular accident. Some studies have shown that recipients of kidneys with expanded donor criteria have slightly diminished graft function, but comparable long-term graft and patient survival (11). Use of ECD kidneys may offer survival advantages to those on dialysis and were previously offered principally to recipients older than 60 years or perhaps allocated to OPOs with longer waiting times (12). As of late 2014, a new kidney allocation scheme (KAS) was implemented. The primary goal of this scheme was to extend the length of time kidney recipients have a functioning transplant by better allocating kidneys to the appropriate recipient. Each donor kidney is now assigned a Kidney Donor Profile Index (KDPI) score, which ranges from 0% to 100% based upon donor factors: age, weight, creatinine, race, hypertension, diabetes, and hepatitis C status. Those kidneys with a KDPI over 85% are comparable to the ECD kidneys and are considered to be of higher risk. The true outcome and long-term consequences of this allocation system will be more evident in the next few years.

In donation after cardiac death (DCD), death is determined by the usual cardiopulmonary criteria, that is, the absence of circulation, and can be used in clinical scenarios in which the donor does not meet brain death criteria. Conditions that may warrant consideration of DCD include irreversible brain injury, end-stage musculoskeletal disease, and high spinal cord injury. Early reports suggest that the time between extubation of the donor and the initiation of cold perfusion of the organs (warm ischemia) should be less than 60 minutes for successful kidney removal and function, though this does vary somewhat between centers (13).

Living donors are people who have been evaluated extensively both medically and psychosocially for possible donor nephrectomy. Medical evaluation should include thorough history and physical examination, laboratory studies (chemistry panel, complete blood count, hepatitis B and C viruses, and HIV testing, ABO typing, tissue typing, cross-match testing), 24-hour urine for creatinine clearance and protein, chest radiograph, computed tomography (CT), or magnetic resonance imaging (MRI) to evaluate both kidneys. Psychosocial evaluation is done to determine the emotional relation of the donor to the potential recipient and to ensure that the donor truly desires to donate and for altruistic reasons (not financial or other gain). An individual should be considered as a potential living donor only if the following basic requirements have been fulfilled:

- Donor and recipient are ABO blood group compatible.
- The warm T-lymphocyte cross-match is negative.
- The person is in excellent physical condition, emotionally stable, and well motivated.
- The individual is willing to undergo donor nephrectomy, is fully informed about the procedure, and is not under pressure from family members to donate a kidney.

The cytotoxic T-cell cross-match must be negative immediately before transplantation in order to proceed with surgery. A positive high-titer B-cell cross-match is also a contraindication to transplantation; however, transplantation may proceed in the presence of a low-titer B-cell cross-match, provided that the T-cell cross-match and the flow cytometry cross-match are negative (14).

**IMMEDIATE PREOPERATIVE MANAGEMENT**

Appropriate recipients are selected based on a list that is generated by UNOS. This list takes into account the following factors: ABO blood type, human leukocyte antigen (HLA) matching, antibody testing, and waiting time. Although potential recipients are familiar to the transplant center physicians, they are carefully evaluated for recent infection or illness with blood tests, chest radiograph, and electrocardiogram (ECG). Because waiting lists are long and patients may have been waiting for several years, other illnesses may have developed in the interim that may contraindicate transplant surgery. Patients may require a treatment of hemodialysis or peritoneal dialysis prior to transplant surgery if there is evidence of hyperkalemia or fluid overload.

**IMMEDIATE POSTTRANSPLANT MANAGEMENT**

Renal transplantation is carried out in the standard fashion through an incision that exposes the iliac fossa. The donor
renal vessels are sutured in an end-to-side fashion to the external iliac artery and vein and a ureteroneocystostomy is created. Patients are monitored with continuous ECG and central venous pressure in the immediate postoperative period. Blood pressures are carefully monitored, as most patients have underlying hypertension and administration of immunosuppressive medications such as corticosteroids can affect blood pressure control. In addition, pain, catecholamine release, and fluid status may contribute to difficulties with blood pressure control. Although adequate blood pressure control is important for the integrity of the renal arterial anastomosis, it is equally important to avoid hypotension and therefore prevent renal hypoperfusion and graft thrombosis.

Urine output is carefully monitored on an hourly basis via an indwelling urinary catheter. This urinary catheter also serves to protect the ureteroneocystostomy during the early postoperative period. Any increase in intravesical pressure due to incomplete emptying of the bladder could compromise the newly created anastomosis between the ureter and bladder. Hematuria occurring early posttransplant may be due to bleeding at the ureteral anastomosis, in the bladder, or along the urethra. This can be managed with gentle flushing of the urinary catheter with 20 to 30 mL of sterile saline; changing the urinary catheter to one of a larger caliber may also help remove clots. Three-way urinary catheters are also used to facilitate continuous bladder irrigation should other measures fail to treat the hematuria.

Blood glucose monitoring is also done on a regular basis. Many transplant recipients have underlying diabetes mellitus and all patients may have hyperglycemia exacerbation related to administration of steroids and other immunosuppressive agents. Use of continuous insulin infusion and frequent blood glucose monitoring may be necessary to maintain good glycemic control. Optimal control of hyperglycemia in the postoperative period and in critically ill patients has been shown to decrease morbidity and mortality (15,16).

Particular attention should be paid to the volume and electrolyte status as the urine output in the immediate posttransplant period can vary from oliguria (frequently due to delayed graft function) to several liters as a result of generous fluid replacement during the surgery and also due to solute-induced osmotic diuresis. Living-donor allografts typically have excellent immediate function and may have prompt and marked diuresis. Most transplant centers utilize a center-specific protocol with a fixed-rate maintenance of intravenous fluids usually with 0.9% normal saline at 50 to 100 mL/hr together with replacement fluid at two-thirds or one-half of previous hour urine output. Some recipients may need hourly fluid replacement on a milliliter-for-milliliter basis in order to keep up with fluid losses. Kidneys from expanded donors or DCD or with longer cold ischemia times may not have immediate function due to acute tubular necrosis (ATN). These recipients should be kept on a maintenance volume of intravenous fluids and the central venous pressure can be used to guide fluid status (Fig. 75.1). Other factors to consider would include the timing of the last dialysis and the amount of urine produced by the patient before transplant. Hemodialysis treatment shortly before the transplant surgery may render a recipient relatively hypovolemic during the perioperative period. Patients who have not yet been started on renal replacement therapy or who make a normal amount of urine may not have issues with hypovolemia.

![Algorithm for the management of low urine output following renal transplant.](image)
Postoperative evaluation of electrolytes should include monitoring of serum sodium, potassium, bicarbonate, calcium, magnesium, and phosphorous. Although some patients require bicarbonate supplements, potassium supplements are usually not necessary. However, supplementation may be required in patients with large-volume posttransplant diuresis.

Prophylaxis with subcutaneous heparin to prevent deep venous thrombosis and with \( \text{H}_2 \) receptor blockers or proton pump inhibitors to prevent gastric and/or duodenal ulcers is often administered. Patients should be evaluated for the need for dialysis based on their electrolyte, metabolic, and volume status.

**EARLY COMPLICATIONS**

The most common complication early posttransplant is an inappropriately low urine output. The differential diagnosis includes obstruction of urine flow anywhere between the renal pelvis and the collection bag; graft hypoperfusion; urinary leak; renal parenchymal disease, usually ATN; and acute rejection in immunologically sensitized patients. If a brisk diuresis was observed in the operating room or has been recorded in previous hours, a sudden reduction in urine flow should immediately raise suspicion of a mechanical problem.

Frequently, blood clots obstruct the urinary catheter. The patient complains of a sense of fullness and need to urinate. “Milking” the urinary catheter tubing poses no risk of contaminating the closed system and usually dislodges the clots. If catheter irrigation is necessary, meticulously sterile technique is used. Sterile saline, 20 to 30 mL, should be instilled retrograde to facilitate mechanically breaking up the clot. Avoid overdistention of the bladder, which risks rupture of the ureteroneocystostomy or bladder closure. If irrigation fails to evacuate the clot, removal of the Foley catheter and replacement with a larger catheter (number 18 through 20 French) is recommended. If clots still accumulate, a triple-lumen urinary catheter permits continuous bladder irrigation; rarely, cystoscopy is required to evacuate clots.

Other mechanical problems include obstruction of the ureter or urine leak (17). These should always be suspected when there has been a history of brisk urine flow noted at surgery, but little or none has been noticed since bladder closure. Urine leak can present as severe wound pain, ascites, scrotal or labial edema, and fluid draining from the wound or operative drains with urea nitrogen and creatinine concentrations much higher than serum. Ultrasonography is particularly useful in diagnosing hydroureretor or perinephric fluid collections (18). These problems require immediate operative correction.

After exclusion of outflow problems, factors that determine allograft perfusion should be addressed. Norms for “adequate” blood pressure are higher after transplantation, especially in children receiving adult kidneys and patients with limited cardiac contractility. To some degree, all transplanted kidneys have sustained predonation procurement and reperfusion injuries (19). There is an increase in interstitial edema and increased venocapillary resistance, endothelial swelling and denuding, and activation of vasoactive mediators. The resistance of the renal vascular bed is increased. Renal plasma flow requires a higher mean arterial pressure in this setting. The renal transplant recipient usually requires a blood pressure greater than 120/80 mmHg. The patient’s history of average pretransplant pressures is valuable in targeting perfusion pressure.

Unless there is clear evidence of intravascular volume overload, fluid boluses with normal saline are usually required. A transient response may justify further volume expansion. Most dialysis-dependent patients have total-body fluid overload. Their “dry weight,” used to calculate an end point on dialysis, is always in excess of the dry weight they reach with normal renal function. Several centers use low-dose dopamine (2.5 \( \mu \)g/kg/min) in an attempt to improve renal perfusion, although it is most likely that any increased perfusion actually occurs. In rare circumstances, the intrarenal vascular resistance may be excessively high, and adequate perfusion pressures do not produce sufficient intrarenal blood flow. This problem dramatically increases the risk of further ischemic injury or even thrombosis. Grafts from pediatric donors, especially those younger than 4 years, are prone to thrombosis. As an additional safeguard, in recipients of pediatric en bloc kidneys, low-dose aspirin therapy immediately after surgery to minimize the risk of thrombosis should be considered. Graft thrombosis is rare, but any hope of graft salvage requires immediate return to the operating room.

**DELAYED GRAFT FUNCTION AND ACUTE TUBULAR NECROSIS**

Delayed graft function (DGF) or acute renal dysfunction in the immediate posttransplant period has been a serious and frequent problem in cadaveric renal transplantation, occurring in up to 30% of the recipients (20), and in up to 35% to 40% in ECD and DCD kidney recipients, respectively. However, this diagnosis should be considered only after all other causes are eliminated. ATN is the most common histologic feature in patients with DGF. The risk factors associated with an increased incidence of DGF include donor hypovolemia or hypotension, particularly in the presence of nephrotoxic drugs or vasopressors; prolonged cold or warm ischemia times; kidneys procured from older donors and from donors with hypertension or vascular occlusive disease; injury incurred during procurement, preservation, or implantation; and a high (>50%) panel reactive antibody (PRA) level in the recipient (21–23). Living-donor kidneys are much less likely to have DGF than deceased donor kidneys. The pathophysiology leading to DGF is complex and incompletely understood, but appears to be due to ischemia–reperfusion injury. The short- and long-term deleterious effects on graft survival that have been demonstrated in patients developing this disorder relate to its association with acute and chronic rejection (23,24). Therefore, protocols were developed to administer antilymphocyte antibodies for the preemptive treatment of acute rejection, during this period of graft dysfunction, when a diagnosis of rejection could be difficult. This led to the development of protocols termed sequential quadruple immunosuppressive therapy, where patients receive antibody induction followed by maintenance immunosuppression, usually with three agents.

**IMMUNOLOGIC CAUSES OF EARLY GRAFT DYSFUNCTION**

*Hyperacute rejection* is a rare and largely preventable cause of immediate graft failure. It is caused by preformed antibodies
present in the recipients’ serum at the time of transplantation against donor antigens. These antibodies are the consequence of previous exposure to donor antigens due to blood transfusions, prior transplantation, or pregnancy. It also occurs when transplantation is attempted across ABO-incompatible barriers. The events that lead to hyperacute rejection may occur with such rapidity that the kidney becomes visibly ischemic while the patient is still on the operating table. It always occurs within 24 hours of transplantation. Renal histology shows fibrin thrombi occluding the glomerular capillaries and small vessels with extensive tissue necrosis. Although plasmapheresis and anticoagulation have been advocated, there is no established effective treatment and interventions are seldom successful. A kidney with hyperacute rejection should always be removed promptly. The current cross-match techniques, because of their increased sensitivity, have greatly diminished the incidence of hyperacute rejection.

Antibody-mediated \((C4D)\) acute rejection is another form of early rejection that can occur in previously sensitized patients, but who have an initial negative cross-match. This form of acute rejection is potentially reversible if diagnosed early and treated aggressively with plasmapheresis and intravenous immunoglobulin (25). Eculizumab is a humanized monoclonal antibody that specifically binds to the complement protein \(C5\), thereby inhibiting its cleavage to \(C5a\) and \(C5b\) and preventing the generation of the terminal complement complex \(C5b-9\) is currently in studies for the prevention of antibody mediated rejection \((AMR)\) in renal transplant recipients. Eculizumab is approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria \((PNH)\) and another rare disease, atypical hemolytic uremic syndrome \((aHUS)\) and currently available commercially. It is being evaluated in Phase 2 clinical studies in kidney transplant recipients for prophylaxis of AMR and also for the prevention of DGF (26). Patients receiving eculizumab may have increased susceptibility to infections, especially those with encapsulated bacteria. Life-threatening and fatal meningococcal infections have been reported. Children treated with eculizumab may also be at increased risk of developing serious infections due to Streptococcus pneumoniae and Haemophilus influenzae type b \((Hib)\) (27).

**IMMUNOSUPPRESSION**

The different phases of immunosuppressive therapy after transplantation are as follows:

1. **Induction immunosuppression** in the immediate post-transplantation period when potent therapy is required to prevent rejection.
2. **Maintenance immunosuppression for long-term therapy** to prevent allograft rejection, but at the same time preserving host defense mechanisms against infections.
3. **Intensification of the immunosuppressive therapy** for the treatment of an acute rejection episode.

Antilymphocyte antibodies—available as immunosuppressive agents since the late 1960s—are ideally suited for use as induction immunosuppressive agents and, to some extent, for the treatment of acute rejection. All early forms of antilymphocyte antibodies were polyclonal, made by injecting human lymphocytes into horses, goats, rabbits, or sheep. In contrast to polyclonal antibodies, a monoclonal antibody is highly specific, and recognizes a single antigen epitope. They have a greater potency at lower doses, and have a more predictable and consistent effect. Monoclonal antibodies that have been approved for use in transplantation are directed either at cell surface receptors such as the CD3/T-cell receptor \((TCR)\) complex \((OKT3)\), or the interleukin-2 \((IL-2)\) receptor \((IL-2R)\; daclizumab and basiliximab). OKT3 and daclizumab have been withdrawn and are no longer available. These immunosuppressive agents are classified as depleting-antibody or nondepleting antibody, depending on their ability to deplete lymphocytes from the peripheral circulation.

Current maintenance immunosuppression protocols often use the combination of a calcineurin inhibitor, an antimetabolite, and corticosteroids. However, the principles of the different regimes are similar: more intense immunosuppression in the induction phase with gradual reduction in immunosuppression in the maintenance phase. The immunosuppression protocol an institution implements should provide a balance between preventing rejection and avoiding the consequences of overimmunosuppression such as infection and malignancy.

**Induction Agents**

**Depleting Antibodies**

Rabbit antilymphocyte globulin \((thymoglobulin)\), a polyclonal antilymphocyte antibody, is produced by the immunization of rabbits with human thymocytes. Several mechanisms of action have been proposed to explain the immunosuppressive effect of thymoglobulin. These include complement-mediated cell lysis, clearance of lymphocytes by opsonization and subsequent phagocytosis by macrophages, and antibody-dependent cell-mediated cytolyis (28).

Polyclonal antibody treatment induces marked lymphocyte depletion that persists during the entire treatment period. The number of circulating T cells will gradually increase after the cessation of treatment and reach pretreatment levels in several weeks, with significant variability among patients. Each polyclonal antilymphocyte preparation varies in its constituent antibodies. Due to this unpredictable antibody mixture and batch-to-batch variability, treatment responses and side effects are variable between the different preparations (29).

Thymoglobulin \((antithymocyte globulin)\) is the only polyclonal agent currently available for use in the United States. Thymoglobulin consists of antibodies specific for T-cell epitopes, including CD2, CD3, CD4, CD8, CD11a, CD18, CD25, HLA-DR, and HLA class I. An uncommon, but serious, side effect of thymoglobulin treatment is the cytokine release syndrome, which usually occurs after the administration of the first few doses. This syndrome includes the development of skin rashes, hypotension, acute respiratory distress, and anaphylaxis. Polyclonal antibodies often cross-react with antigens on unrelated cells, resulting in such side effects as granulocytopenia, thrombocytopenia, arthralgia, serum sickness, phlebitis, and immune complex glomerulonephritis. Because these agents severely impair cell-mediated immunity, patients are prone to develop opportunistic infections and posttransplantation malignancies, especially postransplantation lymphoproliferative disorders \((PTLDs)\).

Thymoglobulin is dosed at 1.5 mg/kg/day for a total dose of 6 mg/kg. It is administered as an IV infusion over a period of about 6 hours. Premedication is recommended using high-dose methylprednisolone, an antihistamine, and acetaminophen 1 hour prior to its administration.
Alemtuzumab (Campath-1H) is a humanized monoclonal antibody directed against the CD52 antigen (30,31); it is not approved by the Food and Drug Administration for use in kidney transplant patients but is used off-label in approximately 15% of these recipients. Targeting of CD52 with antibody has shown to be exceptionally lytic of lymphocytes. The mechanism of action of alemtuzumab includes complement-mediated lysis, cell-mediated killing (antibody-dependent cellular cytotoxicity [ADCC]), and induction of apoptosis of targeted cells. Alemtuzumab is a relatively low-affinity antibody, requiring 20 to 50 μg/mL to saturate its receptors (32). Because of the humanization of alemtuzumab, the first-dose effect is relatively mild; there is an associated tumor necrosis factor (TNF)-α and interferon-γ (IFN-γ) release that can be reduced with steroids. First infusion reactions such as fever, rash, nausea, vomiting, headache, and rigors due to a cytokine release syndrome have been reported with alemtuzumab treatment; however, these effects have been of a low-grade nature and limited with steroid pretreatment (32,33). Alemtuzumab effectively depletes immune cells, namely T and B lymphocytes, some natural killer (NK) cells, and some monocyte/macrophage lineage. Results from a number of single-center trials (34,35) and a multicenter trial (36) comparing alemtuzumab induction with that of basiliximab in low–immunologic-risk recipients and with thymoglobulin for high–immunologic-risk recipients have confirmed the efficacy of alemtuzumab as an induction agent.

Rituximab (Rituxan) antibody is a genetically engineered chimeric (human and mouse) monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes (37). Rituximab is approved for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin lymphoma (38,39). Because of its effects on the B lymphocytes, rituximab is believed to be effective in the treatment of patients with antibody-mediated (humoral) acute rejection and is also thought to have a role in decreasing the PRA level in sensitized patients. However, it is not FDA approved for the latter indications and has not gained widespread support for use in transplant recipients, except for treatment in patients with PTLD (40).

Nondepleting Antibody

Basiliximab is an anti–interleukin-2α receptor antibody that is currently used as an induction agent in kidney transplant recipients that are unsensitized and are immunologically at a lower risk for acute rejection. IL-2 is a cytokine responsible for the growth and proliferation of activated T cells. During an immune response, IL-2 exerts its effects by binding to the IL-2R on the surface of the antigen-activated T cell; anti–interleukin-2α receptor antibodies are monoclonal antibodies directed against the IL-2R on activated T cells. These antibodies are used as induction agents for prophylaxis against acute rejection in renal transplant recipients (41).

Basiliximab (Simulect) is a chimeric (human and mouse) IgG1κ monoclonal antibody that is administered as an IV infusion of two doses of 20 mg each. The first dose is given within 2 hours before transplantation, and the second dose is administered 4 days after transplantation. Adverse effects of the IL-2R antibodies are minimal and equivalent to placebo in controlled trials; hypersensitivity reactions have been reported.

Maintenance Agents

Calcineurin Inhibitors

Calcineurin inhibitors are currently considered to be the mainstay of immunosuppression regimens following transplantation. They are potent immunosuppressants, inhibiting T-cell activation by inhibiting calcineurin phosphatase, a key step in the regulation of cytokine expression. The introduction of calcineurin inhibitors in the mid-1980s revolutionized the field of transplantation by dramatically reducing acute rejection rates and improving short-term allograft survival (42).

Cyclosporine A (CsA), the first calcineurin inhibitor approved for use in transplant recipients for maintenance immunosuppression, binds to cyclophilin in the T cell. The CsA/cyclophilin complex, in turn, inhibits calcineurin phosphatase, which is responsible for the transcription of IL-2. CsA is highly lipophilic and water insoluble. Early formulations (Sandimmune) were administered orally as an oil-based solution. In this form, bioavailability was erratic, highly variable, and bile dependent for its absorption. This erratic absorption profile led to the development of a microemulsion formulation (modified cyclosporine, Neoral) that demonstrated a more reliable and predictable absorption. These two formulations are not bioequivalent and are thus not interchangeable. CsA is available in an IV formulation, as an oral solution, and in a capsule form. The IV formulation should be administered as a continuous infusion and should be limited to patients unable to take CsA orally; the patient should be monitored closely during the infusion process. The CsA dosage should be titrated based on whole blood concentration; the recommended starting dose of oral solution or capsules is 10 to 14 mg/kg/day for the nonmodified CsA and 6 to 12 mg/kg/day of the modified CsA, administered 12 hours apart in divided doses. In the United States, use of CsA has been superseded by that of tacrolimus in the majority of kidney transplant recipients and in almost all pancreas transplant recipients.

Tacrolimus (Prograf, FK-506) is a macrolide agent that inhibits IL-2 production in a similar fashion as CsA in the T lymphocyte. However, instead of binding to cyclophilin, tacrolimus binds to the FK-binding protein 12 (FKBP-12), with the resulting complex inhibiting calcineurin phosphatase. Tacrolimus is available in IV injection and oral capsule dosage forms. The IV form of tacrolimus is also administered as a continuous infusion and, because of the risk of neurotoxicity, should be limited to select patients unable to take tacrolimus orally. Tacrolimus is readily absorbed in the stomach and should be given orally or through nasogastric tube whenever feasible. The recommended starting dose of oral tacrolimus is 0.2 mg/kg/day administered 12 hours apart in divided doses.

Astagraf XL is an extended-release formulation of tacrolimus capsule that is indicated for the prevention of rejection in kidney transplant recipients. It shares the same efficacy and side-effect profile as that of immediate-release tacrolimus. It provides a once-daily dosing option and, as a result, may improve compliance (43,44).

Envarsus is also an extended-release formulation of tacrolimus utilizing the proprietary MeltDose drug-delivery technology that significantly increases the bioavailability of tacrolimus; it is designed for once a day administration. In a large-phase III study it showed comparable efficacy to that of immediate-release twice a day tacrolimus. Because of its improved absorption, patients required lower doses of
Envarsus than immediate-release tacrolimus (45). Envarsus is currently available for use in Europe. Final regulatory approval and marketing of this agent in the United States are currently pending and is expected to be available for use soon.

Adverse Effects of the Calcineurin Inhibitors

Both calcineurin inhibitors have a narrow therapeutic window, multiple side effects, and drug interactions. Both drugs are metabolized by the cytochrome P450–3A4 enzyme system; their blood concentrations are affected by drugs that block or induce this cytochrome enzyme system. These drugs interact with some of the commonly used antibiotics, antifungal agents, and antihypertensive agents (Table 75.1).

Both drugs cause acute and chronic nephrotoxicity; the acute nephrotoxicity is due in part to hemodynamic changes secondary to their vasoconstrictor effects on the afferent arteriole of the glomerulus. This results in a reduction in the glomerular filtration rate, manifested by an increase in the serum creatinine concentration. This acute change is dose related and reversible. However, the lesions associated with calcineurin inhibitor–induced chronic nephropathy may lead to end-stage renal failure. These lesions, which consist of tubulointerstitial fibrosis, tubular atrophy, afferent arteriopathy, and global or focal glomerular sclerosis or collapse, have been well demonstrated in patients with autoimmune diseases treated with cyclosporine, as well as in the various organ transplant recipients: heart, liver, renal, and bone marrow (46,47). The other reported adverse effects of CsA and tacrolimus include hypertension, hyperkalemia, hyperlipidemia, and headache. Adverse effects unique to CsA include hirsutism and gingival hyperplasia, whereas those unique to tacrolimus include alopecia, fine tremor, and hyperglycemia. The adverse-effect profiles of both CsA and tacrolimus are compared in Table 75.2.

Dose modifications of both CsA and tacrolimus are based on whole blood trough concentrations. Monitoring of the respective drug concentrations is an essential aid in the management of a transplant recipient for the evaluation of rejection, toxicity, dose adjustments, drug interactions, and compliance. Two methods for monitoring CsA levels in whole blood include high-pressure liquid chromatography (HPLC) and radioimmunoassay, or TDx. For tacrolimus, a microparticle enzyme immunoassay (MELA) or an enzyme-linked immunosorbent assay (ELISA)-based IMx assay are utilized. Target levels of either drug vary, based on the type of assay used, the type of monitoring (trough vs. C2 [drug level 2 hours postdose] vs. AUC [area under the curve]), transplant center standards, time posttransplantation, and the recipients’ risk for acute rejection.

Antimetabolites

Mycophenolate mofetil (MMF) (CellCept) and enteric-coated mycophenolate sodium (MPF) (Myfortic) contain the active moiety mycophenolic acid (MPA), a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a key, rate-limiting step in the de novo pathway of guanosine nucleotide synthesis. Depletion of the guanosine nucleotides inhibits T- and B-cell proliferation as they are dependent on the de novo pathway of purine synthesis rather than salvage pathways.

The recommended dose of MMF is 1,000 mg orally or IV twice daily, divided 12 hours apart. MMF is the prodrug of mycophenolate sodium (MPF) (Myfortic) contain the active moiety mycophenolic acid (MPA), a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a key, rate-limiting step in the de novo pathway of guanosine nucleotide synthesis. Depletion of the guanosine nucleotides inhibits T- and B-cell proliferation as they are dependent on the de novo pathway of purine synthesis rather than salvage pathways.

Adverse effects of MPA include gastrointestinal effects (dyspepsia, nausea, vomiting, diarrhea, and constipation) and bone marrow suppression (leukopenia and thrombocytopenia). Diarrhea, leukopenia, and thrombocytopenia are often dose limiting requiring dose reduction to ameliorate the toxic effects. These patients, however, should be monitored closely, as a relationship exists between an increased incidence of acute rejection and decreased MPA doses (48,49).

Azathioprine (Imuran)—a purine analog that inhibits DNA and RNA production in the T cell—is an imidazole derivative

### Table 75.2 Adverse Effect Profile of Cyclosporine A and Tacrolimus

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<thead>
<tr>
<th>Adverse Event</th>
<th>Cyclosporine A (%)</th>
<th>Tacrolimus (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>52.2</td>
<td>49.8</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>38.2</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>41.5</td>
<td>45.4</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4.0</td>
<td>19.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Headache</td>
<td>37.7</td>
<td>43.9</td>
<td></td>
</tr>
<tr>
<td>Tremors</td>
<td>33.8</td>
<td>54.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1.0</td>
<td>10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>8.7</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>5.3</td>
<td>0.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>8.7</td>
<td>1.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

of 6-mercaptopurine. The initial recommended dose of azathioprine is 3 to 5 mg/kg/day, administered orally or IV once daily. Adverse effects of azathioprine include hematologic toxicities (pancytopenia, macrocytic anemia, thrombocytopenia, and leukopenia), alopecia, pancreatitis, and hepatotoxicity. Dose reductions may be required for myelosuppressive toxicities. A potent drug interaction may be seen with the coadministration of azathioprine and allopurinol (a xanthine oxidase inhibitor). Although it is recommended that the dose of azathioprine should be reduced by 75% when coadministered with allopurinol, it is more prudent to avoid the use of these two agents together.

**mTOR Inhibitors**

Sirolimus (Rapamune) is a macrolide antibiotic produced by *Streptomyces hygroscopicus* and is structurally similar to tacrolimus. Like tacrolimus, sirolimus also binds to FKBP-12. However, unlike tacrolimus, this complex binds to and inhibits the activation of the mammalian target of rapamycin (mTOR). This interferes with biochemical signal transduction from the cell membrane to the nucleus by inhibiting the stimulation of T cells by IL-2, -4, and -6 and by blocking the CD28 costimulatory signal. Sirolimus is available in oral tablets and solution. The recommended initial dose of sirolimus is approximately 6-mg (5 to 10 mg) loading dose, followed by 2-mg once-daily maintenance dose. Dose adjustments are made based on weekly or biweekly trough level monitoring (t1/2 = 62 hours).

Adverse effects of sirolimus include anemia, leukopenia, thrombocytopenia, hyperlipidemia, prolongation of delayed graft function, impaired wound healing, pneumonitis, arthralgia, aphthous mouth ulcers, lymphoedema, and diarrhea. The advantage of sirolimus is due to its lack of nephrotoxicity (50,51). However, when coadministered with CsA, the nephrotoxic effect of CsA can be potentiated (52). Sirolimus is metabolized by the cytochrome P450–3A4 enzyme system and has a similar drug interaction profile as that of the calcineurin inhibitors.

Everolimus (Zortress) is a rapamycin derivative with increased oral bioavailability and a shorter half-life. The recommended initial dose of everolimus is 0.75 mg orally twice daily with dose adjustments made weekly or biweekly to target trough levels between 3 and 8 ng/mL. Everolimus shares some of the same advantages and adverse effects associated with sirolimus; everolimus is used in combination with cyclosporine or tacrolimus and appears to be efficacious even with lower tacrolimus doses (53).

**Costimulation Blockade**

Belatacept represents a new class of immunosuppressive therapy for renal transplantation. It is a selective costimulation blocker that binds to the B7 receptors on the surface of antigen-presenting cells and provides effective immunosuppression while avoiding the toxicities associated with calcineurin inhibitors. It is administered intravenously at monthly intervals in the long term. Although there is a trend toward higher rates of early rejection episodes in patients treated with belatacept, longer-term data have shown superior graft function and reduction of death or graft loss with belatacept (54). A safety issue that must be considered when using belatacept is the potential for increased risk of posttransplant lymphoproliferative disease (PTLD), especially in Epstein–Barr virus (EBV) seronegative recipients or patients treated with lymphocyte-depleting agents. Therefore, belatacept is contraindicated in kidney transplant recipients who are EBV seronegative or serologic status is unknown.

**Corticosteroids**

Corticosteroids exert their immunosuppressive effects through multiple pathways, the most important of which is through their ability to inhibit cytokine and cytokine receptor transcription. Corticosteroids inhibit the expression of various cytokines responsible for the activation of T cells including IL-1, -2, -3, -6, TNF-α, and IFN-γ. Corticosteroids function as both induction and maintenance immunosuppressive agents, as well as for the treatment of acute rejection episodes. Typical induction protocols call for high-dose methylprednisolone, the first dose administered intraoperatively prior to organ perfusion with tapering doses for the first few days posttransplantation. This is followed by oral prednisone with continued tapering to a baseline maintenance dose. Corticosteroids are typically administered once a day in the morning concurrent with intrinsic cortisol release.

Adverse effects of corticosteroids are numerous and include cosmetic changes, avascular necrosis, cataracts, osteoporosis, impaired wound healing, glucose intolerance, hypertension, hyperlipidemia, increased appetite, hypothalamic–adrenal axis (HPA) suppression, and mood swings.

Corticosteroids were the first immunosuppressants used when renal transplants were done in the 1960s. Because of numerous adverse effects, steroid withdrawal has been attempted, but only with moderate success because of increased acute rejection. However, with the advent of newer and more effective immunosuppressive therapy, there has been a renewed interest in early withdrawal or complete elimination of corticosteroids. Short-term success has been achieved in several small single-center trials and a few larger multicenter trials. Early corticosteroid withdrawal has also been associated with a more favorable cardiovascular risk profile, as evidenced by less hypertension, posttransplant diabetes mellitus (PTDM), and hyperlipidemia (55).

**MINIMIZING OPPORTUNISTIC INFECTIONS IN THE TRANSPLANT**

**Recipient**

Within the first month following transplantation, surgical wound-related and nosocomial infections are the most common infections observed in renal allograft recipients. As a result, bacterial infections involving the urinary tract, the respiratory tract, the surgical wound, and/or intravenous lines are the ones frequently encountered. In a few instances, infections may be due to reactivation of pre-existing infection in the recipient such as subclinical bacterial infections, especially urinary tract infections (UTIs) and tuberculosis, or transmission of infections from the donor to the recipient.

Infections in the 1- to 6-month period after transplantation are due to opportunistic organisms, most notably viruses belonging to the herpes group, especially cytomegalovirus (CMV), and due to *Candida* species and *Pneumocystis jiroveci*. Antimicrobial prophylaxis specific to these opportunistic organisms should be given to all renal allograft recipients.
early posttransplantation. Prophylaxis protocols differ among centers in antimicrobial selection and duration of therapy. Prophylaxis with antifungals such as clotrimazole, nystatin, or fluconazole may be used against *Candida* infections of the mouth and throat (thrush). Prophylaxis against *P. jiroveci* pneumonia (PCP) includes sulfamethoxazole/trimethoprim; for those patients with a sulfa allergy, monthly inhaled pentamidine or oral dapsone will provide adequate prophylaxis against PCP. Drug and dose selection of antiviral prophylaxis against CMV infection can be stratified by infection risk based on previous CMV exposure, or the presence of anti-CMV antibodies in the recipient (Table 75.3). Valganciclovir is currently the drug of choice for antiviral prophylaxis against CMV.

Several antimicrobial agents adversely interact with cyclosporine and tacrolimus, and careful consideration should be given to the choice of the antimicrobial agent.

**“STABLE” ALLOGRAFT RECIPIENTS READMITTED TO THE INTENSIVE CARE UNIT**

Successful transplantation restores patients to an active and functional life, but it does not prevent subsequent occurrence of atherosclerotic cardiovascular disease, cancer, trauma, infections, and other major problems. Furthermore, the care of transplant patients with other diseases demands an awareness of the long-term problems that are unique to this patient population, and these are also discussed below.

**INFECTIONS**

**Viral Infections**

**Cytomegalovirus**

CMV is the most important viral infection affecting transplant recipients. CMV infection risk is highest in patients who are CMV IgG-seronegative and received an allograft from a CMV-seropositive donor (see Table 75.3) or who have received CMV-positive blood transfusion. CMV infection often presents clinically with fever after cessation of anti-CMV prophylaxis and in some instances may present as disseminated or tissue invasive CMV disease affecting the gastrointestinal tract, liver, kidney, or lungs with organ-specific symptoms (i.e., pneumonitis). CMV is diagnosed by identification and quantification of the viral DNA in the blood by polymerase chain reaction (PCR). Tissue-invasive disease may be diagnosed by the identification of the characteristic *owl-eye* inclusions on tissue biopsy (56). Treatment of CMV viremia and tissue-invasive CMV disease should be initiated promptly with oral valganciclovir or intravenous ganciclovir. Concomitant treatment with CMV immune globulin may be required in some patients with severe tissue disease. Duration of treatment depends on the extent of the disease and continued positivity of the CMV-DNA by PCR.

**Polyoma (BK Virus) Infection**

With the increased use of potent immunosuppressive agents, there has been an emergence of opportunistic infections such as polyomavirus infection in renal transplant recipients. Polyomavirus is a member of the papovavirus family. The two sub-types—BK and JC virus—were first described in 1971 and named after the initials of the original patients. BK virus is associated with interstitial nephritis and ureteral stenosis in the transplant kidney and with hemorrhagic cystitis in bone marrow transplant recipients. So far, there is no evidence linking polyomavirus infection to any particular immunosuppressive agent. Tissue injury due to recurrent episodes of acute rejection and treatment with potent immunosuppressive agents appears to potentiate polyomavirus infection. Notably, this infection is rarely seen in solid organ transplants other than the kidney. Recent studies have shown that polyomavirus has been implicated as a cause of interstitial nephritis in 5% of renal transplant recipients with subsequent graft failure in as many as 45% of the affected patients. The time from transplantation to the diagnosis of polyomavirus infection is variable, with a range of 2 to 60 months (median 9 months). PCR for polyomavirus DNA in the urine and blood is a sensitive and specific method for detecting the agent; at the present time, there is no specific therapy for polyomavirus infection. Screening with urine and/or blood PCR for polyomavirus prospectively and reduction in immunosuppression in the presence of increasing or high viral loads is indicated and is the most effective option currently available. Many protocols include discontinuation/reduction of antimetabolites such as MMF and/or substitution of tacrolimus with cyclosporine; m-TOR inhibitors are being used increasingly because of their antiviral properties (57–59).

Other viral infections that may occur in the immunosuppressed renal allograft recipient include EBV, which may lead to the development of EBV-positive lymphomas; herpes simplex virus (types I and II); hepatitis B and C viruses; varicella-zoster virus; and the influenza virus. Treatment of viral infections depends on the type of virus and the extent of the disease. All transplant recipients should receive an annual influenza immunization.

**Fungal Infections**

Fungal infections are a major concern in the immunosuppressed renal allograft recipient. As with the general population,

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**TABLE 75.3** Cytomegalovirus (CMV) Risk Stratification and Treatment Options

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Donor CMV IgG Serostatus</th>
<th>Recipient CMV IgG Serostatus</th>
<th>Usual Drug of Choice</th>
<th>Dose</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Positive</td>
<td>Negative</td>
<td>Valganciclovir</td>
<td>450–900 mg daily</td>
<td>180</td>
</tr>
<tr>
<td>Moderate</td>
<td>Positive</td>
<td>Positive</td>
<td>Valganciclovir</td>
<td>450–900 mg daily</td>
<td>90</td>
</tr>
<tr>
<td>Low</td>
<td>Negative</td>
<td>Positive</td>
<td>Valganciclovir</td>
<td>450–900 mg daily</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Valacyclovir</td>
<td>500 mg twice or thrice daily</td>
<td>30</td>
</tr>
</tbody>
</table>


Candida albicans infections resulting from endogenous flora are common. However, with immunosuppression, these infections can become more serious. Other fungal pathogens seen in transplant recipients include nocardiosis, aspergillosis, Cryptococcus, histoplasmosis, coccidiodomycosis, blastomycosis, and mucormycosis. Treatment of fungal infections include the use of antifungals specific to the organism, surgical excision—especially in the case of mucormycosis—and reduction in the overall immunosuppression. Careful consideration should be given to the choice of the antimicrobial agent because of drug interactions (azole antifungals) or additive nephrotoxicity (amphotericin B) in the presence of immunosuppressant agents. Invasive fungal infections in transplant recipients are associated with a high risk of graft loss and mortality. Early diagnosis and aggressive treatment can preserve organ function and can be lifesaving.

Other Opportunistic Infections

UTIs are a frequent complication of renal transplantation. Although UTIs are frequently asymptomatic, they constitute the major source of bacteremia in this patient population. Therefore, all UTIs, even asymptomatic ones, should be treated appropriately. Fortunately, renal dysfunction is an uncommon complication of UTIs in the transplant recipient. It usually occurs with severe pyelonephritis involving the allograft, usually in the setting of ureteral obstruction or vesicoureteral reflux. Chronic UTIs may require daily prophylactic antibiotic administration.

Renal allograft recipients, especially patients with poor allograft function with a background of intensive acute and chronic immunosuppressive therapy for recurrent rejection episodes, are susceptible to a large range of infections. Empiric treatment should be initiated at the first sign of infection as infections can be aggressive and worsen rapidly.

GASTROINTESTINAL COMPLICATIONS

A wide variety of gastrointestinal complications may occur after transplantation due to infections with organisms such as CMV, Candida sp., and Clostridium difficile; adverse effects associated with immunosuppressive agents; posttransplantation complications of pre-existing conditions such as diverticulitis; and other complications such as acute appendicitis, gastrointestinal bleeding, colonic or small bowel perforations, pancreatitis, and ischemic colitis. Diarrhea is a common problem in transplant recipients and may be related to the immunosuppressive drugs, due to opportunistic infections, or due to pre-existing autonomic dysfunction often related to diabetes mellitus.

Peptic Ulcer Disease

Gastroduodenal ulcers account for most of the gastrointestinal complications posttransplantation and occur often soon after renal transplantation or acute rejection therapy. Gastroduodenal ulcers presenting posttransplantation can be attributed to a variety of causes including pre-existing ulcer history, viral pathogens (CMV in 15%, herpes simplex in 2%), and immunosuppressive agents, mainly corticosteroids (60–63). The treatment of posttransplantation gastroduodenal ulcers is the same as with the general population. Proton pump inhibitors and H₂-receptor blocking agents may be used for both therapy and prophylaxis. Intermittent therapy with calcium, aluminum, or magnesium salts can provide immediate relief; however, coadministration of these agents with MMF (CellCept) may inhibit absorption of the active moiety of this drug in the intestinal tract. All kidney transplant recipients diagnosed with gastroduodenal ulcers should be evaluated for Helicobacter pylori and CMV infection. Clarithromycin (Biaxin), commonly used for the treatment of H. pylori, interacts with CsA and tacrolimus (see Table 75.1); therefore, under ideal circumstances, an alternate antibiotic regimen should be used. For CMV-related gastrointestinal lesions, ganciclovir or valganciclovir treatment should be initiated promptly.

Bowel Perforation

Colonic perforation should be suspected in the presence of one or more of the following: abdominal pain, fever, increased white blood cell count, tenderness, and pneumoperitoneum. These clinical criteria may be blunted in the presence of poor renal function, use of high-dose corticosteroids, or based upon the overall state of immunosuppression. A plain abdominal radiograph, CT scan, or colonoscopy may help in the diagnosis. Mortality rates after colonic perforation can be reduced with minimal delay in time to surgery, broad-spectrum antibiotic therapy, and reduction of immunosuppression. Operative intervention has been shown to improve patient survival significantly (64). Screening for colonic diverticula before transplantation should be applied to all patients older than age 50 years, and a segmental colectomy may be required in patients who have experienced clinical symptoms of diverticulitis (60,64).

Acute Pancreatitis

Acute pancreatitis is an infrequent but severe complication following renal transplantation. A review of the literature has documented an incidence of 2.3%, with a mortality rate of 61.3% in 3,253 renal transplant recipients (65). Several etiologic factors have been considered in the etiology of this process. Azathioprine has been reported to cause pancreatitis with rapid improvement after cessation and with recurrence of symptoms with reinstitution (66). Corticosteroids and cyclosporine have also been reported to cause pancreatitis; however, this association is not as convincing as that of azathioprine. Other causes of pancreatitis include hyperparathyroidism, CMV infection, biliary tract disease, alcoholism, and hyperlipidemia (65). Although the diagnosis of pancreatitis depends largely on an increase in the serum amylase and/or serum lipase levels, ultrasonography and CT scan may be useful. Intensive medical management with particular attention to volume replacement, electrolyte balance, and nutrition is essential. Severe diarrhea with ensuing dehydration and acidosis, gastrointestinal bleeding, cholecystitis, and diverticulitis are other commonly encountered gastrointestinal problems in the transplant recipient. Advances in the management of peptic ulcer disease, prophylaxis against CMV disease, and better preparation of recipients prior to transplantation have reduced the overall morbidity and mortality. Several of the gastrointestinal problems may be related to the side effects of...
the immunosuppressive drugs or due to the net state of over-immunosuppression. Careful consideration should be given to the change in the immunosuppressive agent and to decrease in the dosages of these medications.

**Hematologic Complications**

Neutropenia is a frequent complication posttransplantation, often as a result of the adverse effects of immunosuppressive medications. Antithymocyte globulin can cause transient decreases in neutrophils that often rebound after cessation of therapy. Maintenance immunosuppression with mycophenolic acid, mTOR inhibitors, and prophylaxis with ganciclovir and sulfamethoxazole/trimethoprim contribute to the development of neutropenia due to their myelosuppressive effects. Careful dose reduction of these agents and/or use of granulocyte-stimulating factors are often required for persistent neutropenia. Of particular importance is that neutropenia can be a sign of CMV infection, and therefore this should always be excluded in transplant recipients with persistent neutropenia.

Anemia is a frequent occurrence in the early posttransplantation period as a result of pre-existing anemia of ESRD, surgical blood loss, and immunosuppressive medications. Patients with slow or DGF may have a more pronounced and prolonged anemia. Anemia in the late posttransplantation phase can be attributed to a combination of immunosuppressive medications, renal allograft dysfunction, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, and/or iron deficiency (67). As cardiovascular disease is the leading cause of morbidity and mortality in kidney transplant recipients, it is important to manage anemia aggressively in this patient population with the use of erythropoietin. Furthermore, given the high incidence of coexisting cardiovascular disease in this patient population, blood transfusions should not be withheld for acute indications.

Thrombocytopenia is also a frequent occurrence in renal allograft recipients and often is caused by the immunosuppressive medications. Antithymocyte globulin, valganciclovir, and dapsone can cause transient decreases in platelets. Withholding doses or dose adjustments of the responsible agent may be required for the treatment of thrombocytopenia. Platelet recovery is rapid, often returning to baseline within days. In rare circumstances, thrombocytopenia may be due to HUS that is caused by immunosuppressive drugs (calcineurin inhibitors, mTOR inhibitors), severe acute vascular rejection, transmission from donor, recurrence of previous HUS, or causes similar to those in nontransplant recipients.

**CARDIAC AND VASCULAR DISEASES**

**Coronary Artery Disease**

Atherosclerotic vascular disease is the major cause of late morbidity and mortality in transplant recipients, and coronary artery disease is the principal cause of death (68–72). In transplant recipients, risk factors for posttransplantation coronary artery disease include increased age, male gender, history of diabetes mellitus, hypercholesterolemia, smoking history, acute renal allograft rejection episodes, and greater cumulative dose of steroids (73). The key to the early detection of significant coronary artery disease in renal transplant recipients without coronary symptoms is repeated evaluation for the known risk factors. The management of transplant patients with coronary artery disease is similar to that of other patients and should include noninvasive exercise or resting diagnostic testing, coronary arteriography, or both. However, some noninvasive screening tests have been shown to be less useful, especially in the presence of diabetes, uremia, and left ventricular hypertrophy (74). With the increasing number of transplantations performed in the elderly and in patients with diabetes mellitus, cardiovascular disease will continue to be a major cause of posttransplantation morbidity. Of particular note, during cardiac catheterization, femoral arterial puncture on the ipsilateral side to the renal transplant should be avoided whenever feasible to reduce the risks of mechanical injury and atheroembolization to the renal allograft.

**Cerebrovascular and Peripheral Vascular Disease**

Cerebrovascular disease occurs in 1% to 3% of all renal allograft recipients (68,75). There is also an increased risk of peripheral vascular disease (68,71,76,77). A thorough history to elicit symptoms associated with cerebrovascular and peripheral vascular disease and examination of the carotid arteries and peripheral circulation should be performed annually, and the presence of a carotid bruit should be further investigated with duplex ultrasonography and magnetic resonance angiography (MRA). In the presence of more than 60% stenosis of the carotid artery, the patient should be referred to the neurovascular surgeon for further evaluation (78).

Successful transplantation does not reduce the rate of atherosclerosis initiated in renal failure. Factors contributing to the high incidence of vascular disease include hypertension, hyperlipidemia, obesity, cigarette smoking, and the presence of pre-existing diabetes mellitus or the development of posttransplantation diabetes mellitus (68). The mortality rate from coronary artery disease was increased 25-fold to that of age-matched and gender-matched controls in an Australian study (79), was increased 10-fold in a study from Stockholm (80), and was increased 3–4-fold in a Minneapolis study (73). By actuarial analysis, 15% of patients who survived with a functioning allograft for 15 years developed peripheral vascular disease (76).

**HYPERTENSION**

Hypertension is a common complication of renal transplantation and remains an important risk factor for mortality from cardiovascular disease. Posttransplantation hypertension is a major risk factor for graft survival. It is unclear, however, whether this is because of the deleterious effects of hypertension on the structure and function of the renal allograft, or whether hypertension is a marker of underlying renal disease (81,82). The causes of hypertension in renal transplant recipients include acute and/or chronic allograft rejection; recurrent or de novo transplant glomerulonephritis; transplant renal artery stenosis; high renin output state from diseased native kidneys; immunosuppressive agents such as steroids, cyclosporine, and tacrolimus; obesity; hypercalcemia; and new-onset essential hypertension (83).
HYPERLIPIDEMIA

As discussed earlier, cardiovascular disease is the most common cause of posttransplantation morbidity and mortality among long-term renal transplant survivors. As in the general population, posttransplantation lipoprotein abnormalities contribute to the development of cardiovascular and peripheral vascular disease in renal transplant recipients (70,76,84,85). The prevalence of posttransplantation hyperlipidemia ranges from 16% to 78% of recipients (68), depending at which time point posttransplantation serum lipid levels were obtained. Elevations in triglycerides, low-density lipoproteins (LDLs), apolipoprotein B, and total cholesterol levels are common (86–94). The pathogenesis of hyperlipidemia in renal transplant recipients is poorly understood and appears to be multifactorial. The numerous factors that have been shown to be associated with hyperlipidemia after renal transplantation are age, body weight, gender, pretransplantation lipid levels, renal dysfunction, proteinuria, concomitant use of diuretics or β-blockers, diabetes, steroid use, and cyclosporine, everolimus, and sirolimus use (84,86–92,95,96).

NEW-ONSET DIABETES AFTER TRANSPLANTATION

New-onset diabetes after transplantation (NODAT) has been reported in 3% to 40% of transplant recipients with an even higher incidence occurring in African Americans, Hispanics, and patients with a family history of diabetes mellitus, increasing with recipient age and weight (68,69,72,75,97–99). NODAT has been attributed to the use of immunosuppressive agents, especially with tacrolimus and corticosteroids; however, cyclosporine has also been implicated (99–102). Patients with NODAT have a poor outcome in terms of patient and graft survival, with increased mortality resulting from cardiovascular and possibly infectious complications (98,103).

Insulin treatment may be required in patients with NODAT who do not respond to lifestyle modification and oral hypoglycemic agents. About half of patients in whom NODAT develops require insulin. Aggressive treatment with either intravenous or subcutaneous insulin may also be indicated during periods of intercurrent illness and stress.

| TABLE 75.4 Causes of Graft Dysfunction and Failure |
|---------------------------------|---------------------------------|
| **Early (<90 Days Posttransplantation)** | **Late (>90 Days Posttransplantation)** |
| Medical | Medical |
| Hyperacute rejection | Acute rejection |
| Delayed graft function | Calcineurin inhibitor toxicity |
| Acute rejection | Chronic rejection |
| Acute calcineurin inhibitor nephrotoxicity | Dehydration |
| Dehydration | Other drug toxicities |
| Other drug toxicities | Infection |
| Infection | BK virus nephropathy |
| De novo/recurrent disease | De novo/recurrent disease |
| Lymphocele | Renal artery stenosis |
| Ureteric obstruction | Ureteric obstruction |
| Urine leak | Urine leak |
| Vascular thrombosis | Vascular thrombosis |

GRAFT DYSFUNCTION AND GRAFT FAILURE

The differential diagnosis of acute allograft dysfunction can be divided into (a) early, occurring less than 90 days posttransplantation, and (b) late, occurring more than 90 days after transplantation. It can be further differentiated into medical and surgical problems as outlined in Table 75.4. Some of the more common medical and surgical problems are discussed below.

Acute Rejection

Although acute allograft rejection is a common cause of graft dysfunction both in the early and late periods, it most commonly occurs during the first 90 days posttransplantation. Recipients of transplants from living donors have a significantly lower incidence of rejection episodes. Factors significantly associated with the development of acute rejection are fever, oliguria, weight gain, edema, hypertension, and the presence of an enlarged, tender graft. However, these features are frequently absent, and the most common presentation may be an asymptomatic rise in serum creatinine. An increase in serum creatinine above 20% is often the cardinal feature of rejection. Percutaneous needle biopsy of the allograft is the most reliable method of diagnosis of acute rejection. Acute rejection is classified histologically using the Banff 07 classification of renal allograft pathology depending on the severity of lymphocytic infiltration of tubules (tubulitis), arterioles (arteritis), and the renal interstitium and the presence of C4d deposition which can indicate the presence of AMR (106).

The principles and the management of acute rejection include rapid diagnosis, accurate classification, and prompt administration of antirejection therapy. Currently, corticosteroids and antilymphocyte antibodies represent the main components of antirejection treatment protocols. The decision on treatment of acute rejection is based on histologic severity. One approach is to treat mild acute cellular rejection with a course of 250 to 500 mg of intravenous methylprednisolone administered daily for 3 or 4 days, and moderate and severe acute cellular rejection and acute vascular rejection are treated
with a 4- to 7-day course of lymphocyte depleting antibody (thymoglobulin).

**Chronic Rejection**

Chronic rejection is characterized clinically by a progressive decline in renal function, persistent proteinuria, and hypertension; the course of chronic rejection is slow and insidious. Chronic rejection often occurs in conjunction with other histologic causes of allograft dysfunction, namely, acute rejection, calcineurin inhibitor nephrotoxicity, and recurrent or de novo glomerular diseases. The diagnosis of chronic rejection should, therefore, be based on morphologic characteristics of allograft histology and the clinical observation of a gradual decline in renal allograft function. The pathophysiology of chronic rejection is not completely understood, but most likely involves both immune and nonimmune factors. Risk factors for the development of chronic rejection include delayed graft function, ischemia–reperfusion injury, degree of HLA mismatching, histoincompatibility, acute rejection episodes, inadequate renal mass, hypertension, hyperlipidemia, and CMV infection (107). There is no treatment for chronic rejection at the present time.

**UROLOGIC COMPLICATIONS**

Urologic problems have been reported in between 2% and 20% of all renal transplants. These complications can include urinary retention, urine leak, and ureteral stenosis. Urinary retention can occur because of a neurogenic bladder (related to diabetes or a congenital neurologic disorder) or perhaps to undetected prostatic hypertrophy. These can be managed with an initially longer period of urinary catheterization and use of α-antagonists (tamsulosin, terazosin, prazosin) to improve bladder emptying. More extreme cases may require long-term intermittent self-catheterization or surgical urinary diversion. Urine leak or stenosis can occur both early and later after renal transplant and will be manifested by a rising serum creatinine. Urine leaks may also result in increased fluid through an operative drain or fluid leakage through the wound. This fluid can be sent for creatinine level to confirm the presence of a urine leak. Ultrasound studies may demonstrate a fluid collection around the allograft or hydronephrosis in the case of ureteral stenosis. Nuclear medicine scans can also be obtained to confirm the presence of a ureteral stenosis or urine leak. Mild cases of ureteral stenosis/leakage can be managed with percutaneous methods including insertion of ureteral stents and transluminal balloon dilation. Many of these stenoses/leaks will require operative management to reimplant the ureter or a more complex urologic procedure using the recipient’s native ureter or bladder (108–112).

**URINARY STONES**

Urinary calculi are a relatively uncommon complication of renal transplantation. Calculi may have been present in the donor kidney or may develop after transplantation. Predisposing factors include obstruction, recurrent UTI, hypercalciuria, hyperoxaluria, internal stents, and nonabsorbable suture material (113). Open removal of a calculus from the transplanted kidney is rarely necessary. Complete stone removal is usually possible by standard urologic techniques.

**VASCULAR COMPLICATIONS**

Vascular complications including vessel thrombosis or stenosis have been reported in 2% to 12% of all renal transplants. Vascular complications in general are significantly associated with ATN and graft loss. Early graft dysfunction should be evaluated for vascular complications with Doppler ultrasound (114). Patients with underlying thrombophilia are at a higher risk for early allograft loss without appropriate anticoagulation. Screening for thrombophilia in those ESRD patients with a history of a thromboembolic event may be appropriate to prevent this complication. Those patients with graft loss due to vascular thrombosis in the absence of an obvious technical problem should undergo a thrombophilia evaluation before retransplant (115).

**LYMHOCELE**

A lymphocele is a collection of lymphatic fluid around the allografted kidney that can occur due to leakage of small lymphatic channels around the iliac vessels at the time of the transplant. The incidence of lymphoceles has been reported from as low as 0.02% up to 26% following renal transplant (116–118). Consequences of lymphoceles can include distention due to the fluid collection as well as venous or ureteral obstruction and graft compromise. Treatment of lymphoceles can include percutaneous techniques with drainage and sclerosis of the cavity or may include operative marsupialization via the laparoscopic or open technique. Laparoscopic techniques are less invasive, have less morbidity, and are generally the first line of therapy (118).

**POSTTRANSPLANT MALIGNANCIES**

Prolonged and intensive immunosuppression impairs the ability of the body to cope with cancers caused by carcinogens such as sunlight or oncogenic viruses, and may lead to the development of an unusual assortment of malignancies (119,120). Infections with potentially oncogenic viruses are common in immunosuppressed patients, including EBV-related B-cell PTLD, human papillomavirus, hepatitis B and C viruses—related hepatocellular carcinoma, and the human herpes virus 8 (Kaposi sarcoma) (120). Malignancies that occur in transplant recipients have a pattern that is very different from that of the general population. The frequency of the cancers that are common in the general population, such as carcinomas of the lung, prostate, breast, and colon, and invasive carcinomas of the uterine cervix, are not increased among transplant recipients (119). Most patients who develop malignancies posttransplant have received multiple immunosuppressive drugs and no single agent can be implicated. The natural history of tumors associated with immunosuppression used for renal transplantation may be more aggressive than would be expected in patients without immunosuppression or transplantation. Cancers of the lip and skin are the most common malignancies. In contrast to the general population,
Key Points

- Increasing numbers of patients are living with ESRD on renal replacement therapy.
- Renal transplantation is the most effective and cost-effective option for patients with ESRD, but is limited by the number of available kidneys for transplant.
- Immediate posttransplant care involves careful management of fluids and electrolytes in patients who frequently have multiple underlying medical comorbidities.
- Management of renal transplant patients is a balance between preventing acute/chronic rejection with use of immunosuppression and avoiding complications such as infection and malignancy with long-term use of these medications.

References


