5 Management of the successful solid organ transplant recipient

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Advances in early medical and surgical care of solid organ transplant recipients, and especially development of newer immunosuppressive drugs, have resulted in improved long-term patient and graft survival. Transplant recipients generally are followed closely by the transplant center in the early months after transplantation. Although the successful transplant recipient is in most cases "wedded" to the transplant center, a greater part of the long-term management of the patient falls upon non-transplant specialists and primary care physicians. These providers will be managing a growing number of transplant recipients and, often in consultation with the transplant center, will be responsible for managing transplant-related problems as well as overall primary care of the patient. Familiarity with common problems of organ transplant recipients is essential for the appropriate long-term care of these patients. Other chapters in this text provide overviews of management and follow-up of organ-specific issues. As discussed in these chapters, a major cause of graft loss is patient death, mostly as a result of cardiovascular events, infections, and cancer. Transplant recipients face an increased risk of morbidity from these problems partly as a result of side effects of long-term immunosuppressive drugs, so long-term management must include steps to decrease the risk and minimize the impact of these problems. The patient's transplant status and long-term immunosuppression may also impact routine primary care issues and standard recommended algorithms.

The timing of transferring a transplant recipient from the transplant center back to the referring physician and/or primary provider varies between transplant centers. In general, patients tend to be closely managed by the transplant center for at least 3–12 months. Most transplant centers provide a template for recommended laboratory monitoring and follow-up visits, but there is no single standard of practice. The most complete recommendations for transplant follow-up have been proposed for kidney transplant recipients. In 2000, the American Society of Transplantation (AST) published guidelines for early and long-term care of renal transplant recipients. In 2002, the European Renal Association published guidelines for follow-up of kidney transplant recipients beyond the first post-transplant year. International guidelines for the care of the kidney transplant recipient have just been published by the Kidney Disease: Improving Global Outcome (KDIGO) group. The goal of these guidelines is to help improve long-term outcomes of kidney transplant recipients and their allografts while minimizing complications. Standardized guidelines are not as well developed for recipients of other solid organ transplants, but existing guidelines for care of kidney transplant recipients provide a reasonable template for the care of these other patients. The AST's recommended frequency of and rationale for outpatient follow-up of renal transplant recipients are outlined in Table 5.1.

Early follow-up of transplant recipients emphasizes surveillance of allograft function, side effects of anti-rejection drugs, and complications of infectious

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Table 5.1 Recommended frequency and timing of outpatient visits for kidney transplant recipients

Time after transplantation	Interval for routine visits and laboratory monitoring[a]	Rationale
First 30 days	Two to three visits per week	Screen for acute rejection (high risk), postoperative complications, and adverse effects of immunosuppressive medications
1–3 months	Once per week (children) Every 1–3 weeks (adults)	Screen for acute rejection (high risk), opportunistic infections, adverse effects of immunosuppressive medications, and adherence (especially children)
4–12 months	Every 2–4 weeks (children) Every 4–8 weeks (adults)	Screen for acute rejection (moderate risk), opportunistic infections, adverse effects of immunosuppressive medications, adherence (especially children), and growth and development (children)
>12 months	Every month (children), every 2–4 months (adults)	Screen for graft dysfunction
	Every 3–6 months	Screen for graft dysfunction, cardiovascular disease risk, cancer, adverse effects of immunosuppressive medications, general health maintenance, adherence, and growth and development (children)

[a]Visits may be for laboratory tests only or may include contact with transplant nurses, coordinators, and/or physicians, as deemed necessary by either the patient or caregivers.
Adapted from Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. *J Am Soc Nephrol* 2000;**11**:S1–86.

diseases. Beyond 1 year, stability of graft function remains a primary concern, although the causes of acute and chronic graft dysfunction become more varied. Long-term transplant recipients with stable graft function remain at risk for medical complications, often related to chronic immunosuppression. Such complications may contribute to ongoing morbidity, mortality, and impaired quality of life. Table 5.2 outlines common problems encountered in transplant recipients as well as primary care management issues important in this group of patients. It is probably fair to say that the state of chronic immunosuppression and side effects of anti-rejection drugs are responsible for the lion's share of post-transplant problems, sometimes magnifying pre-existing disorders. The primary care provider will generally play the major role in managing stable transplant recipients beyond the first post-transplant year, whereas the transplant center may play a supporting role, seeing patients as infrequently as once a year. However, optimal management of these transplant recipients requires effective communication between the community physician and the transplant center. Table 5.3 lists those situations that require the specialized expertise of the transplant center.

Common symptoms or abnormalities occurring in transplant recipients

Cosmetic issues

Cosmetic problems resulting from immunosuppressive drugs occur commonly in transplant recipients. Chronic use of corticosteroids can cause a cushingoid appearance and dermatologic alterations, including acne. Weight gain is common, usually blamed on steroids, and is discussed later. These complaints can respond to steroid minimization, but this should be done in concert with the transplant center to avoid risking rejection of the graft. Acne usually responds to topical agents such as benzoyl peroxide or antibiotic therapy. Topical erythromycin or clindamycin, or systemic erythromycin, has been used with good results. Systemic macrolide antibiotics interact with the metabolism of the calcineurin inhibitors, so alternative therapy may be preferable. Patients with severe acne may benefit from evaluation by a dermatologist. Acne may be more common with use of cyclosporine than with tacrolimus. Rarely, severe acne has been reported with use of rapamycin and can respond to withdrawal of the drug.

Table 5.2 Common medical problems present in transplant recipients and monitoring recommendation for primary care issue

Cardiovascular problems	
Increased risk of coronary artery disease and cardiac dysfunction	Attention to modifiable risk factors
	Importance of smoking cessation
Increased risk of peripheral vascular disease	Periodic screening tests in high risk patients (e.g., cardiac stress test with nuclear imaging or stress echo)
Hypertension	
Increased infection risk	
	Fever in transplant recipients requires consideration of wide differential of etiology; regular dental care
Increased cancer risk	
Lymphoma	Patients require regular dermatologic and gynecologic screening
Squamous and basal cell carcinoma	Periodic laboratory testing for screening
Cervical and vulvar carcinoma	
Metabolic disorders	
Hyperlipidemia	Drug interactions with lipid-lowering drugs
Obesity	Monitor body mass index, diet, and exercise
New-onset diabetes	
Hyperuricemia	
Hyperkalemia	
Hypomagnesemia	
Hypophosphatemia	
Hematologic abnormalities	
Anemia	May require consultation with transplant center to rule out infection, decide on adjustment of immunosuppressive drugs
Leukopenia	
Thrombocytopenia	
Chronic kidney disease	
	Monitor kidney function and screen for proteinuria; may benefit by referral to nephrology
Metabolic bone disease	
Osteoporosis	Screen high-risk patients for decreased bone density
Avascular necrosis	May be ongoing problem in former end-stage renal disease patients; screen for vitamin D deficiency
Hyperparathyroidism	
Cosmetic problems	
	May benefit from adjustment of immunosuppression in consultation with transplant center
Pregnancy	
	Discuss use of contraceptive measures; desire for pregnancy should be discussed
Depression	
	Screening and consideration for treatment with transplant center
Non-adherence to medications	
	Regular assessment of adherence
Drug interactions	
	Educate patient re discussing initiation of new medications with primary physician knowledgeable with interactions

Table 5.3 Situations requiring consultation with the transplant center

Major changes in the immunosuppressive drug regimen
Difficulty with medication insurance coverage; nearing 36 months after transplantation in a patient not eligible for continued Medicare coverage
Patient non-adherence to immunosuppressive drug therapy
Suspicion of acute or chronic allograft rejection; acute or chronic dysfunction of the graft not explained
Suspected or diagnosed cancer
Unremitting or unexplained febrile illness
Swelling or pain of a renal graft; gross hematuria or new-onset proteinuria
Unexplained or persistent leucopenia or thrombocytopenia
Acute hospitalization
Renal transplant recipient returning to dialysis or to be considered for another transplantation
Patient enrolled in a clinical trial

Adapted from Howard AD. Long-term posttransplantation care: the expanding role of community nephrologists. *Am J Kidney Dis* 2006;**47**(4 suppl 2):S111–24.

Cosmetic complaints attributable to the calcineurin inhibitors (CNIs) are also common. Cyclosporine can cause hirsutism which can be particularly troublesome to female patients. Usually this problem can be managed by periodic hair removal or bleaching. Conversely, some patients on tacrolimus complain of hair loss. In most patients this abates over time, but, in an occasional patient, alopecia may be severe. The use of mycophenolic acid derivatives may contribute to hair loss. Cyclosporine use is also associated with gingival hyperplasia which is occasionally severe, interfering with oral intake or increasing the risk of oral infections. This problem appears to be more pronounced in patients taking non-dihydropyridine calcium channel blockers or phenytoin. These drugs should be discontinued or changed to alternative therapy if possible. Some patients benefit from chronic antibiotic therapy to reduce gum inflammation, but, in severe cases, gingivectomy may be required. Switching from cyclosporine to tacrolimus is often effective, but should be done under the direction of the transplant center.

Case

A 50-year-old man with end-stage liver disease resulting from hepatitis C received a deceased donor liver transplant 1 year earlier. Maintenance immunosuppression included cyclosporine, prednisone, and mycophenolate mofetil. His hypertension was well controlled on metoprolol, nifedipine, and furosemide. In the past 6 months he developed bleeding gums. Examination revealed severe gingival hyperplasia. Nifedipine was discontinued but there was no improvement 2 months later. After consultation with the patient's transplant center, tacrolimus was begun as a substitute for cyclosporine. Over the next 4 months, the gingival hyperplasia resolved.

Hematologic abnormalities

Disorders of red blood cells

Anemia is probably more common in renal transplant recipients than in other solid organ transplant recipients because there is not infrequently an element of renal dysfunction and defective erythropoeitin production. A significant proportion of these patients may be iron deficient, especially in the early post-transplant period, and may require iron supplementation. Beyond the first post-transplant year, 20–30% of patients remain anemic from some combination of impaired renal function, impaired erythropoeitin production, and/or the effects of antiproliferative immunosuppressants (i.e., target of rapamycin [TOR]

inhibitors, mycophenolic acid derivatives, and azathioprine) that directly effect proliferation of red cell precursors or impair the action of erythropoeitin. Correction of anemia theoretically may improve the patient's quality of life and reduce cardiovascular risk.

Anemia is also not uncommon in non-renal transplant recipients, and is particularly prevalent in the presence of renal impairment. Anemia has been associated with the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), but has mainly been reported in renal transplant recipients. This effect appears to be due to an inhibitory effect of these drugs on erythroid precursors. Aplastic anemia due to parvovirus B19 infection has been reported and can respond to intravenous immunoglobulin infusion. Polymerase chain reaction (PCR) testing of the serum or bone marrow for parvovirus DNA is usually required to make the diagnosis. An uncommon cause of anemia, usually associated with thrombocytopenia as well, is the hemolytic–uremic syndrome which rarely complicates the use of CNIs and possibly sirolimus.

Key points 5.1 Causes of anemia in solid organ transplantation

Impaired renal function

Iron deficiency

Antiproliferative immunosuppressants

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

Parvovirus infection

A reported 10–20% of renal transplant recipients may manifest polycythemia or post-transplant erythrocytosis (PTE), usually defined by a hematocrit >51%, Secondary causes such as chronic lung disease, sleep apnea, or stenosis of the renal transplant artery or native renal mass should be excluded. The mechanisms for PTE, although not completely defined, may be related to increased sensitivity of red cell precursors to erythropoietin, possibly involving angiotensin receptors on these cells. Treatment may be required if the patient has symptoms such as malaise, lethargy, or headache, and to avoid thromboembolic events, which can occur in up to 30% of patients. PTE often responds to treatment with ACEIs or ARBs. Those patients who do not respond to these medications may require intermittent phlebotomy. In some patients PTE resolves spontaneously. Treatment should be considered if the hematocrit is consistently >55%.

Leukopenia and thrombocytopenia

Leukopenia and thrombocytopenia seen in transplant recipients are most often drug related. The antiproliferative agents can all affect cell lines, and significant leukopenia or thrombocytopenia may necessitate dose reduction or, sometimes, temporary or even permanent discontinuation of these drugs. Many other drugs commonly administered to transplant recipients can contribute to leukopenia and thrombocytopenia. Some of the anti-lymphocyte antibodies administered as induction therapy or for treatment of acute rejection (e.g., rabbit antithymocyte globulin, OKT3, alemtuzumab) result in lymphopenia that can persist for many months or years. Leukopenia is common with antiviral drugs such as ganciclovir or valganciclovir, and may mandate reduction in dose. Many other antimicrobial drugs, including trimethoprim–sulfamethoxazole, can lower white blood cell or platelet counts idiosyncratically. Finally, leukopenia or pancytopenia may occur in the setting of viral infections, especially infection with cytomegalovirus (CMV). Evaluation of persistent leukopenia or thrombocytopenia of unclear etiology may require extensive infectious disease and hematologic evaluations, possibly including bone marrow biopsy, cultures, or radiologic imaging studies to exclude occult opportunistic infection or hematologic malignancy.

Case

A 40-year-old woman received a kidney transplant from a deceased donor 1 month earlier. She had a 5-day course of rabbit anti-thymocyte globulin followed by maintenance therapy with tacrolimus, and mycophenolate mofetil. She exhibited immediate allograft function and steroids were stopped on postoperative day 5. Before transplantation, the patient tested negative for antibodies to CMV, but the donor was positive, and a 6-month course of valganciclovir (900 mg/day) was prescribed. Routine laboratory test performed 6 weeks after transplantation showed a white blood cell count (WBC) of

1100/mm^3 and a chart review showed that there had been a gradual decline in the count during the previous 3 weeks. Valganciclovir was temporarily held. Three days later, the WBC count was 1600/mm^3. Mycophenolate dose was decreased from 1000 mg twice daily to 750 mg twice daily. Four days later, WBC the increased to 2600/mm^3. Valganciclovir was renewed at a dose of 450 mg/day.

Adjustments in immunosuppression medications for leukopenia or thrombocytopenia should be done in consultation with the transplant center. Drug-related blood dyscrasias may take several weeks to improve despite adjustment or discontinuation of the putative drug. Severe neutropenia as defined by an absolute neutrophil count of <1000/mm^3 can increase the risk of bacteremia and granulocyte colony-stimulating factor (G-CSF) may be beneficial on a short-term basis.

Gastrointestinal problems

Most transplant centers have adopted protocols that include the use of histamine blockers (H_2-receptor blocker) or proton-pump inhibitors (PPIs) to prevent upper gastrointestinal complications (e.g., peptic ulcers or gastric erosions) in the early post-transplant period, particularly in patients treated with high doses of corticosteroids in the perioperative period. Patients on chronic low-dose steroids (e.g., <10 mg/day) should have a lower risk of upper gastrointestinal complications, so that these prophylactic drugs are often discontinued weeks or months later when the steroids have been tapered. Complaints of dyspepsia are often initially managed by switching to a PPI if the patient is on an H_2-receptor blocker, or increasing the dosage of the PPI. Persistent symptoms of dyspepsia should prompt further investigation such as upper endoscopy and search for specific etiologies, including infectious forms of esophagitis or gastritis resulting from *Candida* spp., CMV, or other herpesviruses.

Diarrhea can occur in as many as 50% of transplant recipients. Anti-rejection drugs such as the mycophenolic acid derivatives and tacrolimus are often causative agents. Patients may be taking oral magnesium or phosphorous supplements which can contribute to this problem as well. For the most part, diarrhea is mild and transient. Persistent symptoms usually respond to drug dosage modification. Diarrhea can be caused by elevated serum levels of tacrolimus, and conversely the shorter gastrointestinal transit time in the presence of diarrhea can decrease enteric metabolism of the drug and raise serum levels. Diarrhea in transplant recipients receiving mycophenolic acid derivatives can occasionally be associated with histologic alterations in the colonic mucosa and sometimes resemble those seen in Crohn's disease.

Despite the significant association of diarrhea with certain drugs, these patients should also undergo evaluation for possible infectious etiologies. Table 5.4 lists potential infectious etiologies for diarrhea as well as the diagnostic tests required. Figure 5.1 shows an algorithm for diagnosis and management of diarrhea in transplant recipients derived from the DIDACT study by Maes et al. (see Further reading). Using this schema, this group was able to determine the specific etiology of diarrhea and to provide a cure in approximately 85% of patients. Notably, this approach is based on the premise that reduction of immunosuppression may increase the risk of graft rejection so that other etiologies should be considered and treated before lowering the doses of suspected immunosuppressants. In practice, this algorithm is sometimes reversed with empiric reduction of mycophenolic acid derivatives. Using this practice, further studies should be entertained if diarrhea does not resolve. Moreover, efforts should be made to titrate the dose of immunosuppressants back to baseline once the diarrhea resolves.

Case

A 35-year-old man with type 1 diabetes mellitus received a live donor kidney transplant from his wife 10 years ago. His allograft function had been excellent with a baseline serum creatinine concentration of 1.2 mg/dL. Maintenance immunosuppression consisted of tacrolimus, enteric-coated mycophenolic acid, and alternate-day prednisone. The patient had severe gastroparesis, and 3 weeks ago his primary care physician prescribed erythromycin in an effort to improve gastric emptying. He called his transplant center requesting a second opinion about management of nausea and vomiting. Routine blood tests revealed: blood urea nitrogen (BUN) 65 mg/dL, serum creatinine 4.8 mg/dL, and trough FK506 level 31 ng/mL (target levels had been 5–8 ng/mL). Tacrolimus and erythromycin were both discontinued and serum creatinine returned to baseline within 5 days.

Table 5.4 Potential infectious causes of diarrhea in immunosuppressed transplant recipients

Organism	Diagnostic test
Bacterial	
Salmonella spp.	Stool for expanded enteric pathogens culture
Shigella spp.	
E. coli	
Vibrio spp.	
Aeromonas spp.	
Camphylobacter spp.	
Mycobacterium complex	Acid-fast bacilli culture
Clostridium difficile toxin	Send stool for toxin detection
Viral	
Cytomegalovirus	Serum viral polymerase chain reaction
Adenovirus	
Enterovirus	Stool shedding may not be pathogenic; may require colonic biopsy to document tissue invasion
Rotavirus	
Parasitic	
Isospora belli	Stool for ova and parasites
Cryptosporidia	May require more than one specimen for diagnosis
Microsporidia	Cryptosporidia, microsporidia, *Isospora* spp. require specific orders
Pneumocystis jiroveci	
Balantidium coli	
Giardia spp.	Antigen testing
Fungal	
Candida spp.	Stool culture and direct exam
Cryptococci	
Aspergillus spp.	

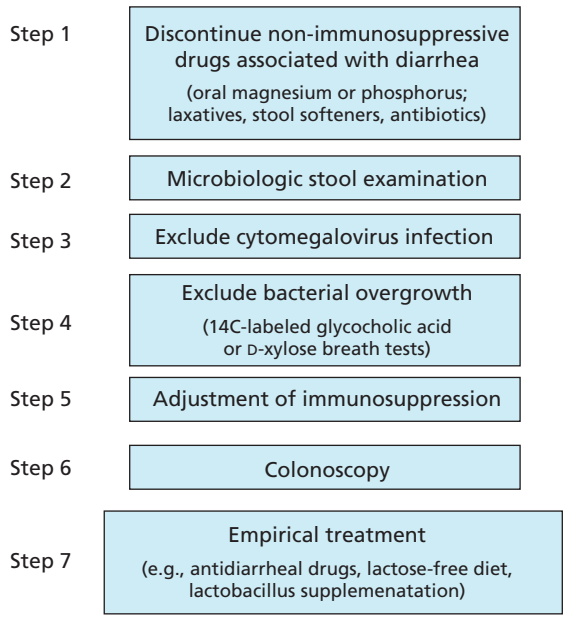


Figure 5.1 Diagnostic flowchart for evaluation of causative factor of severe diarrhea in transplant recipients. (Adapted with permission from Maes B, Haday K, de Moor B, et al. Severe diarrhea in renal transplant patients: Results of the DIDACT study. *Am J Transplant* 2006;**6**:1466–72.)

Fever

The cause of a fever in an immunosuppressed patient may not be readily evident and may present a diagnostic puzzle. Infections are the most common cause of fever in these patients, but common infections may present in an atypical fashion so these patients are at higher risk for atypical or opportunistic infections. Sometimes, neoplasms such as lymphoma can present as fever of unknown origin. A careful physical examination and detailed laboratory and radiologic evaluation are often necessary to correctly diagnose and manage the patient. A standardized approach to evaluation of the persistently febrile transplant recipient is essential. Blood and urine cultures should be performed and a chest radiograph should be obtained even if there are no significant pulmonary symptoms. Obtaining a urinalysis and urine culture is especially important in kidney transplant recipients because graft pyelonephritis may be present without localizing symptoms. Stool studies or nasal and throat cultures may be helpful if symptoms are present. Additional radiologic studies such as sinus radiographs, and chest and/or abdominal computed tomography (CT) can be done if there are localizing symptoms or if unexplained fever persists. Viral studies, especially for CMV or Epstein–Barr virus (EBV) infection should always be considered. Patients can manifest common community acquired infections; however, lack of

clinical response to initial empiric treatment will likely require more intensive evaluation, as discussed in great detail in Chapter 4.

Common metabolic abnormalities

Hyperuricemia and gout

Hyperuricemia is a common metabolic problem in transplant recipients and often results from the use of CNIs that impair renal uric acid secretion. Tacrolimus may be associated with less risk of hyperuricemia than cyclosporine. Impaired renal function, use of diuretics, and the metabolic syndrome can contribute to this problem. Gout has been reported in as many as 10–20% of transplant recipients, can cause significant disability and impaired quality of life, and again is more common in patients receiving cyclosporine than in those receiving tacrolimus. Attention to diet is important but may not be sufficient to significantly reduce hyperuricemia. Allopurinol can be effective, but should not be used in conjunction with azathioprine because of bone marrow suppression. Allopurinol can be used safely with the mycophenolic acid derivatives. Some antihypertensive drugs, namely amlodipine and losartan, are reported to have a uricosuric effect that may be helpful in some patients. Acute gouty flares can respond to increased doses of oral steroids or colchicine. Colchicine may be poorly tolerated due to the increased likelihood of diarrhea when used with immunosuppressant drugs. In addition, metabolic interactions between colchicine and immunosuppressant drugs, in particular cyclosporine, can increase the risk of other symptoms of drug toxicity due to colchicine such as myopathy. Due to their deleterious effects on intrarenal hemodynamics, nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided, especially in renal transplant recipients or non-renal transplant recipients with impaired renal function. However, if there is nothing else that relieves the pain, a short-course NSAID may be used while monitoring kidney function and blood pressure.

Electrolyte abnormalities

Electrolyte imbalances are common in solid organ transplant recipients. In kidney recipients, they are often related to renal tubular dysfunctions that reflect expected abnormalities in a transplanted kidney, compounded by some effects of immunosuppressants. Both tacrolimus and cyclosporine can cause impairment of potassium secretion in the distal tubule similar to that seen in type IV renal tubular acidosis. These patients are commonly on other drugs (e.g., ACEIs, ARBs, β blockers) that also can cause elevated serum potassium via a variety of mechanisms. Clinically significant hyperkalemia usually responds to dietary potassium restriction, drug dosage modification or discontinuation. The addition of diuretics or use of the exchange resin, Kayexalate, may be helpful. Kayexalate should be used cautiously in patients with significant gastrointestinal problems such as motility disorders. Florinef is sometimes used to manage persistent hyperkalemia, but may exacerbate pre-existing hypertension or cause symptomatic extracellular volume excess. Moreover, the long-term effects of using an aldosterone agonist on the myocardium and kidney are not known, but there is concern that such agents could promote cardiac hypertrophy or fibrosis in both organs.

Proximal tubular dysfunction can lead to urinary magnesium and phosphorus wasting. manifesting as hypomagnesemia or hypophosphatemia. Renal magnesium wasting is a side effect of the CNIs perhaps as a result of drug-induced decreases in the apical membrane channel that regulates magnesium uptake. Hypophosphatemia is most typically observed in kidney transplant recipients early after transplantation. It is most often seen in patients with rapid normalization of the glomerular filtration rate, and may result as a consequence of persistently elevated levels of parathyroid hormone or other phosphatonins such as FGF-23. Correcting low serum phosphorus through increased dietary intake is generally much easier than correcting hypomagnesemia. Oral replacement of either electrolyte can be limited by diarrhea.

Hyperlipidemia

Immunosuppressive drugs frequently contribute to dyslipidemia. Transplant recipients treated with CNIs and corticosteroids often have adverse risk lipid profiles with elevated concentrations of low-density lipoproteins (LDLs) and reduced concentrations of high-density lipoproteins (HDLs). Sirolimus can cause moderate-to-severe hypercholesterolemia and hypertriglyceridemia. Hyperlipidemia may contribute to the elevated cardiovascular risk profile already present

in many transplant recipients. Numerous studies have shown that lipid-lowering drugs can be effective in improving abnormal lipid profiles with an acceptable safety profile.

The majority of studies examining lipid-lowering therapy in transplant recipients use hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or "statins," as the therapeutic agent. All statins appear to be effective in lowering LDLs and total cholesterol (TC) and there is little evidence to support recommending one over another. Each of atorvastatin, simvastatin, pravastatin, and fluvastatin has been used in studies of kidney transplant recipients. In general, these agents can decrease TC by 20–30%, and LDL-cholesterol by 35–40%. They are less effective in raising HDL-cholesterol or for treating hypertriglyceridemia, although atorvastatin may have some effect in lowering triglycerides. Recently, in a large, multicenter, randomized, placebo control trial (ALERT study), fluvastatin effectively lowered LDL-cholesterol to a goal of <100 mg/dL, but more importantly demonstrated a 30% decreased risk in fatal and non-fatal cardiac events.

Small short-term studies in liver transplant recipients have demonstrated the efficacy and relative safety of using statins in this population. However, long-term outcome studies in liver transplant recipients are lacking. The use of these drugs in liver patients may be more problematic in the presence of liver allograft dysfunction. The benefit of lipid-lowering therapy has been better defined in cardiac transplantation. In this setting, early use of statins after transplantation has been shown to be effective in controlling hyperlipidemia and decreasing the risk of cardiac allograft vasculopathy. Specifically, pravastatin and simvastatin have been used to this end in randomized trials, and an approximately 20% difference in 4-year survival rate has been shown in patients who received statins. Rates of cardiac allograft vasculopathy were nearly half those of non-treated patients. Cardiac allograft vasculopathy is now recognized to be a manifestation of chronic rejection, and it is believed that statins may be acting by immunomodulatory effects separate from their lipid-lowering effects. The statins may have beneficial effects on mediators that improve endothelial function or that suppress cytokine and natural killer cell activation. Indeed, older studies suggested that the statins exert an immunosuppressive effect in heart and lung transplant recipients. Evidence that statins have similar effects in other organ transplant recipients is lacking.

Certain safety issues should be considered when using statins or other lipid-lowering drugs in transplant recipients (Table 5.5). Hepatic metabolism and excretion of statins are affected by concurrent use of CNIs, thereby increasing the risk of rhabdomyolysis, a rare complication in the general population. This interaction can dramatically increase the blood levels of the statins, whereas converse changes in CNI metabolism in general are not clinically significant. When statins are prescribed to transplant recipients, the lowest dose possible should be used to initiate therapy. One must also be cognizant of other drugs (verapamil, azole antifungals, macrolides, proteinase inhibitors used for HIV infection) that can increase CNI levels and further magnify the risk of statin-induced rhabdomyolysis or liver toxicity. These adverse effects do not necessarily occur early in the course of therapy, and may occur after the drug has been used for a prolonged period. Individual statins may differ with respect to the risk of adverse effects. The extent to which metabolism is affected also varies among the available agents.

Atorvastatin, pravastatin, and fluvastatin appear to be the least myotoxic. Liver function tests and transaminases should be monitored while the patient is on the drug. In the setting of cardiac transplantation, in which statin use is more universal, it has been recommended that creatine phosphokinase (CPK) levels be monitored, even in the absence of symptoms, every 2–3 months after the transplantation, especially when the drug is titrated. In the absence of symptoms, elevations of CPK more than five times the upper limit of normal warrant discontinuation of the drug for some period of time. Less severe elevations warrant consideration of decreasing the dosage of the drug, stopping it, or changing to a different statin that is less likely to have this effect. Whenever a patient presents with significant new muscular complaints, the statin should be stopped at least temporarily and the CPK measured. Fibrates also may cause myotoxicity, most often when they are used in combination with a statin. Fibrates as well as omega-3 fatty acids are generally more effective in controlling hypertriglyceridemia. Cholestyramine may interfere with gastrointestinal absorption of immunosuppressive drugs, although the clinical impact of this appears to be low.

Table 5.5 Use of lipid-lowering drugs in transplant recipients

Type of lipid-lowering drug	Cytochrome P450 3A4 interaction	Dosage adjustment for renal function	Recommended initial daily dosing in mg	Special considerations in transplant recipients
Statins				Higher risk of myositis and rhabdomyolysis when used with CNI
Lovastatin (Mevacor)	Yes	Yes	10–20	
Simvastatin (Zocor)	Yes	Yes	5–10	
Pravastatin (Pravachol)	No	Yes[a]	10	
Atorvastatin (Lipitor)	Yes		5–10	
Fluvastatin (Lescol)	No		10–20	
Rosuvastatin (Crestor)	No		5–10	
Fibric acid derivatives				Increased risk of rhabdomyolysis when used in combination with statins (particularly with gemfibrozil)
Gemfibrozil (Lopid)	Inconsistent inhibition of other CYP isoenzymes	Yes[b]	600	
Fenofibrate (Tricor)		Yes	67	
Bezafibrate		Yes	200	
Clofibrate		Yes	500	
Ciprofibrate		Unknown	200	
Bile acid sequestrants	N/A	N/A		May exacerbate GI complaints due to other required transplant drugs; may interfere with GI absorption of immunosuppressive medications
Cholestyramine (Questran)			4–24 g/day	
Colestipol (Colestid)			5–30 g/day	
Nicotinic acid	None	Significant renal clearance	50–100 mg two to three times a day	Potentiates risk of myopathy when used with statins
Omega-3 fatty acids (fish oil)	None	None	Most studies have used 6–9 g/day	May cause GI upset; most report fishy aftertaste; can inhibit platelet function and increase risk of bleeding; can increase LDL and worsen DM control

[a]Dose reduction recommended for severe renal dysfunction with estimated creatinine clearance of <30 mL/min per 1.73 m^2.
[b]Use of fibrates should be avoided for glomerular filtration rate <15 mL/min per 1.73 m^2.
CNI, calcineurin inhibitor; CYP, cytochrome P450; DM, diabetes mellitus; GI, gastrointestinal; LDL, low-density lipoprotein.

Obesity

Weight gain leading to obesity is a common problem after solid organ transplantation. Corticosteroid use as part of the immunosuppression protocol has usually been viewed as the culprit, but, with the current widespread use of steroid-free regimens, it has become evident that significant weight gain can occur, even with complete avoidance of steroids. Whether other anti-rejection drugs contribute to weight gain is not clear. Improved appetite due to an improved sense of well-being after transplantation is a likely factor. Patients who are overweight pretransplantation have a higher risk of weight gain post-transplantation. Excessive weight gain increases the risk for post-transplant diabetes mellitus (PTDM), hypertension, and hyperlipidemia, thus contributing to overall cardiovascular risk. Despite well-defined adverse metabolic and cardiovascular complications related to obesity, the existing literature is conflicted as to whether obesity impacts transplant graft function and patient survival. Reports of the effect of obesity in renal transplant recipients are fairly evenly split in supporting or not supporting a negative effect on patient and graft survival. An unequivocal negative effect has not been demonstrated in other solid organ recipients, apart from the possible complication of hepatosteatosis in liver transplant recipients and insulin resistance with the development type 2 diabetes mellitus in pancreas transplant recipients.

Successful treatment or avoidance of obesity in the transplant recipient can be challenging, as it is in the general population. Weight loss interventions have not been well studied in the transplant population. Some centers have reported that intensive and individualized dietary advice in the early post-transplant period is successful in preventing subsequent weight gain. Dietary management and establishment of a regular exercise program should receive continued emphasis in the ongoing care of these patients. Effective medications to aid with weight loss are limited. Pharmacologic agents that interfere with fat absorption as a means to lose weight, such as orlistat, have been used with some success in the transplant setting. Unfortunately the resulting fat malabsorption can interfere significantly with the gastrointestinal absorption of many anti-rejection drugs, particularly the CNIs. A significant decrease in the serum levels of these drugs has been reported and in some cases and has precipitated acute rejection. Surgical weight loss procedures, including gastric bypass and gastric banding, have been performed in this population with reported success in many patients. Intestinal bypass procedures resulting in malabsorption would be expected to impact levels and dosages of immunosuppressive drugs.

Post-transplant diabetes mellitus

The development of new-onset type 2 diabetes mellitus has become a significant cause of morbidity in patients after solid organ transplantation. Most patients who develop diabetes mellitus will do so within the first 3 years after transplant, although reports have shown a continued increased incidence for up to 10 years. Up to 10% of patients may require treatment for PTDM in the first year after transplantation. By 10 years, 20% have PTDM and even more patients exhibit impaired glucose tolerance (IGT). Those patients who develop PTDM are at risk for diabetic complications (nephropathy, neuropathy, and retinopathy) in the same time frame expected for people with diabetes in the non-transplant setting. Patients with IGT often manifest this in the setting of metabolic syndrome and, similar to those with overt PTDM, have a higher risk for cardiovascular events as well as for progression to frank diabetes mellitus.

Early reports describing PTDM were flawed by variations in the definition of the disorder, most often based on the need for treatment with insulin. It is now apparent that some patients have less overt abnormalities in glucose metabolism and may be missed by this definition. Therefore, the diagnosis of IGT or diabetes mellitus should be based on criteria outlined by the World Health Organization (WHO).

The increased incidence of abnormal glucose metabolism is associated with the use of the corticosteroids and the CNIs. Both β-cell dysfunction causing impaired insulin release and insulin resistance have been found with the use CNIs. Tacrolimus appears to have a higher diabetogenic effect than cyclosporine. There are some reports showing improved glucose metabolism in patients with PTDM who were switched from tacrolimus to cyclosporine. The incidence of PTDM may be decreased with steroid avoidance or early steroid withdrawal. Late steroid withdrawal appears to be less helpful. In some patients, hyperglycemia is transient and associated

only with higher steroid dosages used at the time of the transplantation or for treatment of rejection. Factors that increase the risk of PTDM include older age, obesity, significant weight gain after transplantation, family history of type 2 diabetes mellitus, a history pregnancy-induced diabetes, and African–American or Hispanic ethnicity. There is also greater association of PTDM with chronic hepatitis C infection and, in some reports, adult polycystic kidney disease.

Key points 5.2 Risk factors for new-onset diabetes mellitus after transplantation

Older age

Obesity

African-American or Hispanic ethnicity

Family history of diabetes mellitus

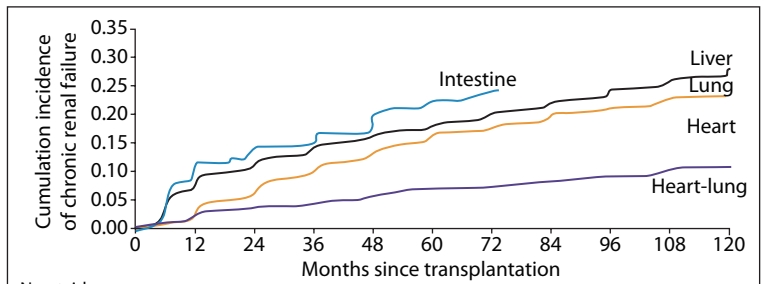
Recent guidelines have recommended screening for abnormal glucose metabolism once weekly for the first month after transplantation using fasting plasma glucose (FPG) and at 3, 6, and 12 months thereafter. Impaired FPG can be further evaluated by an oral glucose tolerance test (OGTT). Measurement of glycated hemoglobin (HbA1c) is generally not useful in the early post-transplant setting because anemia and the high red blood cell turnover typically occur early after transplantation. It is of more use in the ongoing monitoring and treatment of chronic PTDM. The diagnosis of PTDM should lead to treatment. Non-pharmacologic therapy including dietary modification, exercise, and weight loss should be emphasized initially. This is equally important in those with IGT. Even moderate amounts of weight loss can significantly improve glucose tolerance.

All oral hypoglycemic agents have been found to be safe and effective in the treatment of PTDM. However, use of metformin can be limited by impairment of renal function. Many patients with PTDM require insulin therapy. There may be a role for reassessing the immunosuppressive drug regimen in patients with PTDM or IGT, but this should be done only in close concert with the transplant center to avoid precipitating graft dysfunction due to inadequate immunosuppression. Corticosteroid and CNI dosages should be minimized as much as possible. IGT has been shown to be lessened, with lower tacrolimus levels in particular. There may be a role for switching a patient from tacrolimus to cyclosporine or withdrawing the CNI altogether because this has been shown to improve glucose tolerance in some patients, although careful follow-up for the onset of rejection is needed. The goal for treatment is to achieve normal or near-normal glycemia with an HbA1c <7.0%. Less well-controlled PTDM can exacerbate lipid abnormalities and increase the risk of long-term complications. Long-term management of transplant recipients with PTDM should include appropriate screening for retinal complications, neuropathy, and detection of diabetic kidney disease.

Renal disease in transplant recipients

Impairment of renal graft function in kidney transplant recipients has many potential etiologies and can be multifactorial. The evaluation, causes and treatment of renal allograft dysfunction are discussed in Chapter 7. In other solid organ transplant recipients, chronic renal failure after transplantation is becoming an increasing problem, especially as the lifespan of such patients has improved. Chronic nephrotoxicity of CNIs appears to be the major cause of chronic renal failure or chronic kidney disease (CKD), but diabetic nephropathy or glomerulonephritis related to chronic viral hepatitis may also contribute. Among non-renal organ transplant recipients, liver transplant recipients have the highest incidence of CKD, perhaps related to a high rate of renal function abnormalities present before transplantation (including hepatorenal syndrome) and the likely occurrence of hepatitis C-related renal disease in patients who are persistently positive for hepatitis C after transplantation.

Figure 5.2 shows the reported cumulative incidence of CKD in non-renal solid organ transplant recipients in the USA as defined by need for dialysis or a kidney transplant. Among liver transplant recipients, there is an almost 25% incidence of advanced renal failure by 10 years after transplantation. As a group, solid organ transplant recipients who have developed end-stage renal disease (ESRD) represent a growing proportion of the kidney transplant waiting list. In general, these patients appear to do well with kidney transplantation, and prior non-renal transplantation



No. at risk											
Heart-lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,637	12,341	10,022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	3	5	5
Liver	16,849	28,495	24,041	19,508	15,724	12,564	9844	7345	5292	3614	2261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1136	745	468	258	133

Figure 5.2 Cumulative incidence of chronic renal failure among 69 321 people who received non-renal organ transplants in the USA between January 1, 1990 and December 31, 2000. (Used with permission from Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003;**349**:931–40.)

does not exclude them from consideration. As is true in general for patients with ESRD due to primary kidney disease, these patients appear to have better outcomes if they receive a kidney transplant compared with remaining on dialysis.

Solid organ transplant recipients with significant renal function abnormalities should be referred to a nephrologist for evaluation. The presence of significant proteinuria may require a native kidney biopsy to define the cause of kidney disease because this is not typical of CKD due to CNIs. Dosages of CNIs should be minimized as much as possible, but this does not always result in improvement or stabilization of renal function. Conversion from CNIs to sirolimus has met with mixed results and recent evidence indicating that sirolimus can increase urine protein excretion provides a concern in some patients. Non-specific measures such as tight blood pressure control, particularly with the use of ACEIs or ARBs in patients with proteinuria, may be of benefit to slow progression of kidney failure.

Cancer in organ transplant recipients

That transplant recipients are at higher risk for certain cancers, specifically non-melanoma skin cancers, lymphoma, and Kaposi's sarcoma, has been well established. Recently, studies using large established databases, specifically of kidney transplant recipients, have shown that these patients are also at higher risk for many other tumors. The risk of common tumors such as colon, lung, prostate, and breast cancer are roughly twofold higher than that of the general population. The risk for some other tumors is even more pronounced: a threefold increased risk for testicular and bladder cancer and a 15-fold increase in the risk of kidney cancer. Whether other non-renal solid organ transplant recipients are also at higher risk for cancers that have not historically been linked to immunosuppression is not known. It is important to note that dialysis patients waiting on the transplant list also have an elevated risk for development of a variety of neoplasms, suggesting that "uremia" itself may impart a risk of cancer. For kidney transplant recipients, it has been estimated that cancer risk is equivalent to non-transplanted individuals who are 20–30 years older. These findings raise important questions about whether standard guidelines for cancer screening and prevention apply to the transplant population. To say the least, the role of screening for malignancy in transplant recipients is a matter of controversy. It is generally accepted that transplant recipients should receive cancer screening appropriate for age and genetic or hereditary risk factors as outlined by the American Cancer Society. However, in individual cases, the benefit of the screening procedure must be weighed against the cost and considered in the context of the patient's overall life expectancy.

Transplant candidates with pre-existing malignancies require a disease-free waiting period before undergoing transplantation to minimize the risk of future recurrence. The length of waiting time varies according to the natural history and recurrence rates of the specific tumor. This issue is more fully discussed in Chapters 7 and 10. A major concern in these

patients is that immunosuppression may increase the risk of recurrence by affecting the growth of residual tumor or previously dormant metastases. Although there are no extensive data to address this concern, one registry study did suggest a high recurrence rate greater than 26% in cases of bladder cancer, sarcoma, melanoma, and myeloma, and a history of symptomatic renal cell cancer. Moderately elevated rates of recurrence (11–25%) were seen in previous cases of Wilms' tumor, and cancers of the uterus, colon, prostate, and breast. Recurrence rates less than 10% occurred in patients with prior cancers of the cervix, testicles, or thyroid. Incidentally found renal cell cancer and previously treated lymphoma also seem to recur infrequently. Cancers known to be affected by immunosuppression, such as non-melanoma skin cancers and Kaposi's sarcoma, as discussed below, have a significant risk of recurrence. The risk of recurrence in liver transplant recipients previously treated for hepatocellular carcinoma or other hepatobiliary neoplasms is discussed in Chapter 10.

The cancers traditionally associated with the use of immunosuppression are skin cancers, lymphoma, and Kaposi's sarcoma. Increased replication of specific viruses known to be associated with the generation of these tumors may be related to suppression of innate immunity. Human papillomavirus has a strong association with squamous cell carcinoma (SCC), EBV with PTLD, and humanherpes virus 8 (HHV-8) with Kaposi's sarcoma. A guiding principle in the management of these specific tumors as well as any cancer after transplantation is minimization of immunosuppression. This should be done with guidance from the transplant center. Sirolimus is putatively anti-neoplastic and, in some settings, the transplant center may opt to convert a patient to this agent.

Skin cancer

SCC is the most common type of skin cancer seen in transplant recipients. This is a reversal of the pattern seen in the general population, in whom basal cell carcinoma (BCC) is much more common. The risk of a transplant recipient having an SCC has been estimated to be 65–100 times that of the general population. The incidence of SCC increases with duration of time after transplantation and with cumulative immunosuppression. There are reports of a higher incidence of SCC in recipients of heart transplants compared with other organ transplant recipients such as kidneys, but this is probably related to the greater immunosuppression that those patients receive. The highest incidence has been reported in Australia, where 43% of patients develop SCC at 10 years post-transplantation. However, the incidence is still very high in northern climes where skin cancer has occurred in 19% of patients studied in the UK. The occurrence of BCC is also increased, but not as dramatically.

SCCs and BCCs occur in transplant recipients about 30 years earlier than expected for someone in the general population with similar sun exposure. These cancers, especially SCCs, tend to be much more aggressive in transplant recipients, with greater local invasion, higher tendency for multiple locations, and higher risk of recurrence. Metastatic disease in SCC is almost unheard of in the general population, but occurs in 7–8% in transplant recipients. Short-term patient survival is very poor in the presence of metastases disease (1-year survival rate of 39% reported with distant metastases).

Early detection is the key to avoiding complications related to skin cancer. White transplant recipients should undergo a full body skin examination every 1–2 years. Most skin cancers will occur in sun-exposed skin; however, a significant number can involve the trunk. Thus, areas of the body that are normally not exposed need to be examined as well. Patients should be counseled on self-examination, especially if they are at high risk based on previous cancers or actinic keratoses. All patients should be counseled about the risk of sun exposure and the importance of using sunscreen. Use of UVB/UVA sunscreen with a sun protection factor of 15 or greater on all sun-exposed skin on a daily basis is recommended, as is the use of hats and other protective clothing. Not uncommonly, the lips and ears are sites of skin cancer, and these areas may not get adequate protection. White individuals with a history of skin cancer before transplantation are at particularly high risk and should be followed more closely, as should patients who have subsequently developed cancer after their transplant. Non-white recipients are probably at negligible risk and do not require such intensive screening.

If detected early, SCCs and BCCs can generally be treated adequately with local excision. Mohs' micrographic surgery may be required for lesions where tissue conservation is required, such as the face and

scalp. More advanced lesions can require more extensive excision and possibly local node dissection. Premalignant lesions (actinic keratoses) should be treated aggressively. Modalities include cryosurgery, topical 5-fluorouracil, and curettage. Warts are not uncommon in transplant recipients and are sometimes difficult to differentiate from cancers or actinic keratoses, and may require biopsy. In patients with recurrent skin cancers, reduction of immunosuppression should be considered. This should be done together with a transplant center to avoid placing the patient at risk for allograft rejection. The extent to which immunosuppression should be decreased is related to the severity of the cancer and risk of mortality, as well the life-sustaining nature of the transplanted organ. Table 5.6 outlines consensus recommendations for

Table 5.6 Expert consensus on reduction of immunosuppression for specific skin cancer scenarios

Skin cancer scenario[b]	Level of reduction of immunosuppression to consider[a]		
	Kidney allograft	Heart allograft	Liver allograft
1. No history of actinic keratosis or skin cancer	None[c]	None[c]	None[c]
2. History of actinic keratosis (no risk of mortality; marker for increased skin cancer risk in future)	None	None[c]	None[c]
3. History of one or more NMSC per year (negligible risk of mortality, one or fewer minor surgical procedure per year; patients handle this with ease; warning sign of possible future skin cancers)	Mild	None	Mild[c]
4. History of 2–5 NMSCs per year (0·5% risk of mortality over 3 years, minor–moderate surgical procedure two to five times per year; patients can usually handle this, but it starts to bother them; likelihood of numerous future skin cancers)	Mild[c]	Mild	Mild
5. History of 6–10 NMSCs per year (1% risk of mortality over 3 years, minor–moderate surgical procedure 6–10 times per year; patients can usually handle this, but it bothers them; high likelihood of numerous future skin cancers)	Mild[c]	Mild[c]	Mild
6. History of 11–25 NMSCs per year (2% risk of mortality over 3 years, minor–moderate surgical procedure 11–25 times per year; this level of morbidity causes moderate distress and moderate disfigurement; depression may begin; high likelihood of severe future skin cancers)	Mild[c]	Mild[c]	Mild
7. History of > 25 NMSCs per year (5% risk of mortality over 3 years, moderate–severe surgical procedure >25 times per year; this level of morbidity causes severe distress and disfigurement; patients question whether transplant was worth it; depression is common; high likelihood of severe and possibly life-threatening future skin cancers)	Moderate	Mild	Moderate
8. Individual high-risk skin cancer: 1% mortality over 3 years (average-risk SCC; cutaneous and oral KS; stage IA melanoma[d])	Mild[c]	None	Mild
9. Individual high-risk skin cancer: 5% mortality over 3 years (moderate-risk SCC; stage IB melanoma[d])	Mild	Mild	Mild

(*Continued*)

Table 5.6 (*Continued*)

Skin cancer scenario[b]	Level of reduction of immunosuppression to consider[a]		
	Kidney allograft	Heart allograft	Liver allograft
10. Individual high-risk skin cancer: 10% mortality over 3 years (high-risk SCC; early Merkel's cell carcinoma; stage IIA melanoma[d])	Moderate	Mild	Moderate
11. Individual high-risk skin cancer: 25% mortality over 3 years (very high-risk SCC; stage IIB melanoma[d])	Moderate	Mild	Moderate
12. Individual high-risk skin cancer: 50% mortality over 3 years (metastatic SCC; stage IIC/III melanoma[d]; aggressive Merkel's cell carcinoma; visceral KS)	Severe[c]	Moderate	Moderate
13. Individual high-risk skin cancer: 90% mortality over 3 years (untreatable metastatic SCC; stage IV melanoma[d]; metastatic Merkel's cell carcinoma)	Severe[c]	Severe	Severe

KS, Kaposi's sarcoma; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma.
[a]Appropriate level of reduction of immunosuppression should be individualized on the basis of specific patient- and tumor-related data.
[b]Estimates of mortality risk are derived from data in immunocompetent patients; risk may be higher in immunosuppressed patients.
[c]Unaminous opinion.
[d]Melanoma staging derived from the American Joint Commission on Cancer.
Used with permission from Otley CC, Berg D, Ulrich C, et al. Reduction of immunosuppression for transplant-associated skin cancer: expert consensus survey. *Br J Dermatol* 2006;**154**:395–400.

reduction of immunosuppression depending on organ transplant type. as made by an expert group of dermatologists experienced in managing skin cancers in transplant recipients. Results of retrospective studies suggest that sirolimus may have an anti-tumor effect for skin cancer and some centers consider conversion to this drug in patients with multiple SCCs or BCCs.

Lymphoma

PTLD has been reported to occur in 1–8% of transplant recipients. The incidence of PTLD seems to be higher in non-renal transplant patients, probably related to increased amount of overall immunosuppression. Most PTLDs are of B-cell origin and are often associated with reactivation or primary infection with EBV. PTLD can occur as early as the first year after transplantation or as late as 10 years or more afterwards. It can involve any organ in the body, including the allograft. It most commonly involves the lymphoid tissues, central nervous system, and bowel. It can present as unexplained fever, weight loss, or graft dysfunction. Transplant recipients at highest risk for PTLD are those without prior exposure to EBV (i.e., having negative antibody testing before transplantation) who receive an organ from an EBV-positive donor. Other risk factors include cytomegalovirus (CMV) infection and the use of lymphocyte-depleting antibodies for induction therapy or treatment of acute rejection.

Initial treatment for PTLD involves decreasing immunosuppression. Some patients may respond to this measure alone, although generally other therapy is required. In kidney transplant recipients, complete discontinuation of immunosuppression should be considered when the PTLD is severe or extensive because the patient can return to dialysis if the organ is rejected. Significant reductions of immunosuppres-

sion can be more problematic in other organ transplant recipients whose organs are more life sustaining (e.g., heart or lung). Not surprisingly, survival is better if response is seen with immunosuppression minimization alone. Patients with localized disease may respond well to surgery and local radiation. Remission of disease with systemic chemotherapy regimens occurs in as many as 75% of patients who did not respond to decreased immunosuppression alone. However, there may be significant problems with toxicity including bone marrow suppression, sepsis, and cardiotoxicity. Despite the association of PTLD with certain herpes viruses, a beneficial response to antiviral therapy has not been shown consistently. Some groups have used interferon-α or intravenous immunoglobulin with reported success in a small number of patients. A number of reports have shown a fairly good rate of remission with the use of the humanized anti-CD20 monoclonal antibody, rituximab – at least in patients whose tumors are CD20 positive.

Case

A 56-year-old man with a history of end-stage liver disease due to chronic hepatitis B infection underwent liver transplantation. He received induction immunosuppression using basiliximab and subsequently was maintained on tacrolimus, azathioprine, and prednisone. Pretransplant IgG antibody testing for CMV and EBV were positive. Prednisone was discontinued within the first month after transplantation. His liver graft function was excellent and serial protocol liver biopsies did not show rejection or recurrent disease. Two years after transplantation, he noticed a right submandibular mass. Needle aspiration performed by one of his local physicians to rule out infection was unrevealing. It was felt that it might be related to a dental infection. After a root canal and course of antibiotics, the mass continued to enlarge. An excisional biopsy was performed: pathology was consistent with a diffuse large B-cell lymphoma. The cells were positive for CD20 and CD45 markers and negative for CD3. *In situ* hybridization for EBV was negative. Before planned therapy with rituximab could be initiated, he began having episodes of bradycardia, hypotension, and syncope. Imaging showed a sizable mass in the right neck and submandibular region impinging on the carotid artery. He underwent urgent radiation therapy with significant regression of the mass. Immunosuppression was discontinued with the exception of dexamethasone. He then received 4-weekly doses of rituximab. Follow-up CT including of the neck, chest, abdomen, and pelvis was negative for evidence of residual disease. Immunosuppression was reinitiated with low-dose sirolimus. Several months later he complained of progressive low back pain. CT showed a retroperitoneal mass as well as a right axillary mass. Pathology on excisional biopsy of a right axillary node was consistent with recurrent B-cell lymphoma. Chemotherapy was initiated using CHOP (cyclophosphamide–hydroxydaunorubicin–Oncovin [vincristine]–prednisone) and rituximab. Immunosuppression for the liver transplant was completely discontinued. His disease regressed and 2 years later he is still in remission. His liver graft function remains excellent off immunosuppression and he has not had any episodes of rejection.

Cardiovascular disease

Cardiovascular disease contributes to a significant proportion of the morbidity and mortality encountered after solid organ transplantation. This is most evident in and has been most extensively studied in recipients of kidney transplants, but has been shown to occur in other solid organ recipients as well. The presence of "traditional" cardiovascular risk factors, such as advanced age, diabetes, smoking, and hyperlipidemia, can mean that these patients come to transplantation with pre-existing cardiovascular disease. Patients with CKD have a risk of cardiovascular disease that is elevated beyond that accounted for by these traditional factors. Left ventricular (LV) hypertrophy is present in most patients with advanced CKD and may be associated with non-ischemic LV dysfunction. Chronic volume overload, hypertension, and the effects of hyperparathyroidism on myocardial fibrosis are putative causes of cardiovascular disease in the presence of CKD. Hyperphosphatemia and elevated calcium–phosphorus products are associated with high incidence of vascular calcifications, particularly in the coronary arteries. However, the exact relationship between these calcifications and the higher risk for coronary events has not been completely defined. The chronic inflammatory state associated with ESRD and chronic dialysis may play a role. Recipients of other solid organ transplants may not have the same burden of disease, but side effects of immunosuppression may put them at risk for development of cardiovascular problems after transplantation. As noted above, the CNIs, corticosteroids,

and the TOR inhibitors each has variable effects on the development of hyperlipidemia, hypertension, and glucose intolerance – each of which may increase the risk of cardiovascular disease. In both renal and non-renal solid organ transplant recipients, the development of CKD resulting from the nephrotoxicity of CNIs has become an increasing problem and itself increases the risk of cardiovascular disease.

Renal transplantation decreases the risk of cardiovascular events such as myocardial infarction or stroke when compared with equivalent patients remaining on dialysis. However, the risk of cardiovascular events remains elevated two to three times that of age- and sex-matched controls in the general population. A similar risk of ischemic cardiac events and for cardiovascular deaths has been shown in liver transplant recipients, although this has not been as extensively investigated in this population.

Recipients of solid organ transplants have been shown to have an improved outcome when existing coronary artery disease is managed aggressively. Myocardial perfusion imaging, in conjunction with stratification of patients based on risk factors, can help identify patients who warrant further evaluation with coronary angiography. Abnormal myocardial perfusion testing can identify patients who are at high risk for future cardiovascular events. Patients who are aggressively managed, either with coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, appear to have an acceptable rate of complications and outcomes similar to those of non-transplant patients. Available studies do not consistently show a difference in outcome of operative versus percutaneous treatment modalities, although morbidity and mortality are obviously higher with surgical intervention. There may be a higher risk of postoperative infections due to chronic immunosuppression, but this does not appear to cause long-term morbidity. Small studies have shown 1- to 2-year patient survival rates between 85% and 90% in patients who undergo these procedures; 5- and 10-year survival rates are approximately 65% and 40%, respectively.

Patients with significant impairment of renal function, usually defined as a serum creatinine concentration ≥2.0 mg/day, are at risk for acute renal failure with the use of contrast agents. The risk can be minimized with intravenous hydration and possibly with adjunctive use of *N*-acetylcysteine. Acute renal failure after exposure to radiocontrast is sometimes, albeit rarely, irreversible, and may precipitate return to chronic hemodialysis. Temporary discontinuation of ACEIs, ARBs, and diuretics should be considered and some centers routinely recommend holding one or two doses of the patient's CNI before administration of contrast.

Although there is ample evidence documenting risk factors for cardiovascular disease in transplant recipients, there is less evidence documenting the benefit of aggressive risk management. Nevertheless, it seems reasonable to extrapolate from studies done in the non-transplant population documenting benefits of aggressive risk factor modification in those without overt evidence of cardiovascular disease.

Hypertension

The vast majority of renal transplant recipients are hypertensive, even in the presence of good renal graft function. Hypertension also is reported in up to half of liver transplant recipients. In kidney transplant recipients, many factors contribute to the pathophysiology of hypertension, including elevated blood pressure before transplantation, the presence of diseased native kidneys, and, uncommonly, renal artery stenosis involving the transplanted graft. CNIs and corticosteroids also contribute to the pathophysiology of post-transplant hypertension. Renal vasoconstriction due to CNIs, and sodium and water retention due to corticosteroids, are putative mechanisms. Patients are less likely to have hypertension if their immunosuppressive drug regimen does not include a CNI. In addition to being a risk factor for cardiovascular disease, hypertension may contribute to the progression of CKD. Kidney transplant recipients with uncontrolled hypertension have a twofold risk of graft failure. Proteinuria in association with hypertension increases the risk for progression of renal dysfunction in the general population and probably has the same effect in kidney transplant recipients.

Transplant recipients should be treated for hypertension according to the most recent recommendations of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC 7). Blood pressure should be kept below the defined cutoff for hypertension, <140/90 mmHg. However, both cardiovascular risk and progression of renal dysfunction continue to decline with tighter

goals of blood pressure control. As most transplant recipients are considered to have increased cardiovascular risk, including some degree of renal impairment, current recommendations are for target blood pressure <130/80 mmHg as outlined by both JNC 7 and the Kidney Disease Outcomes Quality Initiative (K/DOQI). For those patients who have significant proteinuria (defined by >1 g/day), a blood pressure <125/75 mmHg is a reasonable target.

All classes of antihypertensive agents are effective in treating hypertension in the transplant recipient, although more than one drug is usually required. The choice of agent may be guided by other comorbidities, such as the use of β blockers in cardiac disease, or ACEIs or ARBs in the presence of proteinuria and/or diabetic renal disease. There may be other effects of a drug apart from blood pressure control that may influence choice of an agent (e.g., use of ACEIs in patients with concomitant polycythemia). Pharmacologic interactions between some antihypertensive agents and anti-rejection drugs should always be kept in mind.

Case

A 38-year-old male kidney transplant recipient has exhibited a gradual rise in hematocrit to a recent value of 58%. He has hypertension that has been well controlled on amlodipine and doxazosin. Losartan was substituted for doxazosin. Hematocrit gradually decreased to 44% over the next 6 weeks and blood pressure remained well-controlled.

Calcium channel blockers including dihydropyridine (DHP, e.g., nifedipine and amlodipine) and non-dihydropyridine (NDHP, e.g., diltiazem and verapamil) agents are used effectively in transplant recipients. These agents may mitigate CNI nephrotoxicity by reversing renal vasoconstriction caused by these immunosuppressants. NDHP drugs may also have an antiproteinuric effect which is not seen with DHP agents. NDHP drugs may interfere with the hepatic metabolism of CNIs, often requiring downward dosage adjustments of these drugs. In fact, NDHPs are sometimes used to intentionally decrease the dose and the cost of the CNIs. DHP-type calcium channel blockers often cause peripheral edema that can significantly affect quality of life and may require additional treatment with diuretics. In addition, there is a higher incidence and severity of gingival hyperplasia associated with cyclosporine when used together with DHP calcium channel blockers.

There are several theoretical advantages to using ACEIs or ARBs in transplant recipients. This has been most extensively studied in renal transplant recipients. These agents can decrease proteinuria by 50% or more by their action to decrease intraglomerular pressure as well as their separate effects on glomerular permselectivity. The use of these agents in both diabetic and non-diabetic patients with CKD and proteinuria has been shown to slow the rate of decline of renal function. Studies have also shown that these agents can ameliorate the upregulation of transforming growth factor-β (TGF-β) by CNIs. TGF-β is associated with the tubulointerstitial fibrosis and arteriolopathy that is the hallmark on chronic CNI nephrotoxicity. They may also diminish renal damage mediated by aldosterone.

Despite these theoretical benefits, retrospective studies have provided conflicting data regarding the influence of angiotensin inhibitors on patient or graft survival in kidney transplant recipients. Large randomized trials are lacking. Moreover, the theoretical benefits of these agents must be balanced against potential side effects, some of which are unique to transplant recipients. Use of these antihypertensive drugs may be limited by their tendency to cause hyperkalemia, especially in patients treated with CNIs. Dietary restriction and the use of diuretics in combination with these drugs may alleviate this problem. A small rise in serum creatinine would be expected with use of these drugs due to their effect in decreasing intraglomerular pressure. More significant elevations in creatinine may be seen if they are used with diuretics because of relative intravascular volume depletion. In kidney transplant recipients, a more significant rise in creatinine concentration can be seen in the presence of stenosis of the renal transplant artery and should prompt evaluation with appropriate imaging studies. Finally, ACEIs and ARBs can cause significant, albeit reversible, anemia in a substantial minority of kidney transplant recipients.

Other classes of antihypertensive drugs are useful to control hypertension in transplant recipients, but potential side effects are relevant in this population. β Blockers may contribute to hyperkalemia. Diuretics may contribute to lipid abnormalities, hyperuricemia, and transient renal dysfunction from

volume depletion. α Blockers and other vasodilators may cause edema. These problems can adversely affect quality of life.

Bone disease

Bone disease is common in transplant recipients and multiple factors are involved in its pathogenesis. These factors vary depending on the organ transplanted. In kidney transplant recipients, osteopenia can be influenced by heredity, gender, exercise habits, the presence of diabetes mellitus, and, most importantly, pre-existing renal osteodystrophy. Nutritional factors and chronic liver disease may contribute to pre-existing bone disease in liver transplant recipients. In addition, a number of drugs, including the CNIs and corticosteroids contribute to the pathophysiology of osteopenia. Indeed, as bone density as measured by DXA (dual-energy X-ray absorptiometry) scans decreases by an average of a third in the first 6 months after transplantation, use of high doses of corticosteroids in the early post-transplant period has been incriminated historically as a major culprit. However, many studies have shown that post-transplant osteopenia can be severe, even in patients treated with steroid-free protocols.

A significant number of transplant recipients may lose enough bone mass to become "osteoporotic," thereby increasing the risk for fractures. However, fractures resulting from osteoporosis usually involve the lumbar spine or the hip. Fractures in transplant recipients just as frequently include the non-axial skeleton (especially the feet), supporting the hypothesis that post-transplant bone disease is not a simple form of osteoporosis. Fractures represent a major cause of morbidity and occasional mortality in transplant recipients. Reported fracture rates after transplantation vary from 5% to 35%, much of it occurring in the first year. Fracture risk has been estimated to be between 50 and 100 times higher than that of the normal population.

Numerous studies have shown that bisphosphonates are effective at preventing bone loss when used early after transplantation. They also may help to improve bone density when used late in the setting of established bone loss. Despite this positive effect on bone density, the benefit of these agents in preventing fractures remains a subject of debate. Moreover, there is a concern that these agents may lead to adynamic bone disease when used for prolonged periods of time, at least in kidney transplant recipients. Even so, based on studies showing decreased fracture risk in the non-transplant population, these agents are currently widely prescribed to transplant recipients considered to be at high risk for bone fractures. Several different treatment regimens have been shown to improve bone density in these patients, including daily or weekly oral therapy, or even intermittent intravenous administration.

Other treatment strategies should be considered. Vitamin D replacement alone, either in the form of activated 1,25-dihydroxy-vitamin D (calcitriol), cholecalciferol, or ergocalciferol, when compared head to head with bisphosphonates, is less effective in preserving bone density, but probably better than no therapy. There may be additional benefit to combined therapy. Adequate calcium intake of 1000–1500 mg/day of elemental calcium is recommended and patients should be given oral calcium supplements if dietary intake is not sufficient. Regular weight-bearing exercise should be encouraged. Male patients should be screened for hypogonadism and cautious consideration given to hormone replacement therapy in postmenopausal or amenorrheic women. Thyroid and parathyroid dysfunction should be ruled out.

Screening with DXA bone densitometry can help to identify patients with established bone loss who might benefit from therapy. Optimally, this should occur before transplantation or shortly thereafter in order to decide which patients would benefit from therapy early during the time of greatest bone loss. Some transplant programs screen all patients, but others reserve screening for patients deemed to at particularly high risk (e.g. postmenopausal women). Some programs have standardized protocols using bisphosphonates in the first 1–2 years after transplantation. Patients with known osteoporosis or osteopenia or those at risk who have not previously been screened should be evaluated later in their transplant follow-up according to recommendations established for the general population.

Avascular necrosis

Transplant recipients are at risk for the development of avascular necrosis (AVN), a bone disorder gener-

ally associated with use of corticosteroids. The femoral head is the area most commonly involved, although AVN in the talus, lunate, scaphoid, patella, and humeral head has been reported. Many patients may have more than one joint involved. Overall, the incidence of AVN in transplant recipients appears to be low at around 4–6%, but has been reported to be as high as 40%. Differences in the reported incidence may reflect length of follow-up and the imaging modality used for evaluation. Plain radiographs notoriously lack sensitivity and MRI has emerged as the imaging modality of choice. The risk of AVN has probably decreased over time as a consequence of low-dose steroid or steroid-free regimens. Once established, it is difficult to say whether minimization or discontinuation of steroids is of benefit. AVN can result in significant disability and diminished quality of life for the transplant recipient. Patients may eventually require replacement of the affected joint. Less severe disease may be managed conservatively with bed rest and partial weight bearing. Some patients may benefit by osteotomy or core decompression as a joint-saving technique. The best approach is to avoid the complication by minimizing corticosteroid use as much as possible.

Key points 5.3 Most common skeletal sites for avascular necrosis

Femoral head

Talus

Lunate

Scaphoid

Patella

Humeral head

Hyperparathyroidism

Renal transplant recipients often exhibit persistent secondary hyperparathyroidism or may even develop tertiary hyperparathyroidism related to overactivity of the parathyroid gland which develops routinely in patients with ESRD. Secondary hyperparathyroidism may persist for many months after transplantation and is critically dependent on the level of renal function obtained by transplantation. There is emerging evidence that screening for and correcting 25-hydroxyvitamin D deficiency can be helpful in resolution of this problem. Hypercalcemia may signal tertiary hyperparathyroidism that may not respond to medical therapy and may eventually require surgical parathyroidectomy. The role of cinacalcet in managing such patients is uncertain and requires further study.

Other significant primary care issues in transplant recipients

Reproduction and sexual function

Disturbances in the hypothalamic–pituitary axis related to chronic illness cause infertility and sexual dysfunction in many patients before solid organ transplantation. Sexual dysfunction has been extensively described in patients with CKD and in those with cirrhosis. Menstrual irregularities associated with anovulation occur in women. Most men have low testosterone levels, report erectile dysfunction and decreased libido, and can have impaired spermatogenesis. In general, these disturbances tend to improve in patients who receive a well-functioning organ, but the outcomes are less than uniform. Low testosterone levels have been reported to persist in up to 20% of heart transplant recipients. In the renal transplant population, erectile dysfunction (ED) can persist in as many as 30–50% of men. Age-related changes or comorbidities such as diabetic neuropathy may contribute. Use of certain drugs for common problems in transplant recipients can be associated with ED (e.g. treatment with β blockers, calcium channel blockers, or antidepressants). There are many reports to demonstrate improvement in ED with treatment with sildenafil or its congeners in kidney transplant recipients. Sildenafil is metabolized by the same hepatic pathway as the CNIs and in theory could decrease the serum levels of these drugs. However, small studies of this drug in kidney transplant recipients have failed to find any difference in drug exposure, possibly related to the intermittent nature of usage. There is little available information about the benefit of testosterone replacement in the transplant population. Indeed, the benefit of testosterone replacement in the general male population is uncertain, and must be balanced against significant adverse effects such as sleep apnea, polycythemia, adverse lipid profile, and an increased risk of prostatic disease.

With the possible exception of an association between low testosterone levels and use of corticosteroids, most immunosuppressant medications do not seem to affect sexual function or fertility in males. Although reports are limited, children fathered by transplant recipients do not seem to have a higher incidence of birth defects. The one exception is the TOR inhibitors, which appear to adversely affect spermatogeneis and sperm function quite regularly. Discontinuation of this class of agents may be necessary in male patients wishing to father children.

There is extensive information about pregnancy after solid organ transplantation. As fertility seems to return quickly to age-appropriate levels in female transplant recipients, it is important that an adequate method of contraception is initiated in female recipients of child-bearing age. Transplant status as such should not dictate the choice of contraception measure, although comorbidities in individual patients may limit the use of oral contraceptives. The presence of hypertension, lipid abnormalities, or liver dysfunction may be a relative contraindication to use of these agents. Some but not all transplant professionals feel that contraception using intrauterine devices may be ineffective because this method relies on the inflammatory reaction set up by the device, and this inflammation may be reduced by immunosuppression medications. Female transplant recipients desiring pregnancy should be counseled that it is certainly a feasible option, but, as detailed below, the women need to be fully aware of the risks involved.

The National Transplantation Pregnancy Registry has reported the outcome of over 1600 pregnancies in over 1000 female transplant recipients in the USA. Approximately 75% have occurred in kidney recipients, 15% in liver transplant recipients, and approximately 5% each in heart and combined kidney–pancreas transplant recipients. Only a handful have been reported after lung or other combined organ transplants. Recommendations as to the optimal timing of pregnancy are listed in Table 5.7.

Table 5.7 Optimal circumstances for pregnancy in solid organ transplant patients

More than 1 year post-transplantation
Good graft function with no evidence of rejection
No rejection episodes have occurred for 1 year before conception
For kidney transplant recipients: creatinine concentration stable at ≤1.5 mg/dL; no significant proteinuria (<500 mg/day)
Immunosuppression at nadir and stable dosing

Historical registry analyses suggest poorer fetal outcomes with shorter transplant-to-conception time intervals, and this forms the basis for recommending a waiting period of 1–2 years after transplantation before conceiving. In addition, a trend toward more acute rejection episodes has been observed with earlier conceptions. However, a more recent report demonstrated equivalent outcomes for both pregnancy and long-term graft function in a group of renal transplant recipients who became pregnant <1 year after transplantation compared with those >1 year. Therefore, although it is preferable that patients wait at least 1 year after transplantation to ensure optimum graft function and lowest risk of rejection, pregnancies occurring before that time frame do not necessarily mandate recommendation for termination. Most anti-rejection drugs are safe to continue during pregnancy. There is a long track record of safety for cyclosporine, azathioprine, prednisone, and more recently tacrolimus during pregnancy. Overall, there is a higher incidence of low-for-birth-weight infants and prematurity, but no evidence of higher risk of birth defects. Interestingly, azathioprine carries a Food and Drug Administration pregnancy rating of "D," although the literature supports its relative safety during pregnancy in transplant recipients and those treated for autoimmune diseases. A higher incidence of structural abnormalities in newborns has been reported with mycophenolate mofetil exposure during pregnancy and therefore it also carries a pregnancy rating of "D." Although it may be wise to discontinue mycophenolate mofetil either before desired conception or early after pregnancy is detected, the wisdom of this strategy must always be balanced against the risk to the allograft and the mother. There is little experience with the use of sirolimus during pregnancy. Studies in animals have shown some teratogenic potential. Among the handful of women who were reported to the national registry and who were receiving sirolimus at the time of conception, the drug was most often discontinued during the first trimes-

ter. No structural defects were reported. There are only a few case reports of successful outcome of pregnancies for patients in whom sirolimus was continued throughout the entire pregnancy. Consideration also needs to be given to the other drugs that may have teratogenic potential and require discontinuation before conception, such as ACEIs and possibly statins. There is theoretical potential risk of immunosuppressive drug exposure to the infant who is breastfed by a mother who is an organ transplant recipient. Traditionally, breastfeeding has been discouraged because of this risk.

Pregnant transplant recipients should receive prenatal care by an experienced high-risk obstetrician who communicates regularly with the transplant center. These patients are at higher risk for medical complications during pregnancy and require close follow-up. Many patients will require treatment for hypertension during the pregnancy. The incidence of pre-eclampsia appears to be higher, especially in kidney transplant recipients in whom it has been reported in a third of patients. Pre-existing hypertension and/or proteinuria can make it difficult to diagnose superimposed pre-eclampsia. There is a significant incidence of pregnancy-induced diabetes mellitus in transplant recipients. Obstetric risks include intrauterine growth retardation, low-for-birth-weight infants, higher risk of premature birth, and higher incidence of need for delivery by cesarean section. Cesarean section should be performed for obstetric indications alone. In kidney and/or pancreas graft recipients requiring cesarean section, it may be desirable to have the transplant surgeon available to avoid injury to the grafts because of their location.

Dosages of immunosuppressive drugs needed to maintain adequate drug sometimes must be increased due to an increase in volume of distribution, especially during the second and third trimesters. This is particularly true of the CNIs. Drug levels should be followed closely to avoid inadequate exposure that could increase the risk of rejection. Treatment of rejection episodes should be based on standard practice for the non-pregnant transplant recipient. High doses of corticosteroids are generally tolerated well with no appreciable risk to the fetus, and are generally used as first-line agents. Experience with the use of anti-lymphocyte antibodies for the treatment of acute rejection during pregnancy has been limited but IgG does cross the placenta.

Case

A 24-year-old woman is being seen at follow-up for her kidney transplant 2 years ago. She has a history of spina bifida and ESRD due to cloacal extrophy and reflux. Her renal graft drains into a continent neobladder which she catheterized via an umbilical stoma. She is immunosuppressed using tacrolimus and prednisone. Mycophenolate was discontinued in the first few months after transplantation. A biopsy was done in the first 2 months after transplantation when her creatinine, which was 1.4 mg/dL at best, had increased to 2–2.3 mg/dL. This showed subepithelial nodules in arterioles suggestive of CNI toxicity, but no evidence of rejection. The tacrolimus dose was decreased with improvement in renal function but only to serum creatinine concentrations of 1.7–1.9 mg/dL. A repeat biopsy a few weeks later showed mild interstitial fibrosis and tubular atrophy similar to the previous biopsy but no other specific abnormalities. Imaging of her graft did not show any evidence of obstruction. Since her transplant, she has had recurrent urinary tract infections and febrile pyelonephritis requiring several hospital admissions. She consistently has elevation of serum creatinine to 3–3.4 mg/dL concurrent with infections, and then improvement after treatment to 1.7–2 mg/dL. She presents after recently having had a positive pregnancy test performed by a medical facility; she later had vaginal bleeding and a follow-up test was negative. She is currently in a stable relationship with her long-term boyfriend; they use a condom for contraception. She and her boyfriend now want to discuss pregnancy, however. In addition to immunosuppressive medications, she is taking labetolol, sodium bicarbonate, and aspirin.

This patient represents a high-risk obstetric situation. She has significant renal graft dysfunction and would be at high risk for accelerated graft failure during pregnancy. Graft dysfunction would increase the risk of pregnancy-related complications such as pre-eclampsia and prematurity. Recurrent urinary tract infections would likely have additional adverse effects on the graft and pregnancy. She would be at higher risk for requiring a caesarean section which could risk the viability of her neobladder.

In kidney transplant recipients, the risk that pregnancy will adversely affect long-term graft function is low if baseline kidney function is well preserved. With pre-existing renal function impairment as defined by a serum creatinine >1.5 mg/dL, there is an increased risk of further deterioration of graft function during and after pregnancy. Graft loss within 2 years has

been reported in as many as 14% of kidney recipients after pregnancy. This course is similar to what is seen in non-transplant recipients with CKD and is exacerbated by inadequate blood pressure control. Existing proteinuria tends to increase during pregnancy, then return to baseline levels after delivery. The number of reported pregnancies in other solid organ transplant recipients is small. Reported rates of early graft loss after pregnancy have varied from 3–9% in liver transplant recipients to 23% in lung recipients.

Neuropsychiatric problems

Mood disorders

Mood disorders, most notably depression, are common in patients awaiting organ transplantation. Despite an improved quality of life after transplantation, depression persists in a significant number of patients. In the heart transplant population, the incidence of depression has been shown to climb from 15% early after organ transplantation to as high as 25–30% by 3 years. Other solid organ transplant recipients have been less systematically studied, but similarly have elevated rates of mood disorders compared with the general population. Major depressive disorder and post-traumatic stress disorder are the most frequent diagnoses. Not surprisingly, mood disorders can negatively affect quality of life and perceived ability to work, thereby impairing rehabilitation. Rates of depression are higher in those with less socioeconomic support. The patient's expectations of outcome after transplantation appear, however, to also play a role. Expectations are higher in those with higher levels of education and this has, in addition, been associated with development of depression.

Most classes of antidepressants have been used in recipients of organ transplants. Unfortunately, the majority of experience is anecdotal or comes from small non-randomized studies. Although there is little support to recommend any specific antidepressant with regard to efficacy, side effects and/or drug interactions may dictate use of one drug over another. The largest experiences with the use of antidepressants have been reported in kidney and heart transplant recipients. Selective serotonin reuptake inhibitors (SSRIs) have been used most widely and appear to have a favorable efficacy and side-effect profile. SSRIs have an inhibitory effect on the enzymes of the cytochrome P450 system in the liver and can potentially raise levels of tacrolimus, cyclosporine, and the TOR inhibitors. However, the effect is variable and it is reasonable to increase the frequency of therapeutic drug monitoring when these agents are initiated. Dosage adjustment for renal and liver function impairment also warrants consideration. Table 5.8

Table 5.8 Use of antidepressants in the setting of transplantation and potential interaction with hepatic metabolism of calcineurin inhibitors via the 3A4 isoenzyme of the cytochrome P450 system

Drug class	Effect on cytochrome P450 3A4[a]	Dose adjustment for liver disease[b]	Dose adjustment for kidney disease[b]	Special considerations in transplant patients
Serotonin reuptake inhibitors	Inhibits enzyme:			Greatest experience and documented safety using this class of drugs; nefazodone appears to have highest risk of causing CNI toxicity, citalopram the least
Fluoxetine (Prozac)	++	Y	N	
Paroxetine (Paxil)	++	Y	Y	
Citalopram (Celexa)	+	Y	Y (severe)	
Escitalopram (Lexapro)	++	Y	Y	
Sertraline (Zoloft)	+	Y	Y	
Fluvoxamine	++	Y	N	
Nefazodone	++	Y	N	

Table 5.8 (*Continued*)

Drug class	Effect on cytochrome P450 3A4[a]	Dose adjustment for liver disease[b]	Dose adjustment for kidney disease[b]	Special considerations in transplant patients
Monoamine oxidase inhibitors[c]				Little experience in transplant recipients; numerous and serious potential drug and dietary interactions; most recommend avoiding this class of drugs
Phenelzine	–	Y	N	
Tranylcypromine	–	Y	N	
Selegiline	–	Y (severe)	N	
Tricyclic antidepressants[c]				May cause hepatotoxicity; can cause or exacerbate cardiac conduction abnormalities, orthostatic hypotension
Amitriptyline	–	Y	Y	
Imipramine	–	Y	Y	
Desipramine	–	Y	N	
Nortriptyline	–	Y	Y	
Stimulants[c]				May be contraindicated in the presence of significant cardiovascular disease or HTN; can lower seizure threshold; advantage of having more rapid onset of action for treatment severe vegetative depression
Methylphenidate	–	N/A	N	
Dexamfetamine	–	N	N	
Modafinil	+ induces	Y severe	N[c]	
Other				Can markedly decrease levels of CNI and cause allograft rejection; not recommended
St John's wort	++ induces	N/A	N/A	
Bupropion (Wellbutrin)[c] (norepinephrine–dopamine reuptake inhibitor)	–	Y severe	Y	May cause less weight gain than other antidepressants; use with extreme caution with advanced liver disease
Trazadone (5-HT receptor antagonist)	+ not clinically significant	N	N	Can cause sedation and orthostatic hypotension
Mirtazapine (Remeron) (α_2-receptor blocker, serotonin receptor antagonist)	+ not clinically significant[c]	Y	Y	Can cause agranulocytosis, sedation; may exacerbate hyperlipidemia and weight gain
Benzodiazepines (e.g., alprazolam, clonazepam, diazepam)	+ not clinically significant	Y	Y	May cause respiratory depression if significant lung disease; sedating; potential for habituation and abuse

[a]Effect on isoenzyme: more potent (++), less potent (+), or no effect (–).
[b]Y, yes, N, no; severe, in the presence of moderate to severe liver or kidney disease.
[c]Metabolized via other cytochrome P450 isoenzymes; there may be significant interactions with other psychoactive drugs, antiarrhythmics, HMG-CoA reductase inhibitors, antihypertensive, and antifungal drugs.
CNI, calcineurin inhibitor; HTN, hypertension; N/A, not available.

outlines the pharmacologic considerations of the use of the most widely used drugs in these patients.

Tricyclic antidepressants (TCAs) can be effective in this group of patients, but because they also can interact with the hepatic metabolism of CNIs, close drug monitoring and dosage adjustments may be required. As TCAs have well-documented cardiovascular toxicity, such as conduction delay, orthostatic hypotension, and anticholinergic effects, the use of these drugs as a first-line agent in cardiac transplant recipients is not recommended, and they should be reserved for treatment of severe depression unresponsive to other drugs. Benzodiazepines can be useful for short-term treatment of anxiety or insomnia. Use of short-acting agents can avoid problems with drug accumulation in the presence of renal or hepatic dysfunction. They do not have metabolic interactions with immunosuppressive drugs. There is little information on the use of monoamine oxidase inhibitors in solid organ transplant recipients. Their use is not recommended due to severity of complications caused by drug interactions and the need for dietary restrictions (and hypotensive effects). The pharmokinetics of lithium can be significantly effected by other drugs that transplant recipients are commonly taking including diuretics, ACEIs, and β blockers, as well as by changes in renal perfusion due to CNIs. In addition long-term lithium use can cause CKD. For these reasons its use in transplant recipients for the treatment of bipolar disorder is not recommended. St. John's wort is a herbal drug that has long been used as a treatment for depression. Recently, it has been shown to induce the metabolism of CNIs, thereby decreasing drug levels that could put the patient at risk for rejection, so its use should be avoided. Finally, electroconvulsive therapy (ECT) has been used in a small number of patients with severe depression unresponsive to medical therapy with some success. There is concern that cardiac transplant recipients in particular may be at higher risk for complications due to increased sympathetic discharge as a result of the procedure, such that patients undergoing ECT should be carefully selected.

Compliance

Poor compliance with medical therapy is a risk factor for morbidity and mortality after transplantation. Non-compliance with immunosuppressive medications can of course put the patient at risk for rejection of the organ, which can severely decrease longevity of the transplant. The term "non-compliance" in the setting of organ transplantation usually connotes lack of adherence to a prescribed immunosuppressive regimen, although it also can negatively impact the course of a patient if it involves other medications (e.g., for treatment of hypertension or diabetes mellitus), or lifestyle choices, such as smoking and dietary indiscretion. Serious non-compliance with immunosuppressants is estimated to occur in 20–50% of patients. Non-compliance with immunosuppressants can take various forms from partial compliance where patients may take a "drug holiday," to "white coat adherence" where a patient may start taking the drugs shortly before a follow-up visit after a period of non-adherence, or stop taking the drugs altogether and present with irreversible graft dysfunction. Those with life-saving organ transplants such as heart, lung, and liver, would in theory suffer more severe consequences as a result of non-compliance compared with kidney transplant recipients who can restart dialysis if their graft fails; however, there is no documentation that rates of non-compliance differ among these groups. It has been said that the most useful function of monitoring immunosuppressive drug levels in a long-term transplant recipient is to be able to document compliance with these medications, but this measure would be insensitive in picking up patients with intermittent non-adherence who restart their drugs shortly before a follow-up visit. Socioeconomic factors can play a significant role in non-adherence because most drugs used to prevent rejection are costly. Loss of insurance drug coverage can lead to the patient not being able to afford the medication and to complete discontinuation of the medication or taking it less than prescribed in order to make it last longer. Compliance with drug therapy and confirming that the patient is able to afford the drug should be confirmed regularly even in the long-term patient.

There are several other factors that are associated with poor compliance, including pre-transplant non-compliance, substance abuse, poor social support, and personality disorders. Mood disorders themselves are not associated with higher rates of non-compliance. Non-compliance with other medical recommendations, such as smoking cessation, is more likely to be associated with non-compliance with the prescribed

immunosuppressive regimen. Side effects of the anti-rejection medication, either perceived or real, can lead to non-compliance. This is particularly true with the cosmetic side effects that can be seen with corticosteroids or cyclosporine. Rates of non-compliance are higher in the adolescent transplant recipient, which is often related to cosmetic side effects. In kidney transplant recipients, those who receive living donor transplants are reported to have a higher rate of non-compliance, often related to the belief in the less intensive need for immunosuppressive medication in this setting. Although there are no easy answers as to how to prevent non-adherence, proactively addressing concerns about side effects and repetitive education as to the importance of anti-rejection therapy, especially in individuals deemed at high risk, may help to minimize this complication.

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