Abbreviations

# Nephrology III

Abbreviations

PSAP

# LONG-TERM COMPLICATIONS OF KIDNEY TRANSPLANTATION

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## Learning Objectives

1. Assess the risk of a recipient of a kidney transplant experiencing late allograft loss based on analysis of individual risk factors and modify the immunosuppressive regimen to reduce the risk.
2. Construct appropriate therapeutic regimens for the management of diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, and other cardiovascular (CV) risk factors in a recipient of a kidney transplant.
3. Devise a therapeutic plan to modify the immunosuppressive regimen in a patient who experiences various transplant-related complications.
4. Develop strategies to screen, prevent, and treat patients with other long-term complications of kidney transplantation.
5. Analyze the risk-benefit and explain pharmacological considerations of pregnancy after kidney transplantation, and evaluate appropriate therapy for other gender-specific and age-specific issues in recipients of a kidney transplant.

## Introduction

The past decade has seen an increase in the number of potent immunosuppressive drugs available to prevent and treat acute rejection in recipients of a kidney transplant and as a result, allograft loss attributable to acute rejection has decreased significantly. Rejection rates under modern immunosuppressive drugs are now less than 10%–15%, and development of new immunosuppressive drugs now focuses on reducing toxicities associated with existing drugs rather than reducing rejection rates beyond current standards.

Today, the main challenge facing the transplantation community is to keep recipients of transplants alive and healthy long enough to enjoy the benefits afforded to them through transplantation. Currently, leading causes of allograft loss are death with a functioning allograft and chronic allograft nephropathy (CAN). These causes of allograft loss share many risk factors. Interventions to minimize these risk factors may reduce both outcomes. Today's focus is to effectively manage these comorbid conditions to improve patient survival, allograft survival, and the patient's quality of life after transplantation.

## Leading Causes of Allograft Loss

### Death with Function

Unfortunately, kidney transplantation does not completely ameliorate the cardiovascular (CV) risk that patients with chronic disease faced before transplantation. Cardiovascular risk in recipients of a kidney transplant is up to 4 times the risk in the general population, and not surprisingly, CV events cause about one-third of deaths with a functioning allograft in recipients of kidney transplants.

#### Cardiovascular Disease

Risk factors for CV events after kidney transplantation include both traditional and non-traditional factors. Traditional factors such as hypertension (HTN), diabetes mellitus (DM), dyslipidemia, and smoking are important, but additional factors in recipients of kidney transplants include proteinuria, anemia, and elevated homocysteine concentrations. Patients with extrarenal morbidity (CV disease, peripheral vascular disease, or obesity) are at a significantly higher risk of allograft loss and death compared with patients without extrarenal diseases.

Development of *de novo* congestive heart failure after kidney transplantation also leads to increased risk of death and allograft loss. Cardioprotection associated with female gender is not restored by transplantation. Metabolic syndrome (obesity, HTN, dyslipidemia, glucose intolerance, and insulin resistance) is also an important risk factor for CV morbidity and mortality.

## Abbreviations in this Chapter

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| ARB | Angiotensin II receptor blocker |
| AZA | Azathioprine |
| CNI | Calcineurin inhibitor |
| CV | Cardiovascular |
| CAN | Chronic allograft nephropathy |
| CsA | Cyclosporine |
| DM | Diabetes mellitus |
| HMG CoA | Hydroxymethyl glutaryl coenzyme A |
| HTN | Hypertension |
| MMF | Mycophenolate mofetil |
| NODM | New onset diabetes mellitus |
| SRL | Sirolimus |
| TAC | Tacrolimus |

### Screening

The Framingham Heart Study risk algorithm can help estimate risk of CV events in the kidney transplant population, although it appears to underestimate risk, particularly in patients with DM, of older age, and who smoke. In addition, the Framingham algorithm does not incorporate CV risk associated with chronic kidney disease or anemia. The latest research related to CV risk is emerging from corticosteroid minimization trials. In a study of 183 recipients of kidney transplants using the Framingham algorithm (limitations acknowledged), early corticosteroid cessation was found to reduce CV risk by about 10% over the first transplant year.

### Quality Patient Care

Much of this chapter focuses on managing individual conditions known to be modifiable risk factors for CV morbidity and mortality. Nonpharmacological therapy for CV disease includes coronary revascularization procedures as well as lifestyle changes (described later in this chapter). Aspirin therapy provides recipients of kidney transplants with benefits beyond the CV protection seen in the general population. Allograft survival, serum creatinine, and proteinuria are improved in kidney transplant recipients receiving low-dose aspirin compared with those not receiving aspirin, and aspirin therapy has reduced development of CAN. Low-dose aspirin (81 mg/day) is recommended for recipients of kidney transplants who do not have a specific contraindication.

## Chronic Allograft Nephropathy

Chronic allograft nephropathy is a universal problem in kidney transplant recipients and is generally irreversible. Complex interactions of immune- and nonimmune-mediated factors related to the kidney donor, the recipient of a transplant, the transplant process, and calcineurin inhibitors contribute to the development of CAN, which increases the risk of allograft loss by 10-fold. The global nature of CAN results from numerous insults that the kidney sustains both before and after transplantation. Several risk factors are modifiable, including acute rejection, HTN, dyslipidemia, calcineurin inhibitor (CNI) toxicity, and tobacco use. Pathologic changes from CAN include fibrosis, inflammation, tubular atrophy, sclerosis, and smooth muscle proliferation, and although the term "chronic" is used in CAN, the changes are seen as early as 6 months after transplantation. Early pathologic findings are most likely a result of pre-existing abnormalities present in the donor kidney; a pre-implantation biopsy can identify donor-related abnormalities.

### Screening, Prevention, and Diagnosis

Because CAN may develop early after transplantation and there is no "gold standard" or universal treatment for this complication, prevention is the key strategy and focuses on managing modifiable risk factors mentioned above. Patients with CAN typically have a slowly rising creatinine concentration over several months to years (referred to as the "creatinine creep"). Proteinuria (usually 1–2 g/day) and HTN are also common. The gold standard for diagnosing CAN is an allograft biopsy, and severity is graded based on the presence of interstitial fibrosis and tubular atrophy. Early intervention is essential once a diagnosis is made because patients with lower creatinine concentrations at the time of diagnosis have better outcomes.

### Quality Patient Care

Interventions for CAN are aimed at preventing or minimizing progression of the existing damage, and may involve changing to alternative immunosuppressive drugs, minimizing immunosuppressive drugs known to cause progression of CAN, intensive management of comorbid conditions, and/or changing drug therapy used to treat comorbid conditions.

#### *Modification of the Immunosuppression Regimen*

Two general principles apply when modifying a patient's immunosuppression regimen: CNI minimization or CNI withdrawal. Cautious monitoring is necessary to detect acute changes in allograft function that may be caused by acute rejection, regardless of which method is chosen. Adequate alternate immunosuppression is essential, which generally includes either addition or maximization of mycophenolate mofetil (MMF) and/or sirolimus (SRL).

One issue with the use of SRL in CNI minimization and withdrawal strategies is proteinuria and decline in kidney function after conversion from a CNI to SRL. Several studies found that patients with proteinuria (ranging from 0.3 g/day to 0.8 g/day) at the time of conversion to SRL have a significant increase in proteinuria after conversion, which may result from hyperfiltration due to increased kidney blood flow after CNI reduction or withdrawal. However, other mechanisms may be involved because proteinuria has also developed in patients on a CNI-free regimen before introduction of SRL. Some investigators recommend that conversion to SRL be performed when the serum creatinine concentration is less than 2.5 mg/dL and proteinuria is less than 0.8 g/day to prevent deterioration in kidney function. Treatment with an angiotensin-converting

Abbreviations

**Table 1-1. Diagnosing New-Onset Diabetes Mellitus after Transplantation**

| Diagnosis | Fasting Plasma Glucose (mg/dL) | 2-Hour Plasma Glucose after Oral Glucose Tolerance Test (mg/dL) | Casual Plasma (mg/dL) | Comments |
|---|---|---|---|---|
| Impaired fasting glucose | 110–125 | Not applicable | Not applicable | Repeat on 2nd occasion if elevated |
| Impaired glucose tolerance | Not applicable | 140–199 | Not applicable | |
| Diabetes mellitus | ≥ 126 | ≥ 200 | ≥ 200 plus symptoms | |

enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB) before conversion can help prevent proteinuria.

A recent study randomized patients with CAN on cyclosporine (CsA)-based immunosuppression to continue CsA or switch to tacrolimus (TAC). Compared with patients remaining on CsA, patients switched to TAC experienced stabilization of serum creatinine concentrations, significant improvement in lipid profiles, significantly fewer cardiac events, and no cases of new onset diabetes mellitus (NODM). This novel approach to CAN merits further study given the emerging issues with proteinuria in SRL-treated patients.

### *Management of Comorbid Conditions*

By effectively managing the modifiable risk factors for CAN such as HTN and dyslipidemia, assisting the patient with smoking cessation, if applicable, and targeting molecular markers (such as transforming growth factor-β1, a profibrotic protein), kidney function may be maintained for as long as possible. Managing these individual modifiable risk factors is discussed below.

# Important Modifiable Risk Factors in Recipients of a Kidney Transplant

## Diabetes Mellitus

Diabetes mellitus is one of the strongest risk factors for CV disease in the recipient of a kidney transplant. This is true in patients with DM before transplant and patients who develop NODM after transplant. Unfortunately, the true incidence and severity of NODM in the transplant population is underestimated due to the variety of definitions used to diagnose NODM. The New-Onset Diabetes After Transplantation: 2003 International Consensus Guidelines address the definition, risk factors, screening, and treatment of NODM and serve to provide standardization for the definition of NODM.

Many risk factors for NODM in recipients of kidney transplants are similar to those in the general population (such as age, weight, or family history of DM). In a large study reviewing 11,659 Medicare-covered recipients of kidney transplants, the cumulative incidence of NODM was 16% at 1 year and 24% at 3 years post-transplant. Independent risk factors for developing NODM emerged, including obesity at the time of transplantation, hepatitis C infection, and use of TAC as initial immunosuppression. African-American race, Hispanic ethnicity, older age, and male gender were also risk factors for NODM. This study also highlighted the clinical significance of NODM, which led to a significantly higher risk of allograft failure, death-censored allograft failure, and mortality. Immunosuppression choice also impacts development of NODM; corticosteroids induce insulin resistance and increase hepatic glucose production, whereas CNIs decrease insulin synthesis and release, decrease peripheral sensitivity to insulin, and are directly toxic to islet cells. Risks in pediatric recipients of a kidney transplant are also significant, with up to 16% developing NODM.

### Screening

Candidates for kidney transplantation should be evaluated for their risk of post-transplant NODM. Pre-transplant screening, education, and intervention may present the best opportunity to decrease the incidence of this devastating complication. Patients should understand the significance of NODM, the risk factors that contribute to its development, and the early lifestyle intervention(s) that may prevent NODM. Early diagnosis and intervention, when necessary, is needed to minimize the ongoing damage and secondary complications that can result from elevated blood glucose concentrations.

### Diagnosis

Diagnosis of NODM in the transplant population closely follows the diagnostic criteria for the general population, following the World Health Organization and American Diabetes Association criteria. Table 1-1 reviews the plasma glucose concentrations diagnostic of NODM, impaired fasting glucose, and impaired glucose tolerance. When using these criteria, the incidence of NODM is likely to be significantly higher than previously thought because a majority of studies previously used requirement for oral hypoglycemics and/or insulin as criteria for diagnosis.

### Quality Patient Care

Guidelines for managing NODM recommend initiation of drug therapy in patients with a hemoglobin A1c above 6.5%. Hemoglobin A1c should be measured every 3 months, with a goal of maintaining it at less than 7% to prevent long-term complications of DM. Many factors must be taken into account when designing a drug regimen for patients with NODM, including current immunosuppression therapy and other concomitant drugs, risk for rejection, risk factors for CV disease, kidney function, weight, presence of

insulin resistance, and the patient's motivation. Drug therapy for NODM parallels regimens used in the general population, except for transplant-specific issues, as outlined in Table 1-2.

Unfortunately, prospective studies of treatments for NODM after transplantation are lacking. Several small retrospective studies looked at efficacy of newer drugs such as insulin secretagogues and thiazolidinediones. Both pioglitazone and rosiglitazone have been used in patients with NODM, leading to improvements in hemoglobin A1c concentrations, decreased insulin requirements, and decreased fasting blood glucose. Repaglinide has also been used successfully in recipients of kidney transplants with NODM, leading to improvements in hemoglobin A1c concentrations. About 25%–40% of patients in these studies did not respond to the allocated therapy.

Most therapeutic principles that apply to the general population can be applied to recipients of kidney transplants, with certain key limitations, when determining the best drug regimen. For example, metformin should be avoided due to suboptimal kidney function even in kidney transplant patients with normal creatinine concentrations. By using drugs that target different, yet complementary mechanisms, patients may not need insulin injections. The role of inhaled insulin in recipients of transplants remains to be determined; however it may be a viable option for patients requiring insulin therapy.

Incretin mimetics may be beneficial in managing blood glucose in patients with NODM, and may enable weight loss. One issue with their use in recipients of transplants includes additive gastrointestinal adverse effects (particularly nausea, vomiting, and diarrhea) in those patients receiving MMF as part of their immunosuppression regimen. Another issue is the theoretical risk of change in CNI absorption due to delayed gastric emptying. This change in gastric emptying could delay the time to maximal concentration and prolong intestinal transit time, thereby increasing absorption and area under the curve of the CNIs. The delay in time to maximum concentration may be of particular importance to patients receiving CsA whose therapy is managed using 2-hour post-dose concentrations. Until more data are available, CNI concentrations should be monitored closely.

## Hypertension

The complex interaction of risk factors after kidney transplantation makes treatment of HTN difficult. Pre-transplant HTN, immunosuppression drugs, kidney dysfunction, CAN, and renal artery stenosis may affect blood pressure control after transplantation. Given the importance of HTN on CV morbidity and mortality and development of CAN, HTN is an important pharmacotherapeutic target. Unfortunately, blood pressure goals are not met in about one-third of recipients of a kidney transplant, highlighting the need for more effective management. Hypertension occurs in up to 80% of pediatric transplant recipients, increasing the risk of left ventricular hypertrophy.

### Screening

Continuous screening for and control of post-transplant HTN is highlighted in an analysis of over 24,000 kidney transplant recipients. The analysis showed that although persistent maintenance of systolic blood pressure below 140 mm Hg offers patients the best long-term individual and allograft survival, late intervention in patients with poorly controlled blood pressure improves allograft survival compared with patients with sustained elevation in blood pressure.

### Quality Patient Care

Goals for adult recipients of kidney transplants include blood pressure below 130/80 mm Hg or below 125/75 mm Hg if patients have more than 1 g/day of proteinuria. For children, the goal is less than the 95th percentile for age and gender (less than the 90th percentile if the child has DM). Drug therapy considerations in treating HTN in recipients of kidney transplants are presented in Table 1-3. Unfortunately,

**Table 1-2. Important Considerations for Use of Drugs to Treat Diabetes Mellitus in Recipients of Kidney Transplants**

| | |
|---|---|
| Sulfonylureas | Short-acting drugs preferred (glipizide or glimepiride) due to risk of hypoglycemia |
| Insulin secretagogues | Dose adjustment required in moderate to severe kidney function impairment |
| Thiazolidinediones | Do not require dosage adjustment in patients with kidney function impairment |
| Biguanides | Avoided due to risk of lactic acidosis. Kidney transplant allograft function often impaired despite normal creatinine concentration |
| Alpha-glucosidase inhibitors | Dose adjustment required in moderate to severe kidney function impairment<br>Overlapping adverse effects with immunosuppressants (particularly mycophenolate mofetil) |
| Insulin | Dose adjustments required with change in kidney function (subcutaneous insulin)<br>Increase quality of life and ease of administration (inhaled insulin) |
| Incretin mimetics | Overlapping adverse effects with immunosuppressant drugs (particularly mycophenolate mofetil)<br>Not recommended in kidney failure treated with dialysis or creatinine clearance < 30 mL/minute<br>Should not be used in patients with gastroparesis<br>Slows gastric emptying and intestinal transit time for drugs, which could affect immunosuppressant concentrations |

Abbreviations

**Table 1-3. Important Considerations for Use of Antihypertensive Drugs in Recipients of Kidney Transplant**

| | |
|---|---|
| Calcium channel blockers | Counteract afferent arteriolar vasoconstriction caused by CNIs<br>Inhibition of CYP3A4 by diltiazem and verapamil necessitates close monitoring of CNIs<br>Increased risk of ischemic heart disease |
| ACE inhibitors and angiotensin-II receptor blockers | Effective in reducing proteinuria in recipients of kidney transplant<br>Cardiovascular benefits (reduce left ventricular hypertrophy)<br>Effectively decrease hemoglobin in patients with post-transplant erythrocytosis<br>Decrease transforming growth factor-β1 expression in patients with chronic allograft nephropathy<br>Adverse events to consider include hyperkalemia, anemia, and rarely allograft dysfunction |
| β-blockers | First-line therapy for recipients of kidney transplants with established cardiovascular disease<br>Adverse effects to consider include lipid abnormalities and masking hypoglycemia |
| $\alpha_1$-Antagonists | Beneficial in men with benign prostatic hypertrophy |
| Diuretics | Useful in salt sensitive hypertension (associated with cyclosporine) and patients with fluid overload<br>Loop diuretics preferred when creatinine clearance < 30 mL/minute<br>Adverse effects to consider include electrolyte abnormalities and negative effects on bone metabolism |
| Other drugs | Drugs such as clonidine are generally reserved for difficult to treat hypertension |

ACE = angiotensin-converting enzyme; CNI = calcineurin inhibitor; CYP = cytochrome 450.

there is no ideal antihypertensive drug for this population, and no clear guidelines exist for managing HTN in these patients.

In the past several years, the transplantation community's position about using ACE inhibitors and ARBs has changed dramatically. Historically, these drugs were avoided due to concerns of deterioration in allograft function. More recently, several small studies compared ACE inhibitors or ARBs to calcium channel blockers or β-blockers, and demonstrated that although the drug classes are equally effective in lowering blood pressure, ACE inhibitors and ARBs reduce proteinuria more effectively, with few adverse events and with no clinically significant reduction in kidney function. There is also compelling evidence for using ACE inhibitors or ARBs in patients with CAN because in addition to reducing proteinuria, these drugs also reduce expression of profibrotic transforming growth factor-β1 in the allograft. In several studies, patients with CAN who received ACE inhibitor or ARB therapy had improved kidney allograft survival compared with patients with CAN who did not receive these therapies.

Although calcium channel blockers effectively reduce blood pressure, counteract nephrotoxic effects of CNIs, and are generally the first-line drugs for HTN immediately after kidney transplantation, long-term use must be balanced by the increased risk of ischemic heart disease associated with use of dihydropyridine calcium channel blockers. Once allograft function stabilizes after transplantation, converting therapy to an ACE inhibitor or ARB may be beneficial in terms of long-term allograft function and reduction in cardiovascular events. In patients requiring diuretics, loop diuretics are preferred over thiazide diuretics due to decreased efficacy in patients with poor allograft function (particularly patients with a creatinine clearance less than 30 mL/minute). However, metolazone is effective, particularly when used with loop diuretics.

## Dyslipidemia

Dyslipidemia is prevalent in the transplant population, with more than 80% of adults and 50% of children having total cholesterol concentrations above 200 mg/dL and low-density lipoprotein concentrations above 100 mg/dL. Dyslipidemia is poorly managed, with only one-third of patients reaching target lipid concentrations. Similar to patients with chronic kidney disease, recipients of kidney transplants are considered to have a coronary heart disease risk equivalent and should be considered at highest risk for CV disease.

### Screening

Patients should have a complete lipid profile at baseline, within 6 months of transplantation, and annually thereafter. More frequent monitoring should occur in patients receiving lipid-lowering therapy or in patients who had modifications to their immunosuppression regimen that might influence lipid concentrations. In these cases, lipid profiles should be monitored 2–3 months after initiation of therapy and/or change in dosage. In addition, a creatine phosphokinase concentration should be performed before initiating therapy so a baseline can be established in the event that drug-related myopathy occurs.

### Quality Patient Care

Although the therapeutic goals for treating dyslipidemia parallel those of the general population, there are several differences in the treatment of recipients of a kidney transplant; recommendations for adolescents with dyslipidemia differ slightly from adults. Lipid-lowering therapies in recipients of kidney transplants show fairly consistent reduction in lipid concentrations and CV events such as cardiac death and non-fatal myocardial infarction. Hydroxymethyl glutaryl coenzyme A reductase inhibitors have been effective in reaching therapeutic goals with few reports of adverse events such as myalgia and/or rhabdomyolysis. Hydroxymethyl glutaryl coenzyme A

**Abbreviations**

(HMG CoA) reductase inhibitors may also provide immunologic benefit by reducing acute and chronic rejection in recipients of transplants.

Treatment guidelines were published in 2004 by the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. These guidelines recommend aggressive treatment, which is summarized in Table 1-4. Lipid goals for recipients of a kidney transplant include low-density lipoprotein less than 100 mg/dL; triglycerides less than 500 mg/dL (less than 200 mg/dL if non-high-density lipoprotein cholesterol is greater than 130 mg/dL); high-density lipoprotein cholesterol greater than 40 mg/dL; non-high-density lipoprotein cholesterol less than 130 mg/dL. Therapeutic lifestyle changes, discussed later in this chapter, should be implemented in patients with dyslipidemia and continued if therapeutic lifestyle change fails and drug therapy needs to be added. Maximizing drug therapy should be attempted before adding a second-line drug.

The first and only study of primary prevention of CV events in recipients of kidney transplants randomized patients to fluvastatin or placebo. The primary end point was occurrence of the first major adverse cardiac event (a composite end point including cardiac death, nonfatal myocardial infarction, or coronary intervention procedure). After 5 years of follow-up, the 17% reduction in the composite end point in fluvastatin-treated patients did not reach statistical significance, however, individual secondary end points (cardiac death and nonfatal myocardial infarction) were significantly lower in fluvastatin-treated patients. Follow-up of patients in the Assessment of Lescol in Renal Transplantation Trial (ALERT) trial revealed significant reduction in the primary end point after an additional 2 years, supporting early introduction of lipid-lowering therapy in recipients of transplants.

Although fluvastatin was the HMG CoA reductase inhibitor used in the ALERT trial, transplantation centers routinely use other HMG CoA reductase inhibitors due to their effectiveness in reducing lipids to target levels. Augmented blood concentrations and adverse effects of HMG CoA reductase inhibitors have been reported during concurrent CsA therapy. Although the interaction is thought to be primarily due to inhibition of HMG CoA reductase inhibitor metabolism by CNIs (via inhibition of cytochrome P450 isoenzymes), other mechanisms are likely to contribute because pravastatin, which is metabolized via sulfation, is also elevated in the presence of CsA. These interactions should also be considered in patients taking TAC until more data are available for concurrent TAC and HMG CoA reductase inhibitor use. The greatest danger for adverse reactions such as myopathies occurs when a HMG CoA reductase inhibitor is combined with a CNI plus another drug that inhibits cytochrome P450 isoenzymes. Most practitioners recognize that introduction of low doses and slow titration of the dose allows safe use of HMG CoA reductase inhibitors in recipients of transplants in conjunction with patient education about risks and symptoms of myopathy.

The safety and effectiveness of ezetimibe was evaluated in more than 100 recipients of kidney transplants. A majority of patients were started on ezetimibe due to the inability to reach lipid targets with HMG CoA reductase inhibitor therapy alone or after their inability to tolerate HMG CoA reductase inhibitors. These studies found that ezetimibe was effective in lowering total cholesterol (21%–23%), low-density lipoprotein (31%–37%), and triglycerides (13%–40%). Discontinuation of therapy due to nausea and myopathy was reported in several patients.

Based on the experience to date, ezetimibe-treated patients had no significant change in CNI or SRL trough concentrations; however, one study reported wide inter-patient variability in trough concentrations. However, ezetimibe's area under the curve may be increased 2.3–12-fold in the presence of CsA. Although the majority of studies report using 10 mg/day, it may be prudent to initiate therapy at 5 mg/day. Ezetimibe is an excellent addition to the armamentarium of lipid-lowering drugs, and in future guidelines may be considered a second-line drug, particularly for patients intolerant to HMG CoA reductase

**Table 1-4. Management of Dyslipidemia in Recipients of Kidney Transplants**

| Population | Initiate Treatment When: | First-Line Therapy | Second-Line Therapy | Comments |
|---|---|---|---|---|
| Adult | LDL ≥ 100 mg/dL | TLC + statin | BAS | |
| | TG ≥ 500 mg/dL | TLC ± fibrate | Nicotinic acid | |
| | HDL < 40 mg/dL | TLC | None | |
| | Non-HDLC ≥ 130 mg/dL | TLC + statin | Fibrate or nicotinic acid | Treat if LDL < 100 mg/dL and TG ≥ 200 mg/dL |
| Adolescent | LDL ≥ 130 mg/dL | TLC | HMG CoA reductase inhibitor | Try TLC x 6 months |
| | LDL ≥ 160 mg/dL | TLC + statin | BAS | |
| | TG ≥ 500 mg/dL | TLC ± low dose fibrate | Nicotinic acid | |
| | Non-HDLC ≥ 160 mg/dL | TLC | HMG CoA reductase inhibitor | Try TLC x 6 months; treat if LDL < 130 mg/dL and TG ≥ 200 mg/dL |
| Pre-pubescent children | ≥ 95% percentile for age and gender | Diet | Refer to pediatric lipid specialist | |

BAS = bile acid sequestrant; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Non-HDLC = non-high-density lipoprotein cholesterol; TG = triglyceride; TLC = therapeutic lifestyle changes.

Abbreviations

**Table 1-5. Important Considerations for Use of Lipid-Lowering Drugs in Recipients of Kidney Transplants**

| | |
|---|---|
| HMG CoA reductase inhibitors (statins) | Statin concentrations increased by CNI (especially CsA)<br>Dosages should start low and be titrated slowly due to risk of adverse effects |
| Ezetimibe | Inhibition of CYP3A4 by CNI may increase exposure to ezetimibe; therefore, consider starting at 5 mg/day |
| Bile acid sequestrants | Use only if TG < 400 mg/dL<br>Interfere with enterohepatic cycling of MPA and absorption of CsA (separate 2 hours before or 6 hours after dose)<br>Overlapping adverse effects with immunosuppressants (particularly mycophenolate mofetil) |
| Fibric acid derivatives | Gemfibrozil is the drug of choice because dose reduction is not required for impaired kidney function<br>Avoid using in combination with HMG CoA, when possible |
| Nicotinic acid derivatives | Second-line alternative to bile acid sequestrants<br>Hyperglycemia may limit use in this high-risk population |

CNI = calcineurin inhibitor; CsA = cyclosporine; CYP = cytochrome P450; HMG CoA = hydroxymethyl glutaryl coenzyme A; MPA = mycophenolic acid; TG = triglyceride.

inhibitors or those who do not achieve target lipid levels despite titration of HMG CoA reductase inhibitor dose.

Bile acid sequestrants, fibric acid derivatives, and nicotinic acid derivatives can be used as second-line or adjunctive therapies in patients who do not meet goals despite maximization of the HMG CoA reductase inhibitor therapy. However, each drug class has limitations that must be carefully considered in the kidney transplant population as outlined in Table 1-5.

## Obesity

Obesity (body mass index greater than 30 kg/m$^2$) is a risk factor for post-transplantation complications, such as NODM, HTN, dyslipidemia, heart disease, allograft loss, and death, regardless of whether obesity was present before transplantation or occurred post-transplantation. About two-thirds of adult patients are overweight or obese at the time of kidney transplantation, and more than 10% of pediatric patients are obese, leading to an increased risk of death and CV disease. Given the risk of post-transplantation weight gain and association with poor outcomes, obesity should be addressed before transplantation. Obesity plays an important role in the design of the post-transplantation immunosuppression regimen because corticosteroid minimization protocols have been shown to limit post-transplant weight gain.

### Quality Patient Care

Obesity can contribute to altered pharmacokinetics of immunosuppressive drugs, glomerular hyperfiltration, and development or worsening of comorbid conditions, which in turn lead to allograft damage. Unfortunately, weight loss is challenging due to the effects of corticosteroids on appetite, as well as lifting dietary restrictions after successful transplantation. In addition to lifestyle measures, drug therapy and surgery are therapeutic options to treat obesity. Gastric bypass has been successfully performed in patients who are morbidly obese before and after transplantation. Due to the potential for defunctionalized intestine after gastric bypass, increased CNI dosages may be needed to maintain adequate concentrations; gastric banding does not appear to alter CNI pharmacokinetics. Pharmacological options for obesity also present a challenge to clinicians. For example, orlistat not only causes gastrointestinal adverse effects that may be intolerable in patients taking MMF, but may also cause significant alterations in absorption of highly lipophilic CsA by reducing fat absorption. Risk of increased blood pressure and heart rate limits the use of sibutramine in the kidney transplant population. Sibutramine may also elevate CNI concentrations by competing for metabolism via cytochrome P450 3A4.

## Smoking

Smoking is an independent risk factor for allograft loss and death after kidney transplantation. This is true regardless of whether the patient actively smokes before or after transplantation. In addition to the CV risks associated with smoking, recipients of transplants also face increased risk of smoking-associated cancers. Recognizing the detrimental impact of smoking, some transplantation centers will not perform transplantation procedures in active smokers. Pack-years is a strong predictor of outcome, with a greater than 25 pack-year history leading to higher rates of CV disease, malignancies, allograft loss, and death.

### Quality Patient Care

At the time of transplantation, up to 25% of recipients of a kidney transplant are active smokers and 25% have a past history of smoking; the majority of active smokers continue to smoke post-transplantation. Pre-transplantation smoking cessation measures will provide the most benefit to the recipients; however, patients should be approached to assess their interest in quitting regardless of the time in relation to transplant. United States Public Health Service Report guidelines published in 2000 recommend first-line pharmacotherapy with bupropion or nicotine replacement. Second-line therapies include clonidine, nortriptyline, or a combination of nicotine replacement (e.g., patch plus on-demand gum or nasal spray). Varenicline tartrate is a new smoking cessation drug with a novel mechanism of action

that enables about 20% of patients to successfully stop smoking and maintain abstinence for 1 year after initiation of therapy. Although it is unknown what effects varenicline may have in recipients of transplants, considerations include the need to adjust dosage for patients with impaired kidney function (creatinine clearance less than 30 mL/minute) or those receiving dialysis.

Behavioral modification is a key component of smoking cessation, and without the motivation to quit, success rates are low. Patients with low self-motivation should be encouraged to quit through education about the poor outcomes for the transplanted kidney in patients who smoke. Individual and group counseling and telephone support should be provided to patients. Because weight gain associated with smoking cessation can be compounded in recipients of a transplant, patients should be warned of the risk of weight gain while stressing the health benefits of smoking cessation. Patients should be educated about the risks of resuming smoking after transplantation. These patients may quit before transplant and may not be considered to be high risk to resume smoking. However, stressors associated with the transplant could lead to an increased risk of tobacco use in this patient population.

### Anemia

Kidney transplantation does not provide patients with optimal kidney function, and a large percentage of patients with functioning allografts have chronic kidney disease Stage 3 or higher. Post-transplant anemia may be attributed to poor allograft function, transplant-related drugs (MMF, SRL, azathioprine [AZA], ganciclovir, valganciclovir), iron deficiency, erythropoietin resistance, acute rejection, and infection (particularly viral infections such as cytomegalovirus and parvovirus).

Anemia has been associated with increased left ventricular dysfunction, congestive heart failure, and CV mortality in the kidney transplant population. Unfortunately, a significant proportion of post-transplant anemia is treated suboptimally, with studies finding that less than 50% of patients with a hematocrit less than 30% have had iron studies or have received iron supplementation and/or erythropoiesis-stimulating drugs.

#### Quality Patient Care

The goals of anemia management in the kidney transplant patients should follow the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Recipients of a kidney transplant tend to have a higher rate of erythropoietin resistance; therefore, high doses of erythropoiesis-stimulating drugs may be needed. Blood pressure should be monitored closely during treatment with erythropoiesis-stimulating drugs because studies in recipients of kidney transplants have demonstrated increased blood pressure drug requirements. Iron supplementation is important during treatment with erythropoiesis-stimulating drugs; however, consideration must be given to the conflicting data regarding concomitant administration of iron and MMF. Some data suggest that oral iron chelates MMF, reducing its absorption, whereas other studies showed no interaction. When possible, it is prudent to separate the administration of these two drugs until more data are available. Another limiting factor or oral iron supplementation includes poor tolerance due to overlapping gastrointestinal adverse effects with drugs such as MMF. Intravenous iron replacement has not been widely researched in the transplant population; however, this is a viable alternative that could help avoid both the chelation and gastrointestinal complications associated with oral iron preparations.

### Post-Transplant Erythrocytosis

Post-transplant erythrocytosis is a condition in which a patient's hematocrit concentration rises above 50%. This occurs in about 10%–20% of recipients of a kidney transplant, and usually occurs within 3–6 months after transplantation. Although the exact mechanism behind post-transplant erythrocytosis is unknown, it is likely related to complex interactions between high calcium concentrations and both erythropoietin and angiotensin II-mediated erythropoiesis. Risks associated with erythrocytosis include HTN and thrombotic events. Treatment of erythrocytosis includes angiotensin II blockade or therapeutic phlebotomy.

### Proteinuria

Proteinuria is an independent risk factor for both CV disease and allograft loss in the kidney transplant population. Major etiologies of proteinuria include CAN and recurrent or *de novo* glomerular disease. Nephrotic range proteinuria (greater than 3 g/day) can cause dyslipidemia, and treatment with an ACE inhibitor or ARB can reduce both proteinuria and lipid parameters. In patients transplanted more than 12 months earlier, proteinuria may also indicate recurrence of disease such as immunoglobulin A nephropathy or DM. For both diseases, ACE inhibitor or ARB therapy may ameliorate proteinuria and slow disease progression.

### Hyperhomocysteinemia

Elevated homocysteine concentrations can increase the risk of CV death in the kidney transplant population. About 50% of recipients of kidney transplants have elevated homocysteine concentrations, which inversely correlates with kidney function in both adult and pediatric recipients. Normalization of homocysteine concentrations is the goal; however, studies found that while treatment may cause significant reduction in homocysteine concentrations, it is difficult to reach the normal range. Supplementation with folic acid (5 mg/day), vitamin $B_6$, and vitamin $B_{12}$ has been the main therapy for hyperhomocysteinemia.

## Modification of Immunosuppression to Reduce CV Risk

All changes to the immunosuppression regimen should be done after careful assessment of the risk:benefit ratio and in consultation with the transplantation team. Factors to

Abbreviations

analyze include time since transplant, risk of acute rejection, CV risk, and immunosuppression history. When modifying the regimen, the transplantation team rarely discontinues one drug without adding another in its place, and it rarely makes more than one major change to the immunosuppression regimen at a time (except if the dose and/or concentration of multiple agents are higher than needed given the patient's risk for rejection). The team is also cautious when switching from a newer immunosuppressant drug (e.g., TAC or MMF) to an older drug (e.g. CsA or AZA), or when replacing one class of immunosuppressant drug with another (e.g., SRL is potent enough to replace a CNI, but an antimetabolite such as MMF or AZA is not). Tables 1-6 and 1-7 summarize the common immunosuppression-related CV complications and options for modifying the immunosuppression regimen. Trough concentration targets vary at different times post-transplant, and depend on concurrent immunosuppressive drugs and the risk of acute rejection. In addition, adverse effects of immunosuppressant drugs often have a synergistic effect. For example, TAC is associated with a high rate of NODM when used in combination with corticosteroids; however, much lower rates of NODM are reported when TAC is used in a corticosteroid withdrawal regimen.

# Additional Long-Term Issues in Recipients of a Kidney Transplant

### Reproductive Issues

#### Issues in Women

There are many issues that a woman who receives a kidney transplant must consider. Normal menstruation is often restored by successful kidney transplantation; therefore, effective contraceptive measures must be discussed. Traditionally, barrier methods were favored; however, oral contraceptives may be used after considering the risks (e.g., degree of HTN or risk of thrombosis). Routine gynecological screening is important due to the increased risk of malignancy, particularly human papillomavirus-associated cervical and anogenital cancers. The role of the human papillomavirus vaccine in recipients of a transplant is unclear; however, this vaccine has the potential to reduce the risk of post-transplant gynecologic cancers. Due to the transplantation-related increase in CV risk, hormone replacement therapy in menopausal women must also be undertaken with caution.

Although pregnancy is generally safe in women with stable allograft function, the decision to become pregnant should be considered thoroughly as these pregnancies are considered high risk. The incidence of HTN and pre-eclampsia are high, and about 50% of births occur prematurely. Low birth weight due to intrauterine growth restriction is common, and there is a high rate of Cesarean sections. As of 2004, the National Transplantation Pregnancy Registry had collected data on outcomes in pregnancies of 716 women who had received a kidney transplant. The overall rate of major structural malformations in offspring of recipients of kidney transplants is similar to the general population. Because allograft dysfunction or unstable allograft function increases the risk of allograft loss in pregnant women, women should wait at least 2 years after transplantation to attempt pregnancy, should have a creatinine concentration less than 1.5 mg/dL, have little or no proteinuria, and have had no rejection episodes in the prior year.

There is a need for more information about in utero exposure to immunosuppressant drugs because the majority of existing data report on CsA-, AZA-, and prednisone-containing regimens, with little data available for MMF and SRL. There is one case report of severe fetal malformation after in utero exposure to MMF, and in the context of the limited data, leads to some recommendations to transition the woman to an alternative drug (such as AZA) 6 weeks before attempting to conceive. Of course, the risk of acute rejection must be carefully balanced, and women must be closely monitored for acute rejection both during and after pregnancy. Another issue that remains unanswered for the offspring of recipients of transplants is the incidence of neurocognitive and developmental disability that can result from the increase in premature births.

Several factors contribute to a need for increased monitoring in recipients of transplants who are pregnant. Increased volume of distribution and increased metabolic rate (particularly in the third trimester) may necessitate higher doses of a CNI. Serum creatinine concentration tends to decrease during pregnancy due to glomerular hyperfiltration. Another factor that must be considered in the

**Table 1-6. Immunosuppressant Drugs and Cardiovascular Risk**

| Cardiovascular Risk Factor | Immunosuppressants That Increase Cardiovascular Risk | | | |
|---|---|---|---|---|
| | Very Common | Common | Less Common | Rare |
| Hyperglycemia/ new onset diabetes mellitus | Tacrolimus + prednisone | Tacrolimus<br>Prednisone<br>Cyclosporine | Sirolimus | |
| Dyslipidemia | Sirolimus<br>Cyclosporine + prednisone | Cyclosporine<br>Prednisone | | Tacrolimus |
| Hypertension | | Cyclosporine<br>Prednisone<br>Tacrolimus | Sirolimus | |

Abbreviations

**Table 1-7. Modification of the Immunosuppressive Regimen to Manage Comorbid Conditions**

| Drug | Options for Modifying the Immunosuppressive Regimen |
|---|---|
| Cyclosporine | Taper dose to achieve lower trough concentration (trough concentrations about 75–150 ng/mL by 1 year post-transplant)<br>Change to tacrolimus (e.g., in patients with significant hyperlipidemia)<br>Change to sirolimus |
| Prednisone | Taper dose (e.g., decrease from 10 mg/day to 7.5 mg to 5 mg over several months) (most patients can be tapered to 5 mg/day by 3 months post-transplant)<br>Do not discontinue prednisone completely as late (beyond 3 months) discontinuation is associated with high risk of rejection |
| Tacrolimus | Taper dose to achieve lower trough concentration (trough concentrations about 6–8 ng/mL by 1 year post-transplant)<br>Change to sirolimus<br>Change to cyclosporine (e.g., when severe hyperglycemia requires hospitalization) |
| Sirolimus | Taper dose to achieve lower trough concentration (trough concentrations about 6–8 ng/mL by 1 year post-transplant)<br>Change to cyclosporine or tacrolimus<br>Change to mycophenolate mofetil (if patient is also taking a calcineurin inhibitor) |

planning for pregnancy in the recipient of a kidney transplant is the recent data showing that ACE inhibitor or ARB should not be used in the first trimester of pregnancy.

In a study of 54 menopausal recipients of a kidney transplant, hormone replacement therapy was administered using transdermal estradiol and oral progestin. Although 6 months of therapy reduced climacteric symptoms in 75% of women, 31% of patients discontinued therapy due to thrombophlebitis and elevation in liver transaminase concentrations. The decision to begin hormone replacement therapy must be individualized based on analysis of risk and patient preference.

### Issues in Men

Issues faced by male recipients of kidney transplants include fathering children, erectile dysfunction, and benign prostatic hypertrophy. Overall rates of congenital malformations in children of these recipients are not increased compared with the population at large. Erectile dysfunction is common in patients with kidney failure, and kidney transplantation does little to reverse this condition. One randomized, double-blind, placebo-controlled, crossover trial and several retrospective analyses studied the safety and effectiveness of sildenafil in recipients of kidney transplants. Effectiveness was measured by the International Index of Erectile Function, a validated tool for evaluating erectile dysfunction, and significant improvement was reported, similar to results in the general population. Adverse effects were also similar to the general population. No significant changes in CNI concentrations were reported after the introduction of sildenafil. However, sildenafil exposure may be increased by concurrent CNI administration; a pharmacokinetic study found that sildenafil area under the curve and elimination half-life were significantly increased after concurrent TAC administration, and a significant decrease in both systolic and diastolic blood pressure was observed (27 mm Hg and 20 mm Hg, respectively), which is a greater decrease than is normally seen in the general (non-transplant) population. This underscores the importance of using low doses of sildenafil when initiating therapy, and cautious titration of dosage and monitoring of blood pressure. Although experience with tadalafil and vardenafil use in recipients of kidney transplants is limited, concerns are similar to that of sildenafil, including risk of hypotension, interaction with CNIs, and need to adjust dosages in patients with creatinine clearance less than 50 mL/minute.

Benign prostatic hypertrophy often goes undiagnosed before transplantation, particularly in older men who have low or no urine output because they have been on hemodialysis for long time periods. This is treated similarly to the general population of males in which benign prostatic hypertrophy was studied, and some transplantation centers empirically start therapy with tamsulosin and/or finasteride at the time of kidney transplantation.

## Hyperparathyroidism and Bone Disease

A decline in bone mineral density occurs early after kidney transplantation, and many patients experience persistent hyperparathyroidism (tertiary). Pre-existing renal osteodystrophy, post-transplant hypophosphatemia, and immunosuppressants (particularly corticosteroids and CsA) contribute to bone loss. Persistent overproduction of parathyroid hormone can occur despite normal or high calcium concentrations. Overall fracture risk in recipients of kidney transplants is more than 4 times that of the general, non-transplant, population, or about 2% per year; vertebral and metatarsal fractures are most common. Corticosteroid withdrawal has reduced fracture risk.

Bone mineral density via dual energy X-ray absorptiometry scan of the spine, hip, and radius, when possible, should be performed at baseline, and 1 and 2 years post-transplant. Parathyroid hormone, osteocalcin, and alkaline phosphatase concentrations are elevated in patients with active bone resorption. At a minimum, calcium, phosphorus, bicarbonate, and intact parathyroid hormone concentrations should be monitored in the post-transplant period.

Because bone loss occurs rapidly in the early months after transplantation, interventions should begin at the time of transplantation. The goal is to maintain or, if possible, increase bone mass. Electrolyte concentrations should be maintained within the normal range to avoid stimulating the parathyroid gland. Tertiary hyperparathyroidism may persistent for 1 year or longer after transplantation, and parathyroidectomy may be indicated if overproduction of parathyroid hormone does not subside after transplantation.

Post-transplant therapeutic interventions have maintained or increased bone mineral density; however, none have been successful in reducing the risk of fracture. It is clear that calcium and vitamin D supplementation are generally not sufficient to maintain bone mineral density in recipients of a kidney transplant. In a study of stable recipients of a kidney transplant, comparison of alendronate and calcitriol (both in combination with elemental calcium) showed significant increases in both lumbar and femur bone mineral density after 1 year of therapy in both groups. Early bisphosphonate treatment with intravenous pamidronate, administered at the time of transplant and again 1 month later, has had positive effects on bone mass for up to 4 years. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease recommend that recipients of kidney transplants who have a T score less than two standard deviations from normal receive intravenous bisphosphonate therapy. Patients with adynamic bone disease, as evidenced by low parathyroid hormone concentrations, should not receive bisphosphonate therapy because therapy may further reduce the low bone turnover state. Hormone replacement therapy has not been widely studied in the transplant population.

The usefulness of cinacalcet in the kidney transplant population has been demonstrated in several small studies, and offers an alternative to parathyroidectomy. Cinacalcet therapy achieves normalization of calcium and reduction of parathyroid hormone concentrations in patients with persistent post-transplant hyperparathyroidism. However, parathyroid hormone concentrations quickly rebounds after discontinuing therapy. Alkaline phosphatase increases slightly during cinacalcet therapy, and few patients experience gastrointestinal adverse effects.

One major area of concern in pediatric kidney transplantation is short stature resulting from the complex interaction of factors caused by kidney disease that lead to poor growth. Data regarding the use of recombinant human growth hormone in pediatric recipients of kidney transplants have been conflicting, with some studies reporting substantial increase in height and rate of growth, whereas other studies found that growth hormone maintained bone mass but did not affect new bone formation.

### Hyperuricemia and Gout

Hyperuricemia and gout are prevalent in the chronic kidney disease population; up to 28% of recipients of a transplant develop gout. Risk factors in recipients of a kidney transplant include obesity, weight gain, HTN, diuretics, and CsA. Unfortunately, drugs used to treat gout are often avoided in recipients of transplants. Nonsteroidal anti-inflammatory drugs are avoided due to the potential to reduce kidney function in patients taking CNIs, whereas cyclooxygenase 2 inhibitors are avoided due to the potential to increase CV risk. Corticosteroids are a good option, particularly in patients already taking maintenance corticosteroids because the dosage may be titrated up temporarily until the gout resolves. A short pulse of a corticosteroid can also be used in patients on corticosteroid-free regimens. Colchicine should be used with caution in patients with impaired kidney function, and diarrhea may be exacerbated by gastrointestinal adverse effects of MMF. Allopurinol, when dosed according to kidney function is a good option for maintenance therapy; however, caution must be used in patients taking AZA. Allopurinol and AZA share the same metabolic pathway; therefore, when used together, the AZA dose should be reduced by about 75%, with close monitoring for myelosuppression.

### Malignancy

Long-term immunosuppression significantly increases the risk of nonmelanoma skin cancers, in particular squamous cell carcinoma, basal cell carcinoma, and Kaposi's sarcoma. Patients are also at risk for post-transplant lymphoproliferative disease and cervical or anogenital cancers. Antitumor and antiangiogenesis properties of SRL seen in animal studies are now beginning to emerge in human studies. Compared with patients maintained on CsA-SRL regimens, patients who underwent CsA withdrawal 3 months after transplantation experienced significantly lower 5-year rates of both skin and nonskin cancers. Overall, maintenance immunosuppression with SRL appears to decrease risk of developing any post-transplant malignancy by 60%. In addition, transplant malignancy registry data shows that TAC/MMF immunosuppression regimens are associated with a lower rate of *de novo* malignancies compared with CsA/AZA regimens.

Fifteen recipients of kidney transplants whose immunosuppression regimen consisted of CsA, MMF, and a corticosteroid were converted to SRL and corticosteroid after diagnosis of Kaposi's sarcoma. In all patients, complete regression (confirmed visually) of the lesions was seen by 3 months, and was confirmed pathologically at 6 months. No patient developed acute rejection, and kidney function remained stable.

### Preventive Care

The importance of routine screening and preventive care for recipients of kidney transplants cannot be stressed enough. This includes dental examinations, influenza and pneumococcal vaccinations, and cancer screening (e.g., dermatologic, gynecologic, mammogram, prostate, and colonoscopy). Vaccination may not be effective after periods of intense immunosuppression such as early in the perioperative period. For example, the influenza vaccine is generally not given if a patient has been transplanted within 3 months of the vaccination period. Live vaccines (such as varicella vaccine) are generally avoided after transplantation. Patients must be educated about the high risk of skin cancers and preventive measures such as sunscreen and protective clothing. For patients with a prior history of malignancy or at a high risk for developing

Abbreviations

**Table 1-8. Role of the Clinical Transplant Pharmacist[a]**

| Phase | Responsibilities |
|---|---|
| Perioperative | Identify and solve drug-related problems |
| | Educate the recipients of transplants and their families about drugs and adherence |
| | Act as a liaison between patient and multidisciplinary team for drug issues |
| | Prepare for and assist with discharge planning |
| | Provide drug information to multidisciplinary team |
| Post-transplant | Evaluate the drug regimen on a regular basis |
| | Communicate drug issues to appropriate member of multidisciplinary team |
| | Participate in design, implementation, and monitoring of comprehensive care plans |

[a]As described by the United Network for Organ Sharing.

malignancy, an immunosuppression regimen containing SRL should be considered due to the evolving body of evidence supporting the drug's anti-tumor effects. Additional screening should be performed in patients with specific conditions (e.g., ophthalmologic and podiatric screening in patients with DM).

### Lifestyle Modification

Patient education and support is important when attempting lifestyle modifications in the post-transplantation setting. Therapeutic lifestyle changes recommended for managing dyslipidemia may have beneficial effects on control of DM and HTN. General components of therapeutic lifestyle changes include avoidance of saturated fats, weight reduction, increased physical activity, treatment of elevated blood glucose, and avoidance of alcohol.

Practitioners must remember that weight loss can be particularly difficult for patients given the effects of corticosteroids on appetite and the lifting dietary restrictions after transplantation. Managing HTN may also be impaired by increased sodium intake after transplantation while protein intake and alcohol may exacerbate gout. Exercise, while important, does not appear to modify the risk of CV events to a significant degree, most likely demonstrating the multifactorial nature of post-transplant CV disease. Weight-bearing exercise is beneficial in maintaining bone mass.

### Adherence

Poor adherence to prescribed post-transplant regimens continues to be a significant problem in recipients of transplants of all ages, and although difficult to quantify, accounts for a significant proportion of late allograft loss. In adults, nonadherence has been associated with many risk factors; however, few are modifiable. Nonadherence can be linked to patient beliefs about drugs; therefore, education is key. Poor adherence may be linked to the cosmetic adverse effects of immunosuppression or behavioral issues arising from normal development and the need for independence in adolescents.

Late problems with adherence often arise from the economic burden of purchasing the needed drugs, particularly when Medicare coverage of immunosuppressant drugs ends 3 years after transplantation. Follow-up is less frequent by that time; therefore, proactive strategies must be in place to ensure that alternative drug coverage is available. Although Medicare Part D coverage may improve the patient's accessibility to drugs required for transplantation (other than immunosuppressants covered under Part B), significant variations in copays and premiums exist between drug plans, and this may have either positive or negative effects on adherence, depending on the individual patient's coverage. Pharmacists involved in the design of therapeutic regimens for these patients should be knowledgeable about Medicare Part D.

## Role of the Pharmacist

Recipients of kidney transplants surely represent one of the best examples of complex patients who can benefit significantly from pharmaceutical care provided by a knowledgeable and caring pharmacist. The importance of the pharmacist is recognized by the United Network for Organ Sharing, whose bylaws require transplantation programs to have a clinical transplantation pharmacist dedicated to providing pharmaceutical care for recipients of transplants. Within the bylaws, specific responsibilities of the pharmacists are outlined (see Table 1-8), complementing the activities of other members of the multidisciplinary transplantation team. The clinical transplantation pharmacist is encouraged to participate in clinical research studies, quality assurance, and public and professional education. In addition, the therapeutic complexities of the recipient of a kidney transplant represent great opportunities for pharmacists to provide medication therapy management services to patients covered under Medicare Part D and to improve adherence to the transplant drug regimen.

## Conclusion

Managing recipients of kidney transplants involves complex analysis of patients' risk for both transplantation-specific complications, such as rejection and malignancy, and risks related to CV and other post-transplant diseases. The clinical transplantation pharmacist has numerous opportunities to improve the overall care of the patient and is an essential member of the multidisciplinary team, which serves to broaden the focus of care beyond the function of the transplanted kidney.

## Annotated Bibliography

1. Boots JM, Christiaans MH, van Hooff JP. Effect of immunosuppressive agents on long-term survival of renal transplant recipients: focus on the cardiovascular risk. Drugs 2004;64(18):2047–73.

This excellent article reviews the effects immunosuppressant drugs have on the CV system. As pharmacists, we often think about the detrimental effects of CNIs and corticosteroids on our patients' CV health. However, it is not always in the forefront of our minds to consider the effects that drugs such as MMF and AZA may cause, particularly the relationship between anemia and left

ventricular hypertrophy. The authors provide an excellent background on the pathogenesis of atherosclerosis and arteriosclerosis, as well as proposed mechanisms behind the immunosuppressants' effects on HTN, left ventricular hypertrophy, hyperlipidemia, DM, homocysteine concentrations, and fibrinolysis. This article also contains a great table comparing the effects of the immunosuppressive drugs on specific CV risk factors.

2. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernandez D, et al. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. Transplantation 2003;75(S10):SS3–SS24.

   These consensus guidelines offer the transplantation community a place to begin in assessing a transplant recipient's risk of NODM and clear-cut guidelines for diagnosis. The guidelines also address goals of therapy for managing blood glucose, blood pressure, and lipids in patients with DM. However, the information that pharmacists are most interested in is very generalized and because of the date published, the guidelines do not address newer drug classes such as incretin mimetics. No specific guidelines are given for treating recipients of transplants, mostly due to the fact that controlled trials are missing in this population. Treatment of pre-existing DM or NODM is a challenge that falls to pharmacists' clinical judgment and requires close analysis of patient-specific factors such as body habitus, kidney function, and concurrent drugs that will impact the success of the chosen drug regimen.

3. Holdaas H, Fellstrom B, Jardine AG, Holme I, Nyberg G, Fauchald P, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomized, placebo-controlled trial. Lancet 2003;361:2024–31.

   This is a notable study due to the fact that it is the largest, prospective, placebo-controlled trial of HMG CoA reductase inhibitor therapy in recipients of kidney transplants. Reduction in the primary end point (occurrence of first major adverse cardiac event) in fluvastatin-treated patients compared with placebo-treated patients did not reach statistical significance. However, significant reduction in cardiac death and nonfatal myocardial infarction in patients receiving fluvastatin is a clinically important finding. In addition, initiating lipid-lowering therapy in the placebo arm over the course of the study may have affected the results. Application to the transplant population in the United States is somewhat limited by the predominance of Caucasian patients and CsA-based immunosuppression therapy used in this study. Despite the limitations of this study, it highlights the importance of lipid-lowering therapy in the kidney transplant population.

4. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen D, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med 2003;349(24):2326–33.

   This is an interesting study that looked at the development and progression of CAN in 120 patients with type 1 DM who received kidney-pancreas or kidney transplants. By performing pre-implantation and frequent post-transplant biopsies, the authors provide exceptional insight into CAN. These data are particularly interesting because kidney-pancreas donors are typically young and healthy, representing the best quality kidneys that patients might receive. Mild CAN was present in 94% of 1-year biopsies, progressing to severe CAN in 58% of biopsies by 10 years post-transplant. Two distinct phases of CAN were noted. The first (early) phase was influenced by immunologic factors (severe acute rejection and subclinical rejection) and ischemia-reperfusion injury (acute tubular necrosis). The second (late) phase was characterized by progressive hyalinosis, sclerosis, and fibrosis, likely attributable to chronic CNI-related injury. This study demonstrates the importance of acute tubular necrosis and rejection in the initial development of CAN, and CNI toxicity in the progression of CAN.

5. National Kidney Foundation. Clinical Practice Recommendations for Anemia in Chronic Kidney Disease in Transplant Recipients. Am J Kidney Dis 2006;47(5 suppl 3):S110–S116.

   These guidelines offer a comprehensive overview of the mechanisms behind post-transplant anemia, separating the factors into chronic kidney disease and transplantation-specific factors. The guidelines contain an excellent review of the limited studies that have been performed in the kidney transplant population, as well as the limited data available to demonstrate the relationship between post-transplant anemia and CV events. Unfortunately, the authors do not provide specific recommendations for managing recipients of transplants nor do they address the importance of and the practical considerations for iron administration. In addition, there is no mention of post-transplant erythrocytosis, a less common but clinically important condition in which the hematocrit rises above 50%, potentially increasing the patient's risk of HTN and CV events.

6. Waid T; CRAF Study Group. Tacrolimus as secondary intervention vs. cyclosporine continuation in patients at risk for chronic renal allograft failure. Clin Transplant 2005;19:573–80.

   A novel approach to managing patients with CAN is presented in this multicenter, secondary intervention study. The role of CNIs in the development and progression of CAN is established, so it is a novel idea to study the effect of conversion from CsA to TAC. Although this study did not show a difference in allograft loss between the two groups at 2 years, it is likely too early to see such an effect, despite the stabilization of serum creatinine concentration and improvements in lipid profile in TAC-treated patients. All patients in this study are being followed for an additional 3 years, and it will be exciting to see those results. Because much of the data regarding CAN is based on CsA-based therapy, this study will provide important information on any distinction between the two available CNIs in the progression of CAN.

7. Diekmann F, Campistol JM. Conversion from CNIs to sirolimus in chronic allograft nephropathy: benefits and risks. Nephrol Dial Transplant 2006;21:562–8.

   This editorial provides a comprehensive summary of SRL conversion studies in patients with CAN. The authors present the risk:benefit ratio for conversion to SRL based on results of various trials, and recommend characteristics of patients who may benefit most from conversion to SRL. Specific suggestions for the approach to conversion, such as dosing of SRL, time to overlap the CNI and SRL, and recommendations for dosing of concurrent immunosuppressive drugs are reviewed in detail.

8. Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R Jr, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients. Am J Transplant 2004;4(suppl 7):S13–S53.

These guidelines provide a comprehensive overview of the diagnosis and management of dyslipidemia in the recipient of a kidney transplant. In addition to providing detailed guidance about specific drug therapies, the guidelines also provide an in-depth description of therapeutic lifestyle changes, as well as a comprehensive list of Web pages that may benefit the clinician. The guidelines offer therapeutic recommendations for adolescent patients, an age group where guidance is often lacking. The authors provide a comprehensive discussion of every aspect related to dyslipidemia and kidney transplantation, and include many useful tables and figures that summarize the key points of the recommendations.

9. Palmer SC, Strippoli GFM, McGregor DO. Interventions for preventing bone disease in kidney transplant recipients: a systematic review of randomized controlled trials. Am J Kidney Dis 2005;45:638–49.

This meta-analysis provides an excellent analysis of the major, yet small studies using bisphosphonates, vitamin D analogues, calcitonin, and calcium supplementation for the prevention of bone loss after kidney transplantation. Using these data, the authors provide estimates of fracture risk for patients who receive the above-mentioned therapies versus untreated patients. The authors also provide a nice summary of the published guidelines about prevention of bone disease in recipients of transplants. However, the authors do not provide concise recommendations, let alone a specific algorithm for the prevention of bone disease, leaving this to the discretion of the reader.

10. Chisholm MA, Roberts E. Medicare part D coverage and its influence on transplant patients' out-of-pocket prescription expenses. Am J Transplant 2006;6:1737–42.

This article is essential reading material for pharmacists managing recipients of transplants who are covered by Medicare Part D. It is also a useful tool for managing any patient covered under Medicare. The authors provide an excellent summary of the key aspects of Medicare Parts B and D coverage in recipients of kidney transplants and also provide excellent patient case studies that highlight important aspects of this often confusing issue.

11. McKay DB, Josephson MA. Reproduction and transplantation: report on the AST consensus conference on reproductive issues and transplantation. Am J Transplant 2005;5:1592–9.

The proceedings of this important consensus conference provide readers with summaries of registry data about outcomes of pregnancy after kidney transplantation. The report also provides broad recommendations and considerations for managing contraception, pregnancy, breastfeeding, immunosuppression, and treatment of rejection during these important periods in the female transplant recipient of a transplant. There is an excellent table that summarizes recommendations for timing of pregnancy, comorbidities that may affect outcomes, preconception counseling, obstetrical management, and a comprehensive list of research goals that greatly need to be addressed in these women.

12. Bernardo JF, McCauley J. Drug therapy in transplant recipients—special considerations in the elderly with comorbid conditions. Drugs Aging 2004;21(5):323–48.

The care of recipients of kidney transplants has become more complicated as we begin to transplant more elderly patients. These patients, although considered healthy enough to undergo the transplant surgery, generally come to transplant with numerous comorbidities that often challenge practitioners. Older and/or poorer quality donor kidneys are often used in the elderly due to expectations that the life expectancy of these patients will be shorter than in younger recipients. Immunosuppressive regimens are often modified in fear of over-immunosuppressing these patients, who are at increased risk for CV events, infection, and malignancy. This review provides comprehensive information about the effects of aging on the immune system and pharmacokinetics of drugs, as well as an in-depth discussion of the various drug classes used to treat comorbid conditions in this patient population.

# SELF-ASSESSMENT QUESTIONS

Please start new PSAP-VI online test.

1. L.M. is a 42-year-old woman who received a living-related donor transplant 2 years ago. At her latest visit, she had an elevated serum creatinine concentration (2.4 mg/dL from 0.9 mg/dL). After kidney biopsy, the diagnosis made was moderate rejection. She was treated with a corticosteroid pulse followed by rabbit antithymocyte globulin. Which one of the following preventive care measures is most important for L.M. within the next 6 months?
   A. Pneumococcal vaccine.
   B. Influenza vaccine.
   C. Routine cancer screenings.
   D. Bone mineral density screening.

**Questions 2 and 3 pertain to the following case.**
M.P. is a 58-year-old man who received a kidney transplant 3 years ago from a deceased donor. M.P. is currently receiving cyclosporine, mycophenolate mofetil, and prednisone. His comorbidities include type 2 diabetes mellitus, hypertension, and coronary artery disease. After a rise in his creatinine concentration from 1.9 mg/dL to 2.7 mg/dL and rise in proteinuria from 325 mg/day to 1140 mg/day, a kidney biopsy was performed, revealing moderate chronic allograft nephropathy.

2. Which one of the following changes to the immunosuppression regimen is warranted based on the information presented above?
   A. Change cyclosporine to sirolimus.
   B. Change cyclosporine to tacrolimus.
   C. Change mycophenolate mofetil to sirolimus.
   D. Discontinue cyclosporine; adding another drug is not necessary.

3. M.P.'s blood pressure was elevated during his biopsy admission and is 160/85 mm Hg at an outpatient visit 1 week later; he currently takes metoprolol succinate 50 mg/day. Which one of the following interventions is most appropriate for managing M.P.'s blood pressure?
   A. Titrate dose of metoprolol.
   B. Withdraw metoprolol and add lisinopril.
   C. Add nifedipine to current regimen.
   D. Add losartan to current regimen.

4. C.W. is a 38-year-old African-American man with kidney disease secondary to malignant hypertension who started on hemodialysis at age 18. He received his first kidney transplant in 1999, but it failed due to acute rejection within 1 year. He received a second transplant in 2002, has had no rejection episodes, and has been diagnosed with new-onset diabetes mellitus. C.W. is currently receiving tacrolimus (recent trough concentrations of 11–14 ng/mL), mycophenolate mofetil (2 g/day), and prednisone (5 mg/day). The attending nephrologist would like to modify the patient's immunosuppression regimen before starting an oral hypoglycemic or insulin therapy. Which one of the following is the best modification for C.W.?
   A. Taper and discontinue prednisone over 2 months.
   B. Switch tacrolimus to cyclosporine.
   C. Lower the target trough of tacrolimus.
   D. Lower the target trough of tacrolimus and taper prednisone to 2.5 mg/day.

5. K.M. is a 25-year-old woman who received a kidney transplant about 3 years ago and expresses her desire to have children. She had a mild rejection episode 6 months post-transplant and was successfully treated with a corticosteroid pulse. Her current regimen consists of tacrolimus and mycophenolate mofetil. Based on current knowledge about pregnancy after transplantation, which one of the following changes to her immunosuppression regimen is most appropriate?
   A. Switch tacrolimus to cyclosporine.
   B. Switch mycophenolate mofetil to azathioprine.
   C. Switch mycophenolate mofetil to azathioprine and add prednisone.
   D. Switch tacrolimus to sirolimus.

**Questions 6 and 7 pertain to the following case.**
A.B. is a 56-year-old man who received a kidney transplant about 2 years ago. He is concerned about having brittle bones and has recently had a DEXA scan, but the results are not available yet. Laboratory values at this visit include bicarbonate 23 mEq/L, serum creatinine 1.6 mg/dL, calcium 9.9 mg/dL, phosphorus 2.2 mg/dL, and intact parathyroid hormone 202 pg/mL.

6. Which one of the following oral drugs is the best therapy for A.B. at this time?
   A. Calcium carbonate.
   B. Calcitriol.
   C. Vitamin $D_3$.
   D. Sodium bicarbonate.

A.B. returns to clinic 3 months later with the results of his DEXA scan, which shows that A.B. has osteopenia. Laboratory values at this visit include bicarbonate 24 mEq/L, serum creatinine 1.3 mg/dL, calcium 10.6 mg/dL, phosphorus 2.5 mg/dL, and intact parathyroid hormone 449 pg/mL.

7. Which one of the following therapies is most appropriate for A.B. at this time?
   A. Alendronate.
   B. Cinacalcet.
   C. Calcitonin.
   D. Testosterone.

**Questions 8 and 9 pertain to the following case.**
S.A. is a 59-year-old woman with kidney disease from type 2 diabetes. She is 4 years post-transplantation, and despite lifestyle changes and atorvastatin 80 mg/day, her lipid profile reveals total cholesterol 240 mg/dL, low-density lipoprotein 138 mg/dL, high-density lipoprotein 39 mg/dL, and triglycerides 212 mg/dL. Hemoglobin A1c is 10.2% and blood pressure is 138/92 mm Hg. She currently takes cyclosporine (trough 248 ng/mL), mycophenolate mofetil 2 g/day, and prednisone 7.5 mg/day.

8. Which one of the following is the most appropriate way to modify her immunosuppression regimen to improve the lipid profile?
   A. Switch cyclosporine to tacrolimus.
   B. Switch cyclosporine to sirolimus.
   C. Decrease dosages of cyclosporine and prednisone.
   D. Switch mycophenolate mofetil to azathioprine.

Six months later, S.A.'s lipid goals still have not reached target (total cholesterol 229 mg/dL, low-density lipoprotein 114 mg/dL, high-density lipoprotein 42 mg/dL, and triglycerides 235 mg/dL).

9. Which one of the following is the most appropriate drug therapy for the patient at this point?
   A. Add colesevelam.
   B. Add ezetimibe.
   C. Add nicotinic acid.
   D. Add gemfibrozil.

**Questions 10–12 pertain to the following case.**
S.K. is a 60-year-old man who received a kidney transplant 4 years ago. Current medical issues include new onset diabetes mellitus, hypertension, coronary artery disease, tobacco use, and body mass index of 33 kg/m$^2$.

10. At this time, which one of the following lifestyle changes would be most beneficial to his (and his kidney's) survival?
    A. Exercise.
    B. Smoking cessation.
    C. Alcohol avoidance.
    D. Weight reduction.

11. S.K.'s new onset diabetes mellitus is currently being managed only by diet, and his most recent hemoglobin A1c was 9.2%. Which one of the following drugs is the best choice for S.K.?
    A. Pioglitazone.
    B. Glipizide.
    C. Metformin.
    D. Acarbose.

S.K.'s lipid profile obtained 1 week ago shows the following: total cholesterol 208 mg/dL, low-density lipoprotein 90 mg/dL, high density lipoprotein 42 mg/dL and triglycerides 310 mg/dL. S.K. refuses to take a hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitor because he developed severe muscle pain when he took simvastatin in the past.

12. Based on these results, which one of the following interventions is most appropriate for S.K.?
    A. Gemfibrozil.
    B. Colesevelam.
    C. Ezetimibe.
    D. Niacin.

13. Which one of the following maintenance immunosuppression regimens would be most effective in preventing long-term complications in a patient with significant family history of diabetes mellitus, established hyperlipidemia, and a body mass index of 36 kg/m$^2$?
    A. Tacrolimus, mycophenolate mofetil, and prednisone.
    B. Tacrolimus, mycophenolate mofetil, and early corticosteroid withdrawal.
    C. Cyclosporine, mycophenolate mofetil, and prednisone.
    D. Cyclosporine, mycophenolate mofetil, and early corticosteroid withdrawal.

14. F.T. is a 38-year-old woman who received a transplant in 2005. She has had multiple fractures, most recently 2 months ago. Laboratory values at the time included serum creatinine 1.6 mg/dL, proteinuria 280 mg/day, calcium 11.2 mg/dL, and intact parathyroid hormone 1090 pg/mL; she takes tacrolimus, mycophenolate mofetil, and prednisone. Today, F.T. presents to the clinic with pain and swelling in her big toe, which is assumed to be gout. Which one of the following drugs would be the best for this gout flare?
    A. Prednisone.
    B. Ibuprofen.
    C. Celecoxib.
    D. Colchicine.

15. S.W., who received a kidney transplant 22 years ago and still has adequate allograft function, was recently diagnosed with squamous cell carcinoma. His current regimen includes cyclosporine (trough 96 ng/mL) and prednisone 2.5 mg/day. Which one of the following is the most appropriate modification to his immunosuppression regimen?
    A. Switch cyclosporine to tacrolimus.
    B. Switch cyclosporine to sirolimus.
    C. Switch cyclosporine to mycophenolate mofetil.
    D. Discontinue cyclosporine and increase prednisone dose.

**Questions 16 and 17 pertain to the following case.**
M.G. is a 45-year-old recipient of a kidney transplant about 13 years ago who is taking cyclosporine (trough 249 ng/mL), azathioprine (50 mg/day), prednisone (5 mg every other day), metoprolol, diltiazem, atorvastatin, finasteride, and aspirin. He has recently been diagnosed with new-onset

diabetes mellitus and a kidney biopsy for rising creatinine concentration revealed chronic allograft nephropathy. Twenty-four-hour urine collection reveals creatinine clearance of 46 mL/minute and protein excretion of 440 mg/day.

16. Which one of the following changes to his immunosuppressive regimen is the best choice for M.G.?
    A. Switch cyclosporine to sirolimus.
    B. Taper prednisone and cyclosporine dose.
    C. Switch cyclosporine to mycophenolate mofetil.
    D. Switch cyclosporine to tacrolimus.

17. M.G.'s blood pressure is 150/86 mm Hg at his next visit. Which one of the following drugs should be started at this time?
    A. Furosemide.
    B. Hydrochlorothiazide.
    C. Terazosin.
    D. Losartan.

18. D.T. is a 56-year-old man who received a kidney transplant in 2004. He has a history of myocardial infarction and hypertension. He is currently taking metoprolol succinate and clonidine for his blood pressure, and his serum creatinine is 1.4 mg/dL, total cholesterol is 179 mg/dL, and hemoglobin is 15.9 g/dL. Which one of the following drugs should be added for the management of D.T.'s hypertension at this time?
    A. Labetalol.
    B. Minoxidil.
    C. Lisinopril.
    D. Nifedipine.

19. S.L. is a 46-year-old woman who presents for routine follow-up 7 months after her kidney transplant. Current issues include new onset diabetes mellitus (hemoglobin A1c 6.3%), dyslipidemia (total cholesterol 187 mg/dL, low-density lipoprotein 121 mg/dL, high-density lipoprotein 40 mg/dL, and triglycerides 256 mg/dL), and tobacco use. Patient states that "she is starting to go through menopause" and appears nervous and upset. Which one of the following issues is most important to address with pharmacological therapy at this time?
    A. Tobacco dependence.
    B. Perimenopausal symptoms.
    C. Dyslipidemia.
    D. Diabetes mellitus.

20. L.M. is a 29-year-old woman who received a living-donor kidney transplant in 1998 who has a serum creatinine of 1.2 mg/dL, 24-hour creatinine clearance of 58 mL/minute, and microalbuminuria (between 100 mg/day and 225 mg/day). The patient's comorbidities include hypertension (treated with amlodipine and ramipril) and hyperlipidemia (treated with simvastatin). Her current immunosuppressive regimen consists of cyclosporine (trough 145 ng/mL), mycophenolate mofetil, and prednisone. L.M. tells you that she and her husband hope to conceive their second child within the next few months and asks if that is okay. Which one of the following responses is most appropriate?
    A. She can safely become pregnant at this time.
    B. She cannot safely become pregnant at this time.
    C. Further testing is required before she becomes pregnant.
    D. After drug changes, she can become pregnant.

## Abbreviations