Topics in Transplantation Medicine for General Nephrologists

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Before transplantation, the general nephrologist is the primary resource for potential kidney transplantation recipients. After transplantation, the general nephrologist is increasingly managing transplant medications and complications. We provide evidence-based management strategies for common clinical issues. Linking our approach with the data allows the clinician to explore each subject in greater depth to tailor care to individual patients.

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General nephrologists play an ever-increasing role in transplantation care, both pretransplantation and after the procedure. Before the transplant, the general nephrologist is the primary advocate and reference for the patient. As advances in the field have prolonged the survival of kidney transplants and their recipients, the need for long-term management of renal transplant function and long-term monitoring for complications following the transplant has, in turn, also increased. From the patient's perspective, obtaining this management and monitoring from their general nephrologist has distinct advantages. The general nephrologist has a longitudinal relationship with the patient and is often more accessible than physicians at the transplant center. Recognizing the pivotal role of the general nephrologist in the care of the transplant candidate and recipient, this paper provides evidence-based guidance for common clinical questions in the preparation of patients for transplantation and management of patients after their renal transplant.

Which Patients Benefit Most from Receiving Kidneys from Non-Standard Criteria Donors?

The number of people on the wait list for a deceased donor kidney transplant (DDKT) has doubled to more than 80,000 in just the last 10 years (1). In the same time period, the number of deceased donors and living donors has increased only marginally (5800 to 8000 and 4500 to 6300 donors, respectively). Older patients, age 50 to 64 years, are the fastest growing group to be added to the wait list. Average time on the wait list nationally is now approximately 5 years, and longer for minority or highly-sensitized patients (1).

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The increased mortality associated with wait list time has prompted UNOS to create a framework to offer kidney transplants to patients that may benefit most from decreased time on the list (*i.e.*, patients with the greatest risk of death). In 2003, UNOS implemented a system to make use of kidneys from Extended Criteria Donors (ECD, donor age >60 or donor age >50 with 2 of 3 criteria: stroke as cause of death, elevated creatinine, or hypertension). Kidneys meeting these criteria had been used before 2003 (11% of DDKT performed in 1994 and 16% of those in 2003). Since 2003, however, ECD kidneys are only offered to patients on the general wait list who have been counseled on the merits of the ECD program and agreed in advance that it benefits them to accept these kidneys.

There are data showing that shortened time on the wait list provides a survival benefit in addition to the obvious quality of life advantage to older patients and those with co-morbidities, including diabetes (2). Furthermore, at 1, 2, and 3 years post-transplant, in older recipients, there was no significant difference between Standard Criteria Donor (SCD) and ECD kidney transplants in terms of serum creatinine, graft survival, or patient survival (3,4). In some studies, however, transplantation of ECD kidneys has been associated with a greater risk of graft loss (5,6),

Use of Donation after Cardiac Death (DCD) donors is another mechanism for increasing the donor pool. As opposed to SCD donors, who are brain dead, DCD donors have asystole diagnosed before initiation of organ procurement. There is an increase in delayed graft function (dialysis in the first week after transplantation) for recipients of DCD kidneys, and DGF has predicted worse transplant outcomes in other settings (7). However, multiple groups have shown that long-term outcomes are similar between patients who receive standard kidneys and DCD kidneys (8–10).

Selecting appropriate patients for nonstandard kidneys and counseling them appropriately can be a challenge. Consideration of wait list time, overall health status, and desire for

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transplantation must all be considered in selecting patients for ECD kidneys. When hearing about ECD or DCD kidneys, patients may be concerned that these organs are not optimal. Redirection of the conversation to the relative benefits for the individual regarding faster transplantation, potential mortality benefit, and the fact that survival with a functioning graft may still occur with the ECD is recommended.

How Is Patient Cardiovascular Risk Modified by Transplantation?

Cardiovascular disease remains the leading cause of death with a functioning kidney transplant (11). As the age and complexity of transplant recipients increases, the impact of cardiac disease is likely to grow. Strategies to minimize cardiac endpoints have focused on identifying patients before transplantation who are at elevated risk for cardiac complications and on modifying cardiac risk factors post-transplantation. Recent studies have questioned the efficacy of our attempts limit cardiovascular outcomes and have defined heart failure as another post-transplantation complication.

The goal of the pretransplant cardiac evaluation has been to identify patients whose risk for adverse cardiac events warrants further evaluation and possible intervention. Clinical history and noninvasive imaging have been the basis for determining this risk. Current American Society of Transplantation (AST) recommendations suggest screening noninvasive stress tests for transplant candidates with elevated risk for coronary disease with angiography for patients with a positive stress test, and revascularization for patients with stenotic lesions (12 and Figure 1). Traditional cardiac risk factors which have been shown to be relevant in transplant patients include diabetes, age >50 years, history of angina, congestive heart failure, an abnormal EKG, smoking, dyslipidemia, hypertension, and cerebrovascular or peripheral vascular disease. Patients who lack identified risk factors had a low incidence of cardiac events post-transplantation and would be less likely to have significant risk reduction by further cardiac evaluation (13–15).

There are several areas of controversy with these recommendations. These screening guidelines focus on coronary disease despite evidence that cardiovascular pathology in kidney disease is more complex (16). In addition, there is little consensus on what to do with a positive stress test in an asymptomatic candidate for transplantation because revascularization in this setting may not benefit patients. Conversely, because of the extraordinary incidence of coronary disease in patients with renal disease, others contend that coronary angiography should be used as the screening examination for most transplant candidates (17,18).

Coronary revascularization for asymptomatic patients has not proven beneficial for nontransplant patients (19,20), and there are very limited published data for potential transplant recipients. The only study that has attempted to define the role of coronary revascularization using a randomized population of potential transplant recipients into groups receiving revascularization or medical therapy for asymptomatic coronary disease was terminated after enrollment of only 26 patients with nine myocardial infarctions in the medical management arm and two myocardial infarctions in the revascularization arm (21). Not only was this study limited by small sample size and number of events, but also by the definition of medical management, which was limited to aspirin and calcium channel blockers, not standard practice today. We concur with the investigators responsible for that study that revascularization of asymptomatic transplant candidates is worth further study.

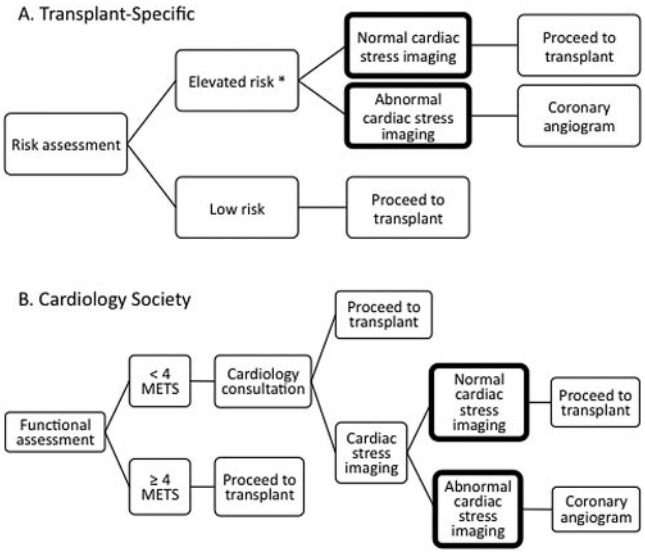

Figure 1. An algorithm of assessment of peri-transplant cardiac risk compared with recommendations of the cardiology societies. Recognizing the high prevalence of cardiac disease in patients with advance renal disease, increased intensity of screening is recommended for many patients before transplantation (A, OHSU application of these recommendations). Elevation of risk in our patients is conferred by presence of diabetes, age >50, history of angina, congestive heart failure, an abnormal EKG, smoking, dyslipidemia, hypertension, and cerebrovascular or peripheral vascular disease. This policy is supported by the ASN and AST, but little prospective data have been collected regarding the efficacy of this screening program. (B) Alternatively, cardiology societies reserve stress imaging for most patients not undergoing vascular surgery who are not symptomatic.

Cardiovascular disease in patients with kidney disease extends beyond coronary vascular plaque formation to myocardial hypertrophy, ventricular dilation, and vascular calcification (16). Recent reports indicate that pretransplantation congestive heart failure (CHF) predicts mortality postevaluation for transplantation and that CHF may be a consequence of transplantation. While it may not be surprising that patients with CHF do worse than those without, the strength of the association and evidence that relatively modest cardiac dysfunction (ejection fraction of 41% to 50% by SPECT imaging) predicts poor outcomes independent of coronary ischemia heightens the concern for patients with this common problem (22). Because kidney transplantation reestablishes the cardiac-renal axis for management of fluid and solutes, one could hypothesize stabilization of myocardial dysfunction after kidney transplantation. However, at least two retrospective studies have found that *de novo* development of CHF is common and carries a poor prognosis (23,24).

Post-transplantation management of cardiac disease is as unsettled as the pretransplantation care. Agents with proven to lower cardiovascular risk in the renal or general population (for example, aspirin, β-blockers, statins, and ACE-Is/ARBs) either have not shown similar efficacy in the post-transplantation or have not been tested. This lack of data may explain why these agents are used with less frequency post-transplantation. The lone randomized trial evaluating medications with established cardioprotective effects in the general population in transplant recipients is the ALERT trial. This randomized trial studied the role of fluvastatin in a largely European transplant cohort. Like studies in the general population, there was a reduction in cardiac events for patients treated with fluvastatin, but the robust mortality benefit with statins in the general population was not seen in transplant recipients (25).

The ALERT study illustrates two important points, that cardiovascular risk is modifiable, and, importantly, that agents need to be tested in transplant populations as results in non-transplant groups may not be generalizable. To this end, the role of ACE inhibitors in reducing cardiovascular outcomes is being evaluated in a randomized study of transplant patients (26). Lack of data, in addition to potential toxicity, may explain the low rates of use of traditional cardioprotective medications for transplant recipients (27). Hopefully, as cardiac issues in kidney transplant patients have now been better defined, we will now accumulate data assessing the efficacy of diagnostic and treatment practices to intervene and prevent the development of debilitating disease.

What Are Common Strategies in the Diagnosis and Management of BK Nephropathy?

BK nephropathy (BKN) has emerged as major cause of kidney allograft dysfunction and graft loss. The clinical presentation of BK nephropathy is usually an asymptomatic worsening of allograft function. Hematuria (gross or microscopic), pyuria, and ureteral stenosis may also occur. Without appropriate treatment, BK nephropathy can lead to the loss of the transplanted kidney. Patients develop viruria, followed by viremia and subsequent nephropathy with incidence of 25%, 10%, and 6%, respectively (28,29). Diagnosis is usually made based on plasma BK PCR and characteristic findings on the kidney transplant biopsy (30). Interstitial nephritis, loss of tubules and viral inclusions in the nuclei of the tubular epithelial cells is the usual pattern on an allograft biopsy showing disease. Some centers decrease immunosuppression if the plasma test detects any virus whereas others use a cut-off of 10^4 copies. A viral load of 10^7 copies in the urine is considered to be clinically significant by centers that screen with urine PCR. More centers are moving toward surveillance strategies and checking BK PCR at predetermined time intervals. This preemptive strategy hopes to diagnose BK disease early and avoid development of irreversible graft dysfunction (31).

Measured reduction in immunosuppression remains the cornerstone treatment for BK viremia and nephropathy (Figure 2). The "net immunosuppressive state" is considered to be the most important risk factor for development of BKN. Currently there are no proven agents available to directly treat the viral infection. As a first step, usually the antimetabolite agent (mycophenolate or azathioprine) is decreased or stopped. Some centers decrease the dose and target level for the calcineurin inhibitor (cyclosporine or tacrolimus) whereas others completely stop the calcineurin inhibitor and maintain patients on a prednisone and sirolimus based regimen. Response to decrease in immunosuppression is monitored by checking plasma BK PCR at regular intervals, usually every 2 weeks. Renal function needs to be monitored closely as there is always concern for precipitating rejection with decrease in immunosuppression (32).

Adjuvant therapies are used if the initial strategy is not

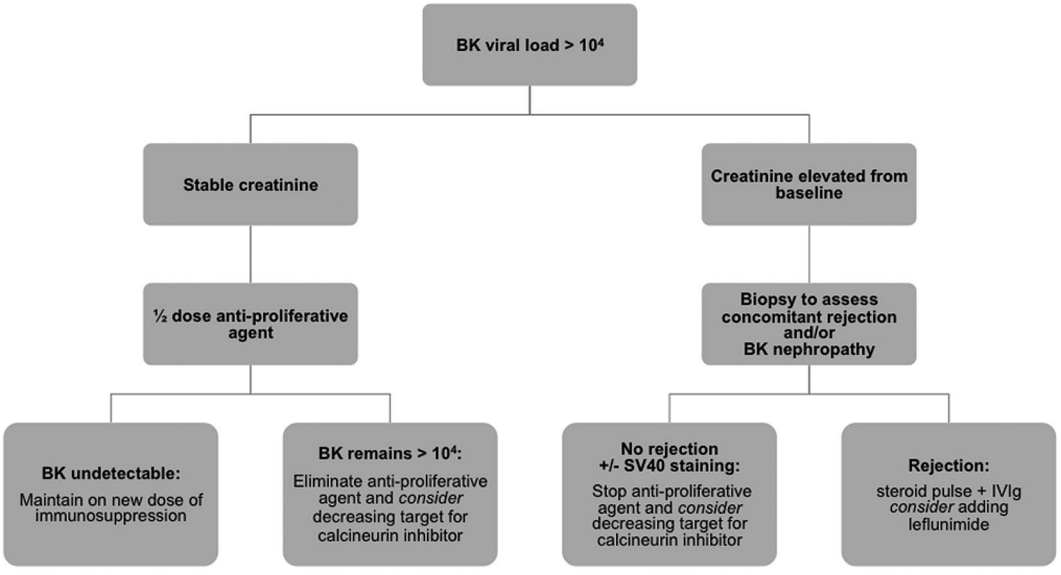

Figure 2. OHSU's algorithm for management of BK viremia. Patients transplanted at OHSU are screened for the presence of BK viremia 1, 3, and 12 months post-transplantation.

successful, the viral burden is very high or there is concomitant rejection on the allograft biopsy. There are no randomized trials evaluating the benefit of these agents when used in addition to lowering immunosuppression. Other agents used include leflunamide, cidofivir, and fluoroquinolones, all of which have *in vitro* activity against BK virus. Leflunamide is given orally, with a loading dose of 100 mg for 3 days followed by daily dosing of 20 to 50 mg with target levels from 50 to 100 ng/ml, although lower levels may be sufficient (33). Despite being nephrotoxic, cidofivir has been administered intravenously in small weekly doses (0.5 mg/kg) to kidney transplant patients with BK nephropathy (34). A National Institutes of Health (NIH)-funded randomized, placebo controlled, multi-center study evaluating safety and efficacy of cidofivir in renal transplant patients with BK virus nephropathy is currently in progress. Ciprofloxacin prophylaxis has been used in hematopoietic stem cell transplant patients and was found to reduce BK reactivation after transplant (35), but data for use of this drug in kidney transplant patients with BKN are lacking.

Coexisting BK infection and rejection presents a therapeutic challenge as one condition requires lowering immunosuppression and the other intensifying it. Some centers first treat the rejection with corticosteroids and then reduce immunosuppression whereas others reduce immunosuppression and give intravenous Ig (IVIg). IVIg is also used when BK virus infection is not responsive to reduction in immunosuppression as it is hypothesized that IVIg may have antiviral effect in addition to its immunosuppressive effects (36).

Many questions remain regarding the optimal way to diagnose and treat BKN (37). Interlaboratory variability in the PCR assay makes the diagnosis challenging (38), and there is no consensus regarding the level of plasma BK PCR that should be treated. We have little idea as to the natural history of patients with low-level viremia and normal allograft function. Distinguishing acute cellular rejection and BK nephropathy on biopsy can be problematic with important therapeutic implications. Management of BKN remains a challenge as there is no consensus regarding how to reduce immunosuppression and for patients receiving adjuvant therapies, the data on intensity and duration of treatment are lacking. Randomized controlled trials are needed to evaluate current adjuvant therapies and more options are needed to better treat patients who develop concomitant BK nephropathy and acute rejection.

Are Generic Immunosuppressive Drugs Safe for Transplant Recipients?

Since approval of the Hatch-Waxman Act in 1983, generic drugs have reduced cost for health care systems. This benefit of lower price is balanced by potential risks concerning equivalency of generic drugs and branded drugs. Because several maintenance immunosuppressive medications have come off patent, particularly tacrolimus and mycophenolate mofetil, and generics have been developed, it is important for nephrologists to understand the role these drugs may have in the treatment of their patients and to be able to explain to patients their decision to continue the branded medication or switch to the generic formulation (39).

The Food and Drug Administration rates generic drugs either "A" (with subclasses "AA" or "AB"), or "B" for bioequivalence. Both classifications of agents are tested for pharmaceutical equivalence (same active ingredients, dosage form, route of administration, strength, and concentration at the receptor). AB-rated drugs have undergone proven bioavailability testing that has deemed that they are equivalent to the branded agent in their rate and extent of absorption, area under of curve concentration and, time to max concentration (C_{max}). AA products have not undergone formal testing but are inherently unlikely to have bioavailability issues (*e.g.*, liquid preparations or drugs that dissolve easily in water). B-rated agents have not undergone *in vivo* testing, and generally are older medications (40). In a study of innovator generic drugs in the US, the difference for in C_{max} and area under the curve (AUC) values between innovator and generic drugs were 4.3% and 3.5% in a 12-year period. Such variation is known even with branded drugs, including Sandimmune (41).

Referring to the experience with the multiple formulations of cyclosporine is useful when looking ahead to generic versions of tacrolimus and mycophenolate mofetil. Teaching patients the importance of adherence to their medicine regimen is a cornerstone of successful transplantation. Therefore, it is not surprising that patients are sometimes reluctant to deviate from established drugs that have led to successful results. Providing patients with the information that there is no evidence documenting differences in outcomes should assuage patient and physician concerns regarding the use of newly released generic formulations of tacrolimus and mycophenolate mofetil (42).

What Is the Role of Sirolimus for Renal Transplant Recipients?

Sirolimus is an alternative to calcinurin inhibitors-based immunosuppression (CNI) that lacks the direct nephrotoxicity of those drugs (43). Despite this obvious advantage, use of sirolimus as primary immunosuppression has halved over this decade, likely because of drug related side effects and trials indicating superior efficacy of CNI-based regimens. Within this context, it appears that sirolimus may still have a role for patients with complications of standard CNI protocols.

In 2001, 17% of patients transplanted in the United States received sirolimus as part of their initial discharge immunosuppressive regimen. However, use of this drug for initial maintenance immunosuppression decreased to 9% of patients by 2006 since patients on sirolimus developed side effects that limited usage, commonly delayed wound healing, edema proteinuria and uncommonly pneumonitis and severe oral lesions (44–46). Publication of the Efficacy Limiting Toxicity Elimination (ELITE)–Symphony trial may further decrease use of sirolimus as primary immunosuppression after renal transplantation (47). This trial compared low-dose sirolimus/mycophenolate mofetil (MMF)/corticosteroids to tacrolimus/MMF/steroids and cyclosporine/MMF/steroids. Three of the four arms in the study had induction therapy with IL-2 receptor blockade. Patients in the sirolimus arm did worse than the calcineurin arms in the primary and important secondary endpoints: rate of acute rejection, overall GFR (GFR), and treatment failure.

The CONVERT trial tested the hypothesis that replacing

calcineurin inhibitors with sirolimus after wound healing has occurred (>6 months post-transplant) would improve outcomes. Patients with stable allograft function were switched to sirolimus from CNI's (tacrolimus or cyclosporine) or maintained on their CNI. For patient with a preserved GFR, switch to sirolimus led to a 3 ml/min improvement in GFR (62.6 ml/min *versus* 59.9 ml/min, $P = 0.009$ at 24 months after the switch). Hopefully, the patients in the study will be followed to assess the biologic significance of this difference. For patients with GFR between 20 to 40 ml/min, 16% developed acute cellular rejection or graft loss at 1 year leading to a cessation of enrollment of this patient group. Thus, for the patients with relatively preserved graft function, there is modest benefit to switching from CNI's to sirolimus. For patients with lower GFR, switch to sirolimus cannot be recommended.

Despite these data, for some patient groups, sirolimus may have important benefits. At least part of the sirolimus mechanism of action affects signaling through molecules like VEGF (vascular endothelial growth factor), which is involved in the vascularization of solid tumors (48–50). For patients with malignancies, eliminating calcineurin inhibitors plus combining the immunosuppressive affects of sirolimus with its anti-neoplastic actions can yield important benefits, especially for Kaposi's sarcoma (51,52). Several studies now report that sirolimus use may decrease the rate of clinically important infections in renal transplant recipients. Cytomegalovirus (CMV) infection remains a major, and possibly a growing, issue for transplant recipients. Sirolimus-based regimens have lower rates of CMV infection and switch to a sirolimus-based regimen has also been successful in cases of CMV that are resistant to standard therapy (53,54).

What Is the Role in Therapeutic Drug Monitoring for Mycophenolic Acid?

Mycophenolic acid (MPA) is a purine antagonist which is approved for the prevention of acute rejection in renal transplant recipients in combination with cyclosporine or tacrolimus and steroids. Currently, there are two forms of mycopholate-based therapies on the US market: Mycophenolate mofetil (CellCept, F. Hoffman La-Roche and generic) and Mycophenolate sodium (Myfortic, Novartis), and 87% of renal transplant patients receive some form of MPA-based therapy at the time of hospital discharge following renal transplantation (11). MPA requires conversion from a pro-drug to the active compound, and the pharmacokinetic profile of mycophenolate compounds can be affected by several factors (renal and liver disease, polymorphism of UGT enzymatic system, albumin level, drug interactions, and choice of calcineurin inhibitors). Because of these factors, therapeutic drug monitoring has been studied for patients on mycophenolate-based therapy (55).

The first study to assess the clinical utility of therapeutic drug monitoring of MPA therapy in renal transplant recipients, APOMYGRE, was the smallest and only one to showing clinical benefit. In this study, 137 renal transplant patients were randomized to a fixed dose (1 g given orally twice a day) or a concentration–controlled (AUC of 40 mg/h/L) MPA therapy. In the concentration-controlled group, mycophenolate monitoring was included a six-point abbreviated MPA-AUC which was measured on day 7 and at months 1, 3, 6, and 12. The overall adverse reaction was similar between both groups, and a lower incidence of rejection was noted in the concentration controlled (7.7%) compared with the fixed dose (24.6%) (56). The second study compared the efficacy and safety of a fixed-dose *versus* concentration-controlled MPA therapy in 905 renal transplant recipients. The target MPA-AUC was 45 mg/h/L, and the same method of abbreviated AUC calculation with six-point measurements were used. The primary objective of this study was to evaluate treatment failure (biopsy-proven acute rejection, graft loss, death) between the groups. There were no significant differences between the groups in treatment failure or acute rejection (57).

Final results of the third study assessing the utility of drug monitoring of MPA levels in renal transplant recipient, Opticept, are yet to be published, but preliminary data indicate no benefit for monitoring levels. In Opticept, patients were randomized to mycophenolate at a dose of 1 g orally twice daily with cyclosporine or tacrolimus. In the two groups, the dose was adjusted to a whole blood MPA level of 1.3 in cyclosporine-treated patients and 1.9 mcg/ml for the tacrolimus-treated patients. In the comparative arm of the study, patients received Mycophenolate mofetil, 1 g given orally twice a day for the duration of the study at a fixed dose. The primary objective of this study was to evaluate treatment failure (biopsy-proven acute rejection, graft loss, death, and renal function at 12 months) between the three groups. Drug level monitoring neither decreased rejection rates nor resulted in less diarrhea, a common side effect attributed to MPA therapy (27).

Even if we follow the results of the APOMYGRE study and neglect the other two larger studies, application of the method of monitoring used in APOMYGRE would test the boundaries of logistical practicality and cost-efficacy. Unfortunately, simpler methods of monitoring, for example, trough plasma concentrations levels, show only a weak correlation with overall drug exposure. Therefore, we monitor levels of MPA only in rare circumstance that a particular patient requires an antiproliferative agent, cannot tolerate switching to azithioprine, and has a dose-related toxicity ascribed to the MPA compound. In this scenario, measurement of MPA levels could potentially allow a decrease in the dose of MPA while maintaining AUC concentrations that we feel provide adequate immunosuppression.

What Are the Most Common Drug Interactions in Transplant Recipients?

Patients come to transplantation with multiple medical issues that require continued, long-term drug therapy. The addition of immunosuppressive medications and antimicrobial agents to their regimens increases the likelihood for complex drug-drug interactions. Drug interactions can be classified as pharmacokinetic or pharmacodynamic. Pharmacokinetic drug interactions refer to agents that alter the plasma concentration of immunosuppressive agents (58). Pharmacodynamic drug interactions reactions are those in which one drug enhances the toxicity of the second drug (*e.g.*, aminoglycoside and calcineurin inhibitors). Tacrolimus and cyclosporine are primarily

Table 1. Cyclosporine and Tacrolimus drug-drug interactions

Drug	Mechanism	Effects	Severity[a]	Comments
ACE-inhibitors	Renal dysfunction in RAS	↑ serum creatinine	3	Physiologic elevation of creatinine; anemia; class effects.
Acyclovir	Inter-renal crystallization	Stone formation	4	Avoid dehydration. Infuse over 1 hour.
Amiodarone	↓ clearance	Nephrotoxicity	3	Very slow onset and offset.
Amlodipine	↓ clearance	↑ CNI level	4	Nifedipine is preferred dihydropiradine.
Amphotericin B	Synergistic nephrotoxicity	Nephrotoxicity	3	Require hydration and electrolyte monitoring.
Carbamazepine	↑ clearance	↓ CNI level	3	Slow onset (up to 7 days).
Cholestyramine	↑ clearance	↓ CNI level	4	Separate doses by 3 hours.
Cimetidine	↓ creatinine secretion	↑ serum creatinine	4	Use other H2 antagonists.
Ciprofloxacin	Possible ↓ CSA effects on IL-2	Pharmacodynamic antagonism	4	May increase risk of rejection.
Clarithromycin	↓ clearance	↑ CNI level	2	Azithromycin is the preferred agent.
Clotrimazole troches	↓ clearance of TAC	Increase TAC level	3	Monitor TAC level closely. No effect on CSA.
Co-trimoxazole	Inhibit creatinine secretion	Increase serum creatinine	4	Preferred agent for pneumocystis *pneumonia*.
Diltiazem	↓ clearance	↑ CNI level	3	Can use to raise CNI level when needed.
Erythromycin	↓ clearance	↑ CNI level	2	Azithromycin is the preferred agent.
Fluconazole	↓ clearance	↑ CNI level	3	Increase LFTs also.
Fluvoxamine	↓ clearance	↑ CNI level	2	
Fosphenytoin	↑ clearance	↓ CNI level	3	Monitor levels carefully.
HMG-CoA reductase inhibitors (Statins)	↓ clearance of statins (greater effect with CSA)	Myopathy/ rhabdomyolysis	3	Less effect with TAC; pravastatin is preferred as it has the least interaction.
Itraconazole	↓ clearance	↑ CNI level	3	Monitor levels carefully. Decrease dosage 50% to 85%.
Ketoconazole	↓ clearance	↑ CNI level	3	Monitor levels carefully. Decrease dosage 25% to 75%.
Methylprednisolone	↓ clearance	↑ CNI level	3	Only at high doses.
Metoclopramide	↓ gastric emptying time	↑ CNI level	3	Increased peak and AUC by 25% to 50%.
Metronidazole	↓ clearance	↑ CNI level	4	
Nafcillin	↑ CNI clearance	↓ CNI level	3	
Nefazodone	↓ CNI clearance	↑ CNI level	3	
Nicardipine	↓ CNI clearance	↑ CNI level	3	
NSAIDs/COX-2 inhibitors	Synergistic nephrotoxicity	Nephrotoxicity	3	CNI-induced vasoconstriction is exacerbated by prostaglandin inhibition.
Phenobarbital	↑ CNI clearance	↓ CNI level	3	Slow onset and slow offset.
Phenytoin	↑ CNI clearance	↓ CNI level	3	
Rifabutin	↑ CNI clearance	↓ CNI level	3	Rifabutin is a less potent hepatic enzyme inducer than rifampin.
Rifampin	↑ CNI clearance	↓ CNI level	2	
Spironolactone	↓ K + Secretion	Hyperkalemia	3	
Verapamil	↓ CNI clearance	↑ CNI level	3	Anticipate decrease in CNI dose.

[a]Scale for severity of interaction: (1) Avoid combination; (2) Usually avoid (use only no other alternative agents available); (3) Monitor closely; (4) No action needed (the risk of Adverse Drug Reaction, ADR, is small).

metabolized in the liver and small intestine via cytochrome P450 enzyme system. Both drugs follow a similar pharmacokinetic behavior following exposure to other drugs which inhibits or induces cytochrome P450 system. In contrast to tacrolimus, cyclosporine is also a strong inhibiter of cytochrome P450 and may affect the plasma concentration of other agents such as statins. Clinically relevant interactions have been reported with azole antifungal drugs, macrolide antibiotics, calcium channel blockers, protease inhibitors, grapefruit juice and St John wort. For mycophenolic acid compounds, drugs that interfere with enterohepatic recirculation of mycophenolate should be avoided or used with caution. Cyclosporine has been shown to reduce mycophenolate plasma concentration. Sirolimus appears to have very similar drug interaction as tacrolimus. A summary of clinically significant drug-drug interactions is provided in Tables 1–3 (59).

For Patients Interested in Becoming Pregnant after Transplantation, How Do We Optimize Kidney Transplant Recipient and Fetal Outcomes?

Good renal function after kidney transplantation improves fertility for male and female recipients. Counseling all patients who are in their reproductive age about pregnancy is important to clarify expectations and explain that are modifiable variables that may optimize patient and fetus outcome.

For contraception, barrier methods are considered inadequate when used alone, and intrauterine devices are not recommended because immunosuppression increases infection risk and decreases efficacy of this method of birth control (60). Progesterone-only oral contraceptives are a safe, effective option for patients unable to tolerate the increased vascular risk of estrogen-progesterone contraception (61).

Pregnancy outcomes are improved for patients who are >1 year post-transplantation, who have a lower creatinine (less than 1.3 mg/dl), and who have low proteinuria (less than 500 mg/d). Under these conditions, patients have no increased graft loss or increased cardiovascular disease after 10 years of follow-up (62,63). Recent KDIGO guidelines recommend patients wait until their renal function is "stable" and are >1 year after transplant (64). Patients can also be advised that acute allograft rejection rates are equal between pregnant and nonpregnant patients (65). Although major malformations are not obviously increased in child of mothers with kidney transplants, our patients should be counseled that fetal loss, preterm labor, low-birth weight, overall developmental abnormalities are likely higher (62,66).

Before pregnancy, we also recommend trying to control BP with medications that are safe during pregnancy as the risk of preeclampsia is increased after transplantation. The anti-hypertensives that are avoided (atenolol, ACE-inhibitors, and angiotensin receptor blockers) and preferred (methyldopa, labetolol, nifedipine, thiazide diuretics, and hydralazine) are the same as in other kidney disease populations. The only added caveat is that drug-drug interactions with immunosuppressive medications should be considered when making adjustments in BP medications.

Discussion of immunosuppression should come with the preamble that none of these medications is considered "safe" based on testing in humans (FDA category "A"), and all have at least some theoretical toxicity to the fetus. We preemptively avoid mycophenolate mofetil and sirolimus based on data and limited experience in this population, respectively (67,68). Steroids and azathioprine have a long history in transplantation. Calcineurin inhibitors probably impact the fetus, but we consider them necessary for transplant and patient health (60). Hopefully, the lower target levels for calcineurin inhibitors that we are now using cause less fetal effects.

Overall, dialogue with patients before pregnancy is critical for managing this high-risk event. McKay and Josephson summarize a more intensive management strategy for patients considering pregnancy after transplantation (69). Coordination with the patient's obstetrical specialist and the transplant center will ease the management of these complicated patients during this critical period.

How Do We Manage Post-Transplant Risk of Cancer?

Malignancies are responsible for up to one-third of deaths of renal transplant patients with a functioning allograft (70,71). This is despite relatively aggressive screening pretransplantation and post-transplantation. Therefore, it is critical that patients are educated about the risk of malignancy while preparing for transplantation.

To address this risk pretransplantation, potential transplant

Table 2. Azathioprine and Mycophenolate drug-drug interactions

Drug	Mechansim	Effects	Severity[a]	Comments
ACE-inhibitors	Synergestic myelosuppression	Anemia, neutropenia	3	Increased bone marrow toxicity.
Allopurinol	Inhibits xanthene oxidase, ↑ AUC of AZA	Severe neutropenia	1	Decrease azathioprine dose by 75%.
Antacids	Decrease absorption of MMF	Decrease efficacy	3	
Cholestyramine	Decrease absorption of MMF		3	Increased bone marrow toxicity.
Co-trimoxazole	Synergestic myelosuppression	Anemia, neutropenia	3	
Ganciclovir	Synergestic myelosuppression	Anemia, neutropenia	3	

[a]Scale for severity of interaction: (1) Avoid combination; (2) Usually avoid (use only no other alternative agents available); (3) Monitor closely; (4) No action needed (the risk of ADR is small).

Table 3. Sirolimus drug–drug interactions

Drug	Mechansim	Effects	Severity[a]	Comments
ACE-inhibitors	Synergestic myelosuppression	Anemia, neutropenia	3	Increase bone marrow toxicity
Amprenavir	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	3	
Carbamazepine	↓ intestinal absorption	↓ sirolimus level	2	
Cholestyramine	↓ intestinal absorption	↓ sirolimus level	3	
Clarithromycin	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	2	Azithromycin is preferred agent
Co-trimoxazole	Synergestic myelosuppression	Anemia, neutropenia	3	
Cyclosporine	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	3	Give 4 hours after the dose
Diltiazem	↑ plasma level of sirolimus	Hyperlipidmia, Anemia, neutropenia	2	Amlodipine is the preferred agent
Erythromycin	↑ plasma level of sirolimus	Hyperlipidmia, Anemia, neutropenia	2	Azithromycin is preferred agent
Fluconazole	↑ plasma level of sirolimus	Hyperlipidmia, Anemia, neutropenia	2	
Ganciclovir	Synergestic myelosuppression	Anemia, neutropenia	3	
Indinavir	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	2	
Itraconazole	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	2	
Metoclopramide	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	3	
Nicardipine	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	2	Amlodipine is preferred agent
Phenobarbital	↑ metabolism of sirolimus	↓ sirolimus level	2	
Phenytoin	↑ metabolism of sirolimus	↓ sirolimus level	2	
Rifabutin	↑ metabolism of sirolimus	↓ sirolimus level	2	
Rifampin	↑ metabolism of sirolimus	↓ sirolimus level	2	
Ritonavir	↑ plasma level of sirolimus	Hyperlipidmia, Anemia, neutropenia	2	
Verapamil	↑ plasma level of sirolimus	Hyperlipidmia, Anemia, neutropenia	2	
Voriconazole	↑ plasma level of sirolimus	Hyperlipidmia, anemia, neutropenia	2	

[a]Scale for severity of interaction: (1) Avoid combination; (2) Usually avoid (use only no other alternative agents available); (3) Monitor closely; (4) No action needed (the risk of ADR is small).

recipients are asked to undergo age-appropriate cancer screening and quit tobacco before transplantation. For patients with a history of cancer, a 2- to 5-year disease-free interval, depending on the cancer type and stage, is recommended before consideration for transplantation. Epstein-Barr virus and CMV serostatus should be determined as uncontrolled infection with either is associated with post-transplantation lymphoproliferative disease (PTLD) (72). The HPV 16 and 18 vaccines are available for young females and should be considered for potential transplant recipients in this population (71).

The most prominent factor for increased cancer rates in transplant recipients is immunosuppression. However, we are learning that all immunosuppression may not carry the same cancer risk. From registry data, anti-thymocyte antibodies (*i.e.*, Thymoglobulin) may carry a higher risk of PTLD than IL-2 receptor blockers (basiliximab or daclizumab) or alemtuzumab (73), but this risk has not been confirmed by randomized trials (74). For chronic immunosuppression, the issue is slightly clearer. The COVERT trial showed that sirolimus decreased cancer rates *versus* calcineurin inhibitors. The effect was greatest for skin cancers (75).

Screening for malignancy after transplantation should also

follow the American Cancer Society's guidelines (71). Because of the 30-fold increase in skin cancers in the kidney transplant population, annual skin examination by a professional is also recommended. Quantitative EBV viral load assays have been looked at for surveillance for early PTLD; however, in studies of pediatric populations, the specificity of detecting true EBV-positive PTLD was varied widely. Because of this lack of specificity and the lack utility in detecting EBV-negative PTLD, there may not be clinical utility of screening for adult patients (76).

Once a diagnosis of cancer is made, a decision needs to be made about how best to handle the immunosuppression medications to optimize patient and allograft survival. The first step is to reduce the amount of immunosuppresion. For PTLD, a reduction in immunosuppresion may lead to a regression of lesions in up to 50% of cases (76). Another option is to convert from a calcineurin inhibitor (CNI) to sirolimus. Randomized trials evaluating the utility of conversion from calcineurin inhibitors to sirolimus for patients with nonmelanoma skin cancers are completed and in progress (*clinicaltrials.gov* NCT00129961, NCT00133887, NCT00866684). The other strategy to consider is decrease target levels of calcineurin inhibitors as it appears as the development of malignancy may be an indication that tissue effects of the drugs are not reflected by serum levels (77).

What Are the Recommendations Regarding Vaccination after Transplantation?

With the obvious increased risk from microbial pathogens in transplant recipients, the rationale for vaccination is readily apparent. Unfortunately, there are several barriers to effective vaccination in our patients. Some of these are concomitant with the biology of transplantation, but others are modifiable. Surprisingly, immunization rates are lower in kidney transplant recipients relative to both the general population and even dialysis patients (78). Greater knowledge regarding the safety and efficacy of vaccination may improve these rates.

Vaccination recommendations for kidney transplant recipients are similar to those of the general population, with a few caveats. Immunologic response to vaccination does not appear to be affected based on use of tacrolimus, cyclosporine or sirolimus; however, both azathioprine and mycophenolate significantly reduced the immune response to most vaccines by 2.5- to 5-fold (79,80). Because vaccination activates cellular immunity, there has also been concern that transplant rejection may be precipitated by vaccination, but the literature does not support this concern (81,82). Live or attenuated vaccines are not recommended for kidney transplant recipients because replication of the pathogen may be enhanced. In addition, oral polio or small pox vaccines should not be administered to household contacts of transplant recipients (83).

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None.

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