

Management of Kidney Transplant Recipients by General Nephrologists: Core Curriculum 2019

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Kidney transplantation is associated with improvement in quality of life and mortality as compared to remaining on dialysis. It is therefore the optimal treatment for kidney failure for most patients. While transplantation nephrologists typically care for the patient in the first 6 months posttransplantation, general nephrologists and internists often care for kidney transplant recipients after this period. Medical management of the kidney transplant recipient can be challenging, and primary care physicians and nephrologists may be unfamiliar with the medical nuances of caring for these patients. This includes drug interactions, which are common and can result in drug toxicities, rejection, and graft injury. Infections and malignancies related to long-term immunosuppression may pose diagnostic and treatment challenges. In this article, we review the mechanisms of immunosuppression, types of rejection, complications of recurrent disease, common infectious diseases, and the nonrenal complications commonly encountered in the kidney transplant recipient.

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Introduction

Kidney transplantation has been standard practice since the 1960s, with more than 440,000 individuals having undergone this procedure in the United States since 1988. In this Core Curriculum, key issues in the care of these patients are reviewed, including basic mechanisms of immunosuppression, common side effects of immunosuppressive agents, drug interactions, infections, and malignancies seen in transplant recipients, as well as contraception and family planning.

Know the Patient and the Transplant

Not all transplants are the same. With the growing organ shortage and the widening gap between organ availability and the numbers of patients on the waitlist, there has been an expansion of the types of donors used. Donor kidneys can be from a living or deceased donor. Living donor kidneys may be through directed donation, a nondirected donation, or an exchange program in which one donor kidney is swapped with another more compatible kidney. The new kidney allocation system, implemented by UNOS (United Network for Organ Sharing) in December 2014, has affected not only organ allocation but also the nomenclature for deceased donor kidneys. Deceased donor kidneys are designated by the Kidney Donor Profile Index (KDPI), ranging from 0% to 100%. The KDPI scoring system integrates factors including hypertension, diabetes, ethnicity, and donor age. The KDPI predicts the life expectancy of

the kidney, with lower scores predicting longer graft survival as compared with higher scores. Most kidneys are from individuals declared brain dead, designated as donation after brain death. Another category is donation after circulatory death, in which medical support has been withdrawn from a non-brain dead donor. Kidney transplantation from donation after circulatory death donors carries an increased risk for delayed graft function compared with kidneys from donation after brain death donors.

In recent guidelines from the Public Health Service, increased-risk donor kidneys include kidneys from donors who have tested negative for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) but have increased risk for exposure due to behavioral risk factors. The risk for transmission of HCV and HIV from these donors is low (about 0.1%-0.3%); for HBV, it is <1.0%. Understanding the potential risks to recipients based on the type of donation is important for optimal care of these patients.

Additional Readings

- ▶ Hart A, Gustafson SK, Skeans MA, et al. OPTN/SRTR 2015 Annual Data Report: early effects of the new kidney allocation system. *Am J Transplant.* 2017;17(suppl 1):543-564.
- ▶ Irwin L, Kotton CN, Elias N, et al. Utilization of increased risk for transmission of infectious disease donor organs in solid organ transplantation: retrospective analysis of disease transmission and safety. *Transplant Infect Dis.* 2017;19(6):e12791.
- ▶ Massie AB, Luo X, Chow EK, Alejo JL, Desai NM, Segev DL. Survival benefit of primary deceased

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

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Immunosuppression and Drug Interactions

Case 1: Three years after deceased donor kidney transplantation, a 50-year-old man with end-stage renal disease (ESRD) due to diabetes is diagnosed with tuberculosis caused by *Mycobacterium tuberculosis*. He is started on treatment with rifampin and continued on his home immunosuppression, including prednisone, mycophenolate mofetil (MMF), and tacrolimus. Three weeks later, his serum creatinine (Scr) level increases to 2.0 from a baseline of 0.9 mg/dL. He has a urinary protein-creatinine ratio of 500 mg/g and urinalysis reveals 5 to 10 white blood cells and 0 to 2 red blood cells. He is asymptomatic.

Question 1: What is the most likely cause of acute kidney injury (AKI)?

- a) Rifampin-induced AKI due to acute interstitial nephritis
- b) Rifampin-induced AKI due to acute tubular necrosis
- c) Allograft rejection
- d) Allograft pyelonephritis

For the answer to the question, see the following text.

At the time of transplantation, patients are typically treated with induction therapy, either a T-lymphocyte-depleting agent (antithymocyte globulin [Thymoglobulin]) or an interleukin 2 (IL-2) inhibitor (basilixumab).

Maintenance immunosuppression is initiated in the hospital and continued for the life of the allograft. The 3-signal approach for T-cell activation and proliferation is an important paradigm for understanding each immunosuppressive agent. Signal 1 leads to initiation of the calcineurin pathway and transcription of IL-2, a T-cell growth factor. However, signal 1 alone is inadequate for T-cell activation and requires a costimulatory signal 2 to facilitate IL-2 and other cytokine expression. Without this costimulatory signal, there is no T-cell activation and instead, apoptosis. Stimulation of IL-2 then leads to signal 3, activation of mammalian target of rapamycin (mTOR), which triggers T-cell proliferation. This multiarmed immune activation is the reasoning behind the use of multiple immunosuppressive agents (Fig 1).

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) work on signal 1 to inhibit T-cell proliferation. Both tacrolimus and cyclosporine exert their effects by binding their respective cytoplasmic receptors, cyclophilin and tacrolimus-binding protein (also known as FK506 binding protein [FKBP]), respectively, thus inhibiting calcineurin and the expression of several cytokines that are integral for lymphocyte proliferation. Randomized controlled trials comparing CNIs and graft outcomes have been inconclusive. However, a meta-analysis concluded that tacrolimus use is associated with improved patient mortality and a decrease in graft loss and allograft rejection.

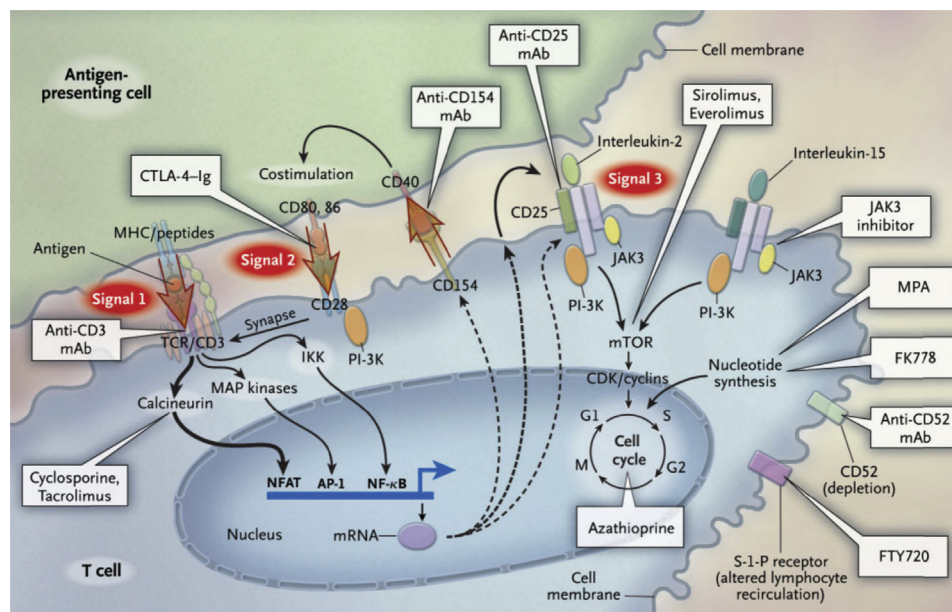


Figure 1. Mechanisms of immunosuppression. Abbreviations: AP-1, activator protein 1; CTLA, cytotoxic T-lymphocyte-associated antigen; FTY, fingolimod; IKK, I κ B kinase; JAK3, Janus kinase 3; MAP, mitogen-activated protein; MHC, major histocompatibility complex; MPA, mycophenolic acid; NFAT, nuclear factor of activated T cells; NF- κ B, nuclear factor κ B; PI-3K, phosphoinositide 3-kinase; S-1-P, sphingosine-1-phosphate; TCR, T-cell receptor. Adapted from Halloran (*N Engl J Med.* 2004;351(26):2715-2729) with permission of the Massachusetts Medical Society; original content © 2004 Massachusetts Medical Society.

Cyclosporine is available in 2 formulations, Sandimmune (cyclosporine) and Neoral (cyclosporine modified). Twelve-hour trough levels are measured for Sandimmune because the levels correlate with drug exposure and toxicity. Neoral drug exposure correlates better with 2-hour peak levels (C2 levels) due to more consistent drug absorption, though monitoring of 12-hour trough levels is more common. Caution should be taken when switching between formulations due to variations in bioavailability, which can lead to toxicities or underdosing and subsequent rejections. Cyclosporine in doses of 6 to 10 mg/kg per day (divided into twice-daily dosing) is used during the immediate postoperative period. Twelve-hour trough levels should be monitored and target levels should be progressively decreased over time after transplantation, from 200 ng/mL during the first year to levels of 50 to 75 ng/mL in the long-term patient.

For tacrolimus, 12-hour trough levels are used for monitoring, which correlates with drug exposure. A target level of 8 to 10 ng/mL is recommended for the first several months posttransplantation. Drug targets should be reduced to 5 to 7 ng/mL after the first year, and a lower target of 3 to 5 ng/mL in the setting of significant infection, malignancy, or BK viremia.

While CNIs have significantly improved graft outcomes, their toxicity profile is extensive and can be intolerable to patients. Nephrotoxicities include afferent arteriolar vasoconstriction and subsequent decrease in renal blood flow and filtration rate. Long term, CNIs can cause chronic interstitial fibrosis. A unique side effect is CNI-induced thrombotic microangiopathy, which may be renal limited or systemic, with manifestations similar to thrombotic thrombocytopenic purpura. CNIs can cause hypertension and sodium retention by several mechanisms, including direct stimulation of sodium chloride reabsorption in the distal convoluted tubule, activation of

the renin-angiotensin-aldosterone axis, activation of the sympathetic nervous system, and decreased nitric oxide production. Hyperkalemia due to a decrease in sodium delivery to the collecting duct may respond to thiazide diuretics. Nonrenal manifestations include alopecia associated with tacrolimus and hypertrichosis associated with cyclosporine. Cyclosporine may induce gingival hyperplasia and increase prolactin levels, leading to gynecomastia in men. CNIs, particularly tacrolimus, may cause islet cell toxicity, conferring an increased incidence of posttransplantation diabetes. CNIs, particularly cyclosporine, are associated with hyperuricemia, gout, and hyperlipidemia. Another complication of CNIs is posterior leukoencephalopathy, which can be associated with headaches and seizures.

There are numerous classes of drugs that interact with CNIs, and for this reason, it is important to consult a transplantation pharmacist or transplantation physician before introducing new medications. Table 1 summarizes common drug interactions. Most drug interactions are due to either induction or inhibition of the hepatic cytochrome P450 system. Rifampin/rifabutin, barbiturates, phenytoin, and carbamazepine induce the P450 system and decrease CNI concentrations. P450 inhibitors such as nondihydropyridine calcium channel blockers (verapamil and diltiazem) can require up to a 40% reduction in CNI dosing. Azole antifungals are also potent P450 inhibitors and may warrant up to an 80% reduction in CNI dose. Other important classes of drugs that inhibit P450 are macrolide antibiotics and protease inhibitors. Caution must be taken when starting or stopping treatment with any of these medications given the risk for rejection or toxicity. In addition to drug interactions, foods such as grapefruit can also increase CNI drug levels. Furanocoumarins, an active chemical compound in grapefruit, are strong inhibitors of the

Table 1. Common Drug Interactions

Agent	Comment
Common Drugs That Increase CNI Level	
Erythromycin, clarithromycin	Potent inhibition of cytochrome P450 <i>Alternatives:</i> Azithromycin is an acceptable alternative in some cases, less impact on drug metabolism
Azole antifungals	Potent inhibition of cytochrome P450
Diltiazem, verapamil	Moderate inhibition of cytochrome P450 <i>Alternatives:</i> Nondihydropyridine calcium channel blockers or β -blockers
Protease inhibitors (eg, ritonavir, darunavir, indinavir)	Very potent inhibitors of metabolism <i>Alternatives:</i> nucleoside reverse-transcriptase inhibitors, non-nucleoside reverse-transcriptase inhibitors, or integrase inhibitors
Common Drugs That Decrease CNI Level	
Rifampin	Inducer of cytochrome P450
Rifabutin	Inducer of cytochrome P450
Carbamazepine	Inducer of cytochrome P450
Phenobarbital	Inducer of cytochrome P450

Note: This is by no means an exhaustive list. It is advised to check for drug interactions when initiating new medications in transplant recipients.
Abbreviation: CNI, calcineurin inhibitor.

P450 system, resulting in elevated CNI levels. It is recommended that transplant recipients on CNI treatment avoid grapefruit and grapefruit juice.

Corticosteroids

Corticosteroids inhibit nuclear factor κ B (NF κ B), a transcription factor necessary for the expression of several cytokines that are integral for T-cell activation. Glucocorticoids also induce lymphopenia as a result of lymphocyte migration from the vascular compartment to the lymphoid tissue. Immediately post-transplantation, high-dose methylprednisolone is administered, followed by a rapid taper to either 5 mg of prednisone daily or steroid withdrawal, a decision based on patient immunologic risk. Patients who are of low immunologic risk (low calculated panel-reactive antibodies, first transplant, negative cross-match, and non-African American) with a non-immune-mediated cause of ESRD (ie, diabetes, hypertension, and polycystic kidney disease) might be considered for early steroid withdrawal. The side effects of high-dose steroids are well described, including osteoporosis, osteonecrosis, impaired wound healing, hyperlipidemia, glucose intolerance, and psychopathologic effects. Although kidney transplant recipients often attribute adverse side effects to the use of corticosteroids, studies from the rheumatoid arthritis literature indicate that the adverse effects of long-term low-dose corticosteroid treatment (<10 mg/d) are modest and rarely different from placebo. Late steroid withdrawal significantly increases the risk for rejection and should not be done.

Antiproliferative Agents

MMF is a prodrug for which the active metabolite is mycophenolic acid (MPA), an inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH catalyzes the generation of guanosine nucleotides from inosine in de novo purine synthesis. MPA specifically inhibits T-cell proliferation because other cell lines are less affected due to a salvage pathway for the production of guanosine nucleotides. MPA also downregulates the expression of adhesion molecules and thus limits lymphocytes from binding to vascular endothelial cells, inhibiting lymphocytes from entering rejection sites.

Providers must be aware of drug interactions with mycophenolate preparations. MMF and MPA should not be administered with azathioprine due to additive hematologic side effects. Cyclosporine inhibits enterohepatic recirculation of mycophenolate, therefore reducing drug exposure to the active metabolite, an effect that is not present with tacrolimus or mTOR inhibitors. MMF intestinal absorption is inhibited by coadministration with proton pump inhibitors, antacids, cholestyramine, sevelamer, and oral ferrous sulfate. MPA is less affected by coadministration with proton pump inhibitors. The most common side effects are heartburn, nausea, and diarrhea.

Azathioprine is a purine analogue that is incorporated into cellular DNA and inhibits purine nucleotide synthesis, gene replication, and ultimately T-cell activation. It also inhibits circulating monocyte differentiation into macrophages, which are key antigen-presenting cells. Azathioprine may be used when patients cannot tolerate the gastrointestinal side effects of mycophenolate preparations or as an alternative in anticipation of pregnancy. The main side effect of azathioprine is bone marrow suppression. Azathioprine is converted to its inactive form by xanthine oxidase. Therefore, concomitant use with xanthine inhibitors such as allopurinol or febuxostat will increase azathioprine levels, resulting in severe myelosuppression. Occasionally, azathioprine can cause reversible hepatitis or cholestasis and rarely can cause pancreatitis.

mTOR Inhibitors

mTOR inhibitors (sirolimus and everolimus) bind to the same cytosolic protein as does tacrolimus (ie, FKBP), but instead inhibit the TOR rather than calcineurin. Inhibition of TOR blocks signal 3, inhibiting cytokine-dependent activation of the cell cycle. The target drug troughs range from 5 to 10 ng/dL based on the clinical scenario. Sirolimus has a long half-life (67.5 hours) and thus drug levels must be checked several days after a dose adjustment. Side effects of mTOR inhibitors include impaired wound healing, lymphocele development, delayed recovery from acute tubular necrosis, reduced testosterone concentration, proteinuria, edema, painful mouth ulcers, skin lesions, hyperlipidemia, thrombocytopenia, pneumonia/pneumonitis, diarrhea, and hyperlipidemia. De novo proteinuria may develop or existing proteinuria may be exacerbated. Proposed mechanisms include a reduction in tubular protein reabsorption and damage to podocyte integrity. Baseline and serial measurements of proteinuria are important and treatment with mTOR inhibitors should be avoided or withdrawn in patients who develop proteinuria with protein excretion > 1 g/d. Noninfectious interstitial pneumonitis has been described with mTOR inhibitors, which can occur at any time posttransplantation. This typically resolves 2 to 3 weeks after drug treatment discontinuation.

Belatacept

Belatacept is an immunosuppressive drug used in patients with low immunologic risk. It is a human fusion protein that binds to CD80/CD86 on antigen-presenting cells, blocking the interaction with CD28 on T cells and inhibiting the costimulatory signal 2. Belatacept typically supplants the use of CNIs and is used in conjunction with MMF or mTOR inhibitors and steroids. Long-term studies have shown improved kidney function but an increased incidence of high-grade cellular rejection. Various immunosuppressive protocols are being evaluated to reduce rejection rates. There is also an increased incidence of posttransplantation lymphoproliferative disease (PTLD)

with belatacept compared to cyclosporine, particularly in Epstein-Barr virus (EBV)-seronegative patients. Belatacept is contraindicated in patients who are EBV seronegative or whose EBV status is unknown.

Immunosuppression Monitoring

Several immunosuppressive agents have a narrow therapeutic window, which necessitates close monitoring of drug levels. In the early weeks and months post-transplantation, the transplantation center will monitor and adjust levels of immunosuppression. As recipients are further from transplantation, target levels for the various immunosuppressive agents are lower. Target levels are influenced by side effects, infectious and malignancy complications, underlying kidney disease, and duration since transplantation. Special consideration must be given to hospitalized patients who are unable to take oral medications. Steroids and MMF can be administered intravenously (IV) when needed, while cyclosporine can be given as a suspension if a small amount of medication can be tolerated orally. Tacrolimus can be dose adjusted (50% reduction) and given sublingually. Administration of immunosuppressive agents by non-oral routes requires consultation with an experienced transplantation pharmacist.

With respect to case 1, rifampin is a potent inducer of cytochrome P450, which results in decreased tacrolimus levels due to enhanced metabolism. Home immunosuppression therapy was continued without monitoring tacrolimus levels after starting rifampin treatment. Due to subtherapeutic tacrolimus levels, this patient likely has AKI from acute rejection. Thus, the correct answer is (c).

Additional Readings

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- ★ **ESSENTIAL READING**
- Lim MA, Kohli J, Bloom RD. Immunosuppression for kidney transplantation: where are we now and where are we going? *Transplant Rev (Orlando)*. 2017;31(1):10-17.

Monitoring Kidney Function

Regular monitoring of kidney function is required throughout the life of the transplanted kidney. Early after transplantation, kidney function is monitored twice weekly for a month, with a gradual decrease in the frequency of monitoring over the first year. Standard practice is to monitor laboratory values indicative of transplant function no less than every 3 months indefinitely. Should a recipient develop an acute illness, especially a viral illness or urinary tract infection, it is wise to check the Scr concentration after the illness because a generalized immune response can trigger rejection. A general rule in monitoring transplant recipients is that a 20% to 25% increase in Scr concentration above baseline warrants attention. Evaluation includes at a minimum kidney ultrasound to rule out obstruction, as might be seen with inadequate bladder emptying, stone, or ureteral stricture. Doppler studies should be included with the ultrasound to assess vascular inflow if blood pressure is elevated or bruit is appreciated over the kidney. Assessment for BK viremia can also shed light on the cause of an elevated Scr level. Serum viral load > 10,000 copies is associated with BK

Table 2. Differential Diagnosis of Acute Kidney Injury in Kidney Transplant Recipients

	Comments	Evaluation
Decreased Kidney Perfusion		
Volume depletion	Poor intake or diarrhea	Physical examination, assess electrolytes
Renal artery stenosis	Typically associated with hypertension	Ultrasound with Doppler study
Calcineurin inhibitor toxicity	Causes vasoconstriction	Tacrolimus or cyclosporine level
Obstructive Causes		
Ureteral stricture	May be seen with BK infection	Ultrasound with evaluation of the ureter
Bladder dysfunction	Neurogenic bladder	Ultrasound, postvoid residual
Bladder outlet obstruction	Prostatic enlargement	Ultrasound and postvoid residual
Intrinsic Kidney Injury		
Acute cellular rejection	Can be triggered by recent infection or immunosuppression reduction	Renal allograft biopsy
Acute antibody-mediated rejection	Especially if immunosuppression has been reduced	Donor-specific antibodies, renal allograft biopsy
Drug toxicity	Calcineurin inhibitors, antibiotics	Therapeutic drug level monitoring, kidney allograft biopsy
Infection	Transplant pyelonephritis, BK virus infection	Urine culture, BK viral load in plasma
Posttransplantation lymphoma	Rare occurrence	EBV plasma viral load, kidney allograft biopsy
Recurrent disease	IgA, MN, FSGS, MPGN, immune complex disease	Kidney allograft biopsy

Abbreviations: EBV, Epstein-Barr virus; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.

nephropathy. Table 2 summarizes major causes of AKI in kidney transplant recipients.

Proteinuria is another indication for kidney allograft biopsy. Non-nephrotic-range proteinuria may be seen with early transplant glomerulopathy associated with chronic antibody-mediated rejection (CAMR). Nephrotic-range proteinuria can be associated with transplant glomerulopathy as well, but may be an indicator of diabetes or recurrent or de novo diseases such as focal segmental glomerulosclerosis (FSGS), membranous glomerulopathy, or other immune complex deposition diseases.

The gold standard in assessment of an increased Scr concentration is the kidney allograft biopsy. The biopsy may identify acute or chronic rejection, recurrent or de novo kidney disease, viral or other infections, or progressive scarring with interstitial fibrosis and tubular atrophy. Acute and chronic rejection is graded based on severity, typically using Banff criteria. Biopsy tissue should be evaluated by a nephropathologist familiar with transplant pathology.

Rejection

Case 2: A 24-year-old woman with ESRD secondary to lupus nephritis who received a deceased donor kidney transplant 4 months ago presents with low-grade fever (99.5°F) and decreased appetite with associated nausea. Scr level is elevated to 1.3 mg/dL from a nadir of 0.8 mg/dL. Urinalysis shows 3 to 5 white blood cells, 3 to 5 red blood cells, and trace protein. Kidney ultrasound shows resistive indexes of 85% to 90%, patent renal artery and vein, and mild pelviectasis. She has not been seen in the clinic or had laboratory measurements performed for 2 months. She is admitted to the hospital and continued on her home medications. Tacrolimus trough is 4 ng/mL. Urine culture results are negative and a kidney allograft biopsy is scheduled.

Question 2: What is the most likely cause of AKI?

- a) Allograft pyelonephritis
- b) Volume depletion due to poor appetite and nausea
- c) Rejection due to medication nonadherence
- d) Tacrolimus-induced nephrotoxicity

Owing to the advent of CNIs, the risk for cellular rejection has decreased significantly. However, antibody-mediated rejection is the cause of 30% to 50% of acute rejection episodes and 60% of late graft failures. Unexplained AKI in a kidney transplant recipient warrants referral of the patient to the transplantation center for biopsy and treatment. The transplantation nephrologist will have access to HLA antigen laboratory testing and donor information that can also be used to guide treatment.

Cellular Rejection

Cellular rejection is most likely to occur in the early weeks to months posttransplantation, though it can manifest later, especially if immunosuppression is

reduced, either through patient nonadherence, provider recommendation, or after immune stimulation associated with acute illness. Cellular rejection commonly presents as an asymptomatic increase in Scr level. Symptoms of rejection including fever, graft tenderness, oliguria, and hypertension are uncommon. Cellular rejection can take the form of tubulointerstitial or vascular rejection. In tubulointerstitial rejection, T lymphocytes, monocytes, and plasma cells infiltrate the interstitium and invade renal tubules, causing tubulitis. The degree of interstitial infiltration and tubulitis define the degree of type 1 cellular rejection according to the Banff classification. Cell-mediated vascular rejection manifests as lymphocytes, monocytes, and macrophages invading the sub-endothelium and intima of arteries and corresponds to type 2 rejection. Type 3 rejection manifests with transmural arterial fibrinoid necrosis.

Treatment of rejection is dependent on the severity and degree of background chronicity. Type 1 cellular rejections are typically treated with glucocorticoids alone, either IV methylprednisolone, 500 to 1,000 mg, daily for 3 to 6 consecutive days or oral pulse steroids. Type 2 and greater rejections, with little background scarring, are treated with lymphocyte-depleting agents in conjunction with glucocorticoids. According to a 2016 systematic review, complete renal response (defined as Scr within 125% of the pretreatment Scr or a 25% decrease in Scr from pretreatment peak Scr) was noted in 52% to 80% of treated Banff 2A rejections, 73% to 75% of treated Banff 1B rejections, and 10% of treated Banff 2B rejections, with a pooled 1A and 1B complete functional response rate of 44%. Worse treatment responses are reported in cellular rejections with vascular involvement (Box 1).

Humoral Rejection

Hyperacute rejection, an extremely rare occurrence, develops within seconds of implantation as a result of high levels of antibodies against antigens on the endothelium of glomeruli and microvasculature of the donor kidney. This process leads to complement activation, platelet deposition, and endothelial necrosis. Improvements in the detection of donor-specific antibodies (DSAs) and sophisticated cross-matching techniques have largely eliminated this complication.

Acute antibody-mediated rejection (AMR) occurs within the first weeks to years after transplantation. The most common mechanism underlying AMR is an anamnestic antibody response that results from prior antigenic exposure such as pregnancy, blood transfusions, or prior transplants. Through both complement-mediated and -independent mechanisms, the interaction of these antibodies with the vascular endothelium results in cell death, loss of vascular integrity, and subsequent ischemic injury. Diagnosis using Banff criteria requires 3 features to be met for diagnosis: morphologic changes, including

Box 1. Revised Banff 2017 Classification of Antibody-Mediated and T-Cell-Mediated Rejection in Kidney Allografts**Active ABMR; All 3 Criteria Must be Met for Diagnosis**

- Histologic evidence of acute tissue injury, including ≥ 1 of the following:
 - Microvascular inflammation ($g > 0$ and/or $ptc > 0$), in the absence of recurrent or de novo GN, although in the presence of acute TCMR, borderline infiltrate, or infection, $ptc \geq 1$ alone is not sufficient and g must be ≥ 1
 - Intimal or transmural arteritis ($v > 0$)
 - Acute TMA, in the absence of any other cause
 - Acute tubular injury, in the absence of any other apparent cause
- Evidence of current/recent antibody interaction with vascular endothelium, including ≥ 1 of the following:
 - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
 - At least moderate microvascular inflammation ($[g + ptc] \geq 2$) in the absence of recurrent or de novo GN, although in the presence of acute TCMR, borderline infiltrate, or infection, $ptc \geq 2$ alone is not sufficient and g must be ≥ 1

Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated

- Serologic evidence of DSA (to HLA or other antigens). **C4d staining or expression of validated transcript/classifiers as noted in criterion 2 may substitute for DSA; however, thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met**

Chronic Active ABMR; All 3 Criteria Must Be Met for Diagnosis

- Morphologic evidence of chronic tissue injury, including ≥ 1 of the following:
 - Transplant glomerulopathy ($cg > 0$) if no evidence of chronic TMA or chronic recurrent/de novo GN; includes changes evident by EM alone ($cg1a$)
 - Severe peritubular capillary basement membrane multilayering (requires EM)
 - Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no history of TCMR, but are not required
- Identical to criterion 2 for active ABMR
- Identical to criterion 3 for active ABMR, including strong recommendation for DSA testing when criteria 1 and 2 are met

Acute TCMR

Grade IA: Interstitial inflammation involving $>25\%$ of nonsclerotic cortical parenchyma ($i2$ or $i3$) with moderate tubulitis ($t2$) involving ≥ 1 tubule, not including tubules that are severely atrophic

Grade IB: Interstitial inflammation involving $>25\%$ of nonsclerotic cortical parenchyma ($i2$ or $i3$) with severe tubulitis ($t3$) involving ≥ 1 tubule, not including tubules that are severely atrophic

Grade IIA: Mild to moderate intimal arteritis ($v1$), with or without interstitial inflammation and/or tubulitis

Grade IIB: Severe intimal arteritis ($v2$), with or without interstitial inflammation and/or tubulitis

Grade III: Transmural arteritis and/or arterial fibrinoid necrosis of medical smooth muscle with accompanying mononuclear cell intimal arteritis ($v3$), with or without interstitial inflammation and/or tubulitis

Abbreviations: ABMR, antibody-mediated rejection; cg, Banff chronic glomerulopathy score; g, Banff glomerulitis score; GN, glomerulonephritis; DSA, donor-specific antibodies; EM, electron microscopy; i, inflammation; IF, immunofluorescence; IHC, immunohistochemistry; ptc, Banff peritubular capillaritis score; TCMR, T cell-mediated rejection; TMA, thrombotic microangiopathy; v, arteritis.

Adapted from Haas et al (*Am J Transplant*. 2018;18:293-307; <https://doi.org/10.1111/ajt.14625>) with permission of John Wiley and Sons; original content is © 2018 Haas et al.

microvascular inflammation characterized by neutrophils and mononuclear cells in glomeruli and peritubular capillaries, acute tubular injury, thrombotic microangiopathy, or intimal or transmural arteritis; evidence of complement activation by C4d deposition in the peritubular capillaries or within arterial fibrinoid necrosis; and presence of DSAs (Box 1).

Treatment of AMR is less standardized and less effective. Given the critical role of DSAs and complement in the pathogenesis of AMR, plasmapheresis or immunoadsorption is the fastest way to temporarily remove circulating DSAs and complement from the peripheral blood. In the United States, plasmapheresis is used in preference to immunoadsorption. Despite the efficacy of antibody removal with plasmapheresis, there is no inhibition of active antibody synthesis and thus there is a risk

for significant rebound. Adjuvant therapies are used in conjunction with plasmapheresis, such as IV immunoglobulin (IVIG). Multiple mechanisms for IVIG action have been proposed, including enhanced antibody clearance, inhibition of complement, and negative regulatory signals through Fc receptors.

While plasmapheresis and IVIG aim to remove DSAs, other therapies target the production of new antibodies. Rituximab, a chimeric monoclonal antibody, eliminates CD20-positive B cells. Following exposure to donor HLA antigens, CD20-positive lymphocytes present antigens to helper T cells that release cytokines that allow B cells to differentiate into antibody-secreting plasma cells. Rituximab may inhibit DSA production by depleting CD20-positive B cells. Rituximab also downregulates CD40 to inhibit interaction between B and T cells.

Rescue therapies for AMR include eculizumab and bortezomib. Eculizumab, a humanized monoclonal antibody, blocks C5, inhibiting the formation of the C5b-C9 membrane attack complex, thus inhibiting complement activation. Eculizumab, US Food and Drug Administration (FDA) approved for the treatment of paroxysmal nocturnal hemoglobinuria, has shown some promise in the treatment of refractory AMR. Finally, bortezomib, a proteasome inhibitor that is FDA approved for the treatment of multiple myeloma, has been used to deplete plasma cells. The physiologic role of a proteasome is to break down misfolded proteins when tagged by ubiquitin, and bortezomib inhibits this process, leading to plasma cell apoptosis. Recent evidence indicates that the use of proteasome inhibitors may be ineffective in AMR due to rebound repopulation of lymphoid germinal centers. More clinical trials are necessary to further elucidate the role of these therapies.

Chronic AMR

CAMR is clinically recognized as a cause of a slow and progressive decline in graft function, often in the setting of hypertension and proteinuria. CAMR is the most common cause of graft failure in the United States. Pre-existing or de novo DSAs deposit on the vascular endothelium, resulting in injury to glomerular and peritubular capillaries. The pattern of injury includes cellular hypertrophy; sub-endothelial deposition of fibrillary material; expansion and duplication of the glomerular basement membrane, designated as transplant glomerulopathy; and complement deposition.

Diagnosis using Banff criteria requires all 3 of the following criteria to be met. First, there must be tissue evidence of chronic injury, including one of the following: transplant glomerulopathy, severe multilayering of basement membrane, or new-onset intimal arterial fibrosis. Second, there must be evidence of antibody interaction with the vascular endothelium, seen as C4d deposition in the peritubular capillaries or moderate microvascular inflammation. Last, there must be serologic evidence of DSAs (Box 1). Unfortunately,

there is no clear evidence supporting therapies for CAMR and practice is based on observational studies and center experience. The only treatment regimen with some reported success is a combination of glucocorticoids, IVIG, and rituximab. A 2017 study showed that in 36 patients with CAMR for whom who IVIG and rituximab had failed, tocilizumab, an anti-IL-6 monoclonal antibody, stabilized kidney function, reduced DSAs, and improved pathologic markers for CAMR. Further studies are required to define optimal therapies and treatment outcomes in larger cohorts.

Returning to case 2, this patient with a new transplant has had no laboratory measurements for 2 months, suggesting a pattern of treatment nonadherence. Young patients are particularly at risk for rejection due to nonadherence. Younger patients underestimate the benefits of immunosuppressive medications and are more intolerant of drug side effects, leading to a statistically significant association with rejection due to nonadherence. Thus, the answer is (c).

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Recurrent and De Novo Disease

Thirty percent to 50% of kidney transplant recipients have glomerular disease as the underlying cause of ESRD. The cumulative incidence of allograft glomerulonephritis, both recurrent and de novo, is 5% at 1 year, 22% at 5 years, and 42% at 10 years post-transplantation. Allograft glomerulonephritis, both recurrent and de novo, accounts for 18% to 22% of death-censored graft failure. The rate of recurrent

Table 3. Recurrent Glomerulonephritis Posttransplantation

Diagnosis Pretransplantation ^a	N ^b	Year 1	Year 3	Year 5	Actual Graft Survival	P ^c	Follow-up, mo
No GN	1,282	—	—	—	82.6%	—	87.5 ± 46
FSGS	148	10.5%	30.7%	35.1%	73.0%	0.009	90.3 ± 49
MN	49	18.9%	45.4%	55.0%	79.6%	0.908	99.7 ± 51
MPGN	52	18.3%	41.4%	41.4%	53.8%	<0.0001	81.3 ± 49
IgAN ^d	165	12.5%	42.0%	51.0%	80.9%	0.382	96.2 ± 45

Abbreviations: FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis.

^aPretransplantation diagnoses in 1,965 kidney recipients who underwent transplantation at a single center from 1998 to 2011. Not included are 269 recipients with other GN types before transplantation.

^bThe relatively low numbers of patients in each group did not allow accurate determinations of incidence of recurrence beyond 5 years posttransplantation.

^cLog-rank test comparing death-censored graft survival in recipients with each of the GN diagnoses with that of recipients with pretransplantation diagnoses other than GN.

^dPatients with IgAN had significantly longer follow-up ($P = 0.028$).

Adapted from Cosio & Cattran (*Kidney Int*. 2017;91(2):304-314; <https://doi.org/10.1016/j.kint.2016.08.030>) with permission of the International Society of Nephrology (ISN); original content © 2016 ISN.

glomerulonephritis varies based on pretransplantation underlying disease (Table 3).

Focal Segmental Glomerulosclerosis

Secondary FSGS can result from glomerular hyperfiltration, reflux nephropathy, drug exposures (pamidronate and heroin) and viral infections (HIV and parvovirus B19) and does not recur. Primary FSGS can be familial or idiopathic. Familial FSGS, caused by mutations in podocyte proteins, does not recur posttransplantation. However, ~30% of idiopathic FSGS will recur after transplantation. Risk factors for recurrent disease include younger age, rapid progression to ESRD, mesangial hypercellularity of native kidneys, European ancestry, male sex, nephrotic-range proteinuria before transplantation, or history of previous graft failure due to recurrence. Patients who have FSGS recurrence in the first year after transplantation have >80% risk for recurrence in subsequent grafts. Recurrence can occur within hours of transplantation, with the development of massive proteinuria. Close monitoring of urinary protein-creatinine ratios immediately posttransplantation is essential for identifying early recurrence. Early biopsy is likely to reveal normal light microscopy findings with evidence of diffuse foot-process effacement on electron microscopy.

The standard of care for recurrence is early initiation of plasmapheresis and maintenance of high-dose CNI therapy. Early institution of plasmapheresis is critical because the efficacy of treatment decreases with the development of glomerular segmental sclerosis. Outcomes with the use of rituximab have been variable. Clinical manifestations of late-occurring FSGS include nephrotic-range proteinuria, hypertension, and graft dysfunction. Treatment is supportive with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to decrease proteinuria, along with maintenance of adequate immunosuppression and control of blood pressure.

Membranous Nephropathy

Idiopathic membranous nephropathy (MN) recurs in up to 40% to 50% of cases after kidney transplantation and 10% to 15% develop graft failure from recurrence after 10 years. Recurrent disease should be distinguished from de novo MN, which is the most common de novo glomerulopathy posttransplantation. Recurrent MN occurs on average 10 months posttransplantation, while de novo MN is more insidious and occurs later posttransplantation. Glomerular M-type phospholipase A₂ receptors (PLA₂R) have been discovered as a major target in idiopathic MN. A total of 70% of patients with biopsy-proven idiopathic MN have immunoglobulin G (IgG) antibodies that react with PLA₂R. Patients with anti-PLA₂R antibodies pretransplantation have a 60% to 76% risk for histologic recurrence, whereas antibody-negative patients have a lower risk of 30%. Anti-PLA₂R antibody levels decline in ~50% of recipients posttransplantation due to

immunosuppression and absorption of antibodies into the allograft. CNIs, steroids, and alkylating agents such as cyclophosphamide and rituximab have been shown to be promising in the treatment of recurrent MN. One study compared patient outcomes of 62 PLA₂R-positive and 8 PLA₂R-negative patients with primary MN and found that estimated glomerular filtration rates (GFRs) were significantly lower in the PLA₂R-positive group, with estimated GFRs of 70.5 mL/min compared to 100 mL/min at 32 months posttransplantation.

IgA Nephropathy

IgA nephropathy (IgAN) accounts for 20% of ESRD in kidney transplant recipients. Histologic recurrence of idiopathic IgAN has been reported in 50% to 60% of patients, though clinically significant recurrence is far less. Clinical manifestations are similar to primary IgAN and include microscopic hematuria, proteinuria, and slow decline in kidney function. Despite the high incidence of recurrence, the estimated 10-year incidence of graft loss due to recurrent IgAN is 9.7%. Prior allograft loss due to recurrent IgA is associated with subsequent graft loss. Current data suggest that the recurrence rate of Henoch-Schönlein purpura after transplantation is similar to that of IgAN.

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) can be primary or secondary, related to viral infections such as HCV or HBV, autoimmune disease, or monoclonal gammopathies. Histopathology consistent with MPGN should be differentiated from histologic changes associated with CAMR. What was formerly referred to as MPGN type I recurs in 20% to 50% of allografts, while MPGN type II recurs in up to 80% to 100% of transplants. Risk factors for recurrence include the presence of HLA-B8 and -DR3, living related donors, and previous graft loss from recurrent disease. The overall graft loss at 10 years due to recurrence is ~15%. However, the risk for graft loss from recurrence in a second graft in patients who have had recurrence in the first graft is as high as 80% to 100%.

Antineutrophil Cytoplasmic Antibody–Associated Glomerulonephritis

Antineutrophil cytoplasmic antibody–associated glomerulonephritis is a relatively rare cause of ESRD. In a cohort of 127 patients, recurrence was reported in 17% of patients between 4 and 89 months posttransplantation. The 10-year incidence of allograft loss was 7.7% in patients with antineutrophil cytoplasmic antibody–positive glomerulonephritis. It is recommended to defer kidney transplantation until the disease is quiescent. Patients with relapses have shown good response to cyclophosphamide.

Lupus Nephritis

Lupus nephritis is an important cause of ESRD among transplant recipients. Histologic recurrence has been

reported in up to 30% of transplant recipients; however, clinically significant disease occurs in only 2% to 9% of patients. Clinical quiescence is recommended for 6 to 9 months before transplantation due to higher morbidity and increased risk for recurrent lupus nephritis during active disease. Graft loss due to lupus nephritis is uncommon, occurring in only 2% to 4% of recipients.

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Infections and Infectious Diseases

Case 3: A 56-year-old man with ESRD secondary to diabetes underwent deceased donor kidney transplantation 18 months ago. He received thymoglobulin induction immunosuppression and received 12 months of prophylaxis with valganciclovir and Bactrim. He now presents with nausea and severe watery diarrhea and laboratory results showing a white blood cell count of $1.8 \times 10^9/L$. Cytomegalovirus (CMV) viral load by polymerase chain reaction is 30,000 copies per milliliter and colonic biopsy samples are positive for CMV colitis.

Question 3: What medication is most appropriate for treatment?

- A. Oral valganciclovir
- B. IV ganciclovir
- C. IV foscarnet
- D. IV cidofovir

For the answer to the question, see the following text.

Urinary tract infections are common posttransplantation. In the early posttransplantation period, this may be related to manipulation of the urinary tract with Foley catheters or ureteral stents. The ureteral anastomosis to the bladder is not an antirefluxing anastomosis and may contribute to infected urine refluxing into the transplanted kidney. In addition, bladder dysfunction related to diabetes or bladder outlet obstruction from an enlarged prostate may contribute to urinary stasis and urinary tract infections. Sexually active women should be counseled on postcoital voiding and perineal hygiene

techniques. Patients with recurrent urinary tract infections should be evaluated for anatomic abnormalities such as bladder diverticula, perinephric abscesses, kidney or bladder stones, or severe reflux. A kidney ultrasound is the initial step in evaluation, and in some cases a voiding cystourethrogram to evaluate for reflux is indicated.

Treatment of recurrent urinary tract infections is not standardized. Use of prophylactic antibiotics poses a risk for developing resistant organisms and limited availability of antibiotics to treat infection. Methenamine hippurate taken twice daily can reduce infections by ~50%. It is metabolized to formaldehyde and actively secreted in urine, creating a hostile environment for microbial growth. Urinary pH should ideally be <6.0 for maximal effectiveness. Methenamine hippurate combined with cranberry extract tablets provides protection for many patients. Patients should also be advised to “double void” and void on a regular basis. In extreme cases in which significant reflux is identified by means of a voiding cystourethrogram, patients may benefit from ureteral reimplantation to their native ureter, which eliminates the reflux of urine into the transplant ureter.

Viral infections are particularly troublesome posttransplantation. Current immunosuppression primarily blocks T-lymphocyte activation because these cells are predominantly responsible for cellular rejection. T cells are also responsible for screening and controlling malignancies and viral and fungal infections. CMV is common in transplant recipients, especially if a seronegative recipient receives a kidney from a seropositive donor. CMV infection often presents with diarrhea, fevers, and malaise but can also present with pulmonary symptoms. Leukopenia is common with CMV. The mainstay of treatment is valganciclovir (oral) or ganciclovir (IV) for tissue-invasive disease.

All recipients are encouraged to receive annual influenza vaccines. However, because live virus vaccines are contraindicated in transplant recipients, they should not receive nasal influenza vaccine. Other vaccines contraindicated for this reason include MMR (measles, mumps, and rubella) and yellow fever and shingles vaccines. A new recombinant vaccine for herpes zoster (Shingrix) has been released and appears safe in this population, though it has not yet been adequately tested in transplant recipients.

Polyoma (BK virus) has plagued transplant recipients since the advent of improved immunosuppression in the early 1990s. Approximately 20% of transplant recipients develop BK viremia posttransplantation. Approximately 80% of adults have antibody evidence of exposure to BK virus, with exposure occurring around school age. The virus is most likely transmitted from the donor organ because recipients of pediatric kidneys are much less likely to develop BK viremia. There is no proven antiviral therapy for BK virus, leaving reduction in immunosuppression as the only effective therapy. The use of IVIG may provide passive immunity and help clear the virus. Studies using cidofovir have not been conclusive, and there is a

significant risk for nephrotoxicity. Despite in vitro evidence of fluoroquinolone having anti-BK virus activity, a randomized controlled trial was negative. Leflunamide is sometimes substituted for MMF/MPA, but again studies are not conclusive and its efficacy may be related to overall decreased immunosuppression.

Influenza has been particularly troubling recently, with increased virulence and inadequate protection from vaccines. Transplant recipients are more likely to face severe illness. West Nile virus has also posed increased morbidity and mortality in transplant recipients. Recipients are encouraged to avoid mosquito bites, eliminate stagnant water, and use mosquito repellants. The risk for viral infections and the inability to receive live vaccines is the greatest limiting factor for traveling abroad for transplant recipients. Any transplant recipient planning to travel abroad should check entry requirements (eg, yellow fever vaccine certificate) and discuss required vaccines with their physician. The Centers for Disease Control and Prevention has an excellent website with travel information for immunosuppressed patients.

Transplantation candidates are screened for tuberculosis before transplantation either with a purified protein derivative (PPD) skin test or an interferon γ release assay (QuantiFERON-TB Gold) assay. All patients who have positive results are further evaluated for active disease and treated either for active or latent tuberculosis.

Fungal infections in kidney transplant recipients can prove fatal. Aspergillus and mucormycosis historically have been associated with high morbidity and mortality risk. The mainstay of treatment is marked reduction in immunosuppression. Survival has improved slightly when this is combined with newer antifungal agents. Given regional variations in endemic fungal prevalence, patient residence and travel history need to be considered in the evaluation of a patient. Blastomyces is endemic in the Ohio and Mississippi River Valleys and the Great Lakes regions. Histoplasmosis is endemic in central and eastern states, as well as parts of Central and South America, Africa, Asia, and Australia. Coccidiomycosis is endemic in the Southwestern United States, especially the San Joaquin Valley of California. Lifelong prophylactic fluconazole therapy is used by some transplantation centers to prevent coccidiomycosis infections for patients residing in endemic areas. The presentation of coccidiomycosis ("valley fever") can be respiratory symptoms, joint infections, or disseminated disease with a characteristic rash.

Considering case 3, this patient is at high risk for CMV infection given thymoglobulin induction and recently completed prophylaxis. He is now presenting with tissue-invasive disease, as evidenced by colonic biopsy, which requires IV ganciclovir for optimal initial treatment. Treatment duration is typically a minimum of 3 weeks (he can convert to oral valganciclovir as symptoms improve) with undetectable viral DNA on polymerase chain reaction amplification of serum samples and resolution of clinical symptoms. This is

followed by another 3-month course of prophylaxis with oral valganciclovir. Thus, the answer is (b).

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Malignancy Posttransplantation

The most common malignancy posttransplantation is nonmelanotic skin cancer. Squamous cell skin cancer risk is 100-fold increased among transplant recipients, especially in Latinos and whites as compared to the general population. All transplant recipients should wear sunscreen and be screened annually by a dermatologist. Though squamous cell skin cancers do not typically metastasize, if untreated, metastasis can occur. Recurrent skin cancers should prompt consideration of conversion to an mTOR inhibitor, which has better efficacy in control of epithelial cell-derived skin cancers.

PTLD is seen in $\sim 0.8\%$ of adult and $\sim 2.6\%$ of pediatric recipients. The majority of PTLD cases are driven by an EBV infection. The higher prevalence in children is due to a lack of acquired immunity to EBV. EBV infection or reactivation results in clonal expansion of B lymphocytes, resulting in lymphoma. PTLD often presents with infiltration of the internal organs, central nervous system, or intrathoracic or intra-abdominal lymph nodes. Palpable lymphadenopathy is uncommon. Presenting symptoms include low-grade fevers, shortness of breath, headaches, or abdominal discomfort. Physicians should have a low threshold for computed tomography (CT) in patients presenting with these symptoms. Initial treatment is reduction in immunosuppression, followed by chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Renal cell cancers are seen more frequently in the transplantation population, likely related to malignant degeneration of cysts in patients with underlying polycystic or acquired cystic disease. There are no accepted guidelines for screening transplant recipients for renal cell

cancer. However, hematuria in a transplant recipient warrants urologic evaluation that includes ultrasonography or CT of both the native and transplanted kidney.

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Contraception, Family Planning, and Pregnancy

Case 4: A 30-year-old woman underwent living related kidney transplantation for ESRD secondary to IgAN 5 years ago. Scr level is stable at 1.0 mg/dL and she is receiving prednisone, 5 mg, once daily, MMF, 1,000 mg, orally twice daily, and tacrolimus, 2 mg, orally twice daily with a level of 5.0 ng/mL. Blood pressure is well controlled with amlodipine, 5 mg, once daily. She was married a year ago and wishes to discuss family planning.

Question 3: What advice should you to give to her?

- A. Her kidney function and blood pressure are well controlled so no contraindications to pursuing pregnancy
- B. Pregnancy is not advised and will likely cause a decline in kidney function
- C. Her immunosuppressives should be adjusted, with discontinuation of MMF due to the risk for fetal malformations
- D. She should stop treatment with both MMF and tacrolimus and remain on prednisone alone

For the answer to the question, see the following text.

In patients of child-bearing age, contraception and family planning need to be discussed early and frequently. Risk Evaluation and Mitigation Strategy (REMS) mandated by the FDA indicates that all patients starting therapy with mycophenolate agents be counseled about the risks for fetal loss or birth defects associated with these agents. The preferred method of contraception is the Mirena intrauterine device. Contrary to early concerns that the immunosuppression would render an intrauterine device ineffective, this is not true. Oral contraception is not favored in early the post-transplantation period due to an increased risk for thromboembolic disease, but may be used later in patients at low risk for thromboembolism. Depot Provera is another option for sustained contraception.

Women who wish to conceive are encouraged to discuss this with their physicians. The optimal scenario for conception is for the patient to: (1) substitute azathioprine for mycophenolate 3 months before conception; (2) be at least 1 year post-transplantation; (3) have a stable estimated GFR with

Scr level < 1.5 mg/dL, with no recent rejection episodes; (4) have no significant proteinuria; and (5) have well-controlled blood pressure and not be using an ACE inhibitor or ARB. Pregnant transplant recipients should be comanaged by transplantation nephrology and high-risk obstetrics. Tacrolimus levels need to be monitored closely because its metabolism by the placenta and dilution by an increased volume of distribution can result in subtherapeutic levels.

Male fertility may be affected by immunosuppressive medications. mTOR inhibitor use in men can result in oligospermia and reduced testosterone levels, which can contribute to infertility and erectile dysfunction. Erectile dysfunction can be treated with phosphodiesterase inhibitors if medical comorbid conditions do not pose a contraindication. Erectile dysfunction can also be treated with penile implants in those with contraindications to the use of phosphodiesterase inhibitors.

Pregnancies are common posttransplantation with generally good outcomes. The International Transplant Pregnancy Registry is a voluntary registry and a good resource for information regarding pregnancy after organ transplantation. Gestation is typically closer to 34 to 36 weeks, with newborns often being small for gestational age. Vaginal births are safe and cesarean sections should be performed only for the standard obstetrical indications. Breast feeding is no longer considered contraindicated for women using glucocorticoids, azathioprine, tacrolimus, cyclosporine, or sirolimus because drug levels of immunosuppressive medications are minimal in breast milk. Data are lacking regarding belatacept and mycophenolate.

Returning to case 4, pregnancy is safe in kidney transplant recipients as long the recipient has stable kidney function and is at least 1 year posttransplantation with well-controlled blood pressure. Mycophenolate treatment should be discontinued before conception due to the risk for fetal malformations. Prednisone, azathioprine, and tacrolimus are safe in pregnancy. Delivery is typically early, around 36 weeks. Thus, the answer is (c).

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Extrarenal Considerations in the Kidney Transplant Recipient

Cardiovascular Health

Cardiovascular disease is the leading cause of death in kidney transplant recipients 1 year posttransplantation. Chronic kidney disease is a risk factor for cardiovascular disease, along with diabetes and hypertension.

Several factors posttransplantation contribute to the increased cardiovascular risk, including hypertension, hyperlipidemia, and physical inactivity. ACE inhibitors and ARBs are often underused.

A lack of focus on cardiovascular risk factors by the transplantation providers, and a fear of doing harm by the primary care providers, often results in inadequate management of these patients.

Weight Control and Exercise

Weight gain is common posttransplantation. The cause of the weight gain is multifactorial and likely related to a combination of improved appetite with restoration of kidney function, a more liberal diet, and a lack of regular exercise. The long-term use of low-dose steroids may have some effect on appetite, though weight gain appears comparable in steroid-withdrawal and steroid-maintenance patients. Patients need to be counseled routinely and frequently on the benefits of a healthy diet and regular exercise.

Electrolyte Abnormalities

Electrolyte abnormalities are common posttransplantation. Hyperkalemia can be associated with CNIs, sulfamethoxazole, ACE inhibitors, and ARBs and with reduced GFR. CNIs can cause hyperkalemia with hyperchloremic metabolic acidosis due to downregulation of specific tubular transport proteins. Hypomagnesemia (magnesium, 1.2-1.7 mg/dL) is seen in most transplant recipients as a result of renal magnesium wasting due to tacrolimus. In addition, proton pump inhibitors may also contribute to hypomagnesemia. Oral magnesium replacement should target a level > 1.5 mg/dL because levels > 2.2 mg/dL are rarely achieved and usually result in magnesium-induced diarrhea.

Bone Health

Optimal management of calcium and phosphorus is not well defined in the kidney transplant population. Elevated parathyroid hormone (PTH) levels before transplantation are predictive of posttransplantation hypophosphatemia. After transplantation, PTH levels may slowly decline as hyperplastic parathyroid tissue involutes over the course of the year. PTH levels should be monitored posttransplantation, with a target level of 1-2 times the upper limit of normal. Oversuppression of PTH can lead to adynamic bone disease, while undercorrected hyperparathyroidism can contribute to increased bone turnover and osteoporosis. Vitamin D levels should be monitored and supplemented as needed.

Gastrointestinal Health

Common side effects of mycophenolate preparations are gastrointestinal toxicity, with diarrhea occurring in up to one-third of patients. The gastrointestinal side effect profile of enteric-coated MPA (Myfortic) is not significantly different from MMF. Mycophenolate-

induced colitis can result in severe diarrhea and requires substitution with a different class agent, such as azathioprine. mTOR inhibitors can also cause diarrhea significant enough to require drug treatment cessation. Tacrolimus can also cause diarrhea, especially at supratherapeutic levels. Diarrhea can also be associated with increased paracellular absorption of tacrolimus, resulting in a further increase in tacrolimus levels and perpetuation.

Hematologic Considerations

Bone marrow suppression is a common consequence of immunosuppressive agents. Leukopenia is a common side effect of antiproliferative agents and mTOR inhibitors. Posttransplantation erythrocytosis can also be seen. The mechanism is not entirely clear. In patients with native kidneys, it is prudent to screen for renal cell carcinoma with CT or ultrasonography. Posttransplantation erythrocytosis (hematocrit > 54%) may be managed by the introduction of an ACE inhibitor or ARB, and in rare cases with phlebotomy.

New-Onset Diabetes After Transplantation

Tacrolimus, more than cyclosporine, is toxic to pancreatic islet cells. New-onset diabetes after transplantation (NODAT) affects up to 40% of transplant recipients, though the accuracy of this statistic is limited by controversy about the definition of NODAT. Risk factors for the development of NODAT are obesity, African American and Hispanic ethnicities, family history of diabetes, and HCV infection. Those with known diabetes before the development of ESRD are likely to require more intensive therapy.

Neurologic Complications

Neurologic side effects of immunosuppression can plague transplant recipients. Fine resting tremors are a common side effect and more prevalent in patients using tacrolimus. Tremors are most frequently noted in the hands, but tongue tremors may also be observed. Vague symptoms of atypical chest pain and peripheral neuropathy are also common with CNIs. However, the most concerning neurologic side effect is posterior leukoencephalopathy that can manifest with altered mental status, visual changes, headaches, or seizures. Diagnosis is made using magnetic resonance imaging because CT (with or without contrast) is unrevealing. Treatment is supportive, along with discontinuation of treatment with the CNI.

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Correction Notice: This article was amended on April 23, 2019 to correct an error in [Table 1](#).