

Managing Your Adult Patients Who Have a **KIDNEY TRANSPLANT**

Implications for Primary Care in:

- ▶ Kidney Transplant Recipients and Chronic Kidney Disease
- ▶ Immunosuppressive Medications
- ▶ Managing Adverse Events
- ▶ Long-Term Care
 - Acute Rejection and Kidney Allograft Dysfunction
 - Cardiovascular Disease Risk Reduction
 - New-Onset Diabetes After Transplant
 - Infection
 - Cancer
 - Other Complications



KIDNEY TRANSPLANT RECIPIENTS AND CKD

All kidney transplant recipients (KTRs) are considered to have CKD based on:

- Damage to native kidneys
- Presumed damage to the kidney transplant based on studies of “protocol biopsies”
- Need for lifelong care caused by complications of prior CKD and chronic allograft nephropathy.

Primary care management of KTRs:

- Early detection of kidney allograft dysfunction to allow for timely diagnosis and treatment
- Prevention, assessment, and management of adverse events (cardiovascular disease, new-onset diabetes after transplant, infection, cancer)
- Reducing risk for acute kidney injury

STAGING SEVERITY OF CHRONIC KIDNEY DISEASE WITH TRANSPLANT

Stage	Description	GFR mL/min/1.73m ³	CKD Clinical action plan*
1T	Kidney damage with normal or increased kidney function	≥90	Diagnosis and treatment of CKD Treatment of comorbid conditions Slowing progression CVD risk reduction
2T	Kidney damage with mildly decreased kidney function	60-89	Estimating progression
3T	Moderately decreased kidney function	30-59	Evaluating and treating complications due to CKD prior to and after transplant Manage transplant-specific issues
4T	Severely decreased kidney function	15-29	Referring to nephrologist if evidence of CKD progression Preparation for kidney replacement therapy (patient and family education, dialysis access, preemptive transplant)
5T	Kidney failure	<15 (or dialysis)	Kidney replacement therapy (if uremia present)

T=transplant. *Refer to nephrologist if clinical action plan cannot be carried out. Includes actions from preceding stages.

Serum creatinine-based estimated glomerular filtration rate (eGFR) should be used to assess level of kidney function (serum creatinine alone is not sufficient). Calculate eGFR to determine CKD stage and appropriate clinical action plan. eGFR can be automatically calculated at www.kidney.org/gfr

MONITORING KIDNEY ALLOGRAFT FUNCTION

Detecting kidney allograft dysfunction as soon as possible will allow timely diagnosis and treatment that may improve outcomes.

Serum creatinine and urine protein measurements are readily available and are useful for detecting acute and chronic allograft dysfunction.

Increased serum creatinine that is not explained by dehydration, urinary obstruction, high calcineurin inhibitor (CNI) levels or other apparent causes is most likely due to an intragraft parenchymal process, such as acute rejection, chronic allograft injury (CAI), drug toxicity, recurrent or *de novo* kidney disease, obstruction or BKV nephropathy.

Ultrasound is relatively inexpensive and reasonably accurate for diagnosing treatable causes of kidney allograft dysfunction.

Proteinuria, or a substantial increase in proteinuria, may indicate a potentially treatable cause of graft dysfunction.

Screening tests for urine protein excretion include dipstick tests for total protein or albumin, as well as randomly collected “spot” urine to measure protein-to-creatinine or albumin-to-creatinine ratios.

SOME CAUSES OF PROTEINURIA AFTER KIDNEY TRANSPLANTATION

Persistent Disease in the Native Kidneys

Allograft Rejection and Drug Toxicity

- Acute rejection
- Thrombotic microangiopathy
- CAI
- Transplant glomerulopathy

De novo and Recurrent Glomerular Diseases

- Minimal change disease
- FSGS
- IgA glomerulonephritis
- Membranous glomerulonephritis
- Membranoproliferative glomerulonephritis
- Postinfectious glomerulonephritis
- Thrombotic thrombocytopenic purpura
- HUS
- Vasculitis
- Diabetic nephropathy
- Systemic lupus erythematosus
- Amyloidosis
- Light- and heavy-chain deposition diseases

CAI, chronic allograft injury; FSGS, focal segmental glomerulosclerosis; HUS, hemolytic-uremic syndrome; IgA, immunoglobulin A.

DIAGNOSTIC CRITERIA FOR ACUTE KIDNEY INJURY

Criteria: An abrupt (within 48 hr) reduction in kidney function currently defined as an absolute increase in serum creatinine of ≥ 0.3 mg/dL (≥ 26.4 μ mol/L), a percentage increase in serum creatinine of $\geq 50\%$ (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/hr for more than 6 hr).

Notes: The above criteria include both an absolute and a percentage change in creatinine to accommodate variations related to age, gender and body mass index (BMI), and to reduce the need for a baseline creatinine but do require at least two creatinine values within 48 hr.

KDOQI Commentary:

Improvement in short-term outcomes has not translated into significant improvements in long-term outcomes in KTRs. The lack of significant improvement in long-term survival may be related to posttransplant

complications. Frequent posttransplantation monitoring may improve long-term outcomes by reducing chronic graft failure or death with a functioning graft.

MANAGING IMMUNOSUPPRESSIVE MEDICATIONS

Maintenance immunosuppressive medication (IS) is a long-term treatment to prevent acute rejection and deterioration of graft function.

Tailoring immunosuppressive therapies to the individual patient's risk profile (both risk for acute rejection and risk for adverse effects) is considered standard practice.

KDOQI Commentary:

In the United States, IS protocols used may vary from center to center based on their particular patient population, organ source, experience and opinion of the transplant team, ease of use, and cost of therapy. IS agents are used in combinations to achieve sufficient immunosuppression, while minimizing the toxicity associated with individual agents. Monitor KTRs for potential adverse interactions between immunosuppressants and other medications.

In general, the transplant community (patients, healthcare providers, and policy makers) needs to embrace the concept of cost containment and the risk(s) to the patient and graft from these measures. This needs to be balanced between who benefits and how much risk is at stake.



TOXICITY PROFILES OF IMMUNOSUPPRESSIVE MEDICATIONS

Adverse effect	Steroids	CsA	Tac	mTORi	MMF	AZA
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leucopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

AZA, azathioprine; CsA, cyclosporine A; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s); Tac, tacrolimus.

↑ indicates a mild-moderate adverse effect on the complication.

↑↑ indicates a moderate-severe adverse effect on the complication.

(↑) indicates a possible, but less certain adverse effect on the complication.

Nonadherence is associated with a high risk of acute rejection and allograft loss. Provide all KTRs and family members with education, prevention, and treatment measures to minimize nonadherence to IS medications.

[R 11.1 (not graded)]

Consider providing KTRs at increased risk for nonadherence with increased levels of screening for nonadherence.

[R 11.2 (not graded)]

Risk Factors for Medication Nonadherence

- Nonadherence behavior prior to transplantation
- Psychiatric illness
- Personality disorders
- Poor social support
- Substance abuse and other high-risk behavior
- Adolescence
- High education level
- Time since transplantation (higher earlier)
- Lack of adequate follow-up with transplant specialists
- Inadequate pretransplant education
- Multiple adverse effects from medications
- Complex medication regimens

SCREENING OF KTRS

Some tests need to be performed routinely to detect abnormalities that may lead to treatment or prevention of complications that are common in KTRs.

LONG-TERM ROUTINE SCREENING AFTER KIDNEY TRANSPLANTATION		
Screening Test / Evaluation	Screening Intervals by Time after Transplantation	
	7-12 months	>12 months
Blood pressure, pulse, height, BMI, weight*	Each clinical visit	
Creatinine and eGFR	Monthly	Every 2-3 months
Urine protein and/or urine albumin	Every 3 months	Annually
Complete blood count	Monthly	Annually
Fasting plasma glucose, GTT or HbA _{1c}	Every 3 months	Annually
Lipid profile (fasting)	–	Annually
BKV NAT	Every 3 months	–
EBV NAT (seronegative)	Every 3 months	–
Tobacco use	–	Annually

*Measure waist circumference when weight and physical appearance suggest obesity but Body Mass Index <35 kg/m². [R 16.4.1 (not graded)]

BKV, BK polyoma virus; BMI, body mass index; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; GTT, glucose tolerance test; HbA_{1c}, hemoglobin A_{1c}; NAT, nucleic acid testing

KDOQI Commentary:

It may not be practical to require BK virus screening exclusively with quantitative plasma nucleic acid testing (NAT) because many US centers use initial urinary screening and then test plasma only if urine screening results are positive. However, some type of screening for BK virus is critical to avoid BK nephropathies.

Current practice regarding EBV screening varies among centers in the US and many do not routinely screen for EBV posttransplant, even in

recipient-negative donor-positive cases. In many centers, EBV screening is reserved for children, who are much more commonly EBV-negative pretransplant than adults. If screening is someday to be routinely implemented in US centers, details regarding the best method of screening and levels of viremia above which a clinical intervention should be triggered need to be better defined.



INFECTION

Risk Reduction of Infection

Typically, a greater degree of immunosuppression may reduce the risk of rejection, but may also increase the risk of infection.

The harm of different infections, and thereby the potential benefits of vaccinations, vary by geographic region. Most vaccines produce an antibody response, albeit diminished, in immunocompromised individuals, including KTRs.

Annual use of influenza vaccination is recommended for both KTRs and their household contacts. Even while KTRs are receiving high levels of immunosuppression, the benefits of timely vaccination outweigh the risks of delaying vaccination.

RECOMMENDED VACCINES AFTER KIDNEY TRANSPLANTATION

- Diphtheria—pertussis—tetanus
- Haemophilus influenza B
- Hepatitis A*
- Hepatitis B
- Pneumovax
- Inactivated polio
- Influenza types A and B (administer annually)
- Meningococcus (administer if recipient is at high risk)
- Typhoid Vi

*For travel, occupational or other specific risk, and endemic regions.

Consider providing booster polysaccharide pneumococcal vaccination every 3 to 5 years.

CONTRAINDICATED VACCINATIONS AFTER TRANSPLANTATION

- Varicella zoster
- Bacillus Calmette-Guérin (BCG)
- Smallpox
- Intranasal influenza
- Live oral typhoid Ty21a and other newer vaccines
- Measles (except during an outbreak)
- Mumps
- Rubella
- Oral polio
- Live Japanese B encephalitis vaccine
- Yellow fever

KDOQI Commentary:

It is now standard of care to use vaccinations in KTRs as long as the vaccine does not contain live or attenuated virus. It is also routine to screen for or use prophylaxis to prevent several posttransplant viral infections. Neither revaccination

against hepatitis after transplant nor following up hepatitis B antibody titers annually is a common practice in the US.



Infections with Increased Risk for KTRs

- BK polyoma virus
- Cytomegalovirus
- Epstein-Barr virus
- Herpes simplex virus 1, 2
- Varicella zoster virus
- Hepatitis C virus
- Hepatitis B virus
- Tuberculosis
- *Candida*
- Human immunodeficiency virus
- *Pneumocystis jirovecii* pneumonia

Advise Your Patients to:

- Promptly report wounds, injuries, the presence of urinary tract infection symptoms, or respiratory ailments
- Inform you well in advance of planned travel
- Maintain good hygiene habits around pets
- Avoid close contact with people who have contagious illnesses
- Avoid secretions of children recently vaccinated with live vaccines
- Wash hands.

CARDIOVASCULAR DISEASE

CVD Risk Factor Management

The incidence of CVD is high after kidney transplantation. KTRs should be considered to be at the highest risk for CVD and managed accordingly.

The annual rate of fatal or nonfatal CVD events in KTRs is 3.5-5.0%, 50-fold higher than in the general population.

Most of the traditional CVD risk factors in the general population, including cigarette smoking, diabetes, hypertension and dyslipidemias, are also risk factors for CVD in KTRs.

Consider managing CVD in KTRs as intensively as with the general population, with appropriate diagnostic tests and treatments. [R 17.1 (not graded)]

Suggest using aspirin (65-100 mg/day) in all patients with atherosclerotic CVD, unless there are contraindications. [17.2 (2B)]

Offer treatment to all patients who use tobacco. [16.3.2 (not graded)]

It is recommended that patients should be strongly encouraged to follow a healthy lifestyle, with exercise, proper diet, and weight reduction as needed. [R 26 (1C)]

Diabetes

New-onset diabetes after transplantation (NODAT) is defined by the World Health Organization and American Diabetes Association as diabetes that develops for the first time after kidney transplantation.

The incidence of NODAT is highest in the first 3 months after transplantation. The cumulative incidence of NODAT by the end of the first year has generally been found to be 10-30% in adults receiving cyclosporine or tacrolimus plus corticosteroids.

If NODAT develops, consider targeting HbA_{1c} 7.0-7.5%, and avoid targeting HbA_{1c} ≤6.0%, especially if hypoglycemic reactions are common. [R 15.2.2 (not graded)]

Dyslipidemias

In the general population, there is strong evidence that reducing LDL-cholesterol decreases the risk for CVD events.

In KTRs, the prevalence of dyslipidemia is high enough to warrant screening and intervention.

In KTRs, there is little reason to believe that reducing LDL-C would not be safe and effective in reducing CVD events.

In adults, consider targeting LDL <100mg/dL and non-HDL <130 mg/dL. [R 16.2.2.3]

In KTRs, there is moderate evidence that dyslipidemias contribute to CVD and that treatment of increased LDL-C with a statin may reduce CVD events, if appropriate dose modification of statins is made for patients treated with CNIs. Agents implicated in causing dyslipidemias include corticosteroids, CsA, and mTORi.

Hypertension

In KTRs, blood pressure is a risk factor for CVD and chronic allograft injury.

Recommend measuring blood pressure at each clinic visit. [R 16.1.1 (1C)]

Suggest maintaining blood pressure at <130/80 mm Hg if ≥18 years of age. [R 16.1.2 (2C)]

To treat hypertension, use any class of antihypertensive agent and monitor closely for adverse effects and drug-drug interactions. [R 16.1.3 (not graded)].

KDOQI Commentary:

CVD risk reduction strategies should include regular screening for new-onset diabetes (using ADA-based definitions) in the posttransplant period in previously nondiabetic patients, good glycemic regulation for diabetic patients according to current ADA guidelines, and lipid management and blood

pressure control according to KDOQI recommendations. In addition, promotion of a healthy lifestyle through weight control, exercise, and smoking cessation should be a central part of posttransplant counseling and care.



CANCER AFTER TRANSPLANTATION

KTRs from around the world are at greater risk of developing cancer, compared to the general population. This is especially true for cancers associated with viral infections (e.g., EBV-associated lymphomas). Others are rare, but occur at a substantially higher rate in KTRs (e.g., Kaposi's sarcoma). There are also cancers that may cause stage 5 CKD, and are therefore seen more commonly in KTRs (e.g., myeloma and renal cell carcinoma).

It is suggested that a qualified health professional, with experience in diagnosing skin cancer, perform annual skin and lip examination on KTRs, except possibly for KTRs with dark skin pigmentation. [R 18.4 (2D)]

Screen for the following cancers as per local guidelines for the general population [R 19.2 (not graded)]:

- Women: cervical, breast and colon cancer
- Men: prostate and colon cancer.

CANCERS CATEGORIZED BY SIR FOR KIDNEY TRANSPLANT PATIENTS AND CANCER INCIDENCE

	Common Cancers	Common cancers in Transplant Population (estimated)	Rare Cancers
High SIR (>5)	Kaposi's sarcoma	Kaposi's sarcoma Vaginal Non-Hodgkin lymphoma Kidney Non-melanoma skin Lip Thyroid Penis Small intestine	Eye
Moderate SIR (>1-5, p <0.05)	Lung Colon Cervix Stomach Liver	Oro-nasopharynx Esophagus Bladder Leukemia	Melanoma Larynx Multiple myeloma Anus Hodgkin's lymphoma
No increased risk shown	Breast Prostate Rectum		Ovary Uterus Pancreas Brain Testis

SIR, Standardized incidence ratio. The ratio of the observed to the expected new cases of cancer. [Adapted from Table 29.]

KDOQI Commentary:

There is increased evidence to suggest that specialty dermatology clinics for organ transplant recipients improve outcome measures, including compliance with photoprotection and increased awareness of skin cancer.

The resources required for these specialty clinics make implementation difficult for community nephrology groups that do not have direct access to a transplant center.



OVERVIEW OF OTHER COMPLICATIONS IN KTRS

Transplant bone disease	<ul style="list-style-type: none"> • The risk of fractures following kidney transplantation is high. • Bone disease is multifactorial, and most KTRs have preexisting CKD-MBD. • Treatment with calcitriol, alfacalcidol, or vitamin D has been suggested to improve BMD in KTRs. • Base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD. [R 21.2 (not graded)]
Hematological complications	<ul style="list-style-type: none"> • In KTRs, anemia is associated with morbidity and mortality, neutropenia with infection, and thrombocytopenia with bleeding. In addition, these hematologic abnormalities may be an indication of treatable, but potentially life-threatening, underlying disorders. • In KTRs, monitoring and identifying the underlying cause and treatment will reduce the morbidity and mortality of anemia, neutropenia, and thrombocytopenia. • Assess and treat anemia by removing underlying causes whenever possible and using standard measures applicable to CKD. [R 22.2 (not graded)]
Hyperuricemia and gout	<ul style="list-style-type: none"> • Hyperuricemia is very common in KTRs. It increases the incidence of gout and other complications in KTRs, and it may be associated with loss of kidney function and CVD. • Suggest treating hyperuricemia in KTRs when there are complications, such as gout, tophi, or uric acid stones. [R 23.1 (2D)] • Suggest colchicine for treating acute gout, with appropriate dose reduction for reduced kidney function and concomitant CNI use. [R 23.1.1 (2D)] • Recommend avoiding allopurinol in patients receiving azathioprine. [R 23.1.2 (1B)] • Suggest avoiding NSAIDs and COX-2 inhibitors whenever possible. [R 23.1.3 (2D)]
Mental health	<ul style="list-style-type: none"> • Depression and anxiety are more common in KTRs than in the general population. • Depression and anxiety may be associated with medication nonadherence, sleep disorders, and other adverse effects that make the diagnosis and treatment of depression and anxiety important. • Include direct questioning about depression and anxiety as part of routine follow-up care after kidney transplantation. [R 27 (not graded)]
Sexual function and fertility	<ul style="list-style-type: none"> • Sexual dysfunction is common in male and female KTRs, and many patients will not spontaneously report it. • Evaluate adults for sexual dysfunction after kidney transplantation. [R 25.1.1 (not graded)] • Include discussion of sexual activity, and counseling about contraception and safe sex practices in follow-up of adult KTRs. [R 25.1.2 (not graded)] • Refer pregnant patients to an obstetrician with expertise in managing high-risk pregnancies. [R 25.2.6 (not graded)] • Recommend that MMF and enteric-coated mycophenolate sodium (EC-MPS) be discontinued or replaced with azathioprine before pregnancy is attempted. [R 25.2.2 (1A)] • Suggest that mTORi be discontinued or replaced before pregnancy is attempted. [25.2.3 (2D)]

KDOQI Commentary:

Metabolic complications are common posttransplant and attention to the prevention and treatment of these issues, many resulting from side effects of IS drugs, constitute a

large part of posttransplant care. Mental health and lifestyle are important areas that require more attention in the medical care of KTRs.



KDOQI Disclaimer

Section I: Use of the Clinical Practice Guideline

This Commentary on the Clinical Practice Guideline document is based upon the best information available at the time of publication. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

Section II: Disclosure

The National Kidney Foundation Disease Outcomes Quality Initiative (NKF-KDOQI®) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Biographic and Disclosure Information section, and is on file at the National Kidney Foundation (NKF).

Grade for Strength of Recommendation	Strength	Wording	Grade for Quality of Evidence	Quality of Evidence
Level 1	Strong	"We recommend...should"	A	High: We are confident that the true effect lies close to that of the estimate of the effect.
Level 2	Weak	"We suggest....might"	B	Moderate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
			C	Low: The true effect may be substantially different from the estimate of the effect.
			D	Very low: The estimate of effect is very uncertain, and often will be far from the truth.

Note: Ungraded statements are used in areas where guidance was based on common sense and/or the question was not specific enough to undertake a systematic evidence review.

On all panels of this resource, R stands for recommendation.

References:

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