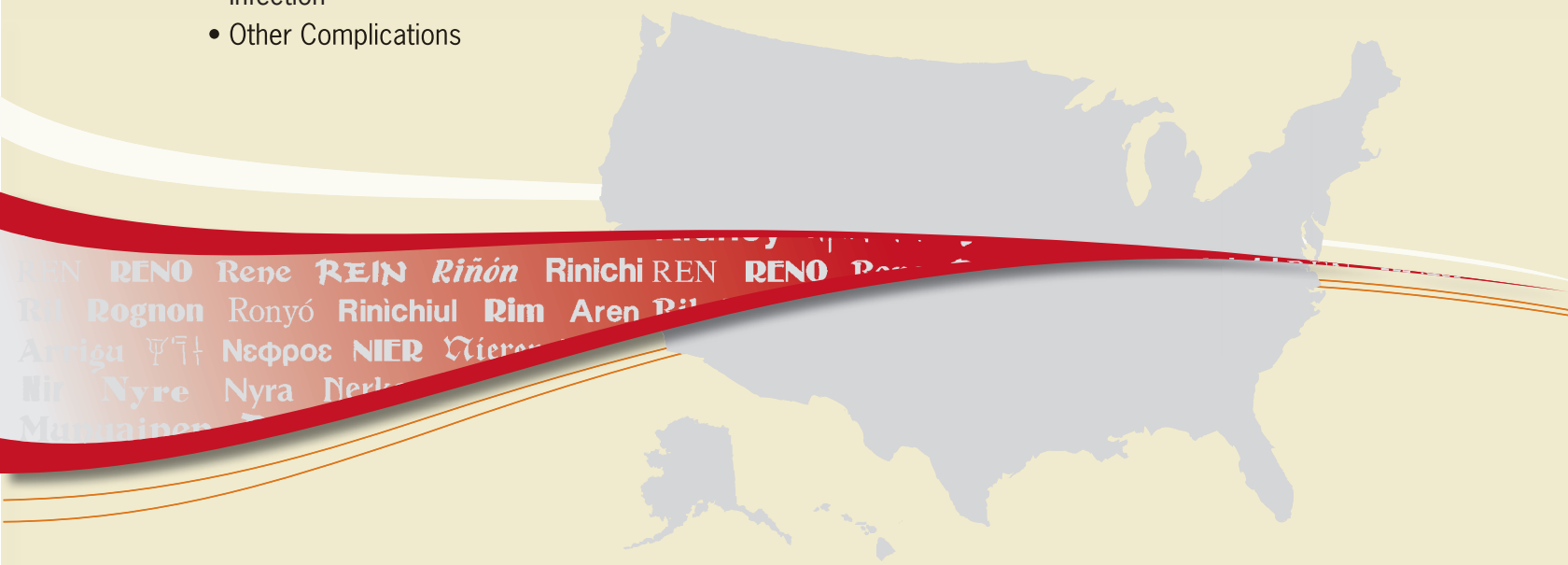
National Kidney Foundation®
KDOQI

Managing KIDNEY TRANSPLANT RECIPIENTS

A CLINICAL GUIDE for Nephrology and Transplant Professionals on:

- Induction Therapy
- Maintenance Immunosuppression
- Managing Adverse Effects
  - Acute Rejection and Chronic Allograft Injury
  - Screening and Graft Monitoring
  - Cardiovascular Disease
  - Cancer
  - Infection
  - Other Complications



Based on select guidelines from KDOQI US Commentary on the *2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients*. To view full publication, visit **www.kdoqi.org**

INITIAL IMMUNOSUPPRESSION

Recommend starting combination immunosuppressive (IS) therapy before, or at the time of, transplant [R 1.1 (1A*)] except perhaps for transplantation between identical twins.

INDUCTION THERAPY

- Recommend a biologic agent as part of initial IS medication. [R 1.2 (1A)]
- Intended to improve the efficacy of immunosuppression by:
  - Reducing acute rejection, or
  - Allowing a reduction of other components of the regimen, such as calcineurin inhibitors (CNIs) or corticosteroids.

First-line induction therapy: recommend using an interleukin 2 receptor antagonist (IL2-RA). [R 1.2.1 (1B)]

Induction therapy for high immunologic risk: recommend using lymphocyte-depleting agent. [R 1.2.2 (2B)]

KDOQI Commentary:

Individual US transplant centers determine immunosuppression protocols based on their particular patient population, organ source, experience, ease of use, and cost of therapy. Ethnic diversity of the population and the number of high-risk patients vary in different regions of the US, which explains in part variations in protocols used in different centers.

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.

*See table on page 11: Rating Guideline Recommendations.

MAINTENANCE IMMUNOSUPPRESSION

INITIAL MAINTENANCE

- Recommend using a combination of IS medications as maintenance therapy, including a CNI and an antiproliferative agent, with or without corticosteroids. [R 2.1 (1B)]
- Recommend measuring CNI blood levels [R 5.1 (1B)]:
  - Every other day during the immediate postoperative period until target levels are reached (2C)
  - Whenever there is a change in medication or patient status that may affect blood levels (2C)
  - Whenever there is a decline in kidney function that may indicate nephrotoxicity or rejection (2C).
- Suggest using tacrolimus as the first-line CNI. [R 2.2 (2A)] Suggest monitoring tacrolimus using 12-h trough (C_0). [5.1.2 (2C)]
- Suggest using mycophenolate as the first-line antiproliferative agent. [R 2.3 (2B)] Suggest monitoring mycophenolate mofetil (MMF) levels. [5.2 (2D)]
- Suggest that in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. [R 2.4 (2B)]

LONG-TERM MAINTENANCE

- Suggest using the lowest planned doses of maintenance IS medications by 2 to 4 months after transplantation if there has been no acute rejection. [R 3.1 (2C)]
- If using prednisone beyond 1 week after transplantation, continuation is suggested over withdrawal. [R 3.2 2C)]
- Nonadherence is associated with a high risk of acute rejection and allograft loss. Consider providing all kidney transplant recipients (KTRs) and family members with education, prevention, and treatment measures to minimize nonadherence to IS medications. [R 11.1 (not graded)]

2006 OPTN/SRTR ANNUAL REPORT

Induction Immunosuppression

- 78% used induction therapy, composed of:
  - Thymoglobulin in 39%
  - Interleukin 2 receptor antagonist in 28%
  - Alemtuzumab in 9%
  - Other in 2%
- 22% did not receive induction therapy

Initial Immunosuppression (at discharge)

- 94% on CNI, composed of:
  - 15% CsA
  - 79% Tac
- 87% on MPA
- 9% on mTOR inhibitor
- 26% steroid free

Maintenance Immunosuppression (1 year and beyond)

- 99% on CNI
- 87% on MPA
- 18% on mTOR inhibitor
- 20% steroid free

CNI, calcineurin inhibitors; CsA, cyclosporine; MPA, mycophenolic acid compounds; mTOR, mammalian target of rapamycin; OPTN/SRTR, Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients; Tac, tacrolimus.

KDOQI Commentary:

In the US, decisions on immunosuppression are made by the transplant center and any alterations should always be made in concert with them. Dosing of immunosuppression should at all times take into account the individual patient's risk profile, balancing rejection with the adverse effects of medications.

Community nephrologists need to coordinate any alterations in IS medications with the transplant center and be vigilant for potential drug interactions with the addition of any new 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. However, this needs to be balanced between who benefits and how much risk is at stake.

Although data about the efficacy and safety of steroid-free regimens are still evolving, it is clear that if steroids are to be eliminated, this should be done in the early transplant period and not later (after 1 year).

ACUTE REJECTION and CHRONIC ALLOGRAFT INJURY

POSSIBLE RISK FACTORS FOR ACUTE REJECTION

- The number of human leukocyte antigen (HLA) mismatches
- Younger recipient age
- Older donor age
- African-American ethnicity (in the United States)
- Panel-reactive antibody (PRA) >30%
- Presence of a donor-specific antibody
- Blood group incompatibility
- Delayed onset of graft function
- Cold ischemia time >24 hours

TREATMENT OF ACUTE REJECTION

- Recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. [R 6.1 (1C)]
- Treat subclinical and borderline acute rejection. [R 6.2 (2D)]
- Suggest adding MMF, if appropriate. [R 6.5 (2D)]

Acute Cellular Rejection

- Recommend using corticosteroids for the initial treatment. [R 6.3 (1D)]
- Suggest adding or restoring prednisone in patients not on steroids who have a rejection episode. [R 6.3.1 (2D)]
- Suggest using lymphocyte-depleting antibodies or OKT3 if [R 6.3.2 (2C)]:
  - Nonresponsive to corticosteroids
  - Acute cellular rejection is recurrent.

Antibody-Mediated Acute Rejection

- Suggest treating with one or more of the following alternatives, with or without corticosteroids [R 6.4 (2C)]:
  - Plasma exchange
  - Intravenous immunoglobulin
  - Anti-CD20 antibody
  - Lymphocyte-depleting antibody.

TREATMENT OF CHRONIC ALLOGRAFT INJURY (CAI)

- Recommend a kidney allograft biopsy for all patients with declining kidney function of unclear cause to detect potentially reversible causes. [R 7.1 (1C)]
- For patients with CAI and histological evidence of CNI toxicity, suggest reducing, withdrawing, or replacing the CNI. [R 7.2 (2C)]
  - Withdrawing the CNI should occur only after attempts at decreasing the dosage have failed. One also must ensure that all other causes of CAI are excluded to avoid inappropriate drug adjustments or missed treatment options

KDOQI Commentary:

Decision making regarding appropriate initial treatment for acute rejection should be based on clinical and pathologic information. Regular surveillance of the patient's kidney function, at the transplant center or in the nephrologist's office, offers an opportunity to enhance patient adherence to medication, diet, and healthy lifestyle.

SCREENING and GRAFT MONITORING

- Detecting kidney allograft dysfunction as soon as possible will allow timely diagnosis and treatment that may improve outcomes.
- Suggest including a kidney allograft ultrasound examination as part of the assessment of kidney allograft dysfunction. [R 8.4 (2C)]

ROUTINE SCREENING AFTER KIDNEY TRANSPLANTATION

Screening Test	Screening Intervals by Time After Transplantation					
	1 week	1 month	2-3 months	4-6 months	7-12 months	>12 months
Creatinine[a]	Daily	2-3 per week	Weekly	Every 2 weeks	Monthly	Every 2-3 months
Urine protein[b]	Once		Every 3 months			Annually
Complete blood count[c]	Daily	2-3 per week	Weekly	Monthly		Annually
Diabetes[d]	Weekly		Every 3 months			Annually
Lipid profile[e]	–	–	Once	–	–	Annually
Tobacco use[f]	Prior to discharge		–	–	–	Annually
BKV NAT[g]	Monthly			Every 3 months		–
EBV NAT (seronegative)[h]	Once	Monthly		Every 3 months		–
Blood pressure, pulse, height, body weight	Each clinical visit					

BKV, BK polyoma virus; EBV, Epstein-Barr virus; NAT, nucleic acid testing.
[a]Serum creatinine. Suggest estimating GFR whenever serum creatinine is measured [R 8.3.1 (2D)] using one of several formulas validated for adults (2C), or the Schwartz formula for children and adolescents (2C).
[b]Urine total protein and/or urine albumin.
[c]Complete blood count, including white blood count, hemoglobin and platelet counts.
[d]Screen for diabetes with fasting blood glucose, glucose tolerance test, or HbA_{1c} level.
[e]Lipid profile includes fasting cholesterol, LDL-C, HDL-C, and triglycerides.
[f]Screen for tobacco use.
[g]Screen for BKV using plasma NAT.
[h]Screen for EBV using plasma NAT in patients with no antibody to EBV at transplant.

- Screening for treatable recurrent kidney disease may result in early diagnosis and treatment that may be beneficial.

SCREENING FOR RECURRENT DISEASES

Disease	Screening (in addition to serum creatinine)	Minimum Screening Frequency	Diagnostic Tests (in addition to kidney biopsy)	Potential Treatment
FSGS[a]	Proteinuria	Daily for 1 week, weekly for 4 weeks, every 3 months for 1 year, then annually		Plasmapheresis
IgA nephropathy[b]	Proteinuria, microhematuria	Once in the first month, every 3 months in the first year, then annually		
MPGN[b]	Proteinuria, microhematuria		Serum complement levels	
Anti-GBM disease[b]	Proteinuria, microhematuria		Anti-GBM antibodies	Plasmapheresis
Pauci-immune vasculitis[b]	Proteinuria, microhematuria		ANCA	Cyclophosphamide and corticosteroids
HUS[c]	Proteinuria, platelet count	During episodes of graft dysfunction	Platelet count, peripheral blood smear, LDH	Plasmapheresis

ANCA, antineutrophil cytoplasmic antibody; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HUS, hemolytic-uremic syndrome; IgA, immunoglobulin A; LDH, lactate dehydrogenase; MPGN, membranoproliferative glomerulonephritis.
[a]See R 10.1 (2C)
[b]See R 10.2 (2C)
[c]See R 10.3 (2D)

CARDIOVASCULAR DISEASE

- The incidence of CVD is high after kidney transplantation.
- Most of the "traditional" risk factors in the general population, including cigarette smoking, diabetes, hypertension and dyslipidemias, are also risk factors for CVD in kidney transplant recipients (KTRs).
- KTRs should be considered at highest risk for CVD and managed accordingly.
- Suggest using aspirin (65-100mg/day) in all KTRs with atherosclerotic CVD, unless there are contraindications. [R 17.2 (2B)]

OVERVIEW OF RISK FACTORS AND TREATMENT GOALS FOR CVD

Reduce Risk for:	Goals
New-onset diabetes after transplantation (NODAT)	• HbA_{1c}: 7.0-7.5% [R 15.2.2 (not graded)] • Avoid targeting HbA_{1c} ≤6.0%, especially if hypoglycemic reactions are common. [R 15.2.2 (not graded)]
Hypertension	• <130/80 mm Hg if ≥18 years of age [R 16.1.2 (2C)] • <90th percentile for sex, age, and height if <18 years old [R 16.1.2 (2C)]

Dyslipidemias	• Adults:
	  • LDL: <100 mg/dL [R 16.2.2.2]
	  • Non-HDL: <130 mg/dL [R 16.2.2.3]
	• Adolescents:
	  • LDL: <130 mg/dL [R 16.2.2.2]
	  • Non-HDL: <160 mg/dL [R 16.2.2.3]

Obesity	• Assess at each visit. [R 16.4.1 (not graded)]
	  • Measure height and weight at each visit, in adults and children.
	  • Calculate body mass index (BMI) at each visit.
	  • Measure waist circumference when weight and physical appearance suggest obesity, but BMI is <35 kg/m^2.
	• Offer a weight reduction program to all obese KTRs.

KDOQI Commentary:

Since cardiovascular disease is the most common cause of patient death among KTRs, a concerted effort to minimize risk factors for heart disease will likely have as great or an even greater impact on optimizing patient and graft outcomes than the discovery of new antirejection therapies. CVD risk reduction strategies should include: regular screenings for new-onset diabetes (using ADA-based definitions) in the posttransplant period among previously nondiabetic patients, good glycemic regulation for diabetic patients according to current ADA guidelines, as well as lipid management and blood pressure control according to KDOQI recommendations.

CANCER

- KTRs are at greater risk of developing cancer compared to the general population.
- Develop an individualized screening plan that includes past medical and family history, tobacco use, competing risks for death, and the performance of the screening methodology. [R 19.1 (not graded)]
- Suggest that a qualified health professional perform annual skin and lip examinations. [R 18.4 (2D)]
- Important factors for consideration in reducing IS medications for KTRs with cancer include [R 20.1.1 (2C)]:
  - Stage of cancer at diagnosis
  - If cancer is likely to be exacerbated by immunosuppression
  - Therapies available for the cancer
  - Whether IS medications interfere with ability to administer standard chemotherapy.

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:

Skin cancer is common in US transplant patients and screening and prevention are critical. However, implementation of guidelines for doing so, including the KDIGO guidelines, is a challenge because of patient preferences against the routine use of sunscreen, as well as time constraints during office visits. Although many posttransplant cancers are viral-mediated and related to immunosuppression, it is less clear how to alter immunosuppression after malignancy has occurred. Although age-specific screening for malignancy should be incorporated into care, consideration must be given to the risk of screening in patients with limited life spans (<5 years) because of comorbid conditions.

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 edemic 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 common practice in the US.

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.

SELECT RECOMMENDATIONS FOR MANAGING INFECTION	
BK polyoma virus	Suggest screening all KTRs with NAT [R 13.1.1 (2C)]: • Monthly for the first 3 to 6 months after transplantation (2D), then every 3 months until the end of the first posttransplant year (2D) • Whenever there is an unexplained rise in serum creatinine (2D) • After treatment for acute rejection. (2D) Suggest reducing IS medications when BKV plasma NAT is persistently >10^7 copies/L. [R 13.1.2 (2D)]
Cytomegalovirus	Recommend KTRs receive chemoprophylaxis with oral ganciclovir or valganciclovir [R 13.2.1]: • For at least 3 months after transplantation (1B) • For 6 weeks after treatment with a T-cell-depleting antibody (1C) • Except when both donor and recipient have negative CMV serologies. In patients with CMV disease, suggest weekly monitoring of CMV by NAT or pp65 antigenemia. [R 13.2.2 (2D)]
Epstein-Barr virus	Suggest reduction or cessation of IS medication in patients who have EBV disease, including PTLD. [R 13.3.3 (1C)]
Herpes simplex virus 1, 2	Recommend treating superficial HSV 1, 2 infection [13.4.1 (1B)] with an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir, or famciclovir) until all lesions have resolved. [13.4.1 (1D)]
Varicella zoster virus	Recommend treating primary VZV infection with either IV or oral acyclovir or valacyclovir and a temporary reduction in IS medication. [13.4.4 (2D)]
Hepatitis C virus	Suggest treating HCV-infected KTRs only when the benefits of treatment clearly outweigh the risk of allograft rejection due to interferon-based therapy (e.g. fibrosing cholestatic hepatitis, life-threatening vasculitis). [R 13.5.1 (2D)]
Hepatitis B virus	Suggest interferon treatment should generally be avoided in HBV-infected KTRs. [R 13.6.2 (2C)] Suggest prophylaxis with tenofovir, entecavir, or lamivudine in HBsAg-positive KTRs. [R 13.6.3 (2B)]
Human immunodeficiency virus	To determine antiretroviral therapy, refer HIV-infected KTRs to an HIV specialist, who should pay special attention to drug-drug interactions and appropriate dosing of medications. [R 13.7.2 (not graded)]
Pneumocystis jirovecii pneumonia	Recommend administering prophylaxis with daily trimethoprim-sulfamethoxazole for 3 to 6 months after transplantation. [R 14.2.1 (1B)] Suggest prophylaxis for at least 6 weeks during and after treatment for acute rejection. [R 14.2.2 (2C)]
Tuberculosis	Suggest that prophylaxis and treatment regimens be the same as would be used in the local general population who require therapy. [R 14.3.1 (2D)] Recommend monitoring CNI and mTORi blood levels in patients receiving rifampin. [R 14.3.2 (1C)] Consider substituting rifabutin for rifampin to minimize interactions with CNIs and mTORi. [R 14.3.2.1 (not graded)]
Candida	Suggest oral and esophageal prophylaxis with oral clotrimazole lozenges, nystatin, or fluconazole [R 14.4.1 (2C)] for: • 1 to 3 months after transplantation • 1 month after treatment with an antilymphocyte antibody.

SELECT RECOMMENDATIONS FOR MANAGING OTHER COMPLICATIONS

Bone disease	Recommend measuring serum calcium and phosphorus at least weekly during the immediate posttransplant period, until stable. [R 21.1 (1B)] After the immediate posttransplant period, 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)] Suggest treatment with calcitriol, alfacalcidol, or vitamin D be considered in KTRs with eGFR >30 mL/min/1.73m^2 and low bone mineral density. [R 21.6 (2D)]
Hematological complications	Assess and treat anemia by removing underlying causes and using standard measures applicable to CKD. [R 22.2 (not graded)] Include treatment of underlying causes whenever possible for neutropenia and thrombocytopenia. [R 22.3 (not graded)] Recommend using ACE-Is or ARBs for initial treatment of erythrocytosis. [R 22.4 (1C)]
Hyperuricemia and gout	Suggest treating hyperuricemia 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 decreased 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	Include direct questioning about depression and anxiety as part of routine follow-up care. [R 27 (not graded)]
Sexual function	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)]
Growth and development	Recommend measuring growth and development in children [R 24.1 (1C)]: • At least every 3 months if <3 years old (including head circumference) [(not graded)] • Every 6 months in children ≥3 years until final adult height. [(not graded)] Recommend using rhGH 28 IU/m^2/week (or 0.05 mg/kg/day) in children with persistent growth failure after kidney transplantation. [R 24.2 (1B)] Suggest minimizing or avoiding corticosteroid use in children who still have growth potential. [R 24.3 (2C)]

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. Bisphosphonates are not commonly used in KTRs in the US. 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 Level 2	Strong Weak	"We recommend…should" "We suggest….might"	A	High: We are confident that the true effect lies close to that of the estimate of the effect.
			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:

KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Kidney Dis*. 2010;56:189-218.

Kidney Disease: Improving Global Outcomes. Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(Suppl 3):S1–S157.

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