



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

The full text of the *KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients* is available at www.kdigo.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)]

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 back panel: Rating Guideline Recommendations.

MAINTENANCE IMMUNOSUPPRESSION

Initial Maintenance

- Tailor IS regimen to the individual patient's risk profile.
- 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 monitoring cyclosporine using 12-h trough (C_0), 2-h post-dose (C_2) or abbreviated AUC. [5.1.1 (2D)]
- 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)]
- If using mammalian target of rapamycin inhibitor (mTORi), recommend starting after graft function is established and surgical wounds are healed. [R 2.5 (1B)] Suggest monitoring mTORi levels. [5.3 (2D)]

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)]
- Continuation of CNI is suggested over CNI withdrawal. [R 3.2 (2B)]
- If using prednisone beyond 1 week after transplantation, continuation is suggested over withdrawal. [R 3.2 (2C)]
- Suggested strategies that may reduce drug costs include use of [R 4.1.1]:
 - A nondihydropyridine calcium-channel blocker to minimize CNI dose (2C)
 - Azathioprine rather than mycophenolate (2B)
 - Adequately tested bioequivalent generic drugs (2C)
 - Prednisone long-term. (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)]

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. [R6.5 (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)]
- Suggest replacing the CNI with a mTORi in patients with CAI, *if* [R 7.2.1 (2D)]:
 - eGFR >40 mL/min/1.73 m², and
 - Urine total protein excretion <500 mg/g creatinine (or equivalent proteinuria by other measures).

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.

^aSerum 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)

^bUrine total protein and/or urine albumin.

^cComplete blood count, including white blood count, hemoglobin and platelet counts.

^dScreen for diabetes with fasting blood glucose, glucose tolerance test, or HbA_{1c} level.

^eLipid profile includes fasting cholesterol, LDL-C, HDL-C, and triglycerides.

^fScreen for tobacco use.

^gScreen for BKV using plasma NAT.

^hScreen 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.

^aSee R 10.1 (2C)

^bSee R 10.2 (2C)

^cSee 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 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • <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	<ul style="list-style-type: none"> • Adults: <ul style="list-style-type: none"> • LDL: <100 mg/dL [R 16.2.2.2] • Non-HDL: <130 mg/dL [R 16.2.2.3] • Adolescents: <ul style="list-style-type: none"> • LDL: <130 mg/dL [R 16.2.2.2] • Non-HDL: <160 mg/dL [R 16.2.2.3]
Obesity	<ul style="list-style-type: none"> • Assess at each visit. [R 16.4.1 (not graded)] <ul style="list-style-type: none"> • 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/m². • Offer a weight-reduction program to all obese KTRs.

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.

INFECTION

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

SELECT RECOMMENDATIONS for MANAGING OTHER COMPLICATIONS

Bone disease	<p>Recommend measuring serum calcium and phosphorus at least weekly during the immediate post-transplant period, until stable. [R 21.1 (1B)]</p> <p>After the immediate post-transplant 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)]</p> <p>Suggest treatment with calcitriol, alfacalcidol, vitamin D or bisphosphonates be considered in KTRs with eGFR >30 mL/min/1.73m² and low bone mineral density. [R 21.6 (2D)]</p>
Hematological complications	<p>Assess and treat anemia by removing underlying causes and using standard measures applicable to CKD. [R 22.2 (not graded)]</p> <p>Include treatment of underlying causes whenever possible for neutropenia and thrombocytopenia. [R 22.3 (not graded)]</p> <p>Recommend using ACE-Is or ARBs for initial treatment of erythrocytosis. [R 22.4 (1C)]</p>
Hyperuricemia and gout	<p>Suggest treating hyperuricemia when there are complications, such as gout, tophi, or uric acid stones. [R 23.1 (2D)]</p> <p>Suggest colchicine for treating acute gout, with appropriate dose reduction for decreased kidney function and concomitant CNI use. [R 23.1.1 (2D)]</p> <p>Recommend avoiding allopurinol in patients receiving azathioprine. [R 23.1.2 (1B)]</p> <p>Suggest avoiding NSAIDs and COX-2 inhibitors whenever possible. [R 23.1.3 (2D)]</p>
Mental health	<p>Include direct questioning about depression and anxiety as part of routine follow-up care. [R 27 (not graded)]</p>
Sexual function	<p>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)]</p>
Growth and development	<p>Recommend measuring growth and development in children [R 24.1 (1C)]:</p> <ul style="list-style-type: none"> • 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)] <p>Recommend using rhGH 28 IU/m²/week (or 0.05 mg/kg/day) in children with persistent growth failure after kidney transplantation. [R 24.2 (1B)]</p> <p>Suggest minimizing or avoiding corticosteroid use in children who still have growth potential. [R 24.3 (2C)]</p>

SELECT RECOMMENDATIONS FOR MANAGING INFECTION

BK polyoma virus	<p>Suggest screening all KTRs with NAT [R 13.1.1 (2C)]:</p> <ul style="list-style-type: none"> • Monthly for the first 3 to 6 months after transplantation (2D), then every 3 months until the end of the first post-transplant year (2D) • Whenever there is an unexplained rise in serum creatinine (2D) • After treatment for acute rejection. (2D) <p>Suggest reducing IS medications when BKV plasma NAT is persistently $>10^7$ copies/L. [R 13.1.2 (2D)]</p>
Cytomegalovirus	<p>Recommend KTRs receive chemoprophylaxis with oral ganciclovir or valganciclovir [R 13.2.1]:</p> <ul style="list-style-type: none"> • 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. <p>In patients with CMV disease, suggest weekly monitoring of CMV by NAT or pp65 antigenemia. [R 13.2.2 (2D)]</p>
Epstein-Barr virus	<p>Suggest monitoring high-risk (donor EBV seropositive/recipient seronegative) KTRs using NAT. [R 13.3.1 (2C)]</p> <p>Suggest reduction or cessation of IS medication in patients who are EBV-seronegative with an increasing EBV load. [R 13.3.2 (2D)]</p> <p>Suggest reduction or cessation of IS medication in patients who have EBV disease, including PTLD. [R 13.3.3 (1C)]</p>
Herpes simplex virus 1, 2	<p>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)]</p>
Varicella zoster virus	<p>Recommend treating primary VZV infection with either IV or oral acyclovir or valacyclovir and a temporary reduction in IS medication. [13.4.4 (2D)]</p>
Hepatitis C virus	<p>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)]</p>
Hepatitis B virus	<p>Suggest interferon treatment should generally be avoided in HBV-infected KTRs. [R 13.6.2 (2C)]</p> <p>Suggest prophylaxis with tenofovir, entecavir, or lamivudine in HBsAg-positive KTRs. [R 13.6.3 (2B)]</p>
Human immunodeficiency virus	<p>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)]</p>
<i>Pneumocystis jirovecii</i> pneumonia	<p>Recommend administering prophylaxis with daily trimethoprim-sulfamethoxazole for 3 to 6 months after transplantation. [R 14.2.1 (1B)]</p> <p>Suggest prophylaxis for at least 6 weeks during and after treatment for acute rejection. [R 14.2.2 (2C)]</p>
Tuberculosis	<p>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)]</p> <p>Recommend monitoring CNI and mTORi blood levels in patients receiving rifampin. [R 14.3.2 (1C)]</p> <p>Consider substituting rifabutin for rifampin to minimize interactions with CNIs and mTORi. [R 14.3.2.1 (not graded)]</p>
Candida	<p>Suggest oral and esophageal prophylaxis with oral clotrimazole lozenges, nystatin, or fluconazole [R 14.4.1 (2C)] for:</p> <ul style="list-style-type: none"> • 1 to 3 months after transplantation • 1 month after treatment with an antilymphocyte antibody.

Section I: Use of the Clinical Practice Guideline

This Clinical Practice Guideline document is based upon the best information available as of March 2009. 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

Kidney Disease: Improving Global Outcomes (KDIGO) 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), Managing Agent for KDIGO.

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.

Reference: 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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