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**KDOQI  
COMMENTARY**

## KDOQI US Commentary on the 2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients

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In response to recently published KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for the care of kidney transplant recipients (KTRs), the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) organized a working group of transplant nephrologists and surgeons to review these guidelines and comment on their relevance and applicability for US KTRs. The following commentaries on the KDIGO guidelines represent the consensus of our work group. The KDIGO transplant guidelines concentrated on aspects of transplant care most important to this population in the posttransplant period, such as immunosuppression, infection, malignancy, and cardiovascular care. Our KDOQI work group concurred with many of the KDIGO recommendations except in some important areas related to immunosuppression, in which decisions in the United States are largely made by transplant centers and are dependent in part on the specific patient population served. Most, but not all, KDIGO guidelines are relevant to US patients. However, implementation of many may remain a major challenge because of issues of limitation in resources needed to assist in the tasks of educating, counseling, and implementing and maintaining lifestyle changes. Although very few of the guidelines are based on evidence that is strong enough to justify their being used as the basis of policy or performance measures, they offer an excellent road map to navigate the complex care of KTRs.

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**INDEX WORDS:** Kidney transplant recipients (KTRs); calcineurin inhibitor (CNI); mycophenolate compound (MPA compound); inhibitor of mammalian target of rapamycin (mTOR inhibitor); KDIGO; KDOQI.

In 2007, there were 16,119 kidney transplants performed in the United States (10,082 deceased donor and 6,037 living donor)<sup>1</sup> and 158,739 US patients living with a functioning

kidney allograft. KDIGO (Kidney Disease: Improving Global Outcomes) is an international initiative formed to "improve the care and outcomes of kidney disease patients worldwide

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through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines.”<sup>2</sup> To this end, a KDIGO work group has recently published a new comprehensive set of recommendations for the care of kidney transplant recipients (KTRs).<sup>3</sup> The last clinical practice transplant guideline for US patients was published in 2000 by the American Society of Transplantation (AST) and was based primarily on expert opinion. Previous KDIGO practice guidelines have been published for the care of patients with hepatitis C and chronic kidney disease (CKD)<sup>4</sup> and CKD–mineral and bone disorders (CKD-MBD).<sup>5</sup> Because global guidelines need to be adapted to the regional context in which they are used, the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) program organized a work group of transplant nephrologists and surgeons to review the newest KDIGO guideline and comment on the relevance and applicability for US KTRs.

### KDIGO GUIDELINE PROCESS

The KDIGO transplant guideline concentrated mainly on aspects of transplant care most important to this population in the posttransplant period, such as immunosuppression, infection, malignancy, and cardiovascular care. The guidelines do not address pretransplant evaluation or issues related to patients returning to dialysis therapy with a failed allograft. The target audience for the guideline is physicians, coordinators, pharmacists, and other medical professionals who directly or indirectly care for KTRs. The KDIGO guideline was based on published evidence and graded according to the strength of the data (Fig 1). Because of the paucity of evidence in many

areas, only 25% of recommendations were graded 1. Furthermore, evidence for only 2% of recommendations were graded A, 13.6% were graded B, 38.9% were graded C, and 45.5% were graded D.<sup>3</sup> The KDIGO authors make it clear that for guidelines in which the evidence was meager, they chose to give guidance rather than remain silent. They also make it clear that the guideline was not developed for regulatory agencies; this is important to keep in mind because so few of the recommendations are based on evidence that is strong enough to justify their being used as the basis of policy or performance measures.

### KDOQI PROCESS FOR INTERPRETATION OF THE KDIGO GUIDELINE IN THE CARE OF US TRANSPLANT PATIENTS

Differences in target population, individual patient immunologic risk, prevalence of concomitant diseases (such as diabetes mellitus), availability of resources, and systems of payment must all be considered in interpreting global recommendations to specific regions. The following commentaries on the KDIGO guideline represent the consensus of a work group convened by KDOQI to evaluate the relevance and applicability of the guideline to US patients and practices. It is beyond the scope of our review to make a comment on each of the more than 150 KDIGO recommendations. We chose instead to address guidelines for which we questioned applicability to US KTRs, as well as those that we believed needed reinforcement or clarification. Emphasis is placed not on critiquing the guidelines, but on determining their appropriateness for our US patients. The relative importance of a recommendation, relevance to US patients, comparison to

Grade*	Wording	Grade for Quality of Evidence	Quality of Evidence
Level 1	"We recommend"	A	High
Level 2	"We suggest"	B	Moderate
		C	Low
		D	Very low

**Figure 1.** Rating guideline recommendations. Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D. \*The additional category Not Graded typically was used to provide guidance based on common sense or when the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. Ungraded recommendations generally are written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2. Adapted from the KDIGO transplant guideline<sup>3</sup> with permission of KDIGO.

existing guidelines, and ease of implementation form the basis of these commentaries.

Members of the KDOQI commentary work group reached consensus on most commentaries and have indicated when this was not the case. We have relisted each KDIGO recommendation by section with the grade for evidence supporting it, followed by our work group's rationale and commentary on the guideline. If a guideline recommendation statement was classified by the KDIGO work group as important enough to become a strong recommendation (category 1), the statement is highlighted by showing the guideline text in bold.

## COMMENTARY ON SECTION I OF THE KDIGO TRANSPLANT GUIDELINE: IMMUNOSUPPRESSION

### KDIGO Recommendations in Chapter 1: Induction Therapy

- 1.1: **We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. (1A)**
- 1.2: **We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)**
  - 1.2.1: **We recommend that an IL-2-RA [interleukin-2 receptor antagonist] be the firstline induction therapy. (1B)**
  - 1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL-2-RA, for KTRs at high immunologic risk. (2B)

### KDOQI Rationale and Commentary

It clearly is important to start immunosuppression before or at the time of transplant. Induction therapy with a biologic agent, such as interleukin 2 (IL-2) receptor antagonists or thymoglobulin, decreases the frequency of acute rejection and now is used in up to 80% of US transplant centers. However, 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 United States, which explains in part variations in protocols used in different centers. Applicability of the recommended KDIGO guidelines in this section must be inter-

### Box 1. 2006 OPTN/SRTR Annual Report

#### Induction Immunosuppression<sup>a</sup>

- 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 inhibitors
- 20% steroid free

Abbreviations: 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.

Data source: Andreoni et al.<sup>6</sup>

preted with these differences in mind. The last published survey of immunosuppression use in US transplant centers was in the 2006 Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) Annual Report<sup>6</sup> and reported on the use of calcineurin inhibitors (CNIs), mycophenolate acid compounds (MPA), mammalian target of rapamycin (mTOR) inhibitors, and induction therapy (Box 1).

Guidelines for induction therapy will be most relevant not to community nephrologists, but to those working in transplant centers in which induction is used. Not all patients need induction therapy. The cost of induction therapy is substantial and should be viewed in the context of risk/benefit for a particular donor/recipient profile. In the United States, the use of lymphocyte-depleting antibodies (thymoglobulin and alemtuzumab) for induction is increasing.<sup>6</sup> Many centers will use these agents in low-risk patients to minimize exposure to other maintenance drugs (ie, steroids). It is unlikely that the current KDIGO guidelines recommending IL-2 receptor antagonists as first-line induction therapy will alter US

transplant practices in which these decisions tend to be transplant-center specific and based on factors described previously.

### **KDIGO Recommendations in Chapter 2: Initial and Maintenance Immunosuppressive Medications**

- 2.1: **We recommend using a combination of immunosuppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. (1B)**
- 2.2: We suggest that tacrolimus be the first-line CNI used. (2A)
  - 2.2.1: We suggest that tacrolimus or CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA)
- 2.3: We suggest that mycophenolate be the first-line antiproliferative agent. (2B)
- 2.4: We 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. (2B)
- 2.5: **We recommend that if mTOR inhibitors are used, they should not be started until graft function is established and surgical wounds are healed. (1B)**

### **KDOQI Rationale and Commentary**

#### *Initial Immunosuppression*

We agree that optimum initial maintenance therapy includes a CNI and an antiproliferative agent and that tacrolimus is the preferred CNI for most patients. The Symphony Study, a large multicenter clinical trial, showed that the combination of low-dose tacrolimus, mycophenolate mofetil (MMF), and steroids with daclizumab induction provided superior efficacy without the negative impact on renal function compared with either cyclosporine or a CNI-free regimen of low-dose sirolimus.<sup>7,8</sup> However, in a small number of patients, other issues, such as age, ethnicity, risk of new-onset diabetes mellitus, and previous toxicity with tacrolimus, may result in the initial use of cyclosporine. Immediate CNI use has not been shown to cause a delay in renal recovery. Although many centers briefly hold or modify the CNI dose in the setting of delayed graft function, especially when using antilymphocyte-depleting induction agents, treatment with these drugs should be initiated before or at the time of discharge from the hospital and not withheld because of delayed graft function. As

stated, mycophenolate compounds (MMF and mycophenolate sodium) are used as the initial antiproliferative agent of choice in most US transplant centers.

#### *Steroid Therapy Discontinuation*

Steroid sparing with discontinuation within the first few weeks after transplant has gained widespread acceptance in the United States, with more than 25% of patients being discharged after transplant off steroid therapy.<sup>6</sup> Although the KDOQI work group agreed that steroid therapy could be discontinued in low-risk patients after induction therapy, we did not think that this suggestion should be accepted as a universal guideline for several reasons. Although short- and medium-term results in corticosteroid therapy discontinuation protocols show equivalent patient and graft survival, there may be a price to pay in the long term. Acute rejection rates are higher in well-designed randomized clinical trials of steroid withdrawal. In addition, the presence of chronic interstitial fibrosis and tubular atrophy may be greater in corticosteroid-free patients, portending decreased long-term graft function. The heterogeneity of the US donor and recipient population may have a role in this issue. Newer transplant regimens decrease prednisone dosage to 5 mg/d. Apart from less bone disease, the potential metabolic benefits of corticosteroid-free protocols versus 5 mg/d seem to be less significant. What is clear is that discontinuation of steroid therapy early after transplant seems to be associated with less risk of rejection than discontinuation of steroids later (>1 year). It should be noted that there are no studies of different times in the first year to determine when corticosteroid therapy can be discontinued safely. In some centers, steroid therapy discontinuation is accomplished up to 6 months posttransplant. Late discontinuation of steroid therapy (>1 year posttransplant) is no longer recommended and forms the basis of KDIGO guideline 2.5, with which we agree. It also must be emphasized that steroid therapy withdrawal should be performed only when there is close frequent monitoring of the patient.

#### *Early Use of mTOR Inhibitors*

Sirolimus and everolimus (agents known as mTOR inhibitors) delay wound healing, prolong

delayed graft function, and are no longer used in the early posttransplant period (KDIGO recommendation 2.5). Furthermore, studies show an increased rejection rate with early use of these compounds in place of CNIs. The Symphony Study showed that the highest rejection rate occurred in the arm using low-dose sirolimus with MMF and steroids.<sup>7,8</sup>

### **KDIGO Recommendations in Chapter 3: Long-term Maintenance Immunosuppressive Medications**

- 3.1: We suggest using the lowest planned doses of maintenance immunosuppressive medications by 2-4 months after transplantation, if there has been no acute rejection. (2C)
- 3.2: We suggest that CNIs be continued rather than withdrawn. (2B)
- 3.2: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (2C)

### **KDOQI Rationale and Commentary**

#### *Decreasing Immunosuppressive Dosage*

Although our work group agreed with suggestion 3.1, we stress that dosing of immunosuppression should at all times take into account the individual patient's risk profile, balancing rejection with the adverse effects of medications. In some patients, this may mean higher drug dosing/drug levels to account for a higher risk of rejection. Although most US transplant centers now strive for a lower dose of immunosuppressive medication after the early posttransplant period, the transplant center should define each patient's target drug dosing based on immunologic risk, which depends on ethnicity, age, history of previous transplant, and level of HLA antibodies.

#### *Continue or Withdraw CNI Therapy*

Although we agreed that mTOR inhibitors should not be used in the early posttransplant period,<sup>7,8</sup> newer clinical trials have explored switching from CNIs to mTOR inhibitors 3-6 months posttransplant.<sup>9,10</sup> Early results suggest relative safety with improvement in renal function. Whether the trade-off of less nephrotoxicity with a different side-effect profile of mTOR inhibitors will be beneficial in the long term remains to be determined. The work group believed that suggestion 3.2 to continue CNI therapy indefinitely in all patients required

more study before it could be accepted as a guideline.

#### *Steroid Therapy Withdrawal*

We agree that late steroid therapy withdrawal (>1 year) is inadvisable, but stress that the definition of "early" steroid discontinuation has not been well defined and may occur after the first week (see commentary under Chapter 2).

### **KDIGO Recommendations in Chapter 4: Strategies to Reduce Drug Costs**

- 4.1: If drug costs block access to transplantation, a strategy to minimize drug costs is appropriate, even if use of inferior drugs is necessary to obtain the improved survival and quality of life benefits of transplantation compared with dialysis. (Not Graded)
  - 4.1.1: We suggest strategies that may reduce drug costs include:
    - limiting use of a biologic agent for induction to patients who are high-risk for acute rejection (2C);
    - using ketoconazole to minimize CNI dose (2D);
    - using a nondihydropyridine CCB to minimize CNI dose (2C);
    - using azathioprine rather than mycophenolate (2B);
    - using adequately tested bioequivalent generic drugs (2C);
    - using prednisone long-term. (2C)
- 4.2: Do not use generic compounds that have not been certified by an independent regulatory agency to meet each of the following criteria when compared to the reference compound (Not Graded):
  - contains the same active ingredient;
  - is identical in strength, dosage form, and route of administration;
  - has the same use indications;
  - is bioequivalent in appropriate bioavailability studies;
  - meets the same batch requirements for identity, strength, purity and quality;
  - is manufactured under strict standards.
- 4.3: It is important that the patient, and the clinician responsible for the patient's care, be made aware of any change in a prescribed immunosuppressive drug, including a change to a generic drug. (Not Graded)
- 4.4: After switching to a generic medication that is monitored using blood levels, obtain levels and adjust the dose as often as necessary until a stable therapeutic target is achieved. (Not Graded)

### KDOQI Rationale and Commentary

Drug costs are becoming an increasing issue in transplantation that impacts on patient adherence and ultimately affects graft survival. Currently, immunosuppressive drugs in the United States are covered by the Centers for Medicare & Medicaid Services (CMS), the primary insurer for many KTRs, for 3 years after transplant, although legislation is being considered to continue this coverage for the life of the kidney. Most KTRs are using many other medications in addition to immunosuppressive drugs. In general, the transplant community (patients, health care providers, and policy makers) need to embrace the concept of cost containment and the risk(s) to the patient and graft by these measures. However, this needs to be balanced by who benefits and how much risk is at stake.

Use of drugs that block the cytochrome P-450 3A system in an attempt to decrease CNI dosing and costs are rarely used in the United States. The concern is that inadvertent cessation of treatment with these drugs, causing a significant decrease in drug levels, could result in an acute rejection episode. Therefore, the work group did not think that many of the 4.1.1 suggestions should be accepted as a guideline. Switching from a mycophenolate compound to an azathioprine compound in the later posttransplant period may be considered in some patients as another cost-saving maneuver, especially in view of recent US registry data showing similar long-term survival with these drugs.<sup>11</sup> Although we agree with the suggestions outlined in 4.2, it should be recognized that many generic formulations have never been tested in transplant patients. Patient confusion with medications when a different generic formulation or even different strengths of the same drug from different manufacturers is dispensed at each refill can lead to inadvertent medication errors, possibly affecting outcomes. Patient education is crucial to avoid errors in medication administration. We agree with recommendation 4.4 that it is crucial to monitor patients after an immunosuppressive dosage change, brand change, or change to a generic drug. However, it needs to be recognized that implementation of this guideline can become burdensome as practices become inundated with inquiries from patients, payors, and

pharmacies regarding medications. Transplant centers and practices that see many transplant patients bear an inordinate part of this burden.

### KDIGO Recommendations in Chapter 5: Monitoring Immunosuppressive Medications

- 5.1: **We recommend measuring CNI blood levels (1B)**, and suggest measuring at least:
- 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)
- 5.1.1: We suggest monitoring CsA using 12-h trough (C0), 2-h post-dose (C2) or abbreviated AUC. (2D)
- 5.1.2: We suggest monitoring tacrolimus using 12-h trough (C0). (2C)
- 5.2: We suggest monitoring MMF levels. (2D)
- 5.3: We suggest monitoring mTOR inhibitor levels. (2C)

### KDOQI Rationale and Commentary

Because immunosuppressive drugs are classified as narrow therapeutic agents, drug-level monitoring is a necessary tool to maximize efficiency and minimize toxicity. The blood drug level is not synonymous with level of immunosuppression, but may correlate imperfectly with this effect. In most US transplant centers, levels of CNI and mTOR inhibitors are monitored. MPA monitoring is problematic because of the poor correlation between trough levels and area under the curve (AUC) exposure. Optimal monitoring of MPA requires a 4- to 6-hour abbreviated AUC measurement, which is logistically difficult in the outpatient setting. Although studies show that monitoring MPA levels in the early posttransplant period may be helpful in cyclosporine-treated patients, recent evidence suggests that such monitoring may be less important in patients on tacrolimus therapy.<sup>12</sup> With most US KTRs now being started on tacrolimus as the CNI of choice, MPA monitoring is not routine in many US transplant centers. Although one person in our work group believed there may still be some value in monitoring MPA levels, the other members questioned the value and applicability of this practice (KDIGO suggestion 5.2). Currently, many US centers measure MPA only in the setting of possible drug-related toxicities or side effects. Although we agree with suggestion 5.3 to monitor mTOR inhibitor levels, it should

be appreciated that therapeutic levels of this agent have yet to be defined in controlled studies.

### KDIGO Recommendations in Chapter 6:

#### Treatment of Acute Rejection

- 6.1: **We recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. (1C)**
- 6.2: We suggest treating subclinical and borderline acute rejection. (2D)
- 6.3: **We recommend corticosteroids for the initial treatment of acute cellular rejection. (1D)**
  - 6.3.1: We suggest adding or restoring maintenance prednisone in patients not on steroids who have a rejection episode. (2D)
  - 6.3.2: We suggest using lymphocyte-depleting antibodies or OKT3 [muromonab-CD3] for acute cellular rejections that do not respond to corticosteroids, and for recurrent acute cellular rejections. (2C)
- 6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C):
  - plasma exchange;
  - intravenous immunoglobulin;
  - anti-CD20 antibody;
  - lymphocyte-depleting antibody.
- 6.5: For patients who have a rejection episode, we suggest adding mycophenolate if the patient is not receiving mycophenolate or azathioprine, or switching azathioprine to mycophenolate. (2D)

#### KDOQI Rationale and Commentary

We concur that biopsies should be performed on all KTRs suspected of having an acute rejection (recommendation 6.1). Expert interpretation of the biopsy specimen by pathologists accustomed to reading kidney transplant biopsies is as important as expertise in performing the biopsy. It is controversial whether subclinical and borderline rejections should be treated (recommendation 6.2 supported by low evidence [2D]). Subclinical rejections are diagnosed in patients who have protocol biopsies performed by design, not for deterioration in kidney function. Recent data suggest that the risk of subclinical rejection in patients on tacrolimus and mycophenolate compound therapy is so low that protocol biopsies may no longer be indicated.<sup>13</sup> Whether this is true in patients with high immunologic risk or patients on minimization protocols (ie, steroid-free protocols or lower CNI doses) is uncertain. Whether borderline rejection should be treated or some infiltrates may be protective also is uncertain. In most US centers, steroids are used

most frequently as first-line treatment for acute rejection, followed by lymphocyte-depleting antibodies in steroid-resistant rejection, but there may be exceptions to this approach. Decision making regarding appropriate initial treatment for acute rejection should be based on clinical and pathologic information. Timing of the rejection episode posttransplant, type of induction agent used before rejection, degree of deterioration in kidney function at the time of rejection, and histologic grade of the rejection may influence selection of the appropriate initial antirejection therapy. There is increasing recognition of the role of antibody-mediated mechanisms in acute rejection. This process requires special blood tests (to detect donor-specific antibodies) and histochemical stains (immunofluorescence for C4d) for diagnosis.<sup>14</sup> Coordination with the transplant center is critical to ensure that all appropriate testing is performed and specific treatment is initiated. After treatment of an acute episode, optimizing overall immunosuppression is required. Considerations should include changing the CNI, adding a mycophenolate compound or increasing the dose, adding corticosteroids to previously steroid-free regimens, or adding/substituting an mTOR inhibitor. More than 85% of patients are already using MPA agents, so the number available for switching will be relatively small.

### KDIGO Recommendations in Chapter 7:

#### Treatment of Chronic Allograft Injury (CAI)

- 7.1: **We recommend kidney allograft biopsy for all patients with declining kidney function of unclear cause, to detect potentially reversible causes. (1C)**
- 7.2: For patients with CAI and histological evidence of CNI toxicity, we suggest reducing, withdrawing, or replacing the CNI. (2C)
  - 7.2.1: For patients with CAI, eGFR >40 mL/min/1.73 m<sup>2</sup>, and urine total protein excretion <500 mg/g creatinine (or equivalent proteinuria by other measures), we suggest replacing the CNI with a mTOR inhibitor. (2D)

#### KDOQI Rationale and Commentary

We agree with the need for kidney transplant biopsy in patients with decreasing kidney function (7.1) and again stress the importance of expertise in pathologic interpretation. Important causes of chronic allograft injury (CAI), which include rejection, BK nephropathy, CNI toxicity, or recurrent disease, require special histochemical stains for diagnosis that are not readily available in all labora-

tories. Therefore, coordination with the transplant center where these techniques are available is essential. For patients with CAI caused by CNI toxicity, 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. Although our work group thought that KDIGO suggestion 7.2.1 may be reasonable in some patients, we also want to emphasize that the role of mTOR inhibitors in the treatment of CAI/CNI toxicity is poorly defined. It is clear that switching from a CNI to an mTOR inhibitor should be avoided in patients with severely decreased glomerular filtration rate (GFR) and/or the presence of proteinuria; however, the exact guidelines for when to switch are still evolving.

#### SUMMARY OF COMMENTARY ON SECTION I: IMMUNOSUPPRESSION

In the United States, immunosuppressive 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. 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 late (after 1 year). Community nephrologists need to coordinate any alterations in immunosuppressive medications with the transplant center and be vigilant for potential drug interactions with the addition of any new medications. Drug monitoring is an essential monitoring tool throughout the post-transplant course, but not always applicable to every immunosuppressive medication. Transplant biopsies frequently are necessary to determine the cause of renal dysfunction, and the interpretation must be performed by pathologists with resources and experience in handling and reading the transplant biopsy specimen.

#### COMMENTARY ON SECTION II OF KDIGO TRANSPLANT GUIDELINE: GRAFT MONITORING AND INFECTIONS

##### KDIGO Recommendations in Chapter 8: Monitoring Kidney Allograft Function

- 8.1: We suggest measuring urine volume (2C):
- Every 1-2 hours for at least 24 hours after transplantation (2D);
  - Daily until graft function is stable. (2D)
- 8.2: We suggest measuring urine protein excretion, (2C) at least:
- Once in the first month to determine a baseline (2D);
  - Every 3 months during the first year (2D);
  - Annually, thereafter. (2D)
- 8.3: We recommend measuring serum creatinine, (1B) at least:
- Daily for 7 days or until hospital discharge, whichever occurs sooner (2C);
  - 2-3 times per week for weeks 2-4 (2C);
  - Weekly for months 2 and 3 (2C);
  - Every 2 weeks for months 4-6 (2C);
  - Monthly for months 7-12 (2C);
  - Every 2-3 months, thereafter. (2C)
- 8.3.1: We suggest estimating GFR whenever serum creatinine is measured, (2D) using:
- One of several formulas validated for adults (2C); or
  - The Schwartz formula for children and adolescents. (2C)
- 8.4: We suggest including a kidney allograft ultrasound examination as part of the assessment of kidney allograft dysfunction. (2C)

#### KDOQI Rationale and Commentary

##### *Routine Screening Tests and Time and Frequency of Monitoring*

Regular surveillance and vigilant monitoring of kidney allograft function are important in improving short- and long-term outcomes. Early detection of kidney allograft dysfunction will allow timely diagnosis and treatment that may improve patient and graft survival. Frequency and types of routine screening tests after kidney transplant are shown in Fig 2. Although there is no standard protocol for the frequency and type of monitoring, recommendations are guided by the likelihood of problems specific to the particular transplant population. In the early posttransplant period, when rejection and complications are the most likely, testing is performed more frequently. Thereafter, the follow-up interval will depend in part on the patient's general condition and the development of additional problems. The AST recommended routine posttransplant 2-3 visits per week during month 1, every 1-3 weeks during month 2-3, every 4-8 weeks during months 4-12, and every 2-4 months after the first year. These early visits often are provided by the transplant physician or surgeon of the transplant center. After 3-6 months, monitoring may be performed by the transplant physician or community nephrologist.<sup>15</sup> In a recent

**Figure 2.** Routine screening after kidney transplant. Complete blood cell count includes white blood cells, hemoglobin, and platelets. Screen for diabetes is by fasting blood glucose level, glucose tolerance test, or hemoglobin A<sub>1c</sub> level. Lipid profile includes fasting cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels. Screens for BK polyoma virus (BKV) and Epstein-Barr virus (EBV) use plasma nucleic acid testing (NAT); EBV screen is for patients with no antibody to EBV at transplant. Adapted from the KDIGO transplant guideline<sup>3</sup> with permission of KDIGO.

Screening Test	Screening Intervals by Time after Transplantation					
	1 wk	1 mo	2-3 mo	4-6 mo	7-12 mo	>12 mo
Serum creatinine	Daily	2-3 per wk	Weekly	Every 2 wk	Monthly	Every 2-3 mo
Urine protein and/or urine albumin	-----	Once -----	-----	Every 3 mo -----	-----	Annually
Complete blood count	Daily	2-3 per wk	Weekly	----- Monthly -----	-----	Annually
Diabetes	-----	Weekly -----	-----	Every 3 mo -----	-----	Annually
Lipid profile	--	--	Once	--	--	Annually
Tobacco use	Prior to discharge		--	--	--	Annually
BKV NAT	-----	Monthly -----	-----	----- Every 3 mo -----	-----	--
EBV NAT (seronegative)	Once	----- Monthly -----	-----	----- Every 3 mo -----	-----	--
Blood pressure, pulse, height, body weight	----- Each clinic visit -----					

survey of posttransplant outpatient visits in Medicare beneficiaries in the United States, frequency of visits to transplant centers varied by center and region; most visits were to nephrologists.<sup>16</sup>

At each clinic visit, education regarding medication adherence, diet, and healthy lifestyle should be given. Screening for tobacco use should be implemented before discharge and annually. Although the work group did not agree that screening all adults for Epstein-Barr virus (EBV) was of value (see commentary under Chapter 13 for EBV), screening for all other elements listed in Fig 2, including screening for proteinuria, is reasonable. In addition to these tests, monitoring for HLA antibodies against the donor (donor-specific antibodies), which is not described in the KDIGO guideline, is becoming more common in some US centers. The optimal timing and frequency of such screening has yet to be determined.<sup>17,18</sup>

#### **Serum Creatinine and Estimated GFR**

Serum creatinine measurement remains the most commonly used index of renal allograft function. It is reliable for detecting acute changes in kidney function. Furthermore, serum creatinine level at year 1 after transplant is a risk factor for subsequent outcomes<sup>19</sup> and may help in the management of the frequency of visits. However, it is less reliable for detecting long-term changes in kidney function in the

kidney transplant recipient. Formulas to estimate GFR using serum creatinine values have been tested in KTRs, but no formula consistently has been shown to be superior to another. As with CKD, considerable renal pathologic states can be present without dramatic changes in serum creatinine levels.

In 2005, the definition of CKD was amended to include all KTRs regardless of markers of kidney damage or GFR.<sup>20,21</sup> Although the work group agreed that CKD staging in KTRs is useful, it must be noted that there is considerable difference in the rate of progression in these 2 groups. Progression is much slower in KTRs in whom kidney half-life is longer at every level of CKD. Renal ultrasound is the preferred imaging study in KTRs (KDIGO suggestion 8.4).<sup>22</sup>

#### **KDIGO Recommendations in Chapter 9: Kidney Allograft Biopsy**

- 9.1: **We recommend kidney allograft biopsy when there is a persistent, unexplained increase in serum creatinine. (1C)**
- 9.2: We suggest kidney allograft biopsy when serum creatinine has not returned to baseline after treatment of acute rejection. (2D)
- 9.3: We suggest kidney allograft biopsy every 7-10 days during delayed function. (2C)
- 9.4: We suggest kidney allograft biopsy if expected kidney function is not achieved within the first 1-2 months after transplantation. (2D)
- 9.5: We suggest kidney allograft biopsy when there is:

- New onset of proteinuria (2C);
- Unexplained proteinuria  $\geq 3.0$  g per gram creatinine or  $\geq 3.0$  g per 24 hours. (2C)

## KDOQI Rationale and Commentary

### Biopsy

Renal allograft biopsy is the gold standard for diagnosing the cause of a change in renal allograft function. It is useful in all clinical situations described in KDIGO suggestions 9.1-9.4. Potential causes of allograft dysfunction include volume depletion; compromised renal blood flow; urinary outflow obstruction; parenchymal causes, such as acute rejection (cellular and/or humoral); chronic allograft nephropathy; recurrent or de novo disease; or BK nephropathy. Patients showing a 20%-25% increase in creatinine level above baseline values warrant consideration for biopsy. Other indications for pursuing renal allograft biopsy would be a less-than-expected response to treatment of acute rejection. The expected response would be dependent on the severity of tissue injury noted on the diagnostic biopsy specimen. Delayed graft function lasting longer than 5-7 days warrants biopsy, with repeated biopsies performed every 7-10 days until graft function recovers. New-onset proteinuria, protein  $\geq 2.0$  g/g creatinine or  $\geq 2.0$  g/24 h, also merits a kidney biopsy. De novo and recurrent glomerular diseases are common causes of new-onset proteinuria. Patients with de novo or recurrent glomerular diseases should be followed up closely by transplant nephrologists or community nephrologists with close communication with the transplant center because treatment of some recurrent kidney diseases may prevent or delay the onset of graft failure.<sup>23,24</sup>

### Safety and Accuracy

The safety of kidney transplant biopsies has been documented and the overall risk of complications is low. Most biopsies are performed in the transplant center by transplant nephrologists. Community nephrologists also may perform biopsies of the kidney in KTRs more than a year posttransplant. It is prudent to obtain a diagnostic ultrasound before biopsy to rule out unexpected alterations in blood flow or urinary tract obstruction. It is imperative that a pathologist familiar with the transplant process interprets the pathol-

ogy, in consultation with the referring nephrologist, using appropriate stains and other studies.

### Molecular Markers

In addition to conventional histopathologic examination, several US transplant centers are using molecular markers, as well as genomic or proteomic methods, to enhance our understanding of the mechanism of immunologic and non-immunologic pathway of injury. As an example, polymerase chain reaction (PCR) has been used to detect messenger RNA for IL-2 and other biomarkers in biopsy samples. Using this approach, IL-2, upregulated during rejection, could be detected 2 days before rejection was apparent using histologic or clinical criteria. Such PCR approaches have been used to detect other gene products upregulated during acute rejection, such as granzyme B, perforin, transforming growth factor  $\beta$ , IL-10, and IL-15.<sup>25-27</sup> These newer methods are performed almost exclusively in transplant centers and may become a standard method of transplant biopsy analysis in the future.

## KDIGO Recommendations in Chapter 10: Recurrent Disease

- 10.1: We suggest screening KTRs with primary kidney disease caused by FSGS for proteinuria (2C) at least:
  - Daily for 1 week (2D);
  - Weekly for 4 weeks (2D);
  - Every 3 months, for the first year (2D); Every year, thereafter. (2D)
- 10.2: We suggest screening KTRs with potentially treatable recurrence of primary kidney disease from IgA nephropathy, MPGN, anti-GBM disease, or ANCA-associated vasculitis for microhematuria, (2C) at least:
  - Once in the first month to determine a baseline (2D);
  - Every 3 months during the first year (2D); Annually, thereafter. (2D)
- 10.3: During episodes of graft dysfunction in patients with primary HUS, we suggest screening for thrombotic microangiopathy (e.g., with platelet count, peripheral smear for blood cell morphology, plasma haptoglobin, and serum lactate dehydrogenase). (2D)
- 10.4: When screening suggests possible treatable recurrent disease, we suggest obtaining an allograft biopsy. (2C)
- 10.5: Treatment of recurrent kidney disease:
  - 10.5.1: We suggest plasma exchange if a biopsy shows minimal change disease or FSGS

- in those with primary FSGS as their primary kidney disease. (2D)
- 10.5.2: We suggest high-dose corticosteroids and cyclophosphamide in patients with recurrent ANCA-associated vasculitis or anti-GBM disease. (2D)
- 10.5.3: We suggest using an ACE-I [ACE inhibitor] or an ARB for patients with recurrent glomerulonephritis and proteinuria. (2C)
- 10.5.4: For KTRs with primary hyperoxaluria, we suggest appropriate measures to prevent oxalate deposition until plasma and urine oxalate levels are normal (2C), including:
- Pyridoxine (2C);
  - High calcium and low oxalate diet (2C);
  - Increased oral fluid intake to enhance urinary dilution of oxalate (2C);
  - Potassium or sodium citrate to alkalize the urine (2C);
  - Orthophosphate (2C);
  - Magnesium oxide (2C);
  - Intensive hemodialysis to remove oxalate. (2C)

### KDOQI Rationale and Commentary

Recurrent disease accounts for a substantial amount of graft loss after renal transplant. It is difficult to assess the percentage of grafts lost to recurrent disease because many patients present with end-stage renal disease without benefit of a diagnostic native renal biopsy. The likelihood of recurrent disease after transplant is dependent on the disease, with certain diseases at particularly high risk of recurrence.<sup>28</sup>

#### *Recurrent Focal Segmental Glomerulosclerosis*

We agree with recommendation 10.1 regarding frequent and regular screening for proteinuria in patients with primary focal segmental glomerulosclerosis (FSGS) as the cause of end-stage renal disease. If the patient is still producing urine at the time of transplant, a preoperative urine protein-creatinine ratio can be a very helpful baseline measure of proteinuria. Early detection of FSGS recurrence, which can present with normal light microscopy, but foot-process effacement on electron microscopy,<sup>29</sup> provides the best opportunity for intervention and amelioration of disease.

#### *IgA Nephropathy*

Recurrence rates of immunoglobulin A (IgA) nephropathy are variable. We agree with recom-

mendation 10.2 for screening routinely for microhematuria. Recurrent disease is confirmed with a renal allograft biopsy. Histologic recurrence of disease is much more common than is clinical disease recurrence. There is no proven therapy for treatment of recurrent disease.<sup>30</sup>

#### *Membranoproliferative Glomerulonephritis*

Recurrence of membranoproliferative glomerulonephritis (MPGN) is common, as high as 80% with MPGN type II (dense-deposit disease). The most common cause of MPGN type I is hepatitis C-associated immune complex formation. We agree with the proposed regularly scheduled screening for microhematuria and proteinuria in recommendation 10.2. Patients with known hepatitis C-associated MPGN pretransplant also may be screened for cryoglobulins, which are associated with MPGN.<sup>31</sup>

#### *Hemolytic Uremic Syndrome*

Hemolytic uremic syndrome (HUS) typically is divided into diarrheal associated ( $D^+$ ) and non-diarrheal associated ( $D^-$ ).  $D^+$  disease occurs mostly in children and rarely recurs post-transplant. However,  $D^-$  HUS is more common in adults and can recur. In HUS associated with a complement abnormality, such as factor H deficiency or factor I mutation, recurrence rates can be as high as 80%. Screening for evidence of recurrence allows for an earlier diagnosis, which will require biopsy in most cases, and provides an opportunity for earlier intervention. There is no comment in the guideline regarding recurrence of thrombotic thrombocytopenic purpura, but early detection of recurrence provides an opportunity for treatment with plasmapheresis and intravenous immune globulin (IVIG).

#### *Biopsy and Treatment*

As stated, kidney biopsy and interpretation by a pathologist with expertise in transplant specimen readings is critical in the diagnosis of disease recurrence. Treatment for most recurrent disease in renal transplantation is based on a combination of case reports, case cohorts, and retrospective reviews. Recurrent diseases post-transplant are not common enough that randomized controlled trials can be implemented; therefore, most recommendations for treatment are based on a consensus of opinion. Despite this, we

agree in general with the recommendations detailed in 10.5.

### **KDIGO Recommendations in Chapter 11: Preventing, Detecting, and Treating Nonadherence**

- 11.1: Consider providing all KTRs and family members with education, prevention, and treatment measures to minimize nonadherence to immunosuppressive medications. (Not Graded)
- 11.2: Consider providing KTRs at increased risk for nonadherence with increased levels of screening for nonadherence. (Not Graded)

### **KDOQI Rationale and Commentary**

Noncompliance or nonadherence to diet and medication is a common problem in KTRs. Nonadherence to medication is associated with a high risk of acute rejection and allograft loss. We agree that early efforts should be made to identify KTRs at increased risk of nonadherence and that these patients should be monitored closely. Prevention, identification, and treatment of nonadherence are integral to the monitoring of kidney allograft function and long-term care of KTRs. Certain subgroup of KTRs, younger patients, African Americans, and those with financial hardships, have an enhanced risk of nonadherence.<sup>32,33</sup>

In addition to identifying patients at risk, it is important to have a system for addressing patient nonadherence. This requires coordinated efforts of social workers, transplant coordinators, financial counselors, pharmacists, primary nephrologists, and the patient's family.<sup>34</sup> A combination of educational, behavioral, and social support interventions provides the best results. Because there is no perfect measure of adherence, consideration should be given to multiple approaches for adherence monitoring. Similar team approaches also are important in other areas requiring adherence, such as diet, exercise, tobacco, alcohol, and drug use.

### **KDIGO Recommendations in Chapter 12: Vaccination**

- 12.1: **We recommend giving all KTRs approved, inactivated vaccines, according to recommended schedules for the general population, except for HBV vaccination. (1D)**
- 12.1.1: We suggest HBV vaccination (ideally prior to transplantation) and HBsAb titers 6-12 weeks after completing the vaccination series. (2D)

12.1.1.1: We suggest annual HBsAb [antibody to hepatitis B surface antigen] titers. (2D)

12.1.1.2: We suggest revaccination if the antibody titer falls below 10 mIU/mL. (2D)

12.2: We suggest avoiding live vaccines in KTRs. (2C)

12.3: We suggest avoiding vaccinations, except influenza vaccination, in the first 6 months following kidney transplantation. (2C)

12.3.1: We suggest resuming immunizations once patients are receiving minimal maintenance doses of immunosuppressive medications. (2C)

12.3.2: **We recommend giving all KTRs, who are at least 1-month post-transplant, influenza vaccination prior to the onset of the annual influenza season, regardless of status of immunosuppression. (1C)**

12.4: We suggest giving the following vaccines to KTRs who, due to age, direct exposure, residence or travel to endemic areas, or other epidemiological risk factors are at increased risk for the specific diseases:

- rabies, (2D)
- tick-borne meningoencephalitis, (2D)
- Japanese B encephalitis—inactivated, (2D)
- Meningococcus, (2D)
- Pneumococcus, (2D)
- Salmonella typhi—inactivated. (2D)

12.4.1: Consult an infectious disease specialist, a travel clinic or public health official for guidance on whether specific cases warrant these vaccinations. (Not Graded)

### **KDOQI Rationale and Commentary**

KTRs are at particular risk of viral infections because of the preferential suppression of T lymphocytes by both induction and maintenance immunosuppression. The risk and consequence of developing a viral infection warrant use of selected vaccines. The suggestions regarding which vaccines are safe and which are contraindicated are based on whether the vaccine contains live or killed virus. Live virus vaccines are contraindicated in immunosuppressed KTRs. The KDIGO recommendations for vaccinations agree with updated guidelines recently published by the AST.<sup>35</sup> Specific comments on the KDIGO suggestions regarding vaccinations are listed in the following sections.

#### **Hepatitis B**

The work group did not concur with KDIGO suggestion 12.1.1. Neither revaccination against hepatitis after transplant nor following up hepa-

titis B antibody titers annually is a common practice in the United States. Hepatitis B is not as prevalent in the United States as in other parts of the world and evidence supporting screening in all patients posttransplant is lacking. However, screening for seroconversion in patients at risk (receiving a hepatitis B core antibody–positive kidney) is appropriate. These patients may benefit from lamivudine or entecavir therapy.<sup>36</sup>

#### **Live Vaccine and Timing of Vaccine**

There is no particular reason for a 6-month lag between transplant and vaccination. The theory is that vaccines are less likely to be effective in the period when immunosuppression is high. In the United States, most individuals are on their baseline maintenance immunosuppression therapy by 3 months posttransplant. Decisions regarding the timing of vaccines are made based on immunosuppression exposure and risk of infection. Recipients also should avoid intimate contact with individuals who have received live vaccines.<sup>37</sup> This includes avoiding close contact with children who have received oral polio vaccine for 3 weeks and may include close contact with adults receiving the attenuated varicella vaccine to prevent zoster. Immunosuppressed individuals are advised to avoid contact for 7 days with individuals who have received live virus nasal sprays for influenza. We concur with the recommendation for flu vaccine, but common practice in the United States is to wait 3-6 months after transplant before it is administered.

#### **KDIGO Recommendations in Chapter 13: Viral Diseases**

##### **13.1: BK POLYOMA VIRUS**

- 13.1.1: We suggest screening all KTRs for BKV with quantitative plasma NAT (2C) at least:
- monthly for the first 3-6 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);
  - and after treatment for acute rejection. (2D)
- 13.1.2: We suggest reducing immunosuppressive medications when BKV plasma NAT is

persistently greater than 10 000 copies/mL ( $10^7$  copies/L). (2D)

##### **13.2: CYTOMEGALOVIRUS**

- 13.2.1: **CMV prophylaxis: We recommend that KTRs (except when donor and recipient both have negative CMV serologies) receive chemoprophylaxis for CMV infection with oral ganciclovir or valganciclovir for at least 3 months after transplantation, (1B) and for 6 weeks after treatment with a T-cell-depleting antibody. (1C)**
- 13.2.2: In patients with CMV disease, we suggest weekly monitoring of CMV by NAT or pp65 antigenemia. (2D)
- 13.2.3: CMV treatment:
- 13.2.3.1: **We recommend that all patients with serious (including most patients with tissue invasive) CMV disease be treated with intravenous ganciclovir. (1D)**
- 13.2.3.2: **We recommend that CMV disease in adult KTRs that is not serious (e.g. episodes that are associated with mild clinical symptoms) be treated with either intravenous ganciclovir or oral valganciclovir. (1D)**
- 13.2.3.3: **We recommend that all CMV disease in pediatric KTRs be treated with intravenous ganciclovir. (1D)**
- 13.2.3.4: We suggest continuing therapy until CMV is no longer detectable by plasma NAT or pp65 antigenemia. (2D)
- 13.2.4: We suggest reducing immunosuppressive medication in life-threatening CMV disease, and CMV disease that persists in the face of treatment, until CMV disease has resolved. (2D)
- 13.2.4.1: We suggest monitoring graft function closely during CMV disease. (2D)

##### **13.3: EPSTEIN-BARR VIRUS AND POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE**

- 13.3.1: We suggest monitoring high-risk (donor EBV seropositive/recipient seronegative) KTRs for EBV by NAT (2C):
- once in the first week after transplantation (2D);
  - then at least monthly for the first 3-6 months after transplantation (2D);
  - then every 3 months until the end of the first post-transplant year (2D);
  - and additionally after treatment for acute rejection. (2D)

- 13.3.2: We suggest that EBV-seronegative patients with an increasing EBV load have immunosuppressive medication reduced. (2D)
- 13.3.3: **We recommend that patients with EBV disease, including PTLN, have a reduction or cessation of immunosuppressive medication. (1C)**
- 13.4: HERPES SIMPLEX VIRUS 1, 2 AND VARICELLA ZOSTER VIRUS
- 13.4.1: **We recommend that KTRs who develop a superficial HSV 1, 2 infection be treated (1B) with an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir, or famciclovir) until all lesions have resolved. (1D)**
- 13.4.2: **We recommend that KTRs with systemic HSV 1, 2 infection be treated (1B) with intravenous acyclovir and a reduction in immunosuppressive medication. (1D)**
- 13.4.2.1: **We recommend that intravenous acyclovir continue until the patient has a clinical response, (1B)** then switch to an appropriate oral antiviral agent (e.g. acyclovir, valacyclovir, or famciclovir) to complete a total treatment duration of 14-21 days. (2D)
- 13.4.3: We suggest using a prophylactic antiviral agent for KTRs experiencing frequent recurrences of HSV 1,2 infection. (2D)
- 13.4.4: We recommend that primary VZV infection (chicken pox) in KTRs be treated (1C) with either intravenous or oral acyclovir or valacyclovir; and a temporary reduction in amount of immunosuppressive medication. (2D)
- 13.5: HEPATITIS C VIRUS
- 13.5.1: We suggest that HCV-infected KTRs be treated 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). (2D) [Based on KDIGO Hepatitis C Recommendation 2.1.5.]
- 13.5.2: We suggest monotherapy with standard interferon for HCV-infected KTRs in whom the benefits of antiviral treatment clearly outweigh the risks. (2D) [Based on KDIGO Hepatitis C Recommendations 2.2.4 and 4.4.2.]
- 13.5.3: We suggest that all conventional current induction and maintenance immunosuppressive regimens can be used in HCV infected patients. (2D) [Based on KDIGO Hepatitis C Recommendation 4.3.]
- 13.5.4: Measure ALT in HCV-infected patients monthly for the first 6 months and every 3-6 months, thereafter. Perform imaging annually to look for cirrhosis and hepatocellular carcinoma. (Not Graded) [Based on KDIGO Hepatitis C Recommendation 4.4.1.] (See Recommendation 19.3.)
- 13.5.5: Test HCV-infected patients at least every 3-6 months for proteinuria. (Not Graded) [Based on KDIGO Hepatitis C Recommendation 4.4.4.]
- 13.5.5.1: For patients who develop new onset proteinuria (either urine protein/creatinine ratio >1 or 24-hour urine protein >1 g on two or more occasions), perform an allograft biopsy with immunofluorescence and electron microscopy. (Not Graded) [Based on KDIGO Hepatitis C Recommendation 4.4.4.]
- 13.5.6: We suggest that patients with HCV associated glomerulopathy not receive interferon. (2D) [Based on KDIGO Hepatitis C Recommendation 4.4.5.]
- 13.6: HEPATITIS B VIRUS
- 13.6.1: We suggest that any currently available induction and maintenance immunosuppressive medication can be used in HBV-infected KTRs. (2D)
- 13.6.2: We suggest that interferon treatment should generally be avoided in HBV infected KTRs. (2C)
- 13.6.3: We suggest that all HBsAg-positive KTRs receive prophylaxis with tenofovir, entecavir, or lamivudine. (2B)
- 13.6.3.1: Tenofovir or entecavir are preferable to lamivudine, to minimize development of potential drug resistance, unless medication cost requires that lamivudine be used. (Not Graded)
- 13.6.3.2: During therapy with antivirals, measure HBV DNA and ALT levels every 3 months to monitor efficacy and to detect drug resistance. (Not Graded)
- 13.6.4: We suggest treatment with adefovir or tenofovir for KTRs with lamivudine resistance (>5 log<sub>10</sub> copies/mL rebound of HBV-DNA). (2D)
- 13.6.5: Screen HBsAg-positive patients with cirrhosis for hepatocellular carcinoma every 12 months with liver ultrasound and alpha fetoprotein. (Not Graded) (See Recommendation 19.3.)
- 13.6.6: We suggest that patients who are negative for HBsAg and have HBsAb titer <10 mIU/mL receive booster vaccination to raise the titer to ≥100 mIU/mL. (2D)

## 13.7: HUMAN IMMUNODEFICIENCY VIRUS

- 13.7.1: If not already done, screen for HIV infection. (Not Graded)
- 13.7.2: 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. (Not Graded).

**KDOQI Rationale and Commentary**

Viral infections are particularly problematic in transplant recipients because of the preferential inhibition of T-lymphocyte function by both induction and maintenance immunosuppression. Use of induction immunosuppression with lymphocyte-depleting agents (thymoglobulin or alemtuzumab) is associated with a greater risk of viral infection posttransplant. In general, the greater the cumulative exposure to immunosuppression, the greater the risk of infectious complications. The presentation of viral infections can be asymptomatic, vague, and nonspecific or life-threatening acute illness. Many viral infections seen in KTRs are rarely seen in immunocompetent patients and therefore do not enter into the differential diagnosis for physicians unfamiliar with transplant recipients. Close communication with the transplant center is crucial in caring for the transplant population. Early detection and institution of therapy provide the best chance for viral eradication.

**BK Virus**

Although the work group agreed with KDIGO suggestions for BK virus screening posttransplant, we did not think it was practical to require 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, there is no disagreement that some type of screening for BK virus is critical to avoid BK nephropathy, for which there is no specific treatment when it is established. Complicating screening for BK virus is the variability in results between laboratories and uncertainty about the level of viremia that should trigger a response to decrease in immunosuppression. In the presence of viremia and increase in serum creatinine level, a renal allograft biopsy is indicated to confirm the presence of BK nephropathy. Because BK viremia and viruria certainly can

be detected beyond the first year, it is not clear how long screening should be continued posttransplant, although most centers screen for the first year only. Ongoing clinical trials are exploring effective treatment for BK nephropathy.<sup>38,39</sup> Decisions about decreases in immunosuppression, currently the mainstay of BK viremia management, always should be made in consultation with the transplant center.

**Cytomegalovirus**

KDIGO recommendation 13.2.1 regarding cytomegalovirus (CMV) prophylaxis is reasonable and applicable to the US population. Universal prophylaxis for CMV now is recommended over initiating pre-emptive treatment after CMV develops.<sup>40</sup> A major concern for US patients is the cost of CMV prophylaxis with oral valgancyclovir. Leukopenia can be observed in patients using mycophenolate preparations when prophylaxis with valgancyclovir is used. Screening for CMV is best performed using NAT methods (13.2.2). CMV antigenemia assays are still in use in many facilities, but are not as sensitive as PCR assays.<sup>41</sup> There is no utility in checking for serologic response to CMV with IgG or IgM titers posttransplant because the immune response is not predictable. Patients with CMV disease should be cared for by clinicians familiar with treating this disease. It is recommended that treatment be continued until viral load is undetectable, followed by prophylactic doses of valgancyclovir for an additional 3 months.<sup>35</sup>

**Epstein-Barr Virus**

Current practice regarding EBV screening varies among centers in the United States and many do not routinely screen for EBV posttransplant, even in recipient-negative donor-positive cases. In contrast to KDIGO recommendation 13.1.1, routine EBV screening is not recommended in AST infectious disease guidelines.<sup>35</sup> In many centers, EBV screening is reserved for children, who are much more commonly EBV negative pretransplant than adults. EBV-induced posttransplant lymphoproliferative disorder (PTLD) affects many more pediatric than adult KTRs. 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.

### *Herpes and Varicella*

Systemic herpesvirus infections can be life threatening in transplant recipients and should be treated aggressively with intravenous antiviral agents, as described in the KDIGO recommendations. Less aggressive cutaneous infection can be treated with oral antiviral agents, as outlined in the KDIGO guidelines.

Varicella exposure is particularly concerning in transplant recipients. The work group disputes the recommended dosing of acyclovir for varicella exposure. Acyclovir at a dose of 10 mg/kg or about 800 mg 4 times daily of oral acyclovir would be standard dosing. We agree with the use of varicella immune globulin and emphasize the need to avoid the varicella vaccine because it is a live virus. Should a transplant recipient develop a systemic varicella infection, hospitalization and high-dose intravenous acyclovir therapy are warranted.

### *Hepatitis C*

Hepatitis C management posttransplant is a challenge. The KDIGO guidelines cited here were based on the recently published KDIGO guideline for hepatitis C in CKD.<sup>4</sup> Hepatitis C typically is not treated posttransplant because of the risk (~50%) of rejection precipitated by interferon therapy, particularly in US KTRs in whom hepatitis C commonly is genotype 1, which is more resistant to treatment with interferon.<sup>42</sup> However, should hepatitis C–related glomerulonephritis develop, the risk-benefit ratio may favor treatment in selected patients. Such decisions always should be made in consultation with hepatology and infectious disease experts and the transplant center. Monitoring liver enzyme levels, specifically alanine aminotransferase (ALT), may reflect a change in hepatitis activity, but monitoring hepatitis C viral load is not recommended because it does not seem to correlate with outcome. Annual monitoring for hepatocellular carcinoma using  $\alpha$ -fetoprotein and imaging is encouraged, but not often practiced.

### *Hepatitis B*

KDIGO recommendations for hepatitis B are reasonable and currently are followed in most US centers, except for recommendation 13.6.6 (see previous recommendation under vaccinations). KTRs with hepatitis C or hepatitis B also should be followed up by a hepatologist.

### *Human Immunodeficiency Virus*

Human immunodeficiency virus (HIV)-positive individuals are now acceptable for transplant if CD4 count is  $\geq 200$  cells/ $\mu\text{L}$  and viral load (VL) is undetectable.<sup>35,43</sup> Transplant should be performed at centers with expertise in managing HIV-positive individuals and care should be coordinated carefully with HIV specialists. Some antiretroviral agents, in particular the protease inhibitors, have potentially serious drug interactions with immunosuppressive agents.<sup>35</sup>

## **KDIGO Recommendations in Chapter 14: Other Infections**

- 14.1: URINARY TRACT INFECTION
  - 14.1.1: We suggest that all KTRs receive UTI prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 months after transplantation. (2B)
  - 14.1.2: For allograft pyelonephritis, we suggest initial hospitalization and treatment with intravenous antibiotics. (2C)
- 14.2: PNEUMOCYSTIS JIROVECI PNEUMONIA
  - 14.2.1: **We recommend that all KTRs receive PCP prophylaxis with daily trimethoprim–sulfamethoxazole for 3-6 months after transplantation. (1B)**
  - 14.2.2: We suggest that all KTRs receive PCP prophylaxis with daily trimethoprim–sulfamethoxazole for at least 6 weeks during and after treatment for acute rejection. (2C)
  - 14.2.3: **We recommend that KTRs with PCP diagnosed by bronchial alveolar lavage and/or lung biopsy be treated with high-dose intravenous trimethoprim–sulfamethoxazole, corticosteroids, and a reduction in immunosuppressive medication. (1C)**
  - 14.2.4: **We recommend treatment with corticosteroids for KTRs with moderate to severe PCP (as defined by PaO<sub>2</sub> <70 mm Hg in room air or an alveolar gradient of >35 mm Hg). (1C)**
- 14.3: TUBERCULOSIS
  - 14.3.1: We suggest that TB prophylaxis and treatment regimens be the same in KTRs as would be used in the local, general population who require therapy. (2D)
  - 14.3.2: We recommend monitoring CNI and mTORi [mTOR inhibitor] blood levels in patients receiving rifampin. (1C)
    - 14.3.2.1: Consider substituting rifabutin for rifampin to minimize

interactions with CNIs and mTORi. (Not Graded)

#### 14.4: CANDIDA PROPHYLAXIS

14.4.1: We suggest oral and esophageal Candida prophylaxis with oral clotrimazole lozenges, nystatin, or fluconazole for 1-3 months after transplantation, and for 1 month after treatment with an antilymphocyte antibody. (2C)

### KDOQI Rationale and Commentary

#### *Urinary Tract Infection*

Urinary tract infections (UTIs) after kidney transplant are very common and account for a large percentage of readmissions posttransplant. UTIs are common because of multiple factors, including the disrupted anatomy of the urinary tract with a ureteroneocystotomy, incomplete bladder emptying because of diabetes or prostatic hypertrophy, and impaired immune responses. Prophylaxis of UTIs usually is undertaken with trimethoprim-sulfamethoxazole for 6 months posttransplant, although infections often occur despite therapy because of the development of drug resistance. Although native kidney pyelonephritis does not always require hospitalization, it is recommended that all KTRs with this diagnosis be hospitalized because the graft dysfunction that usually accompanies transplant pyelonephritis requires aggressive investigation and treatment. Individuals with recurrent UTIs warrant evaluation with urologic assessment. Patients with recurrent UTIs may benefit from long-term suppressive therapy.

#### *Pneumocystic Pneumonia*

We agree that *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis is important for the first 3-6 months posttransplant (14.2.1). After the first month, every-other-day dosing of trimethoprim-sulfamethoxazole or atovaquone is believed to be adequate prophylaxis. In cases in which neither of these agents can be used, an individual may be treated prophylactically with inhaled pentamidine. Our KDOQI work group emphasized that patients who develop PCP should be transferred to the transplant center promptly for management and adjustments in immunosuppression.

#### *Tuberculosis*

Monitoring for latent tuberculosis has posed a challenge in the immunosuppressed population be-

cause of the unreliable nature of skin testing. Newer techniques involving interferon  $\gamma$  release assays are emerging as the new gold standard for detection of latent tuberculosis.<sup>44,45</sup>

#### *Candida Prophylaxis*

Oral candidiasis must be screened for using oral mucosa examination on follow-up visits in KTRs. This is especially true in the early posttransplant period, when immunosuppressive medication dosage is the highest. We agree with these recommendations and emphasize that if fluconazole is used, there is a potential for serious drug interactions because of cytochrome P-450 3A4 inhibition.

### SUMMARY OF COMMENTARY ON SECTION II: GRAFT MONITORING AND INFECTIONS

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 post-transplant complications. Frequent posttransplant monitoring may improve long-term outcomes by decreasing chronic graft failure or death with a functioning graft. Our work group concurred with the recommendation and schedules of routine screening in monitoring kidney allograft function after kidney transplant with a low threshold for performing kidney biopsy in cases of graft dysfunction or proteinuria. Expert tissue processing and interpretation of transplant biopsy specimens by pathologists with transplant experience are critical. 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. Although CKD in KTRs progresses more slowly than CKD in other patients, the work group agreed that the KDIGO guidelines on CKD should be followed in KTRs.

Opportunistic infections are common in KTRs, although advances in diagnosis and treatment have led to improved survival in KTRs with infection. It is now standard of care to use vaccinations in KTRs as long as the vaccine does not contain live or attenuated virus. It also is routine to screen for or use prophylaxis to prevent several posttransplant viral infections. With few exceptions (related to EBV and BK virus screening and hepatitis B vaccination posttransplant), we concurred with KDIGO guidelines for vaccination, screening, and treatment of infection posttransplant.

## COMMENTARY ON SECTION III OF KDIGO TRANSPLANT GUIDELINE: CARDIOVASCULAR DISEASE

### KDIGO Recommendations in Chapter 15: Diabetes Mellitus

- 15.1: Screening for New-Onset Diabetes after Transplantation
- 15.1.1: **We recommend screening all nondiabetic KTRs with fasting plasma glucose, oral glucose tolerance testing, and/or HbA<sub>1c</sub> (1C)** at least:
- weekly for 4 weeks (2D);
  - every 3 months for 1 year (2D);
  - and annually, thereafter. (2D)
- 15.1.2: We suggest screening for NODAT with fasting glucose, oral glucose tolerance testing, and/or after starting, or substantially increasing the dose, of CNIs, mTORi, or corticosteroids. (2D)
- 15.2: Managing NODAT or Diabetes Present at Transplantation
- 15.2.1: If NODAT develops, consider modifying the immunosuppressive drug regimen to reverse or ameliorate diabetes, after weighing the risk of rejection and other potential adverse effects. (Not Graded)
- 15.2.2: Consider targeting HbA<sub>1c</sub> 7.0%-7.5%, and avoid targeting HbA<sub>1c</sub> ≤6.0%, especially if hypoglycemic reactions are common. (Not Graded)
- 15.2.3: We suggest that, in patients with diabetes, aspirin (65-100 mg/d) use for the primary prevention of CVD be based on patient preferences and values, balancing the risk for ischemic events to that of bleeding. (2D)

### KDOQI Rationale and Commentary

#### Diabetic Screening

We agree with screening for new-onset diabetes after transplantation (NODAT) as outlined by the KDIGO work group. Definitions used are similar to those of the American Diabetes Association (ADA). The greater frequency of testing initially is justified by the high risk of NODAT in the early posttransplant period; however, ongoing screening is required because the risk of the development of NODAT continues to increase over time.<sup>46,47</sup> We also point out that prediabetic states (impaired fasting glucose level and impaired glucose tolerance)<sup>48</sup> occur even more commonly than overt diabetes<sup>48</sup> and may be associated with metabolic syndrome, as well as with increased cardiovascular mortality.<sup>49-51</sup> Potential implications of these predia-

betic states emphasize the importance of performing blood tests under fasting conditions. For patients with fasting hyperglycemia, an oral glucose tolerance test or hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) test should be performed. Although more cumbersome to perform, data suggest that an oral glucose tolerance test is a more sensitive indicator of NODAT in hyperglycemic KTRs.<sup>52</sup> This may allow earlier detection of overt diabetes and more prompt institution of treatment.

#### Diabetes Management

Data supporting a substantial benefit in the amelioration or reversal of NODAT using immunosuppression modification in KTRs are very limited. There was consensus in our work group that considering the paucity of data for reversing NODAT by changing immunosuppression and the potential risk of an adverse outcome with such a maneuver, KDIGO suggestion 15.2.1 could not be supported. Certainly if such a step was being considered, it should be done in conjunction with the transplant center. Targeting an HbA<sub>1c</sub> level of 7%-7.5% and avoiding levels <6% is based on data showing increased cardiovascular events with the lower HbA<sub>1c</sub> target.<sup>53,54</sup>

### KDIGO Recommendations in Chapter 16: Hypertension, Dyslipidemias, Tobacco Use, and Obesity

- 16.1: Hypertension
- 16.1.1: **We recommend measuring blood pressure at each clinic visit. (1C)**
- 16.1.2: We suggest maintaining blood pressure at <130 mm Hg systolic and <80 mm Hg diastolic if ≥18 years of age, and <90<sup>th</sup> percentile for sex, age, and height if <18 years old. (2C)
- 16.1.3: To treat hypertension (Not Graded)
- Use any class of antihypertensive agent;
  - Monitor closely for adverse effects and drug-drug interactions; and when urine protein excretion ≥1 g/d for ≥18 years old and ≥600 mg/m<sup>2</sup>/24 h for <18 years old, consider an ACE-I or an ARB as first-line therapy.
- 16.2: Dyslipidemias (These recommendations are based on KDOQI Dyslipidemia Guidelines and are thus not graded).
- 16.2.1: Measure a complete lipid profile in all adult (≥18 years old) and adolescent (puberty to 18 years old) KTRs [Based on

- KDOQI Dyslipidemia Recommendation 1]:
- 2-3 months after transplantation;
  - 2-3 months after a change in treatment or other conditions known to cause dyslipidemias;
  - at least annually, thereafter.
- 16.2.2: Evaluate KTRs with dyslipidemias for secondary causes [Based on KDOQI Dyslipidemia Recommendation 3]
- 16.2.2.1: For KTRs with fasting triglycerides  $\geq 500$  mg/dL ( $\geq 5.65$  mmol/L) that cannot be corrected by removing an underlying cause, treat with:
- Adults: therapeutic lifestyle changes and a triglyceride-lowering agent. [Based on KDOQI Recommendation 4.1];
  - Adolescents: therapeutic lifestyle changes [Based on KDOQI Recommendation 5.1].
- 16.2.2.2: For KTRs with elevated LDL-C:
- Adults: If LDL-C  $\geq 100$  mg/dL ( $\geq 2.59$  mmol/L), treat to reduce LDL-C to  $< 100$  mg/dL ( $< 2.59$  mmol/L) [Based on KDOQI Guideline 4.2];
  - Adolescents: If LDL-C  $\geq 130$  mg/dL ( $\geq 3.36$  mmol/L), treat to reduce LDL-C to  $< 130$  mg/dL ( $< 3.36$  mmol/L) [Based on KDOQI Guideline 5.2].
- 16.2.2.3: For KTRs with normal LDL-C, elevated triglycerides and elevated non-HDL-C:
- Adults: If LDL-C  $< 100$  mg/dL ( $< 2.59$  mmol/L), fasting triglycerides  $\geq 200$  mg/dL ( $\geq 2.26$  mmol/L), and non-HDL-C  $\geq 130$  mg/dL ( $\geq 3.36$  mmol/L), treat to reduce non-HDL-C to  $< 130$  mg/dL ( $< 3.36$  mmol/L) [Based on KDOQI Guideline 4.3];
  - Adolescents: If LDL-C  $< 130$  mg/dL ( $< 3.36$  mmol/L), fasting triglycerides  $\geq 200$  mg/dL ( $\geq 2.26$  mmol/L), and non-HDL-C  $\geq 160$  mg/dL ( $\geq 4.14$  mmol/L), treat to reduce non-HDL-C to  $< 160$  mg/dL ( $< 4.14$

mmol/L) [Based on KDOQI Guideline 5.3].

### 16.3: Tobacco Use

- 16.3.1: Screen and counsel all KTRs, including adolescents and children, for tobacco use, and record the results in the medical record. (Not Graded)
- Screen during initial transplant hospitalization.
  - Screen at least annually, thereafter.
- 16.3.2: Offer treatment to all patients who use tobacco. (Not Graded)

### 16.4: Obesity

- 16.4.1: Assess obesity at each visit. (Not Graded)
- Measure height and weight at each visit, in adults and children.
  - Calculate BMI at each visit.
  - Measure waist circumference when weight and physical appearance suggest obesity, but BMI is  $< 35$  kg/m<sup>2</sup>.
- 16.4.2: Offer a weight-reduction program to all obese KTRs. (Not Graded)

## KDOQI Rationale and Commentary

### Hypertension

The KDIGO work group adapted the KDOQI 2004 recommendations for target blood pressure in KTRs.<sup>55</sup> Self measurement is useful in assessing response to therapy and enhances adherence.<sup>56</sup> In general, we agree that the class of antihypertensive agent does not matter in the treatment of blood pressure elevation in this population and that attention should be given to potential side effects of antihypertensive agents, as well as possible interactions with the immunosuppressive regimen (eg, non-dihydropyridine calcium channel blockers and CNIs). In the absence of adequate randomized controlled trials, it is not known whether angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) prolong recipient or allograft survival. Some, but not all, retrospective studies suggest a benefit; however, all these studies are limited by selection bias.<sup>57,58</sup> Although ACE inhibitors and ARBs commonly lead to some decrease in GFR, treatment with these drugs should be continued unless serum creatinine level increases by  $> 25\%$  to  $30\%$ , in keeping with KDOQI recommendations.<sup>55</sup> In KTRs receiving ACE inhibitors or ARBs, it is important to educate patients to maintain adequate fluid intake during illness to prevent a prerenal

insult to the allograft. Similarly, awareness is necessary when using diuretics in conjunction with therapies that block the renin-angiotensin-aldosterone-system.<sup>59</sup>

### **Dyslipidemia**

The KDIGO work group based their recommendations for evaluation and treatment of hyperlipidemia on the KDOQI dyslipidemia guidelines for KTRs.<sup>60</sup> We agree with these recommendations. CNIs potentiate the toxicity of statins by slowing their metabolism through the cytochrome P-450 system. This interaction occurs more commonly with cyclosporine<sup>61</sup> than with tacrolimus. Dyslipidemia, especially hypertriglyceridemia, frequently complicates mTOR-inhibitor use and lipid-lowering therapy is required in most patients using these agents.

### **Tobacco Use**

Not surprisingly, tobacco use at the time of transplant is associated with decreased patient and graft survival, as well as increased risk of posttransplant cardiovascular disease (CVD). Although the KDIGO work group recommends initial screening and intervention during the hospitalization for transplant, we believe there may be benefit gained by starting counseling in the pretransplant period during the evaluation phase. Unfortunately, this does not occur often because of time and personnel constraints in transplant centers. Ideally, all transplant centers should have smoking-cessation programs available to patients either in-house or through referral. Ideally, systems should be created to continue to screen and monitor for smoking cessation at yearly intervals after transplant because there is a high rate of relapse with this addiction. As outlined in KDIGO Table 25,<sup>3</sup> although all pharmacologic therapies for smoking cessation can be used in KTRs, the starting dose of varenicline should be decreased in patients with GFR  $\leq$ 30 mL/min.

### **Obesity**

Obesity is an epidemic in the United States and the proportion of obese kidney transplant candidates continues to grow. In addition, weight gain after transplant is very commonly observed. Obesity in KTRs is associated with

increased risks of wound complications, delayed graft function, acute rejection, and NO-DAT, resulting in inferior patient and graft outcomes. Attention to this potential complication and counseling should be initiated during the pretransplant evaluation phase. Information regarding pharmacologic therapies for weight loss in KTRs is not available, and we agree with the KDIGO work group that therapeutic lifestyle measures should be encouraged. Data regarding steroid therapy withdrawal and weight gain are controversial. A recent double-blind randomized controlled trial examining early steroid therapy withdrawal did not show a difference in weight gain at 5 years posttransplant compared with the cohort remaining on standard maintenance corticosteroid therapy.<sup>62</sup>

### **KDIGO Recommendations in Chapter 17: Cardiovascular Management**

- 17.1: Consider managing CVD at least as intensively in KTRs as in the general population, with appropriate diagnostic tests and treatments. (Not Graded)
- 17.2: We suggest using aspirin (65-100 mg/d) in all patients with atherosclerotic CVD, unless there are contraindications. (2B)

### **KDOQI Rationale and Commentary**

Although outcomes are favorable compared with remaining on the waiting list, the risk of cardiovascular mortality in KTRs is several-fold higher than observed in the general population,<sup>63</sup> especially in younger age groups and patients with decreasing allograft function.<sup>64</sup> CVD is a major cause of graft loss after the first post-transplant year. In this context, we strongly agree that CVD should be managed in KTRs at least as intensively as in the general population. Ideally, decreasing CVD risk in KTRs requires a multifaceted and multidisciplinary approach. Based on current practice models in the United States, the transplant and nephrology community has not yet been able to achieve these desirable goals.<sup>65</sup> This clearly deserves more attention because control of CVD has the potential to contribute more to long-term kidney graft survival than the discovery of newer drugs that decrease the rate of allograft rejection. Our KDOQI working group agreed with the use of low-dose aspirin in KTRs with evidence of atherosclerosis.

### SUMMARY OF COMMENTARY ON SECTION III: CVD

With the decrease in acute rejection during the past decade in association with improved immunosuppression regimens, patient death now rivals chronic graft dysfunction as one of the leading causes of long-term graft loss. Because CVD is the most common cause of patient death in KTRs, a concerted effort at minimizing risk factors for heart disease likely will have as great or even greater impact on optimizing patient and graft outcomes than the discovery of new antirejection therapies. 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. When immunosuppression modification is being considered to mitigate cardiovascular risk, we recommend that this be in conjunction with the transplant center. In summary, we generally concurred with the suggestions of the work group in this section, but based on current practice standards in the United States, challenges remain with implementation of this guideline.

### COMMENTARY ON SECTION IV OF KDIGO TRANSPLANT GUIDELINE: MALIGNANCY

#### KDIGO Recommendations in Chapter 18: Cancer of the Skin and Lip

- 18.1: We recommend that KTRs, especially those who have fair skin, live in high sun-exposure climates, have occupations requiring sun exposure, have had significant sun exposure as a child, or have a history of skin cancer, be told that their risk of skin and lip cancer is very high. (1C)
- 18.2: We recommend that KTRs minimize life-long sun exposure and use appropriate ultraviolet light blocking agents. (1D)
- 18.3: We suggest that adult KTRs perform skin and lip self-examinations and report new lesions to a health-care provider. (2D)
- 18.4: For adult KTRs, we suggest 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. (2D)
- 18.5: We suggest that patients with a history of skin or lip cancer, or premalignant lesions, be referred to and followed by a qualified health professional with experience in diagnosing and treating skin cancer. (2D)

- 18.6: We suggest that patients with a history of skin cancer be offered treatment with oral acitretin, if there are no contraindications. (2B)

#### KDOQI Rationale and Commentary

##### *Counseling and Sunscreen*

We concur with recommendations 18.1 and 18.2 because skin cancer is a major source of morbidity and sometimes mortality in KTRs. Warning patients at risk of the high danger of skin cancer, a 1C recommendation, is reinforced by a recent prospective case-control study of organ transplant recipients that showed that regular use of broad-spectrum sunscreens that provide UVA and UVB protection may prevent the development of actinic keratosis, invasive squamous cell carcinoma, and, to a lesser extent, basal cell carcinoma.<sup>66</sup> Most cancer-causing radiation is thought to come from the UVB spectrum and newer broad-spectrum sunscreens provide protection against UVA and UVB radiation. Counseling about sunscreen and the need for sun avoidance needs to be incorporated into routine office visits, although it may not always be successful. In a recent study of KTRs in which 91% of patients had been informed about the need for sun protection, only 46% used more than a tube of sunscreen per year.<sup>67</sup>

##### *Dermatology Involvement*

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.<sup>68</sup> The resources required for these specialty clinics make implementation difficult for community nephrology groups that do not have direct access to a transplant center. Transplant patients should be encouraged to have annual visits with their transplant center, and if dermatology specialty clinics are available, attempt to coordinate a skin cancer evaluation annually.

##### *Use of Retinoid-like Compounds*

There is a limited scientific basis for KDIGO suggestion recommendation 18.6. Although retinoids now are used routinely in KTRs with a high skin cancer burden, our KDOQI work group believes that more data are needed before this suggestion should be accepted as a guideline. In

low-immunologic-risk groups and particularly difficult cases, some data suggest that switching from CNI to sirolimus therapy may decrease the incidence of skin cancer<sup>69</sup>; however, the risk versus benefit of this maneuver has not been well studied.

### **KDIGO Recommendations in Chapter 19: Non-Skin Malignancies**

- 19.1: Develop an individualized screening plan for each KTR that takes into account the patient's past medical and family history, tobacco use, competing risks for death, and the performance of the screening methodology. (Not Graded)
- 19.2: Screen for the following cancers as per local guidelines for the general population (Not Graded): Women: cervical, breast, and colon cancer; Men: prostate and colon cancer.
- 19.3: Obtain hepatic ultrasound and alpha feto-protein every 12 months in patients with compensated cirrhosis. (Not Graded) [See Recommendations 13.5.4 (HCV) and 13.6.5 (HBV).]

### **KDOQI Rationale and Commentary**

#### **Screening**

It is recognized that KTRs have a higher incidence of malignancy, particularly those associated with specific viral infections. Although cancer screening may have benefits in this higher risk population, it should be reinforced that some methods of screening have significant risks, which should be considered on an individualized basis, particularly in patients who have projected survival less than 5 years.

#### **Screening for Cancer in Patients With Hepatitis**

Many patients who have underlying cirrhosis in the United States will be followed up by a professional specializing in liver disease, who may provide additional insight into this cancer screening recommendation. Based on a recent questionnaire of US gastroenterologists, only 50% screen patients for hepatocellular carcinoma.<sup>70</sup> Therefore, implementation of this guideline by US clinicians is unlikely to be widespread.

### **KDIGO Recommendations in Chapter 20: Managing Cancer with Reduction of Immunosuppressive Medication**

- 20.1: We suggest consideration be given to reducing immunosuppressive medications for KTRs with cancer. (2C)

20.1.1: Important factors for consideration include (Not Graded):

- The stage of cancer at diagnosis;
- Whether the cancer is likely to be exacerbated by immunosuppression;
- The therapies available for the cancer;
- Whether immunosuppressive medications interfere with ability to administer the standard chemotherapy.

20.2: For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression. (2C)

### **KDOQI Rationale and Commentary**

Table 1 (Table 29 in the KDIGO report<sup>3</sup> and excerpted from Grulich et al<sup>71</sup>) lists cancers that are increased most in immunosuppressed KTRs based on standardized incidence ratios (SIRs), which compare the incidence to matched populations. Cancers with the highest SIRs may be those most likely to respond to a decrease in immunosuppression. Except for Kaposi sarcoma, limited evidence is available for a decrease in immunosuppression in these settings. A strategy to change immunosuppression therapy must occur in consultation with the transplant center. Switching to sirolimus therapy and decreasing immunosuppression in patients who develop Kaposi sarcoma is based on sound scientific rationale.<sup>72,73</sup>

### **SUMMARY OF COMMENTARY ON SECTION IV: MALIGNANCY**

The incidence of cancer posttransplant is 2-20 times higher than that in the general population, and KDIGO guidelines have been written to outline steps for prevention and screening. With few exceptions, we agree with the recommendations as outlined. 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. We agree that 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.

**Table 1.** Cancers Categorized by SIR for Kidney Transplant Patients and Cancer Incidence

	Common Cancers <sup>a</sup>	Common Cancers in Transplant Population (estimated) <sup>b</sup>	Rare Cancers <sup>c</sup>
High SIR <sup>d</sup> (>5)	Kaposi sarcoma (with HIV) <sup>d</sup>	Kaposi sarcoma, <sup>e</sup> vagina, <sup>e</sup> non-Hodgkin lymphoma, kidney, nonmelanoma skin, <sup>e</sup> lip, <sup>e</sup> thyroid, penis, <sup>e</sup> small intestine <sup>e</sup>	Eye
Moderate SIR <sup>d</sup> (>1 to 5; $P < 0.05$ )	Lung, colon, cervix, stomach, liver	Oronasopharynx, esophagus, bladder, leukemia	Melanoma, larynx, multiple myeloma, anus, <sup>e</sup> Hodgkin lymphoma
No increased risk shown <sup>d</sup>	Breast, prostate, rectum <sup>e</sup>		Ovary, uterus, pancreas, brain, testis

*Note:* Cancers listed in approximate descending order of estimated frequency (SIR × rate in general population).

Abbreviations: HIV, human immunodeficiency virus; SIR, standardized incidence ratio.

<sup>a</sup>Incidence in both general and transplant populations ≥10 cases/100,000 people; based on world incidence.<sup>88</sup> Age-standardized rate normalized to world population.

<sup>b</sup>Incidence in general population <10 cases/100,000, but estimated incidence in transplant population (SIR × general population incidence) ≥10 cases/100,000 people.

<sup>c</sup>Incidence in both general and transplant populations <10 cases/100,000 people.

<sup>d</sup>Excerpted from Table 4 of Grulich et al.<sup>71</sup>

<sup>e</sup>Based on US incidence.<sup>89</sup> Age-standardized rate (normalized to US population).

Adapted from the KDIGO transplant guideline<sup>3</sup> with permission of KDIGO.

## COMMENTARY ON SECTION V OF KDIGO TRANSPLANT GUIDELINE: OTHER COMPLICATIONS

### KDIGO Recommendations in Chapter 21:

#### Transplant Bone Disease

- 21.1: In patients in the immediate post kidney transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable. (1B)
- 21.2: In patients after the immediate post kidney transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD. (Not Graded)
- 21.2.1: Reasonable monitoring intervals would be (Not Graded):
- In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and PTH once, with subsequent intervals depending on baseline level and CKD progression.
  - In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
  - In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
  - In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH.

21.2.2: In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for efficacy and side effects. (Not Graded)

21.2.3: It is reasonable to manage these abnormalities as for patients with CKD stages 3–5. (Not Graded)

21.3: In patients with CKD stages 1–5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions. (2C)

21.4: In patients with CKD stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population. (2C)

21.5: In patients with an eGFR greater than approximately 30 mL/min/1.73 m<sup>2</sup>, we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids or have risk factors for osteoporosis as in the general population. (2D)

21.6: In patients in the first 12 months after kidney transplant with eGFR greater than approximately 30 mL/min/1.73 m<sup>2</sup> and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol or bisphosphonates be considered. (2D)

21.6.1: We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases and 25(OH)D. (2C)

21.6.2: It is reasonable to consider a bone biopsy to guide treatment, specifically before the

- use of bisphosphonates due to the high incidence of adynamic bone disease. (Not Graded)
- 21.6.3: There are insufficient data to guide treatment after the first 12 months. (Not Graded)
- 21.7: In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease. (2B)
- 21.8: In patients with CKD stages 4–5T with a known low BMD, we suggest management as for patients with CKD stages 4–5 not on dialysis. (2C)

## KDOQI Rationale and Commentary

### *Measuring Calcium and Phosphorus*

Recommendations for the diagnosis and treatment of posttransplant bone disease were derived from those created by the CKD-MBD KDIGO work group.<sup>5</sup> Our KDOQI work group concurred with the high-level recommendation to measure calcium and phosphorus weekly after transplant because dramatic changes can occur in these elements with restoration of kidney function. Suggestions for intervals of follow-up after the early transplant period are reasonable and based on the frequency of CKD posttransplant. Although there is consensus that parathyroid hormone (PTH) levels should be monitored, it is not clear at what level PTH should be maintained in KTRs. There also are data to suggest that higher than normal PTH levels may be required to preserve bone formation in KTRs on steroid therapy.<sup>74</sup>

### *Measuring and Treating Vitamin D Deficiency*

Vitamin D deficiency is extremely common in KTRs,<sup>75</sup> and low vitamin D levels should be repleted to control secondary hyperparathyroidism. Although vitamin D repletion can lead to a decrease in PTH levels, there are no data for improvement in bone disease with repletion.

### *Bone Mineral Density and Prevention of Bone Loss With Vitamin D Analogues or Bisphosphonates*

Although the current KDIGO suggestion recommendation (21.5) supports previous AST guidelines to obtain an early bone mineral density (BMD) study in KTRs with GFR >30 mL/min, there are no data correlating results of BMD measurements with fracture risk in KTRs. Although bisphosphonate use may result in less

bone density loss in the early posttransplant period, no study has been sufficiently powered to show fracture prevention using these therapies.<sup>76</sup> Furthermore, bisphosphonate use in patients with GFR <30 mL/min or those with low bone turnover may cause adynamic bone disease.<sup>77</sup> All these limitations have made bisphosphonate use less common in US transplant patients in recent years.

Steroid therapy contributes significantly to fractures and loss of bone mass in the first 6–12 months after transplant, a phenomenon observed less commonly with steroid-avoidance protocols or after steroid therapy is withdrawn.<sup>62,78,79</sup> Thus, advocating for a steroid-avoidance protocol, now used in up to 30% of US transplant centers, may be a reasonable plan for patients at high risk of fractures (older, white, diabetic patients and those with previous fractures) to prevent further bone loss post-transplant.

The KDIGO recommendations in this section focus on the bone disease and biochemical abnormalities that contribute to fractures in KTRs, similar to KDOQI recommendations for CKD-MBD. However, the preponderance of fractures in the feet and in patients with diabetes suggest that other factors, such as neuropathy, balance, and level of activity, also may be important factors contributing to the high risk of fractures in KTRs.<sup>80,81</sup>

## KDIGO Recommendations in Chapter 22: Hematologic Complications

- 22.1: Perform a complete blood count at least (Not Graded):
- daily for 7 days, or until hospital discharge, whichever is earlier;
  - two to three times per week for weeks 2–4; weekly for months 2–3;
  - monthly for months 4–12;
  - then at least annually, and after any change in medication that may cause neutropenia, anemia or thrombocytopenia.
- 22.2: Assess and treat anemia by removing underlying causes whenever possible and using standard measures applicable to CKD. (Not Graded)
- 22.3: For treatment of neutropenia and thrombocytopenia, include treatment of underlying causes whenever possible. (Not Graded)
- 22.4: **We recommend using ACE-Is or ARBs for initial treatment of erythrocytosis. (1C)**

**KDOQI Rationale and Commentary****Anemia**

Anemia is a common problem posttransplant and often occurs at higher levels of GFR in KTRs than in other patients with CKD.<sup>82</sup> The authors base their recommendations for evaluation and treatment on KDOQI guidelines for anemia in CKD, which are reasonable and straightforward.<sup>83</sup> Financial coverage must be explored when discharging a new KTR on erythropoietin replacement therapy because reimbursement may be different from when the patient was on dialysis therapy.

**Neutropenia**

KDIGO suggestion 22.3 is reasonable. Now that CMV prophylaxis with valgancyclovir is routine in US transplant centers and induction with lymphocyte-depleting agents frequently is used, significant neutropenia is observed more frequently in the early posttransplant months, especially in patients using mycophenolate compounds. Rejection risk could be increased if MPA dose is decreased; however, CMV disease could occur if valgancyclovir therapy is discontinued. Some centers use granulocyte colony-stimulating factor to treat neutropenia in the early posttransplant period to avoid discontinuing valgancyclovir therapy or decreasing MPA dose. These decisions should always be made by the transplant center.

**Erythrocytosis**

This phenomenon usually occurs only in patients with good kidney function and is important to recognize and treat appropriately. AST guidelines for treatment (hemoglobin >17-19 g/dL, hematocrit >51% to 52%) should be followed. ACE inhibitors are the treatment of choice (KDIGO recommendation 22.4) and low doses of these agents often are effective.

**KDIGO Recommendations in Chapter 23: Hyperuricemia and Gout**

- 23.1: We suggest treating hyperuricemia in KTRs when there are complications, such as gout, tophi or uric acid stones. (2D)
- 23.1.1: We suggest colchicine for treating acute gout, with appropriate dose reduction for reduced kidney function and concomitant CNI use. (2D)
- 23.1.2: **We recommend avoiding allopurinol in patients receiving azathioprine. (1B)**

- 23.1.3: We suggest avoiding NSAIDs and COX-2 inhibitors whenever possible. (2D)

**KDOQI Rationale and Commentary**

Colchicine can be very effective in treating gout; however, higher doses than those described by the authors in the KDIGO guideline often are needed. The occurrence of diarrhea, causing pre-renal azotemia and deterioration in kidney function, limits the use of colchicine in KTRs to an even greater extent than the occurrence of myopathy, which usually occurs only in patients with very poor kidney function. It is critical to avoid the use of allopurinol in patients on azathioprine therapy (KDIGO guideline 23.1.2) because of inhibition of azathioprine metabolism by this drug. If long-term suppression of uric acid synthesis is needed in a patient on azathioprine therapy, one can switch to a mycophenolate compound because these do not depend on xanthine oxidase for metabolism.

**KDIGO Recommendations in Chapter 24: Growth and Development**

- 24.1: **We recommend measuring growth and development in children (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)
- 24.2: We recommend using rhGH [recombinant human growth hormone] 28 IU/m<sup>2</sup>/week (or 0.05 mg/kg/day) in children with persistent growth failure after kidney transplantation. (1B)
- 24.3: We suggest minimizing or avoiding corticosteroid use in children who still have growth potential. (2C)

**KDOQI Rationale and Commentary**

Improving growth in children remains one of the primary goals for pediatric KTRs. There now have been years of experience with the use of recombinant human growth hormone, and the risks seem to be minimal compared with the benefits.<sup>84</sup> Thus, we concur with KDIGO recommendations 24.1 and 24.2. Although it generally is thought to be preferable to avoid steroid therapy in growing children, evidence in support of this approach is limited. Furthermore, the risk of rejection in children has made some US centers reluctant to use steroid-avoidance protocols.

### KDIGO Recommendations in Chapter 25: Sexual Function and Fertility

- 25.1.1: Evaluate adults for sexual dysfunction after kidney transplantation. (Not Graded)
- 25.1.2: Include discussion of sexual activity and counseling about contraception and safe sex practices in follow-up of adult KTRs. (Not Graded)
- 25.2.1: We suggest waiting for at least 1 year after transplantation before becoming pregnant, and only attempting pregnancy when kidney function is stable with <1 g/day proteinuria. (2C)
- 25.2.2: **We recommend that MMF be discontinued or replaced with azathioprine before pregnancy is attempted. (1A)**
- 25.2.3: We suggest that mTORi be discontinued or replaced before pregnancy is attempted. (2D)
- 25.2.4: Counsel female KTRs with child-bearing potential and their partners about fertility and pregnancy as soon as possible after transplantation. (Not Graded)
- 25.2.5: Counsel pregnant KTRs and their partners about the risks and benefits of breastfeeding. (Not Graded)
- 25.2.6: Refer pregnant patients to an obstetrician with expertise in managing high-risk pregnancies. (Not Graded)
- 25.3.1: We suggest that male KTRs and their partners be advised that:
- male fertility may improve after kidney transplantation (2D);
  - pregnancies fathered by KTRs appear to have no more complications than those in the general population. (2D)
- 25.3.2: **We recommend that adult male KTRs be informed of the possible risks of infertility from mTORi. (1C)**
- 25.3.2.1: We suggest that adult male KTRs who wish to maintain fertility should consider avoiding mTORi, or banking sperm prior to mTORi use. (2C)

### KDOQI Rationale and Commentary

#### *Sexual Dysfunction*

Sexual dysfunction is a topic often overlooked in clinic visits, but one that many patients want addressed. Sexual dysfunction has been reported in 30%-60% of KTRs.<sup>85,86</sup> The use of 5-phosphodiesterase inhibitors to improve male erectile dysfunction appears to be safe in KTRs. Although KDIGO recommendations 25.1.1 and 25.1.2 are not graded, our KDOQI work group concurred with these recommendations.

### *Pregnancy and the Effect of Immunosuppressive Drugs on Teratogenicity*

Counseling about contraception in the first year posttransplant, a KDIGO guideline supported by AST consensus guidelines on pregnancy,<sup>87</sup> is important because fertility may return to normal early posttransplant. The effect of transplant immunosuppressive drugs on fertility and teratogenicity must be understood. Mycophenolate compounds are rated as Category D by the US Food and Drug Administration (FDA) and should be discontinued in women contemplating pregnancy (Guideline 25.2.2). Despite the same FDA rating for azathioprine, there have been years of experience with its use in pregnant KTRs. Although it may be prudent to avoid sirolimus therapy during pregnancy, our work group was divided regarding KDIGO recommendation suggestion 25.2.3; some of us agreed that mTOR-inhibitor therapy should be stopped in pregnancy, while others did not think there was enough evidence to support this recommendation. Until further data emerge regarding the safety of mTOR inhibitors in pregnancy, this precaution must be weighed against the risks and inconvenience of changing immunosuppression therapy. All pregnant KTRs are considered high-risk pregnancies and should be followed up by a high-risk obstetric team.

### *Effect of Sirolimus on Spermatogenesis*

mTOR inhibitors can decrease testosterone levels and male fertility and we therefore concur that counseling males treated with this agent is important (KDIGO 25.3.2). Implementation of this recommendation will require awareness on the part of the physician when patients are switched to this drug because it is used infrequently as an initial agent.

### KDIGO Recommendations in Chapter 26: Lifestyle

- 26: **We recommend that patients are strongly encouraged to follow a healthy lifestyle, with exercise, proper diet and weight reduction as needed. (1C)**

### KDOQI Rationale and Commentary

A healthy lifestyle, so important in reaching and maintaining the sense of wellness that we hope patients will achieve posttransplant, requires an interdisciplinary approach. Our work group was in strong support of this recommendation.

### KDIGO Recommendations in Chapter 27: Mental Health

- 27: Include direct questioning about depression and anxiety as part of routine follow-up care after kidney transplantation. (Not graded)

### KDOQI Rationale and Commentary

Depression and anxiety in the transplant population, conditions that may affect adherence, often are overlooked because patients are expected to be content with their “gift of life.” Attention to this area in the short time allotted for patient visits often requires the help of a multidisciplinary team, especially social workers, to survey patients for signs of these disorders and get the help they need.

### SUMMARY OF COMMENTARY ON SECTION V: OTHER COMPLICATIONS

Metabolic complications are common posttransplant and attention to the prevention and treatment of these issues, many resulting from side effects of immunosuppressive drugs, constitute a large part of posttransplant care. For the most part, our KDOQI work group agreed with KDIGO recommendations for the prevention and treatment of bone disease except for having less enthusiasm for the use of bisphosphonates, which now are used uncommonly in KTRs in the United States. We agreed with recommendations for managing hematologic problems, gout, and growth in children. We also concur with recommendations for management of immunosuppressive drugs in pregnancy, although our group was divided about whether mTOR-inhibitor therapy must be discontinued in pregnancy. We applaud the KDIGO group for including sections on mental health and lifestyle because these are important areas that require more attention in the medical care of KTRs.

### RESEARCH

At the end of each section, members of the KDIGO work group made several suggestions for areas of future research. Our KDOQI work group agreed with the critical importance of research in these areas to create evidence upon which future recommendations and guidelines can be based.

### CONCLUSION

The new KDIGO guideline for the care of kidney transplant patients are broad in scope and should serve as guide for all clinicians caring for

KTRs, including transplant clinicians, nephrologists, nurses, and fellows in training. Our KDOQI work group concurred with many of the KDIGO recommendations except in some important areas related to immunosuppression. Decisions about immunosuppression in the United States are largely made by transplant centers and are dependent in part on the specific patient population served. Emphasis in the KDIGO guideline is made for the need for continued monitoring of KTRs with the use of kidney biopsy to determine causes of graft dysfunction even after the early posttransplant period. Because of increasing recognition of entities such as BK nephropathy and antibody-mediated rejection as important causes for graft dysfunction, it is important to have access to proper processing and interpretation of the transplant biopsy specimen by pathologists with expertise in this area. Most, but not all, KDIGO recommendations are relevant to US patients. However, implementation of many may remain a major challenge because of issues of drug cost and limitation in resources needed to assist in the tasks of educating, counseling, and implementing and maintaining lifestyle changes. However, these KDIGO recommendations offer an excellent road map to navigate the complex care of kidney transplant patients.

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### REFERENCES

1. McCullough KP, Keith DS, Meyer KH, et al. Kidney and pancreas transplant in the United States, 1998-2007: access for patients with diabetes and end stage renal disease. *Am J Transplant.* 2009;9:894-906.

2. Eknoyan G, Lameire N, Barsoum R, et al. The burden of kidney disease: improving global outcomes. *Kidney Int.* 2004;66:1310-1414.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9(suppl 3):S19-20.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the prevention, diagnosis, evaluation and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl.* 2008;109:S1-99.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl.* 2009;113:S1-113.
6. Andreoni KA, Brayman KL, Guidinger MK, Sommers CM, Sung RS. Kidney and pancreas transplantation in the United States, 1996-2005. *Am J Transplant.* 2007;7:1359-1375.
7. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med.* 2007;357:2562-2575.
8. Ekberg H, Bernasconi C, Tedesco-Silva H, et al. Calcineurin inhibitor minimization in the Symphony Study: observational results 3 years after transplantation. *Am J Transplant.* 2009;9:1876-1885.
9. Egbuna OI, Davis R, Chudinski R, et al. Outcomes with conversion from calcineurin inhibitors to sirolimus after renal transplantation in the context of steroid withdrawal or steroid continuation. *Transplantation.* 2009;88:684-692.
10. Lebranchu Y, Thierry A, Toupance O, et al. Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study. *Am J Transplant.* 2009;5:1115-1123.
11. Schold JD, Kaplan B. AZA/tacrolimus is associated with similar outcomes as MMF/tacrolimus among renal transplant recipients. *Am J Transplant.* 2009;9:2067-2074.
12. Gaston RS, Kaplan B, Shah T, et al. Fixed or controlled-dose mycophenolate mofetil with standard or reduced-dose calcineurin inhibitors: the Optcept trial. *Am J Transplant.* 2009;9:1607-1619.
13. Rush D, Arlen D, Boucher A, et al. Lack of benefit of early protocol biopsies in renal transplant patients receiving TAC and MMF: a randomized study. *Am J Transplant.* 2007;7:2538-2545.
14. Chang AT, Platt JC. The role of antibodies in transplantation. *Transpl Rev.* 2009;23:191-198.
15. Abbud-Filho M, Adams PL, Alberú J, et al. A report of the Lisbon Conference on the care of the kidney transplant recipient. *Transplantation.* 2007;83(8 suppl):S1-22.
16. Israni AK, Snyder JJ, Skeans MA, Tuomari AV, Maclean JR, Kasiske BL. Who is caring for kidney transplant patients? Variation by region, transplant center, and patient characteristics. *Am J Nephrol.* 2009;30(5):430-439.
17. Lee PC, Zhu L, Terasaki P, Everly MJ. HLA specific antibodies developed in the first year posttransplant are predictive of chronic rejection and renal graft loss. *Transplantation.* 2009;88:568-574.
18. Everly MJ, Terasaki PI. Monitoring and treating posttransplant human leukocyte antigen antibodies. *Hum Immunol.* 2009;70:655-659.
19. Birnbaum LM, Lipman M, Paraskevas S, et al. Management of chronic allograft nephropathy: a systematic review. *Clin J Am Soc Nephrol.* 2009;4:860-865.
20. Levey AS, Eckardt K-U, Tsukamoto T, et al. Definition and classification of Chronic Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2005;67:2089-2100.
21. Jiménez Alvaro S, Marcén R, Teruel JL, et al. Management of chronic kidney disease after renal transplantation: is it different from nontransplant patients? *Transplant Proc.* 2009;41:2409-2411.
22. Burgos FJ, Pascual J, Marcen R, et al. The role of imaging techniques in renal transplantation. *World J Urol.* 2004;22:399-404.
23. Hergesell O, Felten H, Andrassy K, et al. Safety of ultrasound guided percutaneous renal biopsy—retrospective analysis of 1090 consecutive cases. *Nephrol Dial Transplant.* 1998;13:975-977.
24. Mengel M, Chapman JR, Cosio FG, et al. Protocol biopsies in renal transplantation: insights into patient management and pathogenesis. *Am J Transplant.* 2007;7:512-517.
25. Reeve J, Einecke G, Mangel M, et al. Diagnosing rejection in renal transplants: a comparison of molecular- and histopathology-based approaches. *Am J Transplant.* 2009;9:1802-1810.
26. Bunnag S, Einecke G, Reeve J, et al. Molecular correlates of renal function in kidney transplant biopsies. *J Am Soc Nephrol.* 2009;20:1149-1160.
27. Saint-Mezard P, Berthier CC, Zhang H, et al. Analysis of independent microarray datasets of renal biopsies identifies a robust transcript signature of acute allograft rejection. *Transplant Int.* 2009;3:293-302.
28. Gollert WA, Appel GB, Hariharan S. Recurrent glomerulonephritis after renal transplantation: an unsolved problem. *Clin J Am Soc Nephrol.* 2008;3:800-807.
29. Ghiggeri GM, Carraro M, Vincenti F. Recurrent focal glomerulosclerosis in the era of genetics of podocyte proteins: theory and therapy. *Nephrol Dial Transplant.* 2004;19:1036-1040.
30. Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. *Am J Transplant.* 2006;6:2535-2542.
31. Little MA, Dupont P, Campbell E, et al. Severity of primary MPGN, rather than MPGN type, determines renal survival and post-transplantation recurrence risk. *Kidney Int.* 2006;69:504-511.
32. Fine RN, Becker Y, De Geest S, et al. Nonadherence consensus conference summary report. *Am J Transplant.* 2009;9:35-41.
33. Morrissey PE, Flynn ML, Lin S. Medication noncompliance and its implications in transplant recipients. *Drugs.* 2007;67:1463-1481.
34. Vlaminck H, Maes B, Evers G, et al. Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. *Am J Transplant.* 2004;4:1509-1513.

35. AST Infectious Diseases Guidelines 2nd Edition. *Am J Transplant.* 2009;9(suppl 4):S1-281.
36. Akalin E, Ames S, Sehgal V, Murphy B, Bromberg J. Safety of using hepatitis B core antibody or surface antigen-positive donors in kidney or pancreas transplantation. *Clin Transplant.* 2005;19:364-366.
37. Duchini A, Goss J, Karpen S, Pockros P. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. *Clin Microbiol Rev.* 2003;16(3):357-364.
38. A randomized, placebo-controlled, dose-escalation study to assess the safety and effect of cidofovir in renal transplant recipients with BK virus nephropathy. NCT001384424. ClinicalTrials.Gov. Accessed May 17, 2010.
39. A multicenter, randomized, double-blind, placebo-controlled, multiple dose study of the safety, tolerability and population pharmacokinetics of CMX001 in post-transplant patients with BK virus viraemia. NCT00793598. *ClinicalTrials.Gov.* Accessed May 17, 2010.
40. Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, Rohde F. Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. *Am J Transplant.* 2008;8(5):975-983.
41. Weinberg A, Hodges TN, Li S, et al. Comparison of PCR, antigenemia assay, and rapid blood culture for detection and prevention of cytomegalovirus disease after lung transplantation. *J Clin Microbiol.* 2000;38:768-772.
42. Zein NN, Rakela J, Krawitt EL, Reddy KR, Tomimaga T, Persing DH. Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity, and response to interferon therapy. Collaborative Study Group. *Ann Intern Med.* 1996;125(8):634-639.
43. Roland ME, Barin B, Carlson L, et al. HIV-infected liver and kidney transplant recipients: 1- and 3-year outcomes. *Am J Transplant.* 2008;8:355-365.
44. Richeldi L, Losi M, D'Amico R, et al. Performance of tests for latent tuberculosis in different groups of immunocompromised patients. *Chest.* 2009;136(1):198-204.
45. Kobashi Y, Mouri K, Obase Y, et al. Clinical evaluation of Quantiferon TB-2G test for immunocompromised patients. *Eur Respir J.* 2007;30:945-950.
46. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant.* 2003;3:178-185.
47. Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. *Am J Transplant.* 2003;3:590-598.
48. Nam JH, Mun JI, Kim SI, et al. Beta-cell dysfunction rather than insulin resistance is the main contributing factor for the development of postrenal transplantation diabetes mellitus. *Transplantation.* 2001;71:1417-1423.
49. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24:683-689.
50. de Vries AP, Bakker SJ, van Son WJ, et al. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. *Am J Transplant.* 2004;4:1675-1683.
51. Cosio FG, Kudva Y, van der Velde M, et al. New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int.* 2005;67:2415-2421.
52. Armstrong KA, Prins JB, Beller EM, et al. Should an oral glucose tolerance test be performed routinely in all renal transplant recipients? *Clin J Am Soc Nephrol.* 2006;1:100-108.
53. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545-2559.
54. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2560-2572.
55. National Kidney Foundation. KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. *Am J Kidney Dis.* 2004;43(suppl 1):S1-290.
56. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289:2560-2572.
57. Heinze G, Mitterbauer C, Regele H, et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol.* 2006;17:889-899.
58. Opelz G, Zeier M, Laux G, Morath C, Dohler B. No improvement of patient or graft survival in transplant recipients treated with angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers: a collaborative transplant study report. *J Am Soc Nephrol.* 2006;17:3257-3262.
59. Arthur JM, Shamim S. Interaction of cyclosporine and FK506 with diuretics in transplant patients. *Kidney Int.* 2000;58:325-330.
60. Kasiske B, Cosio FG, Beto J, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant.* 2004;4:13-53.
61. Lemahieu WP, Hermann M, Asberg A, et al. Combined therapy with atorvastatin and calcineurin inhibitors: no interactions with tacrolimus. *Am J Transplant.* 2005;5:2236-2243.
62. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg.* 2008;248:564-577.
63. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32(suppl 3):S112-119.
64. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation.* 2003;75:1291-1295.

65. Gaston RS, Kasiske BL, Fieberg AM, et al. Use of cardioprotective medications in kidney transplant recipients. *Am J Transplant.* 2009;9:1811-1815.
66. Ulrich C, Jurgensen HS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of sunscreen: a 24 months, prospective, case-control study. *Br J Dermatol.* 2009;161(suppl 3):78-84.
67. Mahe E, Morelon E, Fermanian J, et al. Renal-transplant recipients and sun protection. *Transplantation.* 2004;78:741-744.
68. Ismail F, Mitchell D, Casabone A, et al. Specialist dermatology clinics for organ transplant recipients significantly improve compliance with photo protection and levels of skin cancer awareness. *Br J Dermatol.* 2008;155(5):916-925.
69. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol.* 2006;17:581-589.
70. Chalasani N, Said A, Ness R, et al. Screening for hepatocellular carcinoma in patients with cirrhosis in the United States: results of a national survey. *Am J Gastroenterol.* 1999;94:2224-2229.
71. Grulich AE, van Leeuwen MT, Falster MO, et al. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet.* 2007;370:59-67.
72. Stallone G, Infante B, Pontrelli P, et al. ID2-VEGF-related pathways in the pathogenesis of Kaposi's sarcoma: a link disrupted by rapamycin. *Am J Transplant.* 2009;9(3):558-586.
73. Duman S, Toz H, Asci G, et al. Successful treatment of post-transplant Kaposi's sarcoma by reduction of immunosuppression. *Nephrol Dial Transplant.* 2002;17:892-896.
74. Rojas E, Carlini R, Clesca P, et al. The pathogenesis of osteodystrophy after renal transplantation as detected by early alterations in bone remodeling. *Kidney Int.* 2003;63:1915-1923.
75. Stavroulopoulos A, Cassidy MJD, Porter CJ, Hosking DJ, Roe SD. Vitamin D status in renal transplant patients. *Am J Transplant.* 2007;7:2546-2552.
76. Palmer SC, Strippoli G, McGregor D. Interventions for preventing bone disease in kidney transplant recipients: a systematic review of randomized controlled trials. *Am J Kidney Dis.* 2005;45:638-649.
77. Coco M, Glicklich D, Fuagere MC, et al. Prevention of bone loss in renal transplant recipients: a prospective randomized trial of intravenous pamidronate. *J Am Soc Nephrol.* 2003;14:2669-2676.
78. Farmer CKT, Hampson G, Abbs IC. Late low-dose steroid withdrawal in renal transplant recipients increases bone formation and bone mineral density. *Am J Transplant.* 2006;6:2929-2936.
79. van den Ham E, Kooman JP, van Hoof CMJP. The influence of early steroid withdrawal on body composition and bone mineral density in renal transplantation patients. *Transplant Int.* 2003;16:82-87.
80. Nisbeth U, Lindh E, Ljunghall S, Backman U, Fellstrom B. Increased fracture rate in diabetics and females after renal transplantation. *Transplantation.* 1999;67:1218-1222.
81. Ramsey-Goldman R, Dunn JE, Dunlop DD, et al. Increased risk of fracture in patients receiving solid organ transplants. *J Bone Miner Res.* 1999;14:456-463.
82. Chadban SJ, Baines L, Polkinghorne K, et al. Anemia after kidney transplantation is not completely explained by reduced kidney function. *Am J Kidney Dis.* 2007;49:301-309.
83. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis.* 2006;47(suppl 3):S1-146.
84. Vimalachandra D, Craig JC, Cowell CT, et al. Growth hormone treatment in children with chronic renal failure: a meta-analysis of randomized controlled trials. *J Pediatr.* 2001;39:560-567.
85. Tsujimura A, Matsumiya K, Tsuboniwa N, et al. Effect of renal transplantation on sexual function. *Arch Androl.* 2002;48:467-474.
86. Raiz L, Davies EA, Ferguson RM. Sexual functioning following renal transplantation. *Health Soc Work.* 2003;28:264-272.
87. McKay DB, Josephson MA, Armenti VT, et al. Reproduction and transplantation: report on the AST Consensus Conference on Reproductive Issues and Transplantation. *Am J Transplant.* 2005;5:1592-1599.
88. GLOBOCAN 2002. In, International Agency for Research on Cancer, Cancer Mondial, 2002.
89. United States Cancer Statistics: 1999-2005 incidence and mortality web-based report. U.S. Cancer Statistics Working Group, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. In (vol 2009), Atlanta, GA, U.S. Cancer Statistics Working Group, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2009.