# A Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient

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An International Conference on the Care of the Kidney Transplant Recipient was convened in Lisbon, Portugal from February 2–4, 2006 under the auspices of the National Kidney Foundation and Kidney Disease: Improving Global Outcomes (KDIGO), and in cooperation with The Transplantation Society. Conference participants included over 100 experts and leaders in kidney transplantation, representing more than 40 countries from around the world, including participants from Africa, Asia, Australia, Europe, North American, and South America (Appendix).

The goal of the conference was to develop recommendations to improve the outcomes of kidney transplant recipients worldwide with regard to the following basic medical issues: cardiovascular disease (Work Group I), cancer and infection (Work Group II), and anemia, bone disease, reproductive issues, growth and development (Work Group III).

Work Groups I, II, and III addressed the preand posttransplant care of kidney transplant recipients by the following components: timelines of pre- and posttransplantation, immunosuppression, level of kidney allograft function, and burden of disease (prior history of dialysis or preemptive transplant and how that history affects outcome).

A graft maintenance section (Work Group IV) addressed: 1) recipient (and donor) selection; 2) surgical aspects and immediate posttransplant care of recipients including consideration of minimal surgical infrastructure; 3) immunosuppression including an assessment of the incremental expected value of more complex and expensive regimens in comparison to simpler and less expensive regimens, generics, mid- and long-term immunosuppression; 4) living donor versus deceased donor transplantation; and 5) mid- and long-term posttransplant care and monitoring of allograft function.

In addition, conference participants were asked to examine the issue of applicability of the recently published Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for chronic kidney disease (CKD) in kidney allograft recipients (*1*). Specifically, Work Group V addressed the role of estimated glomerular filtration rate (eGFR) in monitoring kidney function after transplantation, as well as the stratification for intervention according to eGFR values.

## Work Group I: Cardiovascular Disease

### Bertram Kasiske, Gabriel Danovitch, and Fernando Cosio: Co-Chairs

Chronic kidney disease, before and after transplantation, is an independent risk factor for cardiovascular disease (CVD). Risk for CVD should be managed from the earliest stages of CKD. Although the absolute risk increases with age (*2–5*), the highest relative risk of CVD is in young adults with CKD. Prevention of CVD includes risk factor management and education (professionals and patients). Kidney transplantation provides a better outcome than dialysis, including less occurrence of CVD and a lower cost (*6–8*). Preemptive transplantation may also help to prevent CVD, and is now best accomplished with a living donor.

### Rationale for Assessing CVD Risk in Transplant Candidates

The risk of CVD should be assessed for all potential transplant recipients to maximize safety and informed consent in transplantation and to prevent CVD events. Optimizing graft function may reduce CVD risk. This risk assessment will also optimize the utilization of scarce resources and determine the appropriate level of expertise needed for the transplantation.

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**Pretransplant CVD evaluation**

Assessment should include a history and physical examination to detect symptomatic disease, and an electrocardiogram (ECG). Evaluation of asymptomatic patients at highest-risk for CVD events (defined below) may include noninvasive and/or invasive testing such as a coronary angiography, depending on local expertise and availability. However, there are no data establishing that screening of asymptomatic patients in itself prevents CVD events (*9*).

Highest-risk patients are those with the following conditions:

- Diabetes (*2–5*)
- Prior CVD (*5*, *10–12*)
- Multiple CVD risk factors, such as more than 1 year on dialysis (*13*); left ventricular hypertrophy (LVH) (*14*); age >60 years; smoking (*2*, *4*, *15*, *16*); hypertension (*3*, *11*, *17*); and dyslipidemias (*4*, *10*, *11*)

Highest-risk patients may still benefit from undergoing kidney transplantation. If there is an anticipated wait of over 2 years for transplantation, then assessment of CVD should be repeated annually in high- risk individuals. (*18*, *19*).

**Perioperative Management**

The perioperative period is a time for CVD events, especially for high-risk patients. Perioperative beta-blockade is strongly recommended for these transplant candidates to prevent perioperative CVD events and should be started, whenever possible, at least 1 month prior to surgery (*20*, *21*). Patients not on a beta-blocker immediately before surgery should be assessed for intravenous beta-blockade. Low-dose aspirin prophylaxis in the pretransplant period is not a contraindication to transplantation (*22*).

**Posttransplant Management**

CVD is a major cause of morbidity and premature mortality after transplantation. Death with a functioning graft in the immediate posttransplant period is often caused by CVD. Posttransplant care should include ongoing CVD risk factor management with a special focus on hypertension, dyslipidemia, and diabetes.

*Hypertension*

Hypertension should be managed according to existing guidelines for CKD patients (*23*). Target blood pressure should be <130/80 mm Hg (and probably lower in patients with persistent proteinuria). All classes of antihypertensive agents can be used in transplant recipients and no single class has been proven to be superior to others after kidney transplantation. Physicians should be aware of potential drug interactions in kidney transplant recipients.

There are practical advantages and disadvantages associated with the use of different antihypertensive agent classes in kidney transplant recipients. Because edema is common after transplantation, diuretics often make a logical first choice. On the other hand, diuretics can occasionally cause an increase in serum creatinine that requires additional evaluation. Calcium channel blockers are generally safe and effective in kidney transplant recipients, but they may contribute to edema. Nondihydropyridine calcium channel blockers may increase blood levels of cyclosporine and thereby require a dose-reduction of cyclosporine A (CsA), but this may actually be advantageous by reducing the cost of CsA.

Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are also effective antihypertensive agents in kidney transplant recipients. They may contribute to hyperkalemia, anemia, and occasionally cause an increase in serum creatinine that prompts further evaluation to rule out kidney allograft rejection. Beta-blockers are effective in transplant recipients, and may be particularly advantageous in patients with known coronary artery disease. Vasodilators and other agents are also effective in transplant recipients. Often a combination of several agents is needed to adequately control blood pressure.

When blood pressure control cannot be readily achieved with pharmacological management, consideration should be given to possible graft artery stenosis or stenosis of the iliac artery above the graft. In addition, the native kidneys may contribute to hypertension and, when blood pressure is difficult to control, consideration should be given to native kidney nephrectomy.

*Dyslipidemia*

Dyslipidemia should be managed according to existing guidelines for CKD patients (*24*). Elevated triglycerides are generally only treated to prevent the rare occurrence of pancreatitis. Triglycerides that are persistently ≥500 mg/day (5.65 mmol/L) can cause pancreatitis. If triglycerides are <500 mg/dL (<5.65 mmol/L), but low-density lipoprotein (LDL) is ≥100 mg/dL (≥ 2.59 mmol/L) then patients should be treated with dietary modification and, if necessary, a statin. If LDL is <100 mg/dL (<2.59 mmol/L), but triglycerides are >200 mg/dL (>2.26 mmol/L), and therefore non-HDL cholesterol is >130 mg/dL (>3.37 mmol/L), then patients should also be treated. For transplant patients with LDL 100–129 mg/dL (2.59–3.34 mmol/L), it is reasonable to attempt diet for 2 to 3 months before starting a statin. However, the reduction in LDL that can be achieved with diet and lifestyle changes is usually modest. Therefore, in patients who cannot be expected reduce LDL to <100 mg/dL (<2.59 mmol/L) by diet, a statin should be started along with diet, if there is no evidence of liver disease.

Statins are the drugs of first choice in the treatment of dyslipidemia posttransplant. Physicians should be aware of potential drug interactions in kidney transplant recipients. The dose of statins should generally be reduced in patients treated with CsA, since CsA increases the blood levels of most statins. The addition of other agents that increase both CsA and statin blood levels, such as azole antifungal agents, macrolide antibiotics, and nondihydropyridine calcium antagonists, should prompt a temporary dose reduction or discontinuation of the statin. If diet and a statin are not sufficient to achieve a target LDL <100 mg/dL (<2.59 mmol/L), then adding a second agent can be considered. Fibrates should generally not be used in combination with a statin, due to the risk of myopathy. Perhaps the best choice of a second agent is the new cholesterol uptake inhibitor ezetimibe.

*Diabetes*

Diabetes should be managed according to existing guidelines (*25*). Optimal diabetes control may be difficult to achieve after transplantation. Treatment of diabetes after kid-

ney transplantation is similar to treatment of diabetes in the general population. Oral hypoglycemic agents are effective. The insulin-sensitizing thiozolidinediones can be used after transplantation, but may be associated with edema and even congestive heart failure. Metformin is an effective agent for improving blood glucose control in the general population, and has been shown in clinical trials to reduce the incidence of complications from diabetes. However, metformin can cause severe lactic acidosis in patients with reduced kidney function. Since kidney transplant recipients are prone to develop acute kidney dysfunction, most consider metformin to be contraindicated in kidney transplant recipients. In the end, clinicians and patients are often left with managing diabetes with various strategies of administering short and long-acting exogenous insulin.

A risk of new onset diabetes mellitus after transplantation (NODAT) and NODAT is associated with increased risk for CVD events (*7*, *26*, *27*). Thus, all patients should be counseled before transplantation on the risk for NODAT and periodically screened following transplantation. Treatment and prevention of obesity and choice of immunosuppressive agents may reduce the risk for NODAT, especially in high-risk patients. NODAT should be managed according to existing guidelines for type 2 diabetes (*25*).

*Cigarette Abstinence*

Cigarette abstinence should be strongly encouraged before and after kidney transplantation (*2*, *4*, *28*). Structured smoking cessation programs that include nicotine replacement and other therapies should be made available.

*Aspirin Prophylaxis*

Aspirin prophylaxis should be considered for the highest-risk transplant recipients, unless contraindicated (*29*).

*Therapeutic Lifestyle*

Therapeutic lifestyle changes should be encouraged and facilitated. These include regular exercise, diet (according to existing guidelines), optimal weight maintenance, and moderation in alcohol intake.

### Choice of Immunosuppressive Medications

Maintenance of graft function, which is partially dependent on immunosuppressive medications, may prevent CVD events. If a choice of agents is available, then the immunosuppressive protocol may be tailored to immunological and CVD risk factors of the individual patient. There is no evidence, however, that specific immunosuppressive protocols influence CVD events.

## Work Group II: Recipient Infection and Cancer

### Jeremy Chapman, Günter Kirste, and Atul Humar: Co-Chairs

Donor evaluation was considered at the Lisbon Forum with respect to the risks of transmission of disease to the recipient. No attempt in this report is made to assess the medical risks to be a live organ donor. The Amsterdam Forum on the care of the live kidney donor has addressed that topic comprehensively (*30*). Further, posttransplant immunosuppression was considered only with respect to identifying risks for cancer and infection, and not for the purpose of conducting a risk benefit analysis of immunosuppressive regimens.

Lisbon Forum participants called attention to the international need for a global resource available to all transplant centers that would report up to date information on endemic and epidemic disease. This would allow immediate access to relevant data for testing of donors from diverse geographic regions irrespective of the region of donation. It is envisaged that such a resource could be established under the auspices of the World Health Organization (WHO).

### Tests To Be Performed on Living and Deceased Kidney Donors

In this section, the word "must" is used to mean that the issue under consideration is of such importance that no transplant should be performed without that issue or test being addressed, even in an environment of constrained resources; the word "should" implies that in a fully resourced environment this issue or test is appropriate internationally accepted standard of care; and the word "could" is used to mean that the issue or test has some proponents or is accepted in some environments, but not others, or is not strongly supported by data (*31–33*).

*Must Be Tested in All Donors to Provide a Standard of Care for the Recipient*

A medical history must be obtained on potential live donors to include a review the donor's recent travel experience and the potential exposure to infections by high risk behaviors. Antibody screening for human immunodeficiency virus (HIV), cytomegalovirus (CMV; immunoglobulin [Ig] G), and hepatitis C virus is recommended. The utility and necessity of nucleic acid testing (NAT) testing for hepatitis C virus remains unresolved (*34*). Screening for HepBsAg must also be done. A donor chest radiograph, urine analysis, and culture are standard.

*Should Be Tested in All Donors to Provide a Standard of Care for the Recipient*

Antibody screening for HepBcAb (even if the donor is HepSAg negative), syphilis (nonspecific antibody test) should be performed. Assessment of the live donor for exposure to human T-cell lymphotrophic virus I and II, tuberculosis, schistosomiasis, Chagas disease, dengue fever, toxoplasmosis (IgG), and malaria depends upon endemicity and clinical situation.

Antibody screening of donors for Epstein-Barr virus (EBV [IgG]) should be performed when a potential recipient is serologically negative to EBV.

*Could Be Tested in Donors to Advantage of the Recipient*

Routine assessment of the live donor for exposure to West Nile virus remains controversial but could be tested in areas with high geographic endemicity (*35*).

### Which Results Would Exclude Donors and Which Tests Are Useful for Defining Risk to the Recipient?

HIV reactivity tested by sensitive enzyme-linked immunosorbent assay (ELISA) for HIV1 and 2 exclude kidney donation. Furthermore sensitive tests may be needed for certain areas of high endemicity or for certain high risk donors. Positive tests for other infectious risks do not always exclude donation, for example if the infection is treatable or treated (syphilis), or if the risks of infection are deemed acceptable by

an informed recipient (hepatitis B virus). Further data are needed however into the use of organs from donors testing positive for recipients who are also serologically reactive to the same virus.

Rare instances of disease transmitted by esoteric viruses continue to be reported (rabies, lymphocytic choriomeningitis virus, and West Nile Virus). Transmission of infectious disease cannot be eradicated completely. Donor sample archiving is a useful tactic to determine untoward infections that may only become evident after transplantation.

**What Measures Should Be Taken to Detect and Prevent Transmission of Donor Cancer?**

Cancer has been transmitted through organ donation and the risk of transmission, although remote (0.015% as an overall rate), cannot be fully eliminated (*36*). Deceased and living donors must have a clinical history and examination and routine laboratory investigation (e.g., chest radiograph, blood count, and chemistry) to reduce the risks of transmission of cancer. Common cancers in the relevant general population should be specifically considered with appropriate screening tests used as in those populations. Tumor marker screening tests may be indicated in certain circumstances; for example, deceased female donors of reproductive age with death due to intracerebral hemorrhage must be screened for metastatic choriocarcinoma by testing serum $\beta$-HCG concentration (*37*).

A history of donor cancer would usually exclude donation unless the donor is disease free or the cancer is not transmissible (e.g., basal cell skin cancer). Donors with certain primary intracerebral tumors may be acceptable in specific circumstances that do not violate possible dissemination beyond the blood-brain barrier (*38*, *39*). The widely reported transmission of glioblastoma presents a substantial hazard for recipients of kidneys from deceased donors (*40*).

Deceased donors must have careful examination for potential cancer during donor surgery. Donor autopsy is recommended, with any relevant information provided in a timely manner to the transplant team. Organ procurement agencies must have a record of all transplanted deceased donor organs and tissues and notify transplant teams in an expeditious manner of any relevant information about actual or potential donor cancer diagnosed in other recipients (*41*).

Living donors should be monitored for cancer after donation and any transmissible cancer diagnosed in the living donor should be made known to the transplant team.

**What Tests Must Be Performed on Recipients While on the Pretransplant Waiting List?**

*Must Be Tested in All Recipients to Provide a Standard of Care*

Antibody screening for HIV, CMV (IgG), and hepatitis C virus and direct testing for HepBsAg must be performed at least annually depending upon the anticipated time the patient will remain on the list (*31–33*). An annual chest radiograph, physical examination, and medical history (including recent travel history and high-risk behaviors) must also be performed.

Active fungal, bacterial, or parasitic infections must be adequately treated prior to the time of transplantation, such as tuberculosis, endocarditis, osteomyelitis, access infection/peritonitis, and dental infection.

*Should Be Tested in All Recipients to Provide a Standard of Care*

Antibody screening for HepBcAb (even if the donor is HepSAg negative), Syphilis (nonspecific antibody test), varicella zoster virus (VZV) IgG, EBV IgG, HepBcAb, and HepBsAb should be performed.

Patients with evidence of current hepatitis B infection (HepBsAg positive) should be tested for HepBeAg and HepB DNA viral load and also have a biopsy of the liver. Patients who have decompensated cirrhosis should not undergo isolate kidney transplantation. Patients with active hepatitis should be treated with antiviral therapy (e.g., lamivudine) both prior to and after transplantation, preferably with expert consultation. Patients with evidence of hepatitis C virus infection should be considered for biopsy of the liver and appropriate treatment based on expert consultation (*42*).

Exposure to infectious disease organisms should be assessed but substantial variations in endemicity and immunization practices necessitate these evaluations be selective; for example: a history and supplemental tests to assess the risk of tuberculosis, schistosomiasis, Chagas disease, malaria, and babesiosis. Current recommendations by the American Society of Transplantation (AST) and the European Best Practice Guidelines (EBPG) expert groups suggest pretransplant screening of potential recipients for latent tuberculosis infection, with appropriate treatment of infected patients *43*, *44*. Seronegative patients should be retested at regular intervals dependent upon individual variations in waiting time and exposure. Nevertheless, HIV and hepatitis B and C testing should be done at least annually. These tests may also be repeated at the time of transplantation, depending upon the interval since the last result was determined.

**Vaccination Before Kidney Transplantation**

Vaccination for potential disease threats in each community must be undertaken as soon as patients are considered for transplantation (*45*). Vaccination and selected monitoring of the serological response as appropriate should be considered for the following infections: polio, hepatitis A, tetanus, diphtheria, mumps, measles, rubella, hepatitis B, pneumococcus, influenza, meningococcus, VZV (if seronegative), hemophilus influenza B.

**Vaccination After Kidney Transplantation**

Vaccination after transplantation is less effective than prior to transplantation because of immunosuppression. Seroconversion rates after vaccination are reduced in immunosuppressed patients. Live vaccination is contraindicated in immunosuppressed patients and should thus be avoided after transplantation and within 4 to 6 weeks prior to transplantation. On the basis of evidence supporting vaccination in the general population, the following vaccinations should be considered in transplant recipients (*45*, *46*):

- Influenza: annual
- Hepatitis A with prospective travel risks if nonimmune
- Pneumococcus: every 3 to 5 years
- Meningococcus: in specific high-risk communities

**Posttransplant Infection**

*Cytomegalovirus Prevention and Prophylaxis*

Recipient CMV IgG–negative/donor CMV IgG–negative patients should reduce the risk of CMV transmission with the avoidance of unscreened on unfiltered blood products that might result in primary exposure and infection (*47*, *48*).

Donor CMV IgG–positive/recipient CMV IgG–negative kidney transplants recipients should be given antiviral prophylaxis for 3 months following transplantation. Valganciclovir, ganciclovir, and valacyclovir are appropriate.

Recipients treated with T-cell depleting therapy (ATG/ALG/OKT3/Campath) are at higher risk of CMV disease and should be given prophylactic antiviral therapy or have a preemptive prevention strategy in place.

Recipient CMV IgG–positive may receive prophylaxis, preemptive therapy or only clinical observation depending on the immunosuppression regimen and the risk of CMV.

*CMV Disease Treatment*

Patients with clinical CMV disease must be treated with antiviral therapy (intravenous ganciclovir) and preferably with a concomitant reduction in the intensity of immunosuppression.

*BK Virus Nephropathy*

The reported incidence of BK virus nephropathy varies between 1–10%. Risk factors include the intensity of immunosuppression. Alternative approaches to treatment are not well established except reduction of immunosuppression (*49*).

*Pneumocystis Jiroveci Pneumonitis (Previously Pneumocystis Carinii)*

The reported incidence of disease is approximately 5% in the absence of prophylaxis, but varies widely. Risk factors include the intensity of immunosuppression (*50*, *51*).

All kidney transplant patients should receive prophylaxis for at least 6 months by either trimethoprim/sulfamethoxazole (preferred), aerosolized pentamidine, or dapsone with or without trimethoprim.

*Urinary Tract Infections*

The use of trimethoprim/suphamethoxazole for Pneumocystis prophylaxis will also provide a degree of urinary tract infection prevention. Routine screening by urine culture is not recommended in all patients, but culture and treatment of symptomatic urinary tract infection (UTI) is required (*52*).

Children and adults with urinary tract abnormalities that predispose to urine infection require an aggressive approach to diagnosis and treatment of urinary tract infection.

*Mycobacterium Tuberculosis*

Tuberculosis is more common after transplantation but the incidence varies widely internationally (*51*). In patients from regions with high endemic rates of tuberculosis and in patients with evidence of prior tuberculosis infection, the treatment choice should be determined by local drug availability factors with respect to the number of agents and duration of treatment required to prevent relapse and drug resistance. At least 6 months of antituberculosis treatment is recommended. Pharmacokinetic drug interactions need to be addressed when cytochrome p450–inducing agents are used for treatment.

*Hepatitis C Virus*

Short-term patient survival following kidney transplantation appears to be similar to uninfected patients but long-term outcomes are worse (*53*). (*54*) Treatment with interferon-based regimens posttransplant are poorly tolerated and associated with rejection of the kidney transplant (*42*, *53*, *54*). The optimal immunosuppressive strategy for infected patients has yet to be developed. Efforts to eradicate HCV carriage before transplantation appear to be beneficial in the posttransplantation period with evidence that viral clearance may be sustained in many patients (*55–57*).

*Hepatitis B Virus*

All nonimmune patients must be vaccinated prior to transplantation, but patients on dialysis have low response rates. Nonimmune transplant recipients who have not been vaccinated should be vaccinated after transplantation, despite low response rates. HBsAg positive transplant recipients should receive antiviral therapy (e.g., lamivudine) preferably with expert consultation (*54*).

Nonimmune recipients of a HepBcAb positive donor kidney have a 2% risk of HepB seroconversion and should be monitored for the detection of HBsAg (*9*, *20*). Ideally, these organs should be used for recipients who are HepBsAb positive. Depending on the type of assay used, occasionally HepBcAb serology may be false positive. Also, use of kidneys from donors who are HepBsAg positive may be considered in recipients who are HepBsAg positive or under certain selected situations where the recipient is HepBsAb positive in conjunction with informed consent and antiviral therapy.

**Pretransplant Recipient Cancer**

*What Measures Should Be Taken to Exclude Cancer Pretransplant?*

All recipients must have a clinical history and examination and routine investigations (e.g., chest radiograph, blood count and chemistry, abdominal ultrasound including the native kidneys) to reduce the risks of transplantation with preexisting cancer. Screening should be done for hepatitis B and C infected patients at risk for the development of a hepatoma and for renal cell carcinoma in patients with analgesic nephropathy. Common cancer screening tests in the relevant general population should be specifically considered for transplant patients with appropriate tumor markers as recommended and used in those populations.

*When Should a Recipient Be Considered for Transplantation If They Have a Known Diagnosis of Prior Cancer?*

Patients can be considered for kidney transplantation if the time between clinical eradication of a cancer and transplantation extends to 2 years, and depending upon the exact tumor histology and its staging in each patient. Vigilance should be maintained in all patients because there remains a lack of good information on the exact risks of cancer recurrence after transplantation (*58*). Patients with existing in situ basal and squamous cell skin cancer may undergo transplantation when monitoring for newly developed skin cancers enables prompt excision.

**Posttransplant Recipient Cancer**

A high index of suspicion should be maintained for the development of recipient de novo or recurrent cancer (*59*). Screening programs should be implemented at least at the same ages and the same intervals as in the general population of those without a transplant. To minimize the incidence of de novo cancer after transplantation patients should be advised with respect to: the prevention of ultraviolet/sunburn exposure, self examination to identify and permit early treatment of premalignant or in situ disease (e.g., skin and breast), and the cessation of smoking. The intensity of the immunosuppression should be reduced in patients with cancer after transplantation, depending upon individual patient prognosis.

The following risk factors should be considered with respect to early posttransplant cancer:

- Donor transmitted cancer: detection in donor or paired recipient
- Recurrent recipient cancer: previous disease
- De novo recipient cancer: age and sex
- De novo donor derived cancer: donor age, EBV status

The following risk factors should be considered with respect to posttransplantation lymphoproliferative disease (PTLD) and Kaposi sarcoma:

- PTLD: EBV-positive donor/EBV-negative recipient
- High levels of immunosuppression (ATG/OKT3)
- Coinfection with CMV/hepatitis C virus
- Kaposi sarcoma: Mediterranean, African, or Middle East origin
- Human herpesvirus 8 reactivation or transmitted infection

## Work Group III: Anemia, Bone Disease, Growth and Reproductive Issues

**Patricia Adams, Pierre Cochat, Connie Davis, and Michelle Josephson: Co-Chairs**

**Anemia**

There are currently no national or international registries that capture hemoglobin levels postkidney transplantation. Transplant care physicians are dependent on surveys, single-center studies, or multicenter trials that record hemoglobin levels as part of the study of some other aspect of care, for our knowledge about erythropoiesis after kidney transplant. However, there is a large body of evidence about anemia in the general population, in CKD, and in end-stage renal disease (ESRD). In the latter, therapeutic principles for the use of erythropoietin-stimulating agents (ESA) have been established, well tested, and proven to be of benefit (*60–62*).

Kidney allografts vary considerably in function, and can be classified by the K/DOQI system according to their glomerular filtration rate (GFR) into five stages similar to kidneys with CKD (*63*). The moniker CKD-T has been proposed by some to distinguish this group (see Work Group V). It should be noted that the CKD and CKD-T groups are not identical. For instance, an individual with stage 1 CKD would have a near normal parathyroid hormone (PTH) level. In contrast, a CKD-T stage 1 patient might have considerable hyperparathyroidism as a residual from ESRD. Nonetheless, CKD-T is a useful grouping because the level of GFR predicts the development of certain abnormalities, such as anemia, that can be anticipated and treated. Additionally, there are excellent guidelines available to direct care based on this classification schema (*51*, *64–68*).

The World Health Organization's definition of anemia is a hemoglobin of <13 g/dL in males and <12 g/dL in females. Hemoglobins below these levels should trigger a work-up for anemia prior to transplantation that includes: 1) assessment for underlying disease (sickle cell, thalassemia, malaria, hemoglobinopathies); 2) nutritional deficiencies (iron, folate, B12, pica, aluminum toxicity); 3) other medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or nonsteroidal anti-inflammatory drugs (NSAIDs) (*69*); 4) bleeding (menses, gastrointestinal, coagulopathy); 5) cause of ESRD such as hemolytic uremic syndrome (HUS), polycystic kidney disease, or HIV-associated nephropathy (HIVAN); 6) endocrine disorders; 7) prior cytotoxic therapies; and 8) prior use of ESAs.

Anemia seems to be most severe in the first 6 weeks posttransplant, and again after 1 to 5 years (*70–72*). Erythropoietin (EPO) levels may be elevated in the first few days following transplantation. After a second peak at days 20 to 50 following transplantation, EPO levels normalize (4–26 U/L) despite continued improvement in hemoglobin levels up to the normal range (*73*).

*Posttransplant Treatment of Anemia*

The threshold to begin therapy for anemia is when the hemoglobin drops below 11 g/dL (Table 1). This level represents the lowest 5 percentile of the hemoglobin distribution of the general United States population adjusted for age and sex (*74*). Causes of posttransplantation anemia include all of the pretransplant conditions above, plus: 1) immunosuppressant therapy (*75*); 2) infection (CMV, parvovirus, parasites); 3) interval posttransplant; 4) rejection; 5) lack of EPO production; 6) EPO resistance; 7) other medications (gancyclovir, bactrim, allopurinol); 8) cancer; 9) red blood cell (RBC) aplasia (rapamune, eprex SQ [*76*], aranesp, tacrolimus); 10) hematophagia; and 11) low GFR. The target of therapy should be to maintain hemoglobin levels above the WHO definition of anemia above. The optimal level of hemoglobin to be achieved with anemia therapy posttransplant is unknown, but unlike the ESRD population where there are concerns about inducing vascular access thrombosis, and where there is literature which demonstrates no benefit to raising the hemoglobin above 13 (*77*, *78*), there is no data to refute the assertion that the hemoglobin should be normalized.

Kidney allograft recipients may be particularly susceptible to anemia in the immediate postop period for several reasons. First, ESRD anemia management may not have been ideal. The U.S. Renal Data System has shown, each year since 1991, that at least 20% of the prevalent dialysis population has a hemoglobin of <11 g/dL (*79*). Second, if the new kidney experiences delayed graft function, its innate EPO production may be too low to stimulate erythropoiesis. Finally, if chronic EPO therapy is stopped, the decrease in hemoglobin level is more marked and the recovery more prolonged than if the dose is tapered.

Increasing hemoglobin has been shown to be significantly associated with improvement in left ventricle ejection

**TABLE 1.** Recommended therapies for anemia

| Standard therapy | Other therapies | ESA resistance |
|---|---|---|
| • B12, folate, thyroid supplement as needed<br>• Erythropoietin alpha (Eprex, Erypo) or beta (Epogen, Procrit) (*51*, *64*, *65*)<br>The starting dose of EPO is 50 units/kg twice weekly. Administer SQ. (The packaging problem with Eprex that resulted in several cases of RBC aplasia has been corrected by the manufacturer to the satisfaction of regulatory agencies.) (*212*)<br>Erythropoietin is dosed twice a week in ESRD. Because the kidney allograft presumably has some innate EPO production, however, it is reasonable to expect that weekly dosing may be adequate post transplant. Anecdotal reports support this view. While on therapy, hemoglobin level should be monitored monthly.<br>Or<br>Darbepoietin alpha (Aranesp) (*213*)<br>The starting dose of darbepoetin alpha is 40 mcg SQ weekly (equally effective to EPO but longer dosing interval so preferred by patients). Darbepoetin alpha (see below) is dosed weekly in ESRD and should be started at this dosing interval post-transplant. At least one study indicates that this dosing interval maybe widened as therapy progresses (*214*).<br>• Iron. Supplement initially with oral iron to keep transferrin receptor saturation (TSAT) >20 %, ferritin 100–800 mcg/L. The use of EPO utilizes large amounts of iron. If oral supplement is inadequate to maintain a serum TSAT >20%, initiate IV if available. IV iron is available as iron dextran, iron gluconate, or iron sucrose. Iron dextran is associated with acute reactions when given IV, requires test dosing, and is generally not recommended. The optimal starting dose of IV iron is 25–150 mg/wk but can be given as larger doses such as 200 mg or 500 mg IV with less frequency. | • Androgens (recommended only for males >50 years)<br>• Carnitine (not recommended for general or routine use)<br>• Transfusions (reserve for symptomatic anemia, acute blood loss, or EPO resistance | • ESA resistance is defined as the continued need for >300 IU/kg of EPO (2006 KDOQI guidelines suggest >500 IU/kg) or 1.5 mcg/kg darbepoetin alpha per week in an iron-replete individual. |

fraction posttransplant (*80*). Anemia is a risk factor for progression of LVH in CKD and posttransplantation (*14*, *81*). Quality of life, sleep disorders, cognitive function, and exercise capacity have all been reported to improve with anemia therapy (*61*, *82*). It has even been proposed that tubulointerstitial changes might be attenuated by anemia therapy (*83*). Erythropoietin therapy has been shown to retard progression in some forms of chronic allograft dysfunction (*84*).

**Posttransplant Erythrocytosis**

Posttransplant erythrocytosis affects a number of allograft recipients. Secondary causes should be excluded: pulmonary disease, erythroleukemia, renal cancer, and hepatitis. It is recommended that the hemoglobin be maintained at <17.5 g/dl by ACE inhibitors or ARB even if the patient is normotensive. If the hemoglobin is higher, phlebotomy is recommended.

**Bone Disease**

Kidney transplant recipients have an increased fracture risk compared with the general population and dialysis patients (*85–87*). This is because they have decreased bone strength (*86*). In the general population, a bone mineral density score is a reasonable surrogate for bone strength (*88*). This is not the case in the transplant recipient (*86–89*). The transplant recipient has other pathologic bone processes that affect bone strength in addition to osteoporosis (*86*). These processes result in altered bone turnover (*86*). Measurement of turnover is not easy or realistic due to lack of patient acceptance of bone biopsies. Although the individual with progressively worsening bone mineral density scores may have an increasing risk for fracture, the bottom line is that there are no good surrogate measures that allow us to accurately predict fracture risk in individual transplant patients (*90*). Nevertheless, the focus of care should be to prevent bone fractures, using the best means available.

Posttransplant bone disease is a heterogeneous process (*86*). Care must be individualized based on the underlying and preexisting pathology as well as available resources. Patients with diabetes and with preexisting bone disorders and/or with a history of fractures are of more concern for fracture risk (*85*, *86*, *91–93*). Patients with pretransplant treatments that included active vitamin D analogs, steroids, other immunosuppressive drugs, or anticonvulsant medications are at elevated risk for posttransplant bone disease (*94*). Similarly those with a history of immobilization, malnutrition, impaired gonadal status, and musculoskeletal symptoms have more risk (*94*). After transplantation patients with a low GFR, those who receive treatment with glucocorticoids and/or calcineurin inhibitors have persistent hyperparathyroidism, hypercalcemia and hyperphosphotemia, hypophosphatemia, and hypomagnesemia. Those treated with loop

diuretics or that have persistent hypogonadism are also at increased risks for bone disease (*94*). In the evaluation of a patient's bone health, obtaining information about the individual's dietary intake of calcium, menstrual history, thyroid disorders, and smoking history is also important in assessing risk (*51*).

*What Diagnostic Tests at a Minimum Must Be Performed to Screen For or Determine Risk of Fracture?*

- Calcium and phosphorous blood levels should be monitored following transplantation at least monthly for the first 6 months and then every 2 months until the end of the first year and then annually until normal (*68*).
- PTH levels should be monitored at 6 and 12 months and then annually if either the calcium blood level is elevated or a low phosphate level is observed (*68*).

If resources permit, should follow K/DOQI guidelines for level of kidney function (*95*). Those with low phosphorous (<1.0 mg/dL), must be on replacement (either via high $PO_4$ diet or, if diet is ineffective, through supplements and possibly vitamin D). The phosphate level should be monitored until a stable or normal level is observed.

Those with a fracture history must have the following:

- Radiograph
- PTH (if not already done for elevated calcium)
- 25-hydroxy vitamin D level (if not possible to check level, assume it is subtherapeutic)

Prophylaxis against posttransplant fractures must include:

- Promote preemptive transplant to reduce time with pretransplant bone disorders
- Limit steroid usage
- Calcium supplementation
  - 1,000 to 1,500 mg/day for men and premenopausal women
  - 1,500 to 2,000 mg/day for postmenopausal women
- Maintain normal vitamin D levels, if not contraindicated supplement vitamin D
- 1,200 to 2,000 IU/day Ergocalciferol or equivalent
- 0.25 to 1 $\mu$g/day Calcitriol or other active analog (monitor serum calcium)
- Encourage weight-bearing exercise such as walking, but avoid impact exercise such as jogging, especially for patients taking steroids
- Encourage smoking cessation

Treatment of posttransplant fractures must include the following:

- Replete those patients with low 25-hydroxy vitamin D
- For those with elevated PTH, if calcium allows, treatment with active vitamin D
- If hypercalcemia and elevated PTH persists (with no evidence for improvement), consider parathyroidectomy surgery after 1 to 2 years, depending on severity.

**Growth**

Statural growth has a crucial influence on quality of life and self esteem, and global rehabilitation is enhanced by height. Growth assessment and management should be performed in any growing transplant patient. Growth parameters include: height, body weight, body mass index, and head circumference and arm circumference in children less than 3 years of age; bone age and skin fold thickness are optional. Such growth parameters should be monitored every 3 months in children less than 3 years of age, then every 6 months until reaching final height (growth velocity <2 cm per year). These parameters should be plotted on individual growth charts using either Standard Deviation Score (SDS) or centiles, adapted to sex and local standard measurements. The analysis of individual growth profile is better achieved by combining statural height vs. chronological age, height velocity vs. chronological age, and body mass index vs. chronological age. The target final height (H, in cm) is midparental height vs. population norms (girls=$[H_{mother}+H_{father}-13]/2$; boys=$[H_{mother}+H_{father}+13]/2$).

*Growth Determinants*

Impairment of longitudinal growth in children with CKD is multifactorial (*96*). It is mainly due to disturbances in the growth hormone (GH), insulin-like growth factor (IGF), and IGF-binding protein axis.

The pathophysiology of growth in patients with CKD depends on age. During infancy, nutrition (energy and protein intake) and fluid/electrolytes homeostasis (mainly sodium and bicarbonate) are the most important determinants; thyroid function also plays a role. During childhood, growth is mainly under the influence of GH, IGFs, and sex hormones; insulin resistance also plays a role.

Other important growth determinants may contribute to growth retardation at the time of transplantation. These include: chronological age and growth velocity at the time of both CKD and transplantation; primary disease; tubular impairment; and pretransplantation use of steroids. The timing of transplant, including preemptive transplant, may be adapted to chronological age, growth velocity, and other relevant clinical and developmental factors. In addition, drug compliance can affect growth. Noncompliance is based upon physical appearance (hair, acne, striae), conflicts (parents, school, rules), drug side effects (taste, regimen frequency), and depression (often underestimated) (*97*).

*Interventions on Growth*

Growth velocity can be improved by several approaches, including drug compliance, steroid sparing protocols, correction of metabolic acidosis and salt depletion, and improving nutritional status (Table 2).

*Use of Recombinant Human Growth Hormone (rhGH)*

The growth-inhibiting effects of uremia can be overcome by high-dose rhGH; there is a uniformly positive impact of rhGH on growth velocity and final height in CKD compliant children (*96*, *98*). Kidney transplant per se induces moderate catch-up during the prepubertal growth period and selected patients may benefit from rhGH (*99*).

All parameters concerning growth and bone should be assessed and addressed before rhGH is given. RhGH can be started when height is <third percentile for age and sex *or* height velocity is <25th percentile for age and sex (*100*). The recommended dose is 0.05 mg/kg per day (or 1.4 mg/m$^2$ per day) in prepubertal children. This dose can be increased in

**TABLE 2.** Methods to improve growth velocity

- Drug compliance
- Steroid sparing protocols based on daily low dose or alternate-day treatments; withdrawal/avoidance of steroids is under investigation
- Correction of metabolic acidosis, i.e. correct to $CO_2$ above 22 mmol/L
- Correction of salt depletion by giving oral salt supplementation, with a target plasma sodium >135 mmol/L (salt depletion due to diuretics may stunt growth)
- Improving nutritional status
- Controlling excessive protein loss, either by medical therapy or by native nephrectomy
- Investigating other morbidities which may impair growth, such as chronic inflammation and chronic liver, lung or heart disease
- Using rhGH when appropriate

pubertal children before attainment of final height provided the patient fulfills these additional conditions: acceptable nutritional status, medication compliance, and if epiphyses are not fused. RhGH should be maintained until final height.

*Safety of rhGH Therapy*

A transient increase of intracranial pressure can be observed with rhGH therapy. This often responds to holding or decreasing rhGH dose. Serious adverse events have been associated with rhGH therapy including the onset of rejection (*96*, *98*, *100*). PTH and HbA1C should be measured every 6 months under rhGH therapy.

Bone health is an additional requirement for optimizing longitudinal growth in children with CKD. In pediatric posttransplant patients with CKD stages 2 to 5, bone disease should be managed as per K/DOQI pediatric bone guidelines (*95*). Such a management can be improved by avoiding hypophosphatemia by giving oral phosphate, with a target phosphate >1 mmol/L *and* controlling hyperparathyroidism, especially when growth hormone is used. Long-term fluoroquinolone treatment may increase the risk of cartilage damage.

**Reproductive Essentials**

*Contraception*

Contraception should ideally be started before transplantation (*101*, *102*). The same treatment may be continued after transplantation with the caveat that estrogens should be discontinued several weeks prior to the transplant procedure or other surgical procedure where the risk of deep vein thrombosis may be increased.

Oral contraceptive agents and depo-provera may be used. Intrauterine devices may be less effective and require antibiotic administration at the time of placement to decrease the risk for sepsis, endometritis, and pelvic inflammatory disease. Barrier methods such as diaphragms, caps, gels, and condoms are generally less effective because they are not utilized as they should be. Furthermore, diaphragms may be associated with more urinary tract infections.

*Pregnancy*

Pregnancy is possible in women with end-stage kidney disease but is rare until after successful transplantation. Following transplantation approximately 60% of women between age 18 to 49 regain their menstrual cycle and between 2–25% of women of child-bearing age conceive depending upon age, previous treatment for kidney disease, transplant immunosuppression, and social situation. The outcome of the pregnancy for the mother and child is determined by the mother's level of kidney function and blood pressure. Loss of the pregnancy occurs in approximately 30% of kidney transplant recipients (15–20% therapeutic abortion, 10–15% miscarriage). Mothers with a creatinine of <133 uMol/L will deliver a live baby in >90% of pregnancies if the pregnancy continues beyond the first trimester. A creatinine over 133 uMol/L is associated with a live delivery in 75% of pregnancies (*51*, *101–103*). The suggested predelivery management schedule is listed in Table 3.

The average gestational age at delivery is between 34 to 37 weeks. Pregnancies in transplant recipients may be complicated by hypertension (50–70%), preeclampsia (30%), intrauterine growth retardation (IUGR; 20%), and preterm birth (50%). Other risks include anemia, urinary tract infection, diabetes (5–10%), and decreasing maternal kidney function (in those with impaired function at conception). However, the outcome for the baby is usually good even with IUGR if an environment capable of managing the complications of an early delivery is available including a sterile operating room, neonatologists, and an intensive care unit. Vaginal delivery is preferred but Caesarean sections do not appear to carry a higher risk in transplant recipients if performed in a sterile operating room using sterile techniques.

To date an increased rate of congenital malformations has not been noted if the mother is treated with cyclosporine or tacrolimus, azathioprine, and prednisone. However, human fetal abnormalities have been seen with mycophenolate mofetil use although the magnitude of this risk is not known. Likewise there are no conclusive data on the risk of malformations with sirolimus but use of sirolimus during pregnancy is not advised. Medications that must not be used during pregnancy are ACE inhibitors, ARBs, statin medications (especially lipophilic), and trimethoprim-sulfamethoxazole.

The safety of breast-feeding has not been established due to the risk of exposing the child to immunosuppressive agents. However, breast-feeding is not absolutely contraindicated.

Overall, the safest care of the pregnant patient requires the presence of transplant nephrologists, obstetricians with experience taking care of women with kidney disease, dialysis facilities, fetal monitors and ultrasound. The minimum support available to provide basic obstetric care to a transplant recipient should include the items listed in Table 3 and as recommended by the WHO (*104–106*).

*Libido/Fertility*

Libido returns following kidney transplantation in both men and women (*107*). Many men with ESRD without diabetes frequently have erectile dysfunction (ED). Return of male sexual function may take months as the testes resume production of testosterone. Male fertility posttransplantation correlates with the duration of ESRD and may remain decreased following transplantation due to the persistence of abnormal sperm production. If impotence persists after transplantation it may also be due to medications (usually

**TABLE 3.** Advised conditions before conception and necessary prenatal care

| | AST 2005 | EBPG 2002 | KDIGO |
|---|---|---|---|
| Interval | 1–2 years | >2 years | 1 year |
| Kidney function | Creatinine <133 uMol/L | Same | Same |
| Proteinuria | None or minimal | <500 mg/day | <500 mg/day |
| BP | Normal | Normal | Controlled to <130/80 |
| Blood glucose | N/A | Normal | Normal |
| US | N/A | Normal | N/A |
| Rejection history | None within 1 year | No recent | No recent |
| Immunosuppression dosing | Stable | Stable | Stable |
| Care providers | High risk OB and Txp physician | OB w/kidney disease and transplant physician | Most experienced OB available and transplant physician |
| Initial visit frequency | N/A | Q 2–4 wks | Q 4 wks |
| Third trimester visit frequency | N/A | Should be increased | Q 1–2 weeks. Weekly after wk 34 |
| Post partum follow up | N/A | Out to 3 months | Out to 3 months |
| Lab data to monitor | N/A | Q 2–4 weeks | Q 2–4 weeks |
| BP checks | N/A | Daily (self) | At each visit |
| BP target | N/A | N/A | Not above baseline |
| Fetal monitoring | N/A | Q 2 wks 3rd trimester | N/A |
| Fetal US | N/A | Monthly | N/A |

antihypertensives), neuropathy, psychological problems, or vascular impairment. The evaluation starts with questions about nocturnal penile tumescence, if this is not present then a trial of sildenafil may be started if the man is not taking nitrates and does not have coronary artery disease. Treatment of ED may also include different formulations of prostaglandin E1 (topical, intraurethral suppositories, intrapenile injections) or combinations of sildenifil with PGE1. Individuals with testosterone deficiency should be treated with testosterone (topical, injected). If this is not successful then referral to urology is warranted. The use of implantable devices is associated with an increased risk of perineal infection but may be acceptable.

Women often experience a lack of sexual interest when on dialysis (>50%). After transplantation, libido usually improves. Treatment of decreased libido includes antidepressant agents, dehydroenphiandrosterone, transdermal testosterone, or sildenafil; however, these treatments have not been subjected to rigorous investigation in transplant recipients.

## Work Group IV: Graft Maintenance

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It is now well established that kidney transplantation is the treatment of choice for patients with ESRD as it offers better long-term survival and improved quality of life compared to dialysis (*108*, *109*). It is also proven to be more cost effective than dialysis (*110–112*). However, these benefits are not realized in the immediate postoperative period. Therefore, transplant services should be viewed as a long-term commitment. Care of the recipient must be continued for the duration of kidney allograft function, and kidney transplant services should be performed on a regular basis to maintain medical and technical skills of the transplant team. The following general recommendations are applicable to the establishment of a sustainable kidney transplant program.

- Prior to transplantation, potential kidney transplant candidates and living kidney donors require careful evaluation to verify an acceptable health risk, and adequate living conditions, social support and financial resources to sustain themselves in the early postoperative period and in the long-term following the transplant procedure.
- Prior to donation, deceased kidney donors require careful evaluation to determine adequate kidney function to provide a health benefit to the potential recipient and to exclude the existence of cancers or infections that might place the potential recipient's health at an unacceptable risk.
- Following transplantation, recipients require life-long treatment with immunosuppressive medications to prevent rejection of the transplanted kidney.
- Following transplantation, recipients require lifelong surveillance by both physical examination and laboratory testing to detect changes in allograft function at a time when intervention is still likely to succeed, and to ensure adequate and appropriate immunosuppression that is sufficient to prevent rejection, but not so intense as to place the patient at risk for infection, malignancy, or toxicity from the medications themselves.

The focus of this report is on kidney transplant program sustainability. It is not to define the minimal resources necessary to perform a single kidney transplant under marginal or exceptional circumstances. Thus, it may be possible to perform an occasional kidney transplant with fewer resources than those described below.

### Donor and Recipient Selection

The choice of a live versus deceased donor should reflect the balance of risks to the donor and benefits to the

recipient, and the expertise of the transplant team in live donor and deceased donor transplantation (*113–117*). Selection and management of living donors should follow the Amsterdam living donor recommendations (*30*). When a new transplant program undertakes deceased donor kidney transplantation, it should gain experience with low-risk donors, such as previously healthy individuals who weigh over 25 kg, are less than 60 years of age, have suffered brain death, and whose death did not result from infection or cancer. Cold ischemia (preservation) times (CIT) should be under 24 hours.

New transplant programs may wish to focus their initial efforts on young adult recipients without significant comorbid conditions prior to caring for older age recipients. Age and other limitations can be relaxed as experience grows. Transplant candidates should have:

- Psychosocial stability, and the financial, family and community resources necessary to be compliant with medical recommendations
- A low probability of early recurrence of the original kidney disease
- Minimal surgical risk factors
- No recent sensitizing events. A peak panel reactive antibody (PRA) equal to zero is ideal. However, sensitized candidates should be considered for kidney transplantation when an experienced histocompatibility laboratory, capable of performing crossmatches between recipient sera and donor cells and in identifying the specificity of antidonor antibodies, is available to determine a negative crossmatch.

Pediatric transplantation should be initiated only by institutions with expertise in both pediatric surgery and kidney transplantation.

New programs should avoid kidney transplantation when there is a high risk of subsequent transplant failure including:

- Imminent life-threatening illness (i.e., avoid futility)
- Clinically significant donor or recipient comorbidities such as advanced cardiovascular, peripheral vascular, liver or pulmonary disease, HIV, active hepatitis, active pulmonary or systemic tuberculosis, or morbid obesity
- A severely dysfunctional urinary excretory system
- An original kidney disease that is highly likely to recur
- Third or greater kidney transplantation
- Multiorgan transplants
- Difficult psychosocial circumstances, compliance, or communication
- Transplantation across a positive crossmatch or transplantation requiring candidate desensitization
- ABO-incompatible transplantation
- A research protocol that has the potential to increase live donor or recipient risk (*33*, *118*)

**Surgical Infrastructure**

Successful kidney transplantation requires a stable societal and institutional infrastructure including: 24-hour electricity, water, and transportation; a regulated and transparent legal and ethical framework permitting live donor and deceased donor transplantation; and adequate hospital resources to perform major surgery including a clean operating room environment, clean recovery area, and an intensive care unit. The institution must also have available the following capabilities: acute and chronic dialysis, onsite chemistry, hematology and microbiology laboratory services, an onsite pharmacy stocking all necessary medications, onsite radiology and ultrasound departments, and medical, surgical, and support staff trained in kidney transplantation.

Access to medical specialities including surgeons and nephrologists trained in transplantation and immunology, anesthesiologists familiar with the intraoperative management of kidney transplant recipients, pathologists able to read kidney biopsies, and expertise in infectious disease, cardiology and dermatology should be available (*119–123*). These essential services need not all be present in a single institution, but they should be readily accessible to the transplant program on a 24-hour basis. Continuous professional development and education should be provided for all members of the transplantation team and an institutional transparency with mechanisms to monitor quality control and to audit outcomes should be achieved.

**Preoperative Assessment**

*Basic*

It is essential that the preoperative live donor and recipient evaluation include a current electrocardiogram and recent chest radiograph; measurement of serum electrolytes, glucose, blood count, clotting parameters and liver function tests; determination of blood group and human leukocyte antigen (HLA; class I and II) antigen phenotype; identification of the presence of candidate antibody to HLA class I and class II antigens and of a positive recipient antidonor crossmatch (*124*). For potentially fertile females, a pregnancy test should be performed. Preoperative clinical assessment must also be undertaken. Body mass index (BMI) should be calculated. Examinations to exclude potential infectious foci (dental, urine, and skin) and cancer should be performed including a clinical and serological review for the presence of bacterial, viral, and parasitic disease (see Work Group II). Evaluation of the bladder and ureteral function should be performed in cases were obstructive uropathy is suspected, along with an appraisal of arterial and venous iliac vessels and correlation with distal circulation. For patients with a history of distal urinary obstruction or for males with potential prostratic disease, an evaluation of bladder and ureteral function should be undertaken. Assessment of arterial and venous iliac vessels with correlation with distal circulation should be carried out. Preoperative anaesthesiology review is required. Cardiac evaluation should be performed when there are signs, symptoms, or a history of cardiac disease as well as for members of high-risk populations such as diabetics (see Work Group I). Similarly, abdominal imaging and evaluation for peptic ulcer and colonic diseases should be performed when there are signs, symptoms, or a history of gastrointestinal disease, or indications based upon health maintenance considerations.

Patient education regarding the nature of the transplant surgery, hospitalization, posttransplant care, and the necessity for diligent compliance with medication and follow-up regimens, plus assessment of psychosocial status

and individual and community resources are necessary to sustain health following transplantation (*64*, *125–130*).

*Desired*

It is desirable that the transplant program have the ability to offer, as part of the preoperative assessment: peak expiratory flow and oxygen saturation exercise tolerance testing, cardiac stress imaging, Doppler ultrasound of iliac vessels, urodynamic assessment, thoracic computer-assisted tomography, abdominal and pelvic imaging, pulmonary function testing, and assessment of common coagulopathies (*51*, *131–133*).

*Advantageous*

It is advantageous for the evaluating program to have available for preoperative assessment the ability to provide on indication: coronary angiography, extended coagulopathy assessment, contrast imaging of iliac vessels, and kidney biopsy of the recipient (*134–136*).

**Operative Resources**

*Basic*

It is essential that the intraoperative live donor and recipient care include the capacity to provide: a surgical and anaesthesiology team trained in transplantation surgery; a setting with instrumentation for vascular, urological and general surgery; surgical facilities that are compliant with WHO and the Centers for Disease Control and Prevention guidelines; appropriate choice of solution for allograft perfusion and storage; intraoperative monitoring of blood pressure, pulse oximetry, electrocardiogram, central venous pressure, urinary output and temperature; infection prophylaxis; thrombosis prophylaxis; and urinary stents (*137–142*).

*Desired*

It is desirable that an institution providing surgical care to live donors and recipients have the ability to offer on indication the use of immunological induction agents (see Induction Immunosuppression, next page) in high-risk populations; intraoperative blood flow measurement; surgical teams trained in pediatric and vascular surgery and in urinary tract diversion procedures; operating rooms or an area within the operating rooms that is used only for "clean" surgery; and resources for performing two simultaneous clean and complex surgical procedures to facilitate live donor transplantation.

*Advantageous*

It is advantageous that an institution providing surgical care to live donors and recipients have the capacity to offer a surgical team trained in donation from nonheartbeating donors, machine perfusion kidney preservation, facilities for laparoscopic donor nephrectomy, and urgent preimplantation biopsy of donated kidneys.

**Immediate Postoperative Care**

*Basic*

It is essential that the postoperative live donor and recipient care include: monitoring of blood pressure and urinary output; availability of central venous pressure monitoring; access to acute dialysis on indication; competence in dialysis access surgery; accessible Doppler ultrasound; capacity to perform, process and interpret kidney biopsies; medications necessary to prevent and treat rejection; ability to monitor blood levels of immunosuppressive drug; prophylaxis, detection and treatment of common nosocomial and posttransplant infections; prophylaxis against peptic ulcer and gastroesophageal reflux diseases; and the availability of postoperative care when necessary in an isolation ward setting.

*Desired*

It is desirable that the postoperative live donor and recipient care include: access to interventional radiology, advanced histopathology (electron microscopy, immunofluorescent staining, etc.), renal scintigraphy, respiratory therapy, availability of monoclonal or polyclonal antibody for treatment of rejection, and access to multidisciplinary teams with experience in the management of posttransplant complications.

*Advantageous*

It is advantageous for postoperative live donor and recipient care to include the capacity for a repeat cross match (*143*), plasmapheresis, administration of hyperimmunoglobulins, monitoring and treatment of patients that present special posttransplant problems (such as HIV, hepatitis C virus, hepatitis B virus, Kaposi sarcoma, and PTLD), a dedicated transplant unit, and the availability of a clinical pharmacologist as part of the transplant team.

**Immunosuppression**

Immunosuppressive medications must be used for the duration of allograft function. Most recipients will need two or three oral immunosuppressant medications, taken one or two times daily to prevent transplant rejection. There are three principal classes of oral immunosuppressant medications: calcineurin inhibitors (cyclosporine and tacrolimus), antiproliferative agents (azathioprine, mycophenolate mofetil, mycophenolate sodium, sirolimus and everolimus), and corticosteroids. To limit toxicity, these medications are given in combinations at doses that would be insufficient to provide adequate immunosuppression from any individual agent when taken alone, but that in combination allow for optimal kidney transplant outcomes. In addition, many patients will benefit from a short but intensive course of intravenous antilymphocyte antibodies or anti-interlekin-2 receptor antibodies at the time of their transplant surgery to "induce" a partially immunosuppressed state.

**Maintenance Immunosuppression**

A wide range of regimes provide a desired outcome (i.e., a graft survival rate that exceeds 90% at 1 year). Most common are three-drug regimens consisting of a calcineurin inhibitor in combination with an antiproliferative agent and a corticosteroid. Three-drug regimens are used with or without induction therapy with antilymphocyte antibodies (*144–146*). Immunosuppressive regimens can be individualized in response to clinical circumstances: allograft dysfunction, allograft histology, immunosuppressive drug toxicities, and patient comorbidities and/or immunological risks (*147–159*).

Work group participants reviewed the use of a two-drug regimen consisting of azathioprine and corticosteroids

without a calcineurin inhibitor for transplantation as a "life-saving" exercise in a severely resource-constrained setting. However, outcomes from using only azathioprine and corticosteroid in any situation other than live-donor kidney transplantation from a two-haplotype matched sibling were noted to be poor (60% 1-year graft survival at best). This regimen was deemed unacceptable by current standards for mismatched live or deceased donor kidney transplantation (*160–164*).

Generic medications are available in different parts of the world. With the high prices of proprietary immunosuppressive agents, it is tempting for medical insurance providers, governments, and other health funding agencies to reduce costs by substituting a generic agent. The use of generic drugs has been encouraged by the WHO to facilitate the more equitable delivery of health care, including kidney transplantation, in developing nations. However, it is essential that generic products meet the strict standards of quality and interchangeability with the originator products. Administrative guidance regarding the establishment of standards for bioequivalence is available on the United States Food and Drug Administration Office of Generic Drugs website (http://www.fda.gov/cder/ogd/index.htm). More stringent criteria were recommended by the American Society of Transplantation conference on immunosuppressive drugs and the use of generic immunosuppressants (*162*).

Furthermore, as there have been problems with the production, distribution, and consistency of generic drugs, it is recommended that national regulatory authorities ensure adequate standards are met prior to the release of new generic medications within their country, possibly in the future as part of a prequalification scheme with the support of the WHO (*163*, *164*). Alternatively, developing countries could improve quality by employing only generics that have won regulatory approval in the United States or European Union. As a principle, it is advisable to maintain a single product in an individual patient, especially when that patient has stable allograft function. The cost of treating episodes of rejection and or allograft loss that result from the use of drugs that are not interchangeable may well exceed any savings made by converting to a generic agent.

**Induction Immunosuppression**

Immunosuppressive drug trials have repeatedly demonstrated that antilymphocyte or anti-interlekin-2 receptor antibodies used in the peritransplant period are capable of reducing the incidence of early acute cellular rejection episodes. This apparent benefit has to be balanced, in the case of depleting antilymphocyte antibodies, with slightly increased risks of posttransplant infections and posttransplant lymphoproliferative disorders (*165–171*).

Although there is some registry data suggesting a long-term allograft survival benefit from the use of induction agents, trial data does not support this in the era of calcineurin inhibitors in combination with antimetabolites. It is therefore not an essential requirement that induction agents be used in kidney transplant recipients. Induction may, however, be desirable to reduce the incidence of early rejection in high-risk patients or for those suffering from delayed graft function and calcineurin inhibitor induced nephrotoxicity. Furthermore, recent trials of steroid avoidance have largely been conducted with the addition of induction antibodies. It may therefore be regarded as advantageous to use antibody induction therapy to achieve safe steroid avoidance (*172–176*).

**Monitoring of Immunosuppression**

In the early posttransplant period, monitoring of the recipient's immunosuppressive drug blood levels is necessary to achieve the desired therapeutic effects and to avoid the toxic side effects. The achievement of specific target drug levels at defined time points posttransplant is associated with better immunological control and reduced side effects of therapy. It is highly recommended that therapeutic drug monitoring, especially of calcineurin inhibitor and mTOR-I drug levels, be available as an essential requirement for the establishment of a kidney transplant program. Measurement of mycophenolate blood concentrations may also be useful (*177–182*).

**Posttransplant Follow-Up**

*Short-Term Follow-Up*

It is essential that transplant centers ensure that patients have access to follow-up care delivered by appropriately trained individuals. Professional organizations or accrediting bodies should define and test the minimal knowledge required for care of kidney transplant recipients. Kidney function must be monitored repeatedly during the lifetime of the graft for the detection of acute rejection, nephrotoxicity from medications, recurrent disease, vascular or urological complications, chronic allograft nephropathy, and other causes of acute and chronic kidney failure. It is essential that early outpatient monitoring of allograft function should take place no less frequently than twice weekly during the first month; weekly during the second month, every 2 weeks during the third and fourth month, and monthly during the fifth through twelfth month. Clinical circumstances will dictate more frequent evaluations for most patients. Laboratory monitoring should include determination of serum creatinine, electrolytes and glucose, urinary protein excretion, and immunosuppressive drug levels. Medical examinations should assess the recipient's general health status, vital signs, wound healing, and compliance with medication regimens. It is essential that all transplant programs have rapid access to diagnostic kidney biopsies on indication. It is desirable to have other modalities available to monitor transplant function such as urine collections for measurement of creatinine clearance and urine protein excretion, ultrasound with Doppler, and radionucleotide scans. It is potentially advantageous to have the capacity to perform screening (protocol) biopsies (*51*, *68*, *64*, *183*, *184*).

*Mid- and Long-Term Follow-Up*

Recommended frequencies and content of mid-term (second to fifth posttransplant year) and long-term follow-up (greater than 5 years after transplantation) are summarized in Tables 4 and 5. Assessment after the first posttransplant year necessarily includes the evaluation of both the kidney allograft and the patient. If kidney function or the clinical condition of the recipient changes, it may be necessary to modify the frequency and choice of tests performed. Patients with a

**TABLE 4.** Timing and frequency of clinical and laboratory examinations beyond the first year after kidney transplantation

| | Basic | | Desired | | Potentially advantageous | |
|---|---|---|---|---|---|---|
| Year post transplant | Clinical exams | Labs | Clinical exams | Labs | Clinical exams | Labs |
| Second year | Every 3 months | Every 3 months | Every 2 months | Every 2 months | Every 1 month | Every 1 month |
| Third through fifth year | Every 6 months | Every 3 months | Every 4 months | Every 2 months | Every 2 months | Every 1 month |
| After the fifth year | Every 12 months | Every 6 months | Every 6 months | Every 3 months | Every 4 months | Every 2 months |

**TABLE 5.** Laboratory evaluation of the kidney transplant recipient

| Basic | Desired | Potentially advantageous |
|---|---|---|
| • Creatinine (Cr)<br>• Estimated Glomerular Filtration Rate (eGFR)<br>• Potassium<br>• Blood Glucose<br>• Hemoglobin<br>• White Blood Cell Count<br>• Urinalysis<br>• Therapeutic Drug Level Monitoring (TDM) of Immunosuppressive Medications | All of the tests listed as Basic Laboratory Evaluations, plus:<br>• Fasting Blood Glucose<br>• Electrolytes<br>• Calcium<br>• Phosphorous<br>• Magnesium<br>• Liver function tests, Blood Lipid Profile<br>• Quantification of urinary protein (if any) | All of the tests listed as Desired Laboratory Evaluations, plus:<br>• Urinary and Serum Polyoma Virus (BKV)<br>• Isotopic/non-isotopic Glomerular Filtration Rate<br>• Kidney Transplant Biopsy<br>• Kidney Transplant Ultrasound<br>• Kidney Radionuclear Scans |

These tests are described as those required for evaluation of kidney function.
Any deterioration of kidney function or very low GFR prompts additional tests.

failing kidney transplant should be under the care of a nephrologist (Tables 4 and 5) (*51*, *68*, *64*, *185*, *186*).

**Kidney Allograft Dysfunction**

Stable transplanted kidneys may not have "normal function." Therefore, the diagnosis of acute or chronic allograft dysfunction must be based upon the trend in kidney function in comparison to that individual's historical reference, typically the recipient's best level of kidney function during the first year after transplantation. Allograft dysfunction may be characterized as a clinically meaningful deterioration in one or more functional parameters (such as serum creatinine, measured or calculated glomerular filtration rate (GFR), or urinary protein excretion) and/or by histological criteria demonstrated on kidney biopsy. A proposed consensus definition for the early detection of allograft dysfunction is either a rise in serum creatinine of ≥0.4 mg/dL or a 25% reduction of the recipient's best level of kidney function following transplantation. Lesser increases in serum creatinine may frequently occur and depending on clinical context, also require investigation and intervention (*187*).

Despite stable kidney function and normal urinalysis, biopsy results may demonstrate significant pathology. The diagnostic sensitivity and specificity of deteriorations in functional parameters will be greater if results from other tests (biopsy, ultrasound, and nuclear imaging studies) are available. Interventions must be rapidly implemented to treat reversible causes of allograft dysfunction and to protect remaining kidney function (Table 6) (*188–194*).

**Nonadherence**

Nonadherence to the prescribed regimen of immunosuppressive medications and to other recommendations for laboratory and clinical follow-up is an important cause of kidney transplant failure. The prevention, identification, and treatment of nonadherence are integral to the monitoring of allograft function and the care of the patient. To prevent nonadherence, it is essential to identify patients at risk; minimize, simplify, and maximize the tolerability of medication schedules; plan for coverage of health care costs; and provide pre- and posttransplant education, counseling, medication cards, and laboratory handbooks as aids. It is desired to establish a long-term and consistent relationship between the recipient and the transplant team including access to a social worker, transplant nurse, financial counselor, pharmacist, psychologist, and patient support group, and to encourage the use of a

**TABLE 6.** Causes of chronic kidney transplant dysfunction after the first posttransplant year

1. Chronic allograft nephropathy (CAN)
2. Medication-induced nephrotoxicity
3. Recurrent or de novo glomerular disease
4. Late acute rejection
5. Hypertensive or diabetic nephropathy
6. Transplant glomerulopathy
7. Obstructive uropathy
8. BK (Polyoma) virus nephropathy
9. Transplant renal artey stenosis
10. Malignancy in the transplanted kidney
11. Hyperfitration

The specific cause of chronic kidney transplant dysfunction must be determined. The list describes common, but not all, etiologies that should be considered.

patient medication diary. It is potentially advantageous for the transplant institution to have access to specialty pharmacy involvement within the transplant program, and to new patient adherence monitoring technologies such as personal digital assistants and medication-event-monitoring systems. It is important to customize interventions specifically to the root causes of the recipient's nonadherence (*195–197*).

**Registries and Data Collection**

Systematic collection of data on donors, transplant candidates, and recipients is essential so that transplant centers can monitor patient and allograft outcomes, and for transparency and quality improvement. Establishment of registries must be performed within national legal requirements governing medical confidentiality. Successful registries have mechanisms to promote user friendliness, to collect data on a routine submission schedule, for data validation and security, and for operational security and back-up systems. It is important for the integrity and transparency of national and local transplant systems that waitlist and posttransplant outcomes be evaluated and reported on a regular basis, and that results are available to staff, administrators, regulators, and the public.

## Work Group V: Chronic Kidney Disease and the Kidney Transplant Recipient

**Gregorio T. Obrador, Robert S. Gaston, Lawrence G. Hunsicker: Co-Chairs**

A recent position statement of the Kidney Disease: Improving Global Outcomes (KDIGO) initiative concluded that all kidney transplant recipients should be considered to have CKD, irrespective of GFR or presence or absence of markers of kidney damage (*63*). Work Group V supports this recommendation due to several empiric observations: a) kidney transplantation is a treatment, not a cure, for end-stage kidney disease; b) restoration of GFR by the transplanted kidney does not erase the preexisting burden related to CKD, as evidenced in the persistently high mortality of transplant recipients compared to the general population (*198*) and the impact of dialysis duration prior to transplantation as an adverse risk factor for graft and patient survival (*199–201*); and c) the histology of kidney allografts, even those with excellent GFR, indicates the presence of parenchymal kidney disease (*202*, *203*).

Serial monitoring of allograft function has always been part of managing kidney transplant recipients, traditionally by following serum creatinine levels. Recent trends in CKD care have emphasized the inadequacy of serum creatinine alone in defining GFR and categorizing severity of kidney disease (*1*). Likewise, in transplant recipients, serum creatinine levels often do not accurately reflect true GFR, contributing to incorrect drug dosing and delay in recognizing CKD-associated comorbidity (anemia, bone disease, etc.) that may be amenable to intervention (*63*, *201*). Work Group V agreed that serial determination of GFR should be the norm in posttransplant care, and is most easily estimated by utilizing one of several available formulae to calculate estimated GFR (eGFR). At least two studies in transplant recipients indicate that eGFR more closely correlates with disease burden and outcome after transplantation than serum creatinine levels (*204*, *205*).

Many different formulae are available to estimate GFR from serum creatinine levels, each with its own advantages and disadvantages (*206*). The National Kidney Foundation K/DOQI Guidelines on CKD recommend using the abbreviated Modification of Diet in Renal Disease formula:

$$\text{eGFR (mL/min/1.73 m}^2) = 186 \times [\text{serum creatinine (mg/dL)} \times 0.0113]^{-1.154} \times \text{age (years)}^{-0.203} \ (\times 0.742 \text{ if female}), \times (1.210 \text{ if African American})$$

Alternatively, the Cockroft-Gault formula can be used (*1*, *63*). Unfortunately, these formulae have limitations in patients with near-normal kidney function and have not been validated in certain populations and ethnic groups (*63*). Five recent studies indicate that these and other available formulae may be less precise in transplant recipients than in the nontransplant CKD population (*188*, *206–209*).

Possible reasons for this difference include derivation of formulae in persons other than recipients, alterations in muscle mass due to acute rejection and steroid use in this population, and nonstandardization of serum creatinine measurements in different laboratories. Despite these limitations, the formulae provide reasonable estimates of GFR and are useful for decision making in the routine care of kidney recipients. Work Group V found evidence supporting and refuting the validity of multiple equations, with no consensus to support any specific formula over previous K/DOQI recommendations.

In some situations it may be necessary to measure GFR with direct clearance techniques. These include extremes of age and body size, severe malnutrition or obesity, diseases of skeletal muscle, quadriplegia or paraplegia, vegetarian diet, rapidly changing kidney function, prior to dosing drugs with significant toxicity that are excreted by the kidneys, and pregnancy (*1*). In the opinion of the Work Group, direct measurements should also be used in clinical trials in which precise quantification of allograft GFR is essential. However, these methods require standardization among centers, and thus, eGFR may be the only feasible option.

Assessment of kidney function should also include serial measurements of urinary protein excretion. In kidney transplant recipients, proteinuria is an indicator of adverse outcomes, and is associated with chronic rejection, drug toxicity (cyclosporine or tacrolimus), recurrent disease, and/or transplant glomerulopathy (*210*). Although albuminuria is a sensitive marker of kidney damage and a risk factor for progression of CKD and cardiovascular disease in nontransplant CKD patients, its significance in transplant recipients is not yet established (*63*). Accordingly, although anemia may be clearly linked to declining kidney function, a number of variables unique to transplant recipients also impact hemoglobin levels (*70*). These include acute rejection, medications (immunosuppressive, antiviral, and antimicrobial agents), infections, malignancy, hemolytic-uremic syndrome, and hemolytic anemia associated with minor ABO incompatibility. Thus, while most clinicians follow hemoglobin levels closely in kidney recipients, using those levels as a marker of kidney function in transplant recipients may be problematic.

Work Group V found no reason to exclude transplanted CKD patients from the staging guidelines proposed by NKF-K/DOQI and modified by KDIGO (*1*, *63*). Application of this clas-

**TABLE 7.** A clinical action plan based on CKD stage as recommended by the NKF KDOQI™ Clinical Practice Guidelines on CKD should be followed, with the following modifications (+T represents with transplant):

| CKD stage | Definition | Clinical action plan | |
|---|---|---|---|
| | | Non-Tx CKD (−T) | Tx-CKD (+T) |
| 1 | Kidney damage or post-Tx with normal or ↑ GFR (≥90 ml/min) | Diagnosis and treatment<br>Treatment of comorbid conditions<br>Slowing progression CVD risk reduction | Diagnosis and treatment of CKD<br>Treatment of comorbid conditions<br>Slowing progression<br>CVD risk reduction |
| 2 | Kidney damage or post-Tx with mild ↓ GFR (60–89 ml/min) | Estimating progression | Estimating progression<br>Evaluating and treating complications due to CKD prior and after Tx |
| 3 | Moderate ↓ GFR (30–59 ml/min) | Evaluating and treating complications | Manage Tx specific issues |
| 4 | Severe ↓ GFR (15–29 ml/min) | Preparation for kidney replacement therapy | If evidence of CKD progression, preparation for kidney replacement therapy (patient and family education, dialysis access, preemptive Tx) |
| 5 | Kidney failure (<15 ml/min) | Replacement (if uremia present) | Replacement (if uremia present) |

**TABLE 8.** Recommendations of CKD work group

- All kidney transplant recipients (KTRs) should be considered to have chronic kidney disease (CKD);
- Kidney function of KTRs must be assessed serially by estimated GFR (eGFR), albuminuria and hemoglobin levels;
- Serum creatinine is not sufficient for assessment of kidney function;
- Serum creatinine based estimates of GFR (eGFR) should be used for assessment of kidney function;
- Different formulae can be used for calculation of eGFR in KTRs;
- Measurement of GFR by direct or indirect clearance methods may be necessary in some clinical situations;
- KTRs can be staged by the severity of CKD assessing the eGFR, as recommended by the NKF-K/DOQI Clinical Practice Guidelines on CKD.

sification is supported by two recent reports of an association between CKD stage and burden of disease in kidney recipients. In the first study, Canadian investigators found the mean number of complications (hypertension, calcium and phosphorus abnormalities, anemia, hypoalbuminemia, acidosis, and lipid abnormalities) to progressively increase from 1.1 in CKD stage 1 to 2.7 in CKD stage 5 (*204*). Subsequently, Marcen and colleagues also reported an independent association between CKD stage and 10-year risk of graft failure (*205*).

However, beyond the clinical action plans previously recommended for the management of nontransplant CKD, Work Group V advocates two significant modifications. First, there is no empiric evidence that stepwise interventions recommended for stages 1 to 3 in nontransplant CKD should not be implemented in all kidney transplant recipients. The rationale supporting application of CKD staging to all with a functioning transplant (the preexisting disease burden associated with CKD) also supports continuing all recommended interventions for stages 1 to 3, regardless of eGFR. Second, recognizing that some transplant recipients with eGFR within stage 4 parameters may maintain stable graft function for many years, preparation for reinstitution of dialysis or a new transplant should commence only when accompanied by evidence of progressive decline in eGFR (Tables 7 and 8). This recommendation is based on evidence that rate of progression is highly variable, may be slower in transplant recipients, and is influenced by risk factors not present in nontransplant CKD (*75*, *194*, *211*).

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