Kidney transplantation is the treatment of choice for patients with ESRD. Despite improvements in short-term patient and graft outcomes, there has been no major improvement in long-term outcomes. The use of kidney allografts from expanded-criteria donors, polyoma virus nephropathy, underimmunosuppression, and incomplete functional recovery after rejection episodes may play a role in the lack of improvement in long-term outcomes. Other factors, including cardiovascular disease, infections, and malignancies, also shorten patient survival and therefore reduce the functional life of an allograft. There is a need for interventions that improve long-term outcomes in kidney transplant recipients. These patients are a unique subset of patients with chronic kidney disease. Therefore, interventions need to address disease progression, comorbid conditions, and patient mortality through a multifaceted approach. The Kidney Disease Outcomes Quality Initiative from the National Kidney Foundation, the European Best Practice Guidelines, and the forthcoming Kidney Disease: Improving Global Outcomes clinical practice guidelines can serve as a cornerstone of this approach. The unique aspects of chronic kidney disease in the transplant recipient require the integration of specific transplant-oriented problems into this care schema and a concrete partnership among transplant centers, community nephrologists, and primary care physicians. This article reviews the contemporary aspects of care for these patients.
progression rates (reported as the mean slope of creatinine clearance or eGFR) have consistently been reported in the range of -1.4 to -2.4 ml/min per yr (16,18,19), some patients lose function more rapidly (5 to 20 ml/min per yr), whereas others stabilize their GFR (18,19). The rate of loss of function does not seem to be associated with baseline function of the transplant. Finally, morbidity and mortality rates increase significantly from stage 1 to stage 5 CKD in kidney transplant recipients (15,16). At the same level of kidney function (stage 3), death rates are higher in kidney transplant recipients compared with nontransplant patients with CKD (16). Such data suggest that despite a slower decline in kidney function over time, kidney transplant recipients have marked differences in comorbidity and mortality rates compared with their CKD counterparts. As such, the impact of a 1-ml/min per yr decline in GFR has a greater impact on long-term outcomes in kidney transplant recipients.

Kidney transplant recipients return to a higher level of physical functioning compared with their counterparts on dialysis. Given this, it is important to recognize that immunosuppression and graft function are only one component of their health care. We propose that the objective should be a systematic integration of transplant, CKD, and general health care. The NKF Kidney Disease Outcomes Quality Initiative or K/DOQI (http://www.kidney.org/professionals/kdoqi/guidelines.cfm), the European Best Practice Guidelines (EBPG; http://www.ndt-educational.org/guidelines.asp), and the forthcoming International Kidney Disease Improving Global Outcomes (KDIGO; http://www.kdigo.org/welcome.htm) clinical practice guidelines should be generalized to this unique subset of individuals who have CKD (17,20). This article reviews the contemporary aspects of care for these patients.

Kidney Allograft Function

Reduced kidney allograft function is associated directly with poor graft and patient outcomes (9,10,15,16,21). A close follow-up of kidney allograft function (monthly to every 2 mo in stable cases) therefore is recommended in all of these patients. Transplant recipients whose graft is stable after 2 yr may decrease the frequency of their actual visits to every 3 to 4 mo but are encouraged to continue more frequent laboratory testing. Traditionally, allograft function has been assessed by measurement of serum creatinine values and urinalyses. The Modification of Diet in Renal Disease (MDRD) estimation formula for GFR in patients with CKD (22) provides a low bias and high precision (2.7 and 10.4 ml/min per 1.73 m², respectively) in predicting GFR in kidney transplant recipients (23). The MDRD GFR calculator is available online at http://www.kidney.org/professionals/kdoqi/index.cfm. The advantage of using GFR or creatinine clearance estimation formulas to determine the stage of CKD allows one to implement a clinical action plan that is consistent with CKD guidelines (17).

Cystatin C is a novel and more sensitive marker of kidney function in kidney transplant recipients that also may predict successfully cardiovascular outcomes (24–26). Whether one uses the serum creatinine, cystatin C, or eGFR formula, it still is crucial to screen for graft dysfunction at regular intervals. At no time after transplantation can one assume that the allograft is entirely stable (27). As with native kidney diseases, late allograft dysfunction may be secondary to acute or chronic processes.

Table 1. Causes of late allograft dysfunction

<table>
<thead>
<tr>
<th>Acute Renal Failure in the Late Posttransplantation Period</th>
<th>Late Allograft Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal decreased effective circulating volume volume contraction congestive heart failure liver failure renal transplant artery stenosis drugs CNI ACE-I, ARB NSAID</td>
<td>Chronic allograft dysfunction CAN CNI nephrotoxicity polyoma (BK) virus nephropathy recurrent/de novo glomerular disease chronic rejection (immunologic) acute rejection Patient death with functioning graft</td>
</tr>
<tr>
<td>Renal urinary tract infection and/or pyelonephritis acute rejection acute interstitial nephritis acute tubular necrosis recurrent/de novo glomerular disease</td>
<td>Renal CVD infectious complications malignancies other</td>
</tr>
<tr>
<td>Postrenal hydronephrosis</td>
<td></td>
</tr>
</tbody>
</table>

*ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAN, chronic allograft nephropathy; CNI, calcineurin inhibitor; CVD, cardiovascular disease; NSAID, nonsteroidal anti-inflammatory drugs.

Acute Kidney Injury or Failure

Acute kidney injury or kidney failure in the late posttransplantation period may be divided into basic categories (Table...
Table 2. Factors involved in the development/progression of CANa

<table>
<thead>
<tr>
<th>Modifiable Risk Factors</th>
<th>Nonmodifiable Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonimmune</td>
<td>Nonimmune</td>
</tr>
<tr>
<td>CNI toxicity</td>
<td>early delayed graft function</td>
</tr>
<tr>
<td>hypertension</td>
<td>donor age or poor graft quality</td>
</tr>
<tr>
<td>dyslipidemia</td>
<td>donor genetic factors</td>
</tr>
<tr>
<td>diabetes</td>
<td>donor/recipient size mismatch</td>
</tr>
<tr>
<td>proteinuria</td>
<td>Immune</td>
</tr>
<tr>
<td>oxidative stress</td>
<td>HLA mismatch</td>
</tr>
<tr>
<td>chronic hypoxia</td>
<td>previous sensitization (high PRA)</td>
</tr>
<tr>
<td>CMV infection</td>
<td>previous rejection</td>
</tr>
<tr>
<td>Immune</td>
<td></td>
</tr>
<tr>
<td>chronic rejection</td>
<td></td>
</tr>
<tr>
<td>subclinical rejection</td>
<td></td>
</tr>
<tr>
<td>patient noncompliance</td>
<td></td>
</tr>
<tr>
<td>suboptimal</td>
<td></td>
</tr>
<tr>
<td>immunosuppression</td>
<td></td>
</tr>
</tbody>
</table>

aCMV, cytomegalovirus; PRA, panel of reactive antigens.

1). The principal difference is the possibility of acute rejection. Therefore, the assessment and management of acute injury or failure in these patients should include the history (including adherence with immunosuppressive drugs) and physical examination, serum creatinine, blood urea nitrogen and electrolytes, blood levels of calcineurin inhibitors (CNI) and/or sirolimus, urinalysis, urine electrolytes, urine indices, and ultrasonographic assessment of the allograft. Volume depletion, drugs, and urinary tract infections constitute the largest proportion of causes of acute injury or failure late after transplantation, and management is similar to that undertaken in native kidney disease. It is important to move readily toward treatment, especially for urinary tract infections, because late infections (after at least 12 mo of allograft function) are associated with a reduction in graft survival (28). Acute rejection is a relatively rare entity in this period. Its diagnosis requires a biopsy, preferably at the transplant center, and should be considered when the above diagnostics are negative or the creatinine fails to return to the previous baseline. In general, any change in creatinine ≥0.3 mg/dl (25 μmol/L) needs to be evaluated promptly.

Acute Rejection

Organ Procurement and Transplantation Network data from April 2005 demonstrated that acute rejection rates within 1 yr averaged 14.7% for the 2001 to 2003 period. After the first posttransplant year, acute rejection rates are less prevalent. Not all rejection episodes carry the same negative prognostic impact. The available literature shows that recurrent rejection (5,29), rejection episodes that occur in the setting of potent immunosuppression (30), episodes that occur beyond month 6 (29–32), or episodes with a lack of functional response to therapy (5) have the worst impact on graft survival.

Chronic Allograft Dysfunction

Chronic allograft dysfunction after the first year posttransplantation is secondary to chronic allograft nephropathy (CAN), drug toxicity, recurrent and/or de novo glomerular diseases, polyuria (BK) infections, and late acute rejection (Table 1) (13,14).

CAN. CAN is a condition of altered kidney allograft function at least 3 mo posttransplantation, independent from acute rejection, CNI toxicity, recurrent or de novo disease, or immunologic features that are suggestive of chronic rejection (C4d+ staining in the pericapillary tubules, intimal fibrosis with inflammatory cells, and duplication of glomerular basement membrane) (33–39). The term CAN is preferred to chronic rejection because the latter implies an immunologic mechanism of injury (33,37). However, immune and nonimmune features (including chronic CNI toxicity) often coexist. Therefore, the term CAN practically defines a histologic diagnosis that is characterized by tubular atrophy, interstitial fibrosis, and fibrous intimal thickening with variable glomerular lesions (37–39). Accompanying clinical features include a gradual elevation in serum creatinine, hypertension, and mild to moderate proteinuria (1 to 3 g/24 h) (13,18). These nonspecific pathologic findings result from a proinflammatory milieu in which the level of injury from both immune and nonimmune insults exceeds the capacity of tissue repair (13,38). CAN lesions are present in up to 94% of grafts at 12 mo posttransplantation (13,38,40) along with the noted clinical features.

CAN is associated with significant morbidity and mortality and is the main reason for returning to dialysis after transplantation (38). It is important to appreciate that early and late posttransplantation events play a role in the progression of CAN (Table 2).

CNI Nephrotoxicity. Cyclosporine A (CsA) and tacrolimus play a significant role in progressive kidney dysfunction after transplantation (40–43). Nearly all kidney allografts display histopathologic signs of chronic CNI toxicity by 10 yr posttransplantation (40). CNI manifest nephrotoxicity in several ways (41,44). They can mediate acute nephrotoxicity via reversible afferent arteriolar vasoconstriction, often associated with subtle volume depletion. This is a common cause for transient increases in serum creatinine and needs to be followed up in a timely manner after improved volume repletion. CAN is associated with significant morbidity and mortality and is the main reason for returning to dialysis after transplantation (38). It is important to appreciate that early and late posttransplantation events play a role in the progression of CAN (Table 2).

Antibody-Mediated Rejection. Both cellular and humoral processes contribute to the pathogenesis of chronic allograft rejection (39). Antibody-mediated rejection (AMR) includes all forms of rejection that involve donor-specific antibodies (DSA) against HLA antigens, ABO isoagglutinins, or non-HLA antigens (i.e., anti-endothelial antibodies) and is defined by the presence of DSA in the recipient’s serum and C4d deposition in the peritubular capillaries as a marker of antibody-mediated...
activation of the complement cascade (58). The chronic form of AMR occurs after the first year posttransplantation and is more indolent than its early counterpart (58,59). It has been shown that one third of patients with CAN develop de novo anti-HLA antibodies compared with only 4% in kidney transplant recipients with normal allograft function (60). Likewise, the presence of C4d deposition in the peritubular capillaries has been identified in one third of patients with chronic allograft dysfunction (61). Injury to peritubular capillaries can result progressively in vascular dropout, interstitial fibrosis, and significant scarring of the kidney allograft (62). Clinically, many of these patients present with significant proteinuria that results from transplant glomerulopathy, a specific form of glomerular lesion that is considered to be the result of immune injury.

A large, multicenter, collaborative study of >2231 kidney transplant recipients that was undertaken to determine the frequency of anti-HLA antibodies in renal transplant recipients with functional transplants (63) showed the presence of anti-HLA antibodies in 20% of patients (63). In this study, 478 patients who developed anti-HLA antibodies had a significantly higher rate of allograft loss at 2 yr than 1753 control patients without detectable antibodies (15.1 versus 6.8%; P < 0.0005) (64). Although these findings suggested a role for anti-HLA antibodies as predictors of allograft loss, this predictive value was NS for recipients with serum creatinine levels <2 mg/dl (177 μmol/L) (64).

In summary, the current literature supports AMR as a contributor to chronic allograft dysfunction through an indolent and progressive process. Notwithstanding this evidence, United Network for Organ Sharing data show that 23% of HLA-identical kidneys are lost after 10 yr of transplantation, demonstrating that other factors—including non-HLA antibodies and nonimmunologic processes—also play an important part in the pathogenesis of chronic allograft injury (65). Although there is a role for the monitoring of HLA antibodies in kidney transplant recipients, routine screening of DSA in kidney transplant recipients is not currently recommended. High-risk patients (patients with AMR, sensitized patients with PRA >80%, or patients who undergo desensitization protocols) with increased serum creatinine levels (>2 mg/dl) may benefit from DSA screening and subsequent adjustment of immunosuppression. Many issues remain unsolved concerning the monitoring of anti-HLA antibodies, including the choice of diagnostic techniques (i.e., complement-based versus solid-phase assays), the frequency of testing, and the interpretation of antibody data in the absence of allograft dysfunction.

**Recurrent and/or De Novo Disease.** Glomerulonephritis (GN) is responsible for kidney failure as a primary or contributing cause in 20 to 40% of patients who receive a transplant (66). The incidence rate of GN recurrence posttransplantation ranges between 6 and 19.4% and may result in graft loss in approximately 8.4% of cases (66–68). Because recurrence implies that the patient has biopsy-proven GN in both native and transplanted kidneys (a condition not always fulfilled), many studies group de novo and recurrent GN (66). Considering these limitations, any form of GN may recur at any time posttransplantation (66–68). However, focal and segmental glomerulosclerosis, membranoproliferative GN (MPGN), hemolytic uremic syndrome, and membranous glomerulonephritis (MGN) are more likely to recur within the first posttransplant year, whereas pauci-immune GN, IgA nephropathy, fibrillary GN, lupus nephritis, and diabetes recur typically after the first year (66–68). Principal causes of de novo GN in renal allografts include transplant glomerulopathy, hemolytic uremic syndrome, membranous glomerulonephritis, and MPGN (69). The last two have been associated with hepatitis C virus (HCV) infection, although MPGN (with or without cryoglobulinemia) is more commonly described (70,71). HCV infection may be associated more frequently with glomerular disease in the renal allograft compared with native kidneys possibly because of increased HCV RNA titers that result from immunosuppression (72). Recurrent/de novo GN is associated overall with a two-fold increased risk for graft loss (66–68). It therefore is important to suspect this condition in individuals with proteinuria, hematuria, and a slow decline in allograft function after the first year. The diagnostic approach should include a biopsy with electron microscopy and immunohistology studies in addition to appropriate serologic evaluation (66–68).

Treatment options for recurrent/de novo GN remain limited and tend to be supportive, especially after the first posttransplant year. Because these patients are already on immunosuppressive agents, management focuses on the removal of the underlying cause if identified (infection, drugs, or malignancy) and improved control of BP, proteinuria, and dyslipidemia. The benefits of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) in native kidney disease-mediated proteinuria have not been demonstrated as extensively in the transplant population, yet these agents have important antiproteinuric effects that can improve allograft survival in individuals with significant proteinuria (73). Cytoxic medications such as cyclophosphamide may have limited benefits for specific posttransplantation entities, e.g., MPGN (74), recurrent anti–glomerular basement membrane glomerulonephritis (75), and focal and segmental glomerulosclerosis (76); but their use has to be gauged carefully and other antiproliferative immunosuppressive drug dosages may have to be altered to decrease untoward effects. When graft loss ensues, retransplantation remains an option. However, the risk for recurrence typically increases with the number of transplants (67,77).

**Polyoma Virus Infection.** Polyoma viruses are ubiquitous DNA viruses that infect a variety of animals, including humans. BK virus, a human polyoma virus, was described initially in a transplant recipient (11,78). It has a remarkable tropism for the genitourinary tract. BK virus–induced nephropathy is recognized as an important cause of late allograft failure. The reported incidence of allograft failure has ranged from 15 to 50% in affected individuals (11,79–81). Unfortunately, there are no clinical features that are unique to BK virus infection. There often is an unexplained rise in serum creatinine, asymptomatic hematuria, ureteral stenosis, and/or subacute kidney failure as a result of interstitial nephritis (11,79–81). Diagnosis can be made by biopsy and urine cytology with identification of characteristic cytopathologic changes. Addi-
tional data suggest that assessment and monitoring of serum PCR for viral DNA and viral load may be helpful as an adjunct diagnostic and monitoring test (11,79–82). Unfortunately, specific antiviral therapy for BK nephritis does not currently exist. Clinical trials have suggested efficacy with low-dose cidofovir (0.25 to 0.33 mg/kg every 2 to 3 wk intravenously) (81,83) as well as leflunomide (83,84). Because BK virus infection reflects the overall state of immunosuppression regardless of the choice of CNI or adjuvant therapy (82), the basis of treatment is to decrease immunosuppressive medications (11,79–84). This is another excellent example of the importance of transplant biopsy to investigate an otherwise unexplained, persistent increase in the serum creatinine.

Proteinuria
The evaluation of kidney function in kidney transplant recipients should include routine measurement of urinary protein excretion. Urine protein to creatinine ratios are a reliable substitute for 24-h urine collection (85). Proteinuria may be defined as >200 mg/g creatinine and microalbuminuria >30 mg/g creatinine on spot urine samples (86). The incidence of proteinuria in kidney transplant patients ranges between 10 and 25% (27). Proteinuria from the native kidneys normally resolves within the first 1 to 10 wk posttransplantation (85). The three most common causes of persistent proteinuria after kidney transplantation are CAN, recurrent glomerulonephritis, and drug-related nephrotoxicity (27,68,87–89). Renal vein thrombosis and reflux nephropathy are less common causes of proteinuria after transplantation (Table 3).

Proteinuria reflects the severity of the underlying glomerular and tubulointerstitial injury. Presumably, proteinuria also contributes to ongoing transplant dysfunction and fibrosis through putative mechanisms that involve aberrant proximal tubule protein uptake and tubular cell toxicity (90,91). It is striking that despite the evidence that demonstrates the significance of proteinuria in native kidney–mediated disease, only recently has proteinuria been examined in depth in kidney transplantation. In general, it is an independent risk factor for disease progression, graft failure, and patient death after kidney transplantation (27,86–90,92). It is interesting that proteinuria may be a clinical surrogate for predicting outcomes in conjunction with medication changes. Urinary protein excretion >800 mg/d is the only independent predictor of negative outcomes in patients with chronic allograft dysfunction, converted from CNI to sirolimus (50). Transplant patients therefore should be evaluated regularly for proteinuria every 6 to 12 mo after the first year posttransplantation (27). Because of the cost-effectiveness of these laboratory tests, we suggest that a spot urine protein/creatinine be obtained along with a urinalysis at each actual clinic visit.

Several studies suggest that ACE-I and ARB can have a beneficial effect in prolonging allograft survival, especially in transplant recipients with CAN and proteinuria (73,93–95). It is important to strive for BP control (<130/80 mmHg and potentially lower if proteinuria is >1 g/24 h) (96) and to look for possible adverse effects when using these agents. Although up to a 30% increase in serum creatinine levels after the initiation of antiproteinuric therapy may be acceptable (97), careful monitoring of kidney function, hematocrit (Hct), and serum potassium levels is warranted as these drugs may result in acute kidney failure, anemia, and hyperkalemia in kidney transplant recipients (14).

Cardiovascular and Peripheral Vascular Disease
It is important to recognize that these entities are intertwined in terms of pathogenesis and outcomes. CVD is the principal cause of death in kidney transplant recipients (Figure 2) (9,10,12,96,98,99). Mortality related to cardiovascular causes accounts for nearly one quarter (23%) of all-cause mortality by 15 yr posttransplantation (100). Of note, even a nonfatal posttransplantation myocardial infarction may predict future graft failure and death (101). Peripheral vascular disease (cerebral vascular disease and lower extremity vascular disease) afflicts at least 15% of all kidney transplant recipients in a 10- to 15-yr period posttransplantation (100).

Both traditional and nontraditional cardiovascular risk factors, including the concurrent presence of peripheral vascular disease, contribute to CVD morbidity and mortality in kidney transplant recipients (Table 4) (96,102). The NKF K/DOQI work group on CVD concluded that modifiable risk factors should be targeted for intervention in these patients (Table 4) (96). Traditional CVD risk factors are shared risk factors for both CKD and CVD. Therefore, addressing each should have a dual impact.

Table 3. Proteinuria after kidney transplantation

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Less common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN</td>
<td>renal transplant vein thrombosis</td>
</tr>
<tr>
<td>recurrent/de novo disease</td>
<td>renal transplant artery stenosis</td>
</tr>
<tr>
<td>native disease (usually resolved by third month posttransplantation)</td>
<td>drugs</td>
</tr>
<tr>
<td>urinary tract infections</td>
<td>reflux</td>
</tr>
</tbody>
</table>

Figure 2. Cardiovascular mortality in kidney transplant recipients. Reprinted with permission from reference (98).
Symptomatic patients should undergo prompt functional and/or invasive testing even if angiography is required. Intravenous hydration with bicarbonate (103) or saline, oral N-acetylcysteine (104), and/or ascorbic acid (105) and withholding CNI, ACE-I, and ARB for 12 h before angiography likely will reduce the risk for contrast-induced nephropathy in the allograft. Currently, there is insufficient evidence to recommend for or against routine periodic screening for asymptomatic CVD in kidney transplant recipients (27). However, we believe that individuals who are at high-risk, e.g., two or more traditional cardiac risk factors or a history of a pretransplantation cardiovascular event or a positive pretransplantation screening test may benefit from noninvasive stress imaging every 1 to 2 yr after transplantation.

Hypertension

Both the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high BP and the K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in CKD defined normal BP as <120/80 mmHg (97,106). With this definition, the incidence of posttransplantation hypertension ranges up to 80%. The causes of posttransplantation hypertension are varied and include CNI use, prednisone, preexisting hypertension, primary kidney disease, kidney transplant artery stenosis, and graft dysfunction (100,107). Systolic and diastolic hypertension both are independent risk factors for graft and patient loss in kidney transplant recipients (108–110). Surprisingly, no large, randomized, controlled studies have demonstrated improved long-term outcomes by decreasing BP in kidney transplantation, yet a recent analysis of the Collaborative Transplant Study showed that lower systolic BP (SBP), even after the first posttransplant year, was associated with improved graft and patient survival (111). Patients whose SBP was >140 mmHg at 1 yr posttransplantation but controlled to ≤140 mmHg by 3 yr had significantly improved long-term graft outcome compared with patients with sustained high SBP (relative risk 0.79; 95% confidence interval 0.73 to 0.86; P < 0.001) (111).

As part of best medical practice, it therefore is appropriate to treat posttransplantation hypertension to target BP values whenever possible (27,97,106,112). Both the seventh report of the Joint National Committee and K/DOQI guidelines recommended a target BP of 130/80 mmHg in patients with CKD, although only K/DOQI specifically addresses BP targets in renal transplant recipients (97,106). The American Society of Transplantation (an older guideline) recommends target BP levels of <140/90 mmHg (27), and the EBPG recommend mandatory BP control to levels of <130/85 mmHg in kidney transplant patients without proteinuria and <125/75 mmHg in proteinuric patients (112).

Lifestyle modifications are necessary and should include weight reduction, a DASH (Dietary Approaches to Stop Hypertension) eating plan, dietary sodium reduction, and physical activity (97). All classes of antihypertensive drugs have been used in transplant patients, yet no preferred agents are offered by any of the guidelines. Initial efficacy studies suggested that calcium channel blockers might have greater benefit in achieving BP control and limiting graft loss (107,113), but it has not been shown that calcium channel blockers have a clear benefit over ACE-I on long-term kidney allograft function and survival (112). Furthermore, these drugs may be involved in the development of edema and CsA-induced gingival hyperplasia (114). On the basis of the effect of ACE-I and ARB in slowing the rate of progression in patients with CKD, several groups have used these agents in CAN, proteinuria, and underlying heart disease posttransplantation (73,93–95,115–117). These studies have dissipated initial concerns regarding the safety of ACE-I and ARB because no significant hyperkalemia or acute changes in kidney function were observed. However, caution is advised in individuals with preexisting hyperkalemia, anemia, and suspected transplant renal artery stenosis (118). The use of diuretics in hypertensive renal transplant patients may be effective and often is necessary in combination therapies. These drugs may result in hypercalcemia, hypernatremia, hyperuricemia, and impaired glucose/lipid metabolism in a high-risk group of patients.

In summary, a target BP of ≤130/80 mmHg with lower BP levels (≤125/75 mmHg if proteinuria >1 g/d) is recommended in renal transplant recipients (Figure 3). ACE-I and ARB may be used safely as preferred agents in patients with proteinuria (urine protein/creatinine ratio >200 mg/g), tolerating up to a 35% rise in baseline serum creatinine levels. Combination therapy frequently is required to control posttransplantation hypertension (96,97,106,110); regardless of the agents selected, a close follow-up (weekly for 2 wk, then monthly) of BP, serum creatinine, electrolytes, and hemoglobin (Hb) levels (in case of ACE-I and ARB use) is recommended. It is advised to avoid making changes in BP medications concomitant (within 1 wk) with changes in immunosuppression. This may complicate the differential diagnosis in case of a rapid rise in serum creatinine levels.

Dyslipidemia

Dyslipidemia, alone or as part of the metabolic syndrome, is an established risk factor for CVD mortality in kidney transplant recipients (27,119–121), as it is in the general population. Post-

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### Table 4. Traditional and nontraditional risk factors for CVD in renal transplant recipients

<table>
<thead>
<tr>
<th>Traditional Risk Factors</th>
<th>Nontraditional Risk Factors</th>
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</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Decreased kidney function</td>
</tr>
<tr>
<td>Male gender</td>
<td>CNI</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Anemia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Oxidative stress.</td>
</tr>
<tr>
<td>Low HDL</td>
<td>Advanced glycation end products</td>
</tr>
<tr>
<td>High LDL</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Menopause</td>
<td>Obesity</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Thrombogenic factors</td>
</tr>
</tbody>
</table>

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transplantation hyperlipidemia affects 60 to 80% of patients (122) and is associated with immunosuppressive treatment, including sirolimus, corticosteroids, and CsA (121–123). Other factors, such as preexisting familial dyslipidemia, obesity, kidney dysfunction, proteinuria, and diabetes, also contribute to posttransplantation hyperlipidemia (121,124). Retrospective studies have reported posttransplantation dyslipidemia as a risk factor for long-term graft loss (125). However, the Assessment of Lescol in Renal Transplant (ALERT) trial, the only randomized, double-blind, placebo-controlled study to examine the role of a statin on renal end points, found no significant effect of fluvastatin on kidney transplant outcomes (126). In a post hoc analysis of this trial, fluvastatin significantly decreased the incidence of myocardial infarction and cardiac death (127). Other studies have shown similar findings in that statins can improve patient survival by an average of 24% among kidney transplant recipients (128).

The evaluation and treatment of posttransplantation dyslipidemia should be based on the National Cholesterol Education Program III and the NKF K/DOQI clinical practice guidelines (119,121). Dyslipidemia in kidney transplant recipients should be evaluated at baseline, 2 to 3 mo after a change in treatment, and at least annually thereafter (121). Recommended goals are target LDL, non-HDL cholesterol, and triglyceride levels of <100, 130, and 150 mg/dl, respectively (121). Treatment options include modification of the immunosuppressive regimen when possible, therapeutic lifestyle changes, statins, fibrates, niacin, and bile acid sequestrants (121).

All statins can provide a 30 to 40% reduction in LDL cholesterol levels. Patients who require maximal LDL cholesterol lowering may be treated with atorvastatin or simvastatin, whereas patients with low HDL cholesterol may have a greater advantage from simvastatin use and those with elevated triglycerides may benefit from high-dose atorvastatin. The final choice of statins should be left to the judgment of the treating physician. For the treatment of hypertriglyceridemia, particularly in patients who are treated with sirolimus, gemfibrozil may be the fibric derivative of choice (121). Although nicotinic acid derivatives also could be used, fibric acid derivatives are better tolerated (121). Bile acid sequestrants such as cholestyramine, colestipol, and colesuvelam hydrochloride alter the bioavailability of immunosuppressants and may also increase triglyceride levels (121). Ezetimibe was used recently alone and in combination with statins to reduce LDL cholesterol in a small-size study with renal transplant patients (129). However, larger clinical trials are required to establish the safety and the efficacy of this drug in kidney transplantation. Antilipemic drugs may have significant interactions between the classes and with immunosuppressant agents. Statins and fibrates interact with CNI and may result in hepatitis, myositis, and rhabdomyolysis (121,124). The prevalence of these untoward effects is minimal in our contemporary era of immunosuppression in the absence of high-dose fibrate or statin therapy and with close monitoring.

In summary, adult renal transplant recipients with hypertriglyceridemia (triglycerides ≥300 mg/dl, or 5.65 mmol/L) may be treated with fibrates, and statins can be used for LDL cholesterol levels of ≥100 mg/dl (2.59 mmol/L; Figure 4). Treatment of proteinuria and other causes of secondary dyslipidemia, along with therapeutic lifestyle changes including diet and physical activity, always should be combined. It monitoring of treatment efficacy and observing for clinical and biologic signs of myositis and hepatitis with most current antilipemic agents are recommended.

**Diabetes**

New-onset diabetes after transplantation (NODAT) is defined using the definition of diabetes and impaired glucose tolerance by the World Health Organization and the American Diabetes Association (www.diabetes.org) (130,131). Fasting plasma glucose levels ≥126 mg/dl (7 mmol/L) or 2-h plasma glucose levels ≥200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test defines diabetes (130,131). NODAT has a high incidence in kidney transplant recipients (up to 25%) and significantly decreases patient and graft survival (132–135), and its prevalence increases continuously with time. Immunosuppressive therapy with tacrolimus, older recipient age, deceased-donor status, hepatitis C, rejection episodes, black race, and higher body weight all are independent risk factors for NODAT (Table 5) (132,135,136).
The International Consensus Guidelines on New-Onset Diabetes after Transplantation recommended management strategies to reduce onset and complications are available on the International Diabetes Federation web site (http://www.idf.org) (131). Regular evaluation for diabetic retinopathy, nephropathy, and neuropathy should be performed, and appropriate measures should be taken. Therapy for all kidney transplant recipients with diabetes should be directed at achievable targets, including BP/130/80 mmHg, fasting plasma glucose/126 mg/dl, glycosylated Hb/6.5g/dl, urine protein:creatinine ratio/200 mg/g, and LDL/100 mg/dl (131,137).

In summary, NODAT has been identified as one of the most important factors associated with reduced graft function and patient and graft survival. International Consensus Guidelines on New-onset Diabetes after Transplantation recommend a multifaceted approach of weight control, diet and exercise, oral agent mono- or combination therapy and insulin use for tight glycemic control (Figure 5) (131). Sulfonylureas, meglitinides, biguanides, thiazolidinediones, and -glucosidase inhibitors all may be used depending on the individual characteristics of the patient and risk for possible side effects (Figure 5) (131,137). Proteinuric, dyslipidemia, hypertension, and anemia should be treated accordingly.

Anemia

The American Society of Transplantation defines anemia as Hb levels of <13 g/dl (Hct of 42%) for male patients and <12 g/dl (Hct of 37%) for female patients (27). The NKF K/DOQI clinical practice guidelines define anemia as Hb levels <12 g/dl (Hct of 37%) for male patients and <11 g/dl (Hct of 33%) for premenopausal women and prepubertal patients (138). Anemia is a common complication after kidney transplantation, with an incidence approximating 30 to 40% (139–141). It may result from inadequate erythropoietin production; iron deficiency; malignancies; oxidative stress/inflammation; hemolytic and uremic syndrome; and viral infections, including CMV and Parvovirus B19 infections (Figure 6) (139–141). Although late (>1 yr posttransplantation) anemia has been reported as an independent risk factor for cardiovascular morbidity and mortality in this patient population (143–145), there is insufficient evidence at present as to whether aggressive anemia management can improve outcomes. Pending the results of prospective, randomized trials to determine optimal Hb/Hct levels in kidney transplant recipients, the K/DOQI recommendations for the management of anemia in patients with CKD may be the best guideline (138).

In the late posttransplantation period, Hb/Hct levels should be checked monthly. Anemia workup should be started for Hb levels <12 g/dl, and treatment with erythropoietin-stimulating agents (ESA) should be started for Hb <11 g/dl. Target recommended Hb (Hct) should be the same as in patients with CKD (138), i.e., between 11 (33%) and 12 g/dl (36%), pending the results of prospective, randomized trials. The current recommended subcutaneous dose of epoetin- in dialysis patients is 80 to 120 IU/kg per wk in two to three divided doses (138). In renal transplant recipients with anemia, ESA may be dosed

**Table 5. Risk factors for NODAT**a

<table>
<thead>
<tr>
<th>Recipient characteristics</th>
<th>Donor</th>
<th>Transplant era (after 1995)</th>
<th>Tacrolimus use</th>
<th>HLA mismatch</th>
<th>Acute rejection</th>
<th>HCV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>older age (&gt;45 yr)</td>
<td></td>
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<tr>
<td>higher body mass index (≥30)</td>
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<td>black race</td>
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<tr>
<td>family history of diabetes</td>
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<tr>
<td>Hispanic ethnicity</td>
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<tr>
<td>education (no college degree)</td>
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<tr>
<td>deceased donor</td>
<td></td>
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<td></td>
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<tr>
<td>male gender</td>
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</tbody>
</table>

aHCV, hepatitis C virus; NODAT, new-onset diabetes after transplantation.

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**Figure 5.** Diabetes management after the first posttransplant year.

**Figure 6.** Common causes of posttransplantation anemia. MMF, mycophenolate mofetil; AZA, azathioprine; CMV, cytomegalovirus; TMA, thrombotic microangiopathy.
weekly and their dose changed monthly if needed. If the rise in 
Hct after ESA therapy has been <2% during a 2- to 4-wk 
period, then the ESA dose should be increased by 50% (138). 
Conversely, if Hct levels increase >8% or if the Hb/Hct exceeds 
the target Hb/Hct, then the weekly dose should be decreased 
by 25%. Abrupt discontinuation of ESA therapy may result in 
a collapse of erythropoiesis. Iron supplementation (oral/intra-
venous) is required for transferrin saturation ≤20% and/or fer-
ritin levels ≤100 ng/ml (138).

In summary, posttransplantation anemia is a prevalent com-
pliation and an independent risk factor for cardiovascular 
morbidity and mortality in kidney transplant recipients. Anem-
ia workup should be initiated for Hb levels <12 g/dl, and 
treatment should be targeted to a goal Hb between 11 and 12 
g/dl. This goal may be achieved by the removal of causal 
agents (Figure 6), oral/intravenous iron supplementation, and 
ESA (138,146–149).

Bone Metabolism and Disease

Almost all kidney transplant recipients have some degree of 
osteodystrophy (disorders of bone remodeling and modeling) 
that persists after kidney transplantation (27,150–153). The in-
cidence of osteoporosis (bone mineral density ≤2.5 SD below 
the young adult mean value or T score) approximates 60%, and 
it results in significant morbidity and mortality, including avas-
cular necrosis and fractures (27,150,151). Maximum bone loss 
occur within the first 3 to 6 mo posttransplantation and con-
tinues during the later stages at a slower rate. Etiologic features 
include treatment with corticosteroids and CNI, previous os-
teodystrophy, persistent hyperparathyroidism, hypogonadism, 
metabolic acidosis, and smoking (150,151).

Current management recommendations are based on the 
available clinical trials and extrapolation from findings in pa-
ients with CKD (151,152,154,155). The cornerstone of these 
recommendations is regular follow-up of serum calcium, phos-
phorus, and intact parathyroid hormone levels and annual (at 
least during the first 3 yr posttransplantation) assessment of 
bone mineral density with dual energy x-ray absorptiometry 
scan of the lumbar spine and the dominant hip. Treatment 
strategies to reduce bone loss include testosterone/estrogen 
replacement when appropriate, elemental calcium and vitamin 
D, phosphate binders, correction of metabolic acidosis, weight-
bearing exercise, and oral or intravenous bisphosphonates 
(151,152,154,155). Although these strategies result in the pre-
vention of bone loss, a recent meta-analysis of clinical trials that 
used bisphosphonates, vitamin D analogues, calcitonin, and 
hormone replacement therapy showed no benefit from any 
treatment to reduce the incidence of fractures in kidney 
transplant recipients (156). Despite recommendations for the 
early use of bisphosphonates (152), these antiresorptive agents 
present a clear risk for adynamic bone disease (157) and should 
be used cautiously in patients with impaired kidney function 
after the first year.

The management of tertiary hyperparathyroidism (HPTH) 
after transplantation also may be challenging. The EBPG for 
renal transplantation recommend that individuals with tertiary 
HPTH be observed for 1 yr after transplantation whenever 
possible to allow for a spontaneous involution (158). After the 
first year, persistent HPTH may be treated by surgical parathy-
roidectomy (159), although this procedure may result in de-
creased kidney allograft function through mechanisms that 
remain to be defined (160,161). Recently, calcimimetic cinacal-
cet was used to normalize posttransplantation hypercalcemia in 
patients with persistent HPTH (162,163). This drug may present 
a reasonable alternative to surgical parathyroidectomy. How-
ever, its safety and effectiveness need to be examined in larger 
clinical trials.

Infections

Infections remain the second most common cause of death in 
kidney transplant recipients (9,10,12,13,27,164). The risk for 
infection in these patients is determined primarily by the in-
tensity of exposure to potential pathogens and the net state of 
imunosuppression (165). Overall, the most prevalent oppor-
tunistic infections are viral, and CMV is the primary virus 
involved. However, a host of community-acquired and oppor-
tunistic bacterial, viral, and fungal infections may occur at 
different rates depending on the period after transplantation.

After the first posttransplant year, the majority of patients 
benefit from good allograft function and are maintained on 
minimal immunosuppression. Community-acquired respira-
tory infections are the principal cause of infectious complica-
tions, as in the general population. Opportunistic infections are 
uncommon in this setting except when there is intense expo-
sure to environmental pathogens (165). In a group of patients 
with chronic, progressive viral infections (CMV, Epstein-Barr 
virol, papillomavirus, HBV, or HCV), signs of progressive 
organ damage may be observed (liver or skin cancer or retinitis 
with CMV). Finally, a small proportion of individuals may 
receive increased immunosuppression for acute rejection epi-
isodes. These patients are at high risk for severe opportunistic 
infections, including Pneumocystis carinii, Listeria monocytogenes, 
Nocardia asteroides, Cryptococcus neoformans, and aspergillus 
(165).

To reduce the burden of infection-related morbidity and 
mortality, the American Society of Transplantation has devel-
opled infectious disease guidelines for the prevention and man-
agement of infectious complications of solid-organ transplant-
tion (166). In addition, guidelines on vaccinations, drug 
interactions with anti-infective agents, and strategies for safe 
living after organ transplantation are available on the American 
Society of Transplantation web site (http://www.a-s-t.org/
mobile/index.htm). Briefly, patient vaccination status should 
be reviewed at the first clinic visit, and a vaccination strategy 
should be developed, keeping in mind that live vaccines are not 
given after transplantation and that patients, close contacts, 
and family members should receive injectable influenza vaccine 
yearly (inhaled influenza vaccine should not be given to trans-
plant recipients or family members). Pneumococcal polysaccha-
ride vaccine should be administered before transplantation and 
repeated every 3 to 5 yr after initial vaccination. Vaccination 
series should be restarted approximately 6 mo after transplant-

tion need appropriate counseling and vaccinations before their trip (167).

In brief, infection and rejection are the two ends of the net state of immunosuppression in kidney transplant recipients. A primary goal is the prevention and/or effective treatment of infection. After the first year posttransplantation, most common infections are community-acquired respiratory infections. In subgroups of patients who have chronic viral infections or are receiving increased immunosuppression for late rejection episodes, there is greater risk for malignancies and opportunistic infections. Close monitoring of these patients is required for early diagnosis of complications. Preventive strategies are necessary and encompass counseling and vaccinations.

Malignancies

Posttransplantation malignancies are a major cause of mortality in kidney transplant recipients (10,14,99). These individuals have a significantly increased risk for malignancies compared with age-matched healthy control subjects and even patients who have ESRD and are on the waiting list for a transplant (27,168–170) (Figure 7). General and more transplant-specific factors contribute to the increased incidence of malignancies in this patient population. These include age, smoking, immunosuppression, and chronic viral infections (169–171).

The relative risk for cancer depends on the type of malignancy. It ranges from a two- to three-fold increase for common malignancies such as lung, prostate, breast, and colon to up to a 100-fold increase for entities such as Kaposi’s sarcomas, posttransplantation lymphoproliferative disease and nonmelanomatous skin cancers (168–170) (Figure 7).

After the first posttransplant year, kidney transplant recipients should undergo annual or biannual skin examination. Age-appropriate annual prostate-specific antigen measurements, fecal occult blood testing, digital and rectal examinations, breast examination and mammography, and colonoscopy are indicated as in the nontransplant patient. Unique screening may include hepatobiliary ultrasound and serum alpha-fetoprotein measurements (history of HBV or HCV) as well as cystoscopy (history of cyclophosphamide use; Table 6) (27,169). In addition to specific antitumor therapy, treatment strategies for posttransplantation malignancies include decreasing or modifying the immunosuppressive regimen (169,172,173). The antiproliferative characteristics of sirolimus may have a salutary impact on the treatment of some of these malignancies. In a recent report, regression of cutaneous Kaposi’s sarcoma was observed after a switch from a CsA mycophenolate mofetil regimen to a regimen based on sirolimus in 15 kidney transplant recipients (173). Sirolimus use has also been associated with decreased incidence of cancer (including skin cancers) in the first 2 yr posttransplantation (174).

In summary, with the growing number of kidney transplant recipients, the prevention, early diagnosis, and treatment of posttransplantation malignancies remain an important challenge to both the transplant and the primary care communities (Figure 7, Table 6). The development of any malignancy should mandate contact with the transplant center to coordinate the overall approach to the patient, including tapering of immunosuppression.

Obesity and Metabolic Syndrome

Overweight and obesity, defined by a body mass index >25 and 30 kg/m², respectively, present a major quandary after kidney transplantation (159). Similar to the trend in the general population, 60% of current kidney transplant recipients are overweight or obese at the time of transplantation, representing a 116% increase from 1987 (175). A significant number of patients gain additional weight after transplantation: The average weight gain in the first posttransplant year was reported recently to be approximately 3 kg (176). Both posttransplantation weight gain and obesity are associated with decreased long-term allograft and patient outcomes (176–180). Although it

**Figure 7.** Posttransplantation malignancies. EBV, Epstein-Barr virus; HPV, human papillomavirus; HBV, hepatitis B virus; HBC, hepatitis C virus; NHL, non-Hodgkin’s lymphoma; Skin (NM), skin cancer (nonmelanomas).
The metabolic syndrome (MS) is a condition of impaired glucose and insulin metabolism, overweight and abdominal fat distribution, mild dyslipidemia, and hypertension. It is prevalent in the US population (age-adjusted prevalence 25%) and is associated with subsequent development of type 2 diabetes and CVD (185,186). The working definition of the National Cholesterol Education Program Expert Panel Adult Treatment Panel III defines MS as a condition with three or more of the following: (1) Waist circumference >102 cm in men and 88 cm in women, (2) serum triglyceride level ≥150 mg/dl (1.69 mmol/L), (3) HDL cholesterol level <40 mg/dl (1.04 mmol/L) in men and 50 mg/dl (1.29 mmol/L) in women, (4) BP ≥130/85 mmHg, and (5) serum glucose level ≥110 mg/dl (6.1 mmol/L) (187). Data to address the role of MS in kidney transplantation are scarce (120,188,189). It seems that up to 63% of renal transplant recipients experience MS as a condition with three or more of the following: (1) Waist circumference >102 cm in men and 88 cm in women, (2) serum triglyceride level ≥150 mg/dl (1.69 mmol/L), (3) HDL cholesterol level <40 mg/dl (1.04 mmol/L) in men and 50 mg/dl (1.29 mmol/L) in women, (4) BP ≥130/85 mmHg, and (5) serum glucose level ≥110 mg/dl (6.1 mmol/L) (187).

Table 6. Screening for malignancies after the first year posttransplantation

<table>
<thead>
<tr>
<th>Screening Frequency</th>
<th>30 Days</th>
<th>6 Months</th>
<th>12 Months</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and lip Anogenital</td>
<td>Self-exam</td>
<td></td>
<td>Physical</td>
<td></td>
</tr>
<tr>
<td>Uterine cervix</td>
<td></td>
<td></td>
<td>Physical, pelvic</td>
<td></td>
</tr>
<tr>
<td>Sarcomas (including Kaposi’s)</td>
<td>High-risk ethnic groups</td>
<td></td>
<td>Pelvic, PAP smear ± biopsy</td>
<td></td>
</tr>
<tr>
<td>PTLD</td>
<td>Self-exam</td>
<td></td>
<td>Skin, conjunctiva, oropharyngeal mucosa ± biopsy</td>
<td></td>
</tr>
<tr>
<td>Hepatic (HCV and HBV patients)</td>
<td>Self-exam</td>
<td></td>
<td>Physical α-fetoprotein</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td>Physical, mammogram</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td>Rectal, PSA</td>
<td></td>
</tr>
</tbody>
</table>

*HBV, hepatitis B virus; PAP, Papanicolaou; PSA, prostate-specific antigen; PTLD, posttransplantation lymphoproliferative disease.

remains unknown whether it is the higher incidence of cardiovascular comorbid conditions that affects graft outcomes or obesity-specific issues (hyperfiltration and glomerulopathy), most studies report a higher likelihood of premature death and graft loss in obese kidney transplant recipients (176–181). Female, young, black, low-income patients with type 2 diabetes are at the highest risk for posttransplantation obesity (175,182). The EBPG considers obesity as a risk factor for increased CVD after transplantation and recommends lifestyle measures to address the epidemic (179). However, this complex problem requires a multifaceted approach and a combination of diet, exercise, minimization of steroid therapy, and psychologic support often is needed. Gastric bypass surgery may be a safe and effective means for achieving significant long-term weight loss and relief of comorbid conditions after transplantation (183,184). This approach should be reserved for resistant cases and requires close collaboration with the transplant center.

In summary, weight gain, obesity, and MS are prevalent after the first posttransplant year. Although there is an association between these conditions and decreased long-term patient and allograft outcomes, it remains unknown whether there is underlying causality. A multifaceted approach that includes a combination of diet, exercise, minimization of steroid therapy, psychologic support, and gastric bypass surgery may be required to address this growing epidemic in renal transplant patients.

Quality of Life and Nonadherence

Kidney transplantation produces greater improvements in quality of life (QOL) than does dialysis (190,191). A meta-analysis of prospective studies that evaluated QOL before and after kidney transplantation found consistent improvement among the posttransplantation population (192). When specific domains of QOL were examined, 78% of the studies found improvement in physical functioning, 85% in mental health, and 63% in social functioning (192). However, despite such evidence, many kidney transplant recipients experience adverse effects that affect life satisfaction and QOL (193–195). Sixty-six percent of kidney transplant recipients reported easy bruising/slow wound healing, 61% noted adverse effects related to sexuality, and >50% related problems secondary to changes in physical appearance (193,194).

Transplant recipients are required to take immunosuppressive treatment for the rest of their lives, and, unfortunately, adherence to this regimen often is suboptimal. This may have dramatic effects on graft and patient outcomes because up to 91% of nonadherent patients may experience graft loss or death (196). A recent meta-analysis of 325 studies that were published from 1980 to 2001 and reported the frequency and impact of nonadherence in adult renal transplant recipients showed that a median (interquartile range) of 22% (18 to 26%) of recipients were nonadherent and that the odds for graft failure increased seven-fold (95% confidence interval 4 to 12%) in nonadherent patients compared with adherent patients (197). Psychosocial and financial barriers often contribute to poor adherence with medications; however, these are not the only factors: A 1-yr posttrans-
plantation compliance rate of only 48% was reported in a free multidrug immunosuppressive clinic (198).

**Conclusions**

Kidney transplantation is the optimal treatment for patients with ESRD; however, despite improvements in short-term patient and graft outcomes, there has been no major improvement in long-term outcomes. There is a need for collaboration among the transplant center, community nephrologists, and primary care physicians who are involved in the long-term care of these patients to enhance these outcomes. A number of public resources that provide clinical practice guidelines for the treatment of these patients are available on the Internet (Table 7). Prevention and early management of disease progression, cardiovascular complications, infections, and malignancies constitute the cornerstone of this collaborative effort to extend life span and allograft function.

**Acknowledgments**

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