REVIEW

Primary Care of the Renal Transplant Patient

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There has been a remarkable rise in the number of kidney transplant recipients (KTR) in the US over the last decade. Increasing use of potent immunosuppressants, which are also potentially diabetogenic and atherogenic, can result in worsening of pre-existing medical conditions as well as development of post-transplant disease. This, coupled with improving long-term survival, is putting tremendous pressure on transplant centers that were not designed to deliver primary care to KTR. Thus, increasing numbers of KTR will present to their primary care physicians (PCP) post-transplant for routine medical care. Similar to native chronic kidney disease patients, KTRs are vulnerable to cardiovascular disease as well as a host of other problems including bone disease, infections and malignancies. Deaths related to complications of cardiovascular disease and malignancies account for 60–65% of long-term mortality among KTRs. Guidelines from the National Kidney Foundation and the European Best Practice Guidelines Expert Group on the management of hypertension, dyslipidemia, smoking, diabetes and bone disease should be incorporated into the long-term care plan of the KTR to improve outcomes. A number of transplant centers do not supply PCPs with protocols and guidelines, making the task of the PCP more difficult. Despite this, PCPs are expected to continue to provide general preventive medicine, vaccinations and management of chronic medical problems. In this narrative review, we examine the common medical problems seen in KTR from the PCP's perspective. Medical management issues related to immunosuppressive medications are also briefly discussed.

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INTRODUCTION

Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD).[1] A total of 248,251 kidney transplants had been performed in the US by 2007.[2] The median age of kidney transplant recipients (KTR) has been increasing and was 51 years in 2004.[3] With the use of potent immunosuppressive therapy, improvement in surgical techniques and post-transplant care, short-term graft survival has improved dramatically and currently approaches 90%.[3] Five-year graft survival has also improved and is currently estimated to be approximately 70%.[4,5]

The available infrastructure at transplant centers has not kept pace with the growth in the volume of transplant patients. Thus, many patients start seeing their primary care physicians (PCPs) within 6 months of transplant.[6] PCPs may play a pivotal role in the prevention of morbidity and mortality in the transplant population by appropriate and timely management of many chronic medical diseases. Immunosuppressants and other common drugs prescribed for KTRs affect both the incidence as well as the response to therapy for these medical problems. Screening for malignancies and prevention of infections through immunization are other major components of primary care. The aim of this narrative review is to assist the PCP in the management of common medical issues and address basic aspects of maintenance immunosuppressive therapy used in KTRs.

We searched MEDLINE for English language publications on human subjects aged ≥19 years involving the medical management of KTRs. Consensus Group Guidelines were reviewed and the reference lists of these articles perused to evaluate whether important original articles were missed in the initial search. A list of topics to be included was created and a repeat search conducted with inclusion of specific search terms to look for original randomized or quasi-randomized trials that might not have been included in the initial search.

CHRONIC MEDICAL COMPLICATIONS OF KIDNEY TRANSPLANTATION

Cardiovascular Disease

The annual risk of death due to cardiovascular disease (CVD) in KTRs is 3.5–5%, as opposed to 9% in dialysis patients.[7,8] Aakhus demonstrated that CVD appeared 20 years earlier in KTRs compared with the general population.[9] Despite the

magnitude of the problem, there is a lack of evidence regarding prevention and treatment of CVD in this population. Although the incidence of myocardial infarction decreases after the first 3 months post-transplantation, events related to congestive heart failure (CHF) are one of the most common causes of hospital admissions in KTRs.[10–12] Thus, management of CVD should include modifying risk factors related to both CVD and CHF.[13] Table 1 lists the traditional risk factors associated with the development of CVD. However, traditional risk factors do not fully predict the incidence of cardiovascular disease in KTR.[14] For instance, in an analysis of 1,500 KTRs, calculations based on the Framingham Heart Score underestimated the actual risk of CVD.[15] The implicated non-traditional risk factors include proteinuria, c-reactive protein, homocysteinemia and various immunosuppressive regimens.[14,16–18] Here, we briefly review some major risk factors of CVD.

Obesity

Obesity has been reported in 10–60% of all KTRs.[19,20] Patients can gain an additional 5–15 kg by 1 year post-transplant.[21] Obesity has been associated with an increased risk for developing diabetes, CHF, atrial fibrillation and decreased graft survival.[19,22–25] Weight gain post-transplant has been attributed to the use of corticosteroids as well as an increase in appetite secondary to cessation of dialysis.[26]

Life-style modification remains the mainstay of therapy. Most transplant centers do not have formal weight loss programs for their patients. Thus, there is a need for PCPs to take the initiative in treating obesity. Lopes reported significant weight loss and improvement in low-density lipoprotein (LDL) with dietary intervention.[27] Improvements in high-density lipoprotein (HDL) have been shown to occur with exercise training.[28] Patients should be cautioned to report usage of over-the-counter weight loss preparations. Orlistat, a pancreatic lipase inhibitor, has been reported to be associated with sub-therapeutic calcineurin inhibitor (CNI, e.g., cyclosporine, tacrolimus) levels.[29,30] Gastric bypass surgery might be effective for achieving long-term weight loss in resistant cases, though immunosuppressant doses may have to be increased thereafter due to inadequate drug absorption.[31–33] Although case reports suggest that gastric banding can be associated with complications of band migration or erosion, there is no definite evidence these are more frequent in transplant recipients.[34–37] Laparoscopic sleeve gastrectomy is an attractive but irreversible alternative.[38] Recent data suggest that obesity surgery can be associated with hyperoxaluria and nephrolithiasis, which could potentially compromise the renal allograft.[39–41] Because of these issues, therapeutic options including pharmacotherapy and surgery should be discussed with the transplant center.

Table 1. Prevalence of Risk Factors Associated with Cardiovascular Disease

	General adult population[168–173]	Dialysis patients[4,13,174]	Renal transplant recipients[13,20,175,176]
Obesity (BMI>30)	25–30%	14%	10–60%
Smoking	21%	25%	25%
Diabetes	11%	35%	45–55%
Hypertension	21–29%	80%	60–85%
Hyperlipidemia	25–29%	25%	60%
Chronic kidney disease	13%	100%	100%

BMI: Body mass index

Cigarette Smoking

Smoking confers a 30% risk of death secondary to CVD-related complications.[42,43] In contrast, smoking cessation is associated with a reduction in mortality.[42] Successful kidney transplantation has been demonstrated to be a strong incentive for patients to quit smoking.[44] Thus, this window of opportunity should be exploited by PCPs. Multifaceted programs incorporating both behavioral and pharmacologic therapy have been shown to be effective.[45] Similar to the general population, nicotine replacement therapy can be used.[46] Bupropion has been reported to result in a reduction in cyclosporin concentrations.[47] Some centers report using varenicline without any significant drug-drug interactions.[48,49] Although data are conflicting, caution is advised when using varenicline and bupropion as they carry 'black-box warnings' from the FDA highlighting the risk of serious neuropsychiatric side effects.[50,51]

Hypertension

Similar to the general population, hypertension in KTR is defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure≥90 mmHg.[52] KTRs are likely to have hypertension due to multiple factors including pre-transplant hypertension, allograft dysfunction leading to chronic kidney disease (CKD) and the use of corticosteroids and CNIs.[53–55] Retrospective analyses have demonstrated an incremental association between elevation of blood pressure (BP) and graft failure.[56,57] Unfortunately, no large RCTs analyzing the effect of BP control on graft outcomes have been performed. Based on data from the general population, the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines have recommended BP goals of<130/80 mmHg for all KTRs.[58,59] When possible, ambulatory BP monitoring is recommended because a circadian 'non-dipping' pattern is often seen in KTRs.[60–62] Such patients might require higher doses of anti-hypertensive medications in the evenings.[63]

The management of hypertension should include simultaneous initiation of lifestyle modification and drug therapy. Similar to recommendations for the general population, weight loss (if BMI>25 kg/m^2), regular moderate exercise, limited alcohol intake (≤2 drinks/day in men and≤1 drink/day in women) and dietary sodium restriction (<2.4 g/day) are recommended.[52,58] Though initial therapy should be tailored based upon specific clinical indication, most patients would require combination therapy for optimal blood pressure control.[64] A detailed discussion on specific drugs can be found elsewhere.[65–67] Based on a small trial (n = 154) with a 58% drop-out rate, Midtvedt suggested that nifedipine improved graft function as compared with lisinopril.[68] These benefits could not be confirmed in other studies.[69,70] The newly published Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) should be used as first-line therapy for patients with proteinuria≥1 g/day.[66] Pharmacotherapy needs careful attention because of potential drug interac-

tions. For example, the non-dihydropyridine calcium channel blockers like diltiazem result in an increase in CNI concentration.[71] Thus, drug and dosage modification should be coordinated with the transplant center. Regardless of specific therapeutic agent initiated, close follow-up (weekly for 2 weeks, then monthly) of blood pressure, serum creatinine, electrolytes and hemoglobin levels (when ACEIs or ARBs are used) is recommended.[72] If blood pressure is not controlled despite medical therapy, causes of secondary hypertension, for, e.g., graft renal artery or iliac artery stenosis, should be explored.[73] In contrast to the general population, interventions to correct stenoses have been shown to improve both blood pressure and allograft function.[74–76]

Dyslipidemia

Hypercholesterolemia and hypertriglyceridemia are seen in 40–80% and 40–60% KTRs, respectively.[59,77] Multiple factors including obesity, diabetes, hypothyroidism, proteinuria and diuretic use are implicated.[77] Immunosuppressive agents including CNIs, sirolimus and corticosteroids can result in elevated total cholesterol, LDL, lipoprotein (a) and triglyceride concentrations.[78–82] Serum total cholesterol concentration is an independent predictor of both cardiovascular and peripheral vascular disease in KTRs.[83]

The treatment of dyslipidemia is based on the recommendations of the National Cholesterol Education Program (NCEP) III and the NKF K/DOQI guidelines.[77,84] Recommended target goals are LDL<100 mg/dl, non-HDL cholesterol (calculated as: total cholesterol—HDL cholesterol)<130 mg/dl and a triglyceride concentration<150 mg/dl. Patients should be counseled about diet, weight loss and moderate exercise. Diet composition should include<200 mg/day cholesterol, <7% saturated fat and increased fiber (10–25 mg/day).[84] Statins are the mainstay of pharmacotherapy. The Assessment of Lescol in Renal Transplantation (ALERT) trial is the only large double-blind placebo-controlled RCT performed to assess statin therapy in KTR.[85] Since CNIs can cause elevated statin concentrations resulting in a higher risk of myopathy, fluvastatin was chosen because of a theoretically minimal interaction with CNIs.[86] A total of 2,102 patients were randomized to fluvastatin or placebo and followed for a median of 5.6 years. Though the study failed to show a significant difference in the primary composite end point (fatal and non-fatal myocardial infarction or any coronary intervention), a 35% risk reduction in the incidence of fatal and non-fatal myocardial infarction was seen (p=0.005). The authors commented that the study was underpowered to find a difference in the primary composite end-point because of the lower than expected cardiovascular event rate.

To summarize, fluvastatin has been shown to be safe in a dose of up to 80 mg though atorvastatin and pravastatin can also likely be used, especially in conjunction with tacrolimus, given reported safety data.[77,87] The other statins should be initiated in lower doses of 5–20 mg.[88] If maximal statin dosage is not effective, combination therapy with ezetimibe can be used though some questions have arisen about its effectiveness.[89,90] Hypertriglyceridemia (>500 mg/dl) is usually treated with gemfibrozil, though some centers use niacin or omega-3 fish oils [91] to avoid the additive risk of myopathy when using fibric acid derivatives with a statin.[77,92,93] Bile acid sequestrants should be avoided as they interfere with the enteral absorption of CNIs.[94]

Diabetes

Approximately 20% of KTRs have pre-transplant diabetes.[4] Another 12–25% develop post-transplant diabetes mellitus (PTDM), which is associated with various factors including African-American race, metabolic syndrome, hepatitis C, and therapy with diuretics, CNIs, corticosteroids and sirolimus.[95] PTDM is associated with significantly higher rates of graft loss, cardiovascular morbidity and mortality as well as overall mortality.[95–98] Microvascular complications including neuropathy, nephropathy and retinopathy seem to be accelerated in PTDM.[99]

Diabetes is diagnosed by fasting plasma glucose (FPG) ≥126 mg/dl or a 2-h plasma glucose ≥200 mg/dl during an oral glucose tolerance test.[100] The KDIGO guidelines suggest screening FPG measurements every 3 months for the first year and annually thereafter.[66] Since there are limited data available on the management of diabetes in KTR, consensus guidelines recommend management based on data from trials on the general population.[67,99] Once diagnosed with diabetes, patients should undergo measurements of HbA1c every 3 months (starting at 3 months post-transplant) and annual spot urine protein:creatinine. Recommended goals of care include blood pressure<130/80, FPG<126, HbA1c 7–7.5%, spot urine protein:creatinine ratio<200 mg/g and LDL <100 mg/dl.[66,67] While the International Diabetes Federation recommended a goal HbA1c <6.5%, this aggressive approach might not be suitable for many patients in light of recent findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[101,102]

Table 2. Drugs Used in Management of Diabetes in Kidney Transplantation

Class	Drug	Comments[118]
Sulfonylureas	Glipizide	Preferred agent
α-Glucosidase inhibitors	Acarbose/miglitol	Contraindicated if SCr>2 mg/dl
Thiazolidinediones	Pioglitazone	Avoid in CHF[177]
	Rosiglitazone	Avoid in CHF/CAD[178,179]
Biguanides	Metformin	Contraindicated if SCr>1.5 (men) and >1.4 (females)
Meglitinides	Repaglinide	Preferred agent
Incretin mimetic	Exenatide	No data
DPP-IV Inhibitor	Sitagliptin	No data but use reported by some centers Reduce dose by 50% if eGFR<50 and by 75% if eGFR<30[180]
Insulin	Rapid/intermediate/long-acting	Preferred agents

SCr=serum creatinine; CHF=congestive heart failure; CAD=coronary artery disease; DPP-IV=dipeptidyl peptidase IV; eGFR=estimated glomerular filtration rate

Table 3. Recommendations for Screening of Malignancies among Kidney Transplant Recipients

Malignancy	Mode	Frequency[66,94,150,181]
PTLD	H&P to evaluate organ involvement, imaging as needed	Every 3 months for 1 year and then annually
Skin and lip	Physical, refer to dermatology as needed	Every 6 months for high-risk patients, otherwise annually
Genital/cervical	Physical+Pap smear	Annually
Bladder	Cystoscopy for de novo hematuria	As needed
Kidney	Ultrasound of native kidney	Biennially (for patients with acquired cystic kidney disease)[182]
Liver (hepatitis B and C patients)	AFP	Annually
Breast	Physical exam, mammogram	Annually
Prostate	Rectal exam, PSA	Annually
Colon	Age >50 years, FOBT or colonoscopy	Annual FOBT or colonoscopy every 5–10 years

PTLD: Post-transplant lymphoproliferative disease; H&P: history and physical exam; AFP: alpha-feto protein; PSA: prostate-specific antigen; FOBT: fecal occult blood test

In the absence of significant co-morbidities, weight loss and moderate exercise (30 min/day on most days of the week) is recommended for all diabetics.[103] Almost all KTRs will require pharmacotherapy with at least one agent. The choice of initial therapy might vary based on patient and physician preference. Table 2 lists the medications used for the treatment of diabetes in KTRs. The use of aspirin for primary prevention is recommended in patients with co-existing diabetes and CKD.[67]

Cerebrovascular Disease

The pathogenesis and management of cerebrovascular disease is closely linked with that of CVD. Compared with the general population, the yearly incidence of cerebrovascular events is elevated in KTRs (0.8–1.34%) but lower than patients on dialysis (3.3%).[104,105] Data from the ALERT trial showed that strokes contributed to 17% of all-cause mortality.[106] Prior history of polycystic kidney disease was associated with a higher incidence of hemorrhagic stroke. Unfortunately, lipid-lowering therapy did not result in a reduced risk of stroke. Prevention of stroke requires aggressive management of traditional risk factors, especially hypertension.[107]

Anemia

Anemia, reported in 40–46% of KTR, is an independent predictor for the development of CVD.[72,108–110] Multiple factors including micronutrient deficiency (iron, folate and vitamin B12), CKD, cytomegalovirus, parvovirus and drugs (e.g., immunosuppressants, valgancyclovir, trimethoprim-sulfamethoxazole, ACEI, ARB) can contribute to post-transplant anemia.[108,111–115] Anemia present postoperatively in KTRs tends to resolve over a period of 6 months.[114] Hemoglobin levels should be followed at least once every 3–6 monthly late posttransplant.[116] All patients with anemia should undergo a workup with red blood cell (RBC) indices, reticulocyte count, iron studies and stool hemoccult.[117] For patients being treated with erythropoiesis-stimulating agents, the recommended therapeutic goal for hemoglobin level is between 11–12 g/dl.[118]

Gout

Decreased renal urate clearance can occur after KT leading to hyperuricemia (10–84%) and gouty arthritis (2–28%).[119,120] Risk factors include CNI use (cyclosporin>>tacrolimus), obesity and use of thiazides.[119] In the absence of ESRD, low-dose colchicine (0.15–0.6 mg/d) can be used for therapy, though an abrupt or insidious myo-neuropathy may develop as an adverse reaction.[121–124] Owing to this concern, some centers avoid colchicine and prefer using low-dose corticosteroids instead (20–30 g/day for 3–5 days).[122] Non-steroidal anti-inflammatory drugs (NSAID) should be used cautiously and only for a short duration (<5 days) even in the absence of significant CKD. Gout involving a single, easily accessible joint is probably best treated with an intra-articular corticosteroid injection.[125,126] Allopurinol should be dose-adjusted according to creatinine clearance when used for prophylaxis and, importantly, must not be used in patients prescribed azathioprine due to the risk of significant toxicity.[127,128]

Depression

Up to 22% of KTRs experience moderate to severe depressive symptoms.[129,130] In a retrospective study (n=47,889) based on Medicare claims, Dobbels reported cumulative incidences of 5%,

Table 4. Vaccination Guidelines for Kidney Transplant Recipients

Vaccine	Dose	Frequency[160–162]	Monitor titer	Comment
Influenza	Routine	Annually (October-November)	No	Need for booster dose controversial[183,184]
Pneumovax	Routine	Every 3–5 years	Yes	Many centers do not monitor titers
Tetanus/ pertussis	Routine	Booster every 5 years	No	-
Diphtheria	Routine	Booster no later than 2 years from vaccination and then every 10 years	No	-
Hepatitis A	1,440 ELISA units	0 and 2 months	Yes	For patients not vaccinated before transplant
Hepatitis B	40 μg	0, 1, 2, and 6 months	Yes	For patients not vaccinated before transplant

ELISA: Enzyme-linked immunosorbent assay

Table 5. Maintenance Immunosuppressive Medications Used in Kidney Transplant Recipients

Drugs	Toxicity profile	Trough concentration (ng/ml)*
Calcineurin inhibitors[185]	Acute and chronic renal toxicity, hyperlipidemia, encephalopathy	
Cyclosporin (> >tacrolimus)	Gout, hirsutism, gingival hyperplasia	75–200
Tacrolimus (> >cyclosporin)	Acute neurotoxicity (tremor), alopecia, diarrhea, diabetes	5–15
Sirolimus[186]	Delayed wound healing, edema, diabetes, hyperlipidemia, marrow suppression	5–12
Mycophenolate mofetil[187]	Diarrhea, esophagitis, marrow suppression	Not measured usually; MPA AUC levels measured by some centers
Corticosteroids	Hyperlipidemia, diabetes, osteoporosis	Not applicable

Trough concentration might vary depending upon time from transplant, graft status, concomitant immunosuppressive therapy; MPA AUC: mycophenolic acid area under the curve

7.3% and 9.1% at 1, 2 and 3 years post-transplant, respectively.[131] Diabetes, female sex, obesity and younger age (<65 years) were associated with a higher rate of depression. Though the study had limited demographic information and no data on outcomes based on therapy, a diagnosis of depression was associated with a nearly two times higher risk of graft failure and death with a functioning graft. The authors surmised that the higher rates of graft loss could be related to non-adherence with treatment regimens among depressed patients.[132]

PCPs can play a vital role in systematic screening and periodic assessment of depression. Therapeutic interventions may include individual and group psychotherapy as well as pharmacotherapy with selective serotonin reuptake inhibitors such as citalopram.[133,134]

Bone Disease

Bone disease in KTR differs from 'steroid-induced' osteoporosis seen after transplantation of non-renal solid organs. In KTR, bone disease is worsened by the frequent pre-existing bone damage acquired during dialysis and prior CKD.[135] Osteoporosis is evident in 10–44% of KTRs by 3 years post-transplantation.[136] The fracture risk for KTRs maintained on corticosteroids has been reported to be four times that of the general population.[137,138] K/DOQI guidelines recommend follow-up of serum calcium and phosphorus levels once every 3 months between 6–12 months post-transplant, and then annually.[139,140] Annual parathyroid hormone and BMD measurements at 0, 1 and 2 years post-transplant are also recommended. In a review of 24 trials (n = 1,299), Palmer et al. failed to show a reduction in fracture with any one individual intervention.[141] The meta-analysis did show that the use of bisphosphonate, vitamin D or calcitonin was associated with an improvement in BMD as well as a reduction in fracture risk (relative risk 0.51, 95% confidence interval 0.27 to 0.99).

Treatment recommendations[70,135,138,139] include: (1) minimize steroid dosing; (2) encourage weight-bearing exercise; (3) ensure daily intake of calcium (1,000 mg/day for men and 1,500 mg for postmenopausal women) and vitamin D (400–1,000 IU); (4) treat vitamin D deficiency (<30 ng/ml) when present; (5) treat persistently low serum phosphate (<2.5 mg/dl) with oral supplementation; (6) consider parenteral bisphosphonate therapy for BMD t-score≤-2. In the US, lack of insurance re-imbursement limits the feasibility of parenteral bisphosphonates, and thus oral therapy might be used alternatively.[142,143]

Malignancies

In a retrospective analysis of 37,765 patients using Medicare claims, Kasiske demonstrated an increased risk of multiple common and rare cancers among KTRs.[144] Vajdic reported similar data using national registry data from Australia and New Zealand, although they did not report an increased incidence of breast and prostate malignancies.[145] In a single-center study from Germany, Wimmer reported increased risk of non-melanoma skin cancers, kidney cancers and cancers of the pharynx, larynx and the oral cavity, but not of cancers of the prostate, breast and colon.[146] Owing to these results it has been proposed that the increased risk of malignancy in this population is secondary to viral re-activation because of immune deficiency induced by use of immunosuppressive agents.[147,148] There is an urgent need for development of screening guidelines for these and other chronically immunosuppressed patients. Because of the higher risk of cancers in this population, various groups have recommended a more intensive screening strategy.[116,149,150] Table 3 lists screening recommendations based on consensus opinion. In absence of reliable data, many of these recommendations are based on extrapolation of data from the general population.[151] It is recommended that all KTRs should use a sunscreen with sun protection factor (SPF) >30.[152]

Infections and Vaccinations

Serious infections are responsible for 14–16% of all deaths among KTRs.[153] Most opportunistic infections are seen be-

Table 6. Effect of Selected Drugs on Calcineurin Inhibitor Concentrations

Concentrations increased by[185]	Concentrations decreased by[155,188]
Macrolide antibiotics	Anticonvulsants (phenobarbital, phenytoin,carbamazepine)
Calcium channel blockers (Diltiazem, verapamil)	Rifampicin
Triazole antifungals	Dexamethasone
Protease inhibitors	St John's Wort (used for depression)
Amiodarone	Marijuana
Metoclopramide	Orlistat
Grapefruit juice	Octreotide
Ciprofloxacin	
Selective serotonin reuptake inhibitors (SSRIs)	

tween 2 and 6 months post-transplant.[154] After 6 months post-transplant, the risk of infection diminishes. However, patients with more intense exposure to immunosuppressive agents continue to be vulnerable to opportunistic infections.[155] Bacterial urinary tract infections (UTI) are the most common infection during the late period and are responsible for significant morbidity and mortality.[156] Though some experts recommend screening for bacteriuria, current guidelines do not make any specific recommendations.[140,157] All patients with suspected UTIs should undergo urinalysis and a urine culture. UTIs with no systemic symptoms can be treated empirically with an oral fluoroquinolone or as guided by local sensitivity data.[158,159] Patients with acute pyelonephritis need inpatient admission for parenteral antibiotic administration.[66]

Timely and appropriate vaccination can prevent substantial morbidity and mortality in KTRs. Immune response is best when the vaccine is administered prior to the transplant as the efficacy of vaccination is frequently blunted post-transplant.[160] All KTRs should receive common killed vaccines (Table 4). It should be noted that suggested schedules reflect the increased need for boosters in this population to achieve adequate immunologic response. Live attenuated vaccines (measles-mumps-rubella, nasal influenza, rotavirus, varicella-zoster) are usually contra-indicated.[161] Currently, there are no reported data on the safety of the human papillomavirus (HPV) vaccine in KTRs.[162] Health-care personnel and household contacts should be immunized. Contacts should stay away from KTRs for a minimum of 1 to 2 weeks after receipt of a live vaccine. Patients should be counseled to notify physicians before any travel so that appropriate travel medicine measures can be instituted.[160]

Immunosuppressants

The common medications used for prevention of graft rejection in KTRs are listed in Table 5. Depending upon transplant center and graft status, patients might be on combination 'triple-therapy' (usually a CNI, mycophenolate and prednisone) or single drug (usually tacrolimus) therapy.[163] By the end of 2005, tacrolimus had largely replaced cyclosporin as the CNI of choice. Seventy-nine percent of patients with new kidney transplants were discharged on tacrolimus compared with only 15% on cyclosporin; 87% received mycophenolate compared with 0.6% on azathioprine. Steroid-free regimens were increasingly being used with 20% patients off corticosteroids at 1-year post-transplantation. Sirolimus use was reported to be 9%, though it seems to have declined since then.[153,164]

Calcineurin inhibitors are the mainstay of maintenance therapy. Both cyclosporin and tacrolimus are extensively metabolized by cytochrome P4503A (CYP3A) in the liver and gastrointestinal tract. A plethora of drugs (Table 6) can alter the pharmacokinetic disposition, and hence plasma concentrations of CNIs by inhibiting or inducing CYP3A enzymatic activity, subsequently increasing risk of rejection or toxicity. PCPs should check for drug interactions before introducing new medications and notify the transplant program about changes made. In case of a possible drug interaction, CNI concentrations need to be monitored soon after (usually 2 days) any significant alteration in medication regimen.

CONCLUSION

Despite substantial advances, the survival of KTRs remains inferior to that of the general population.[165] Complications related to CVD, diabetes, depression and infections accelerate graft loss. Mortality among patients after graft failure is significantly worse than transplant-naive ESRD patients.[166,167] PCPs can play a crucial role in improving long-term survivals by taking an active part in the management of these high-risk patients. The optimal therapeutic approach for many conditions remains a subject of research and debate and in those cases the PCP will need to carefully extrapolate the findings from general populations to KTR. Collaboration and communication between transplant professionals and PCPs are vital to ensure quality patient care.

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