Primary Care Issues in Renal Transplant Recipients

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Due to the excellent outcomes of renal transplantation, there is an increasing number of people surviving with, or receiving a transplant, at an older age. While the transplant centre usually manages the immunosuppression and renal problems, these individuals also require primary care. This article will review the common health issues that primary care physicians encounter routinely among these patients. Common problems include managing cardiovascular risk factors, screening for malignancy, vaccinations, treatment of uncomplicated infections, and bone disease. Important drug interactions will be reviewed. Communication between the primary care physician and the transplant centre will also improve care of these patients.

Key words: *renal transplantation, primary care, cardiovascular disease, drug interactions, chronic kidney disease*

Introduction

Renal transplantation is the preferred treatment for individuals with end-stage renal disease.[1] This is based on improved survival among persons who receive a transplant compared to those who are transplant candidates but remain on dialysis.

Increasing numbers of older adults are receiving renal transplants.[2] In the United States in 2006, persons older than 65 received 2,390 transplants, 14% of all renal transplants for that year. Outcomes are excellent, with 1-year graft survival of 87.9% for individuals older than 65 years. Along with an increase in the number transplants, there has been an increase in graft survival.[2] This has led to a growing number of transplant recipients surviving to an older age.

Apart from care of their transplant, individuals who have received transplants also require primary care. Some nontransplant physicians may be reluctant to treat transplant survivors because of concerns related to their immunosuppressed state and medications. In fact, nontransplant physicians can give these patients excellent care for a variety of health issues, typically problems that primary care physicians already contend with on a daily basis and are comfortable managing.

This article will discuss common primary care issues among renal transplant patients; however, it will not cover early post-transplant issues, or graft dysfunction: these issues are managed by the transplant centre.

Immunosuppressive Agents

Transplant recipients must remain on immunosuppression for the life of the graft. There is no single immunosuppressive protocol that is used for all patients.[3] Most patients are assigned to two or three agents, which allows for improved rejection prophylaxis while minimizing adverse effects. The most common combinations include a calcineurin inhibitor (CnI) such as cyclosporine or tacrolimus, an antiproliferative agent (mycophenolate mofetil, enteric-coated mycophenolic acid, or azathioprine) and prednisone. In general, these medications should only be adjusted by the transplant centre. If there is a concern about immunosuppression, communication with the transplant centre is crucial.

A complete discussion of these medications is beyond the scope of this article, however, some of their important characteristics and side effects are described below.

Calcineurin Inhibitors

Cyclosporine (Neoral®) and tacrolimus (Prograf®) are the mainstays of immunosuppression and both inhibit the enzyme calcineurin, which is required for the activation of T lymphocytes. They have a narrow therapeutic window and require monitoring of blood levels. Target levels vary depending on the time from transplantation, other immunosuppressive drugs used, and patient factors.

Calcineurin inhibitors have similar side effect profiles. Both cause renal vasoconstriction, which can lead to a rise in serum creatinine. Patients with volume depletion (for example, from diarrhea) may have a significant rise in serum creatinine, which will usually improve with hydration. Both medications may also cause fibrosis and atrophy of the graft, along with chronic vascular changes. As well, the CnIs have an adverse impact on cardiovascular risk factors. Both CnIs cause hypertension in a majority of patients. Cyclosporine is more likely to cause hyperlipidemia, while tacrolimus is associated with a higher risk of new-onset diabetes mellitus after transplant.[4]

Antiproliferative Agents

Mycophenolate mofetil (CellCept®) is an inhibitor of purine synthesis. Enteric-coated mycophenolic acid (Myfortic®) is a newer formulation of the same active drug. The most common side effect with both medications is gastrointestinal upset, either upper (nausea and vomiting, heartburn) or lower (diarrhea). They may also cause leukopenia and anemia, but less frequently than azathioprine.

Table 1: Common Drugs That Affect Cyclosporine or Tacrolimus Levels

Increase Levels
Macrolide antibiotics: erythromycin, clarithromycin, azithromycin
Azole antifungals: ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole
Calcium channel blockers: diltiazem, verapamil, nicardipine
Protease inhibitors: ritonavir, others
Grapefruit juice
Decrease Levels
Anticonvulsants: barbiturates, phenytoin, carbamazepine
Antituberculous drugs: rifabutin, rifampin
Cholestyramine
Golytely®

Azathioprine (Imuran®) also inhibits purine synthesis. Although its use in de novo renal transplant patients has been largely supplanted by mycophenolate, many long-term recipients remain on this medication. Unlike mycophenolate, it inhibits proliferation of all white blood cells and can cause neutropenia.

Sirolimus

Sirolimus (Rapamune®) is the newest oral agent approved for use in renal transplantation (Figure 1). It is a proliferation signal inhibitor, which acts by blocking the mammalian target of rapamycin protein (mTOR). Inhibition of mTOR prevents DNA synthesis and lymphocyte proliferation. Proliferation of other cells, including fibroblasts, is also inhibited. Sirolimus has been used in combination with a CnI, with mycophenolate, or with steroids.[5]

Side effects of sirolimus include an increase in CnI nephrotoxicity when used in combination compared to a CnI alone. Other side effects include pneumonitis, proteinuria, leucopenia, hyperlipidemia, edema, diarrhea, and oral ulcers.[5]

Sirolimus inhibits the proliferation of fibroblasts and therefore the process of scar formation that normally occurs following an injury is inhibited. This is usually not a concern for ordinary cuts, however, it may prevent healing of a surgical incision. If a patient taking sirolimus requires surgery, the transplant centre should be consulted. In some cases, the patient may be switched to another agent a few weeks before the operation, and changed back after the incision has healed.

Steroids

Most transplant recipients will be maintained on steroids and will be weaned down to 5–7.5 mg/d of prednisone by 6 months post-transplant. The side effects of steroids are well known, and include hypertension, hyperlipidemia, hyperglycemia, osteoporosis and bone disease, and cataracts.

Drug Interactions

Drug interactions with the CnIs are well-described. Cyclosporine and tacrolimus are metabolized via the cytochrome P450 system in the liver. Several medications either up- or down-regulate the activity of this system. Other drugs may affect CnI levels by increasing or inhibiting absorption of the CnI in the gut (Table 1).

When possible, alternate medications that do not interact with CnIs should be used. For example, in the setting of a community-acquired pneumonia, a broad-spectrum cephalosporin or fluoroquinolone should be used instead of a macrolide antibiotic. If a medication known to interact with CnIs must be used, the transplant centre should be contacted for advice as to CnI monitoring and whether the dose should be changed.

Another concern is the increased toxicity of some medications when they are used together with a CnI (Table 2). Known nephrotoxic medications, such as the aminoglycosides, should be avoided if possible. Since nonsteroidal anti-inflammatory drugs (NSAIDs) can affect renal perfusion, they should be avoided for renal transplant recipients.

Cardiovascular Disease Risk Factors

Cardiovascular disease (CVD) is the leading cause of death among individuals who have had renal transplants.[6] These individuals often have multiple risk factors for cardiovascular disease. In addition, many transplant recipients, even those with a well-functioning graft, still do not have normal renal function and meet the definition of chronic kidney disease (CKD).[7] Studies of nontransplant patients have shown that the risk of CVD is inversely proportional to renal function.[8]

Smoking cessation should be encouraged. Smoking has been found to be a risk factor for both graft loss and cardiovascular disease.[9] Among patients with no history of cardiovascular disease, primary prophylaxis with acetylsalicylic acid should be discussed, as they are at high risk for future cardiovascular events.[10] Patients who have had a previous cardiovascular event are at very high risk for another cardiovascular event and should be assigned to antiplatelet therapy.

Hypertension

Hypertension is seen in up to 80% of renal transplant recipients and is an important determinant of late graft loss.[11]

Table 2: Drugs Whose Toxicity Is Increased by Cyclosporine or Tacrolimus

Statins, especially lovastatin
Aminoglycosides
Amphotericin
Nonsteroidal anti-inflammatory drugs (NSAIDs)

Patients with a systolic blood pressure >140 mm Hg are at an increased risk of graft loss and death from cardiovascular disease.[12]

Current guidelines suggest a target blood pressure of <30/80 mm Hg for transplant recipients.[13] Several classes of antihypertensive agents, including diuretics, beta-blockers, calcium-channel blockers, and ACE inhibitors are effective at lowering blood pressure among transplant recipients. As mentioned above, diltiazem and verapamil can raise CnI levels, so renal function and drug levels must be monitored if one of these drugs is started. Other calcium-channel blockers such as nifedipine and amlodipine do not affect CnI levels. Although ACE inhibitors and angiotensin II receptor blockers are preferred agents for the nontransplant population, there is no evidence among transplant recipients showing their superiority to any other class of antihypertensive agent.[14] If used, renal function and potassium should be checked soon after initiating therapy.

Hyperlipidemia

Hyperlipidemia is common among transplant recipients. The most recent guidelines for individuals with chronic kidney disease suggest a target low density lipoproteins (LDL) level <2.59 mmol/L.[15] Given more recent studies showing a benefit of lowering LDL below 2.00 mmol/L among nontransplant patients,[16] renal transplant recipients may also benefit from more aggressive lipid targets.

Treatment of hyperlipidemia includes lifestyle modification, with a diet low in saturated fat and cholesterol, regular exercise, and weight reduction for overweight individuals. However, most patients will still require medication to reach their lipid targets. Statins are the recommended first-line agent. Because CnIs can increase blood levels of statins, treatment should be started at a low dose and titrated upwards. In the ALERT trial, fluvastatin effectively lowered LDL and decreased the risk of cardiac death or nonfatal myocardial infarction (MI). In addition, it was safe, with an incidence of liver enzyme abnormalities (1.2%) and elevations of creatinine kinase (0.6%) similar to placebo.[17]

Ezetimibe, a new agent that inhibits absorption of cholesterol in the small intestine, appears to be safe and effective in renal transplant recipients and can be combined with a statin.[18] Niacin can be used, but may not be tolerated due to its side effects of flushing, pruritus, and gastrointestinal upset. Bile acid sequestrants such as cholestyramine may inhibit the absorption of calcineurin inhibitors and should be taken separately from the CnI (and other immunosuppressants) and more frequent monitoring will be needed. Fibrates (especially in combination with a statin) may increase the risk of rhabdomyolysis, especially among individuals with renal impairment. Their use should be reserved for difficult cases of hyperlipidemia, and require close monitoring.

Diabetes Mellitus

Along with being a common reason for transplantation, diabetes is a well-recognized complication of renal transplantation. Both diabetes and impaired fasting glucose are risk factors for cardiovascular disease post-transplant.[19] A recent trial showed an incidence of new-onset diabetes or impaired fasting glucose after transplantation of 29.8%.[4] Risk factors for diabetes include increasing age, obesity, family history, Black or Hispanic ethnicity, infection with hepatitis C, steroid use, and use of tacrolimus.[20]

Current recommendations suggest using the standard American Diabetes Association criteria for the diagnosis of diabetes. This includes either symptoms of hyperglycemia with a random glucose >11.1 mmol/L; a fasting glucose >7.0 mmol/L; or a 2 hour glucose >11.1 on a standard oral glucose tolerance test. Patients without symptoms of hyperglycemia or metabolic decompensation require a confirmatory test on a separate occasion.[20]

Treatment of diabetes post-transplant is similar to treatment of nontransplant patients. Patients should receive diabetes education and instruction in glucose self-monitoring. They should be assessed routinely for complications of diabetes including retinopathy and neuropathy. HbA1c levels should be monitored every 3 months, with a target level <6.5%. Pharmacologic therapy may include oral hypoglycemic agents (OHAs) as monotherapy or in combination, and insulin, either in combination with OHAs or as part of a single- or multidose regimen. Among patients with renal dysfunction, the risk of lactic acidosis with metformin and hypoglycemia with sulfonylureas is increased, and these drugs may need to be avoided.

Malignancy

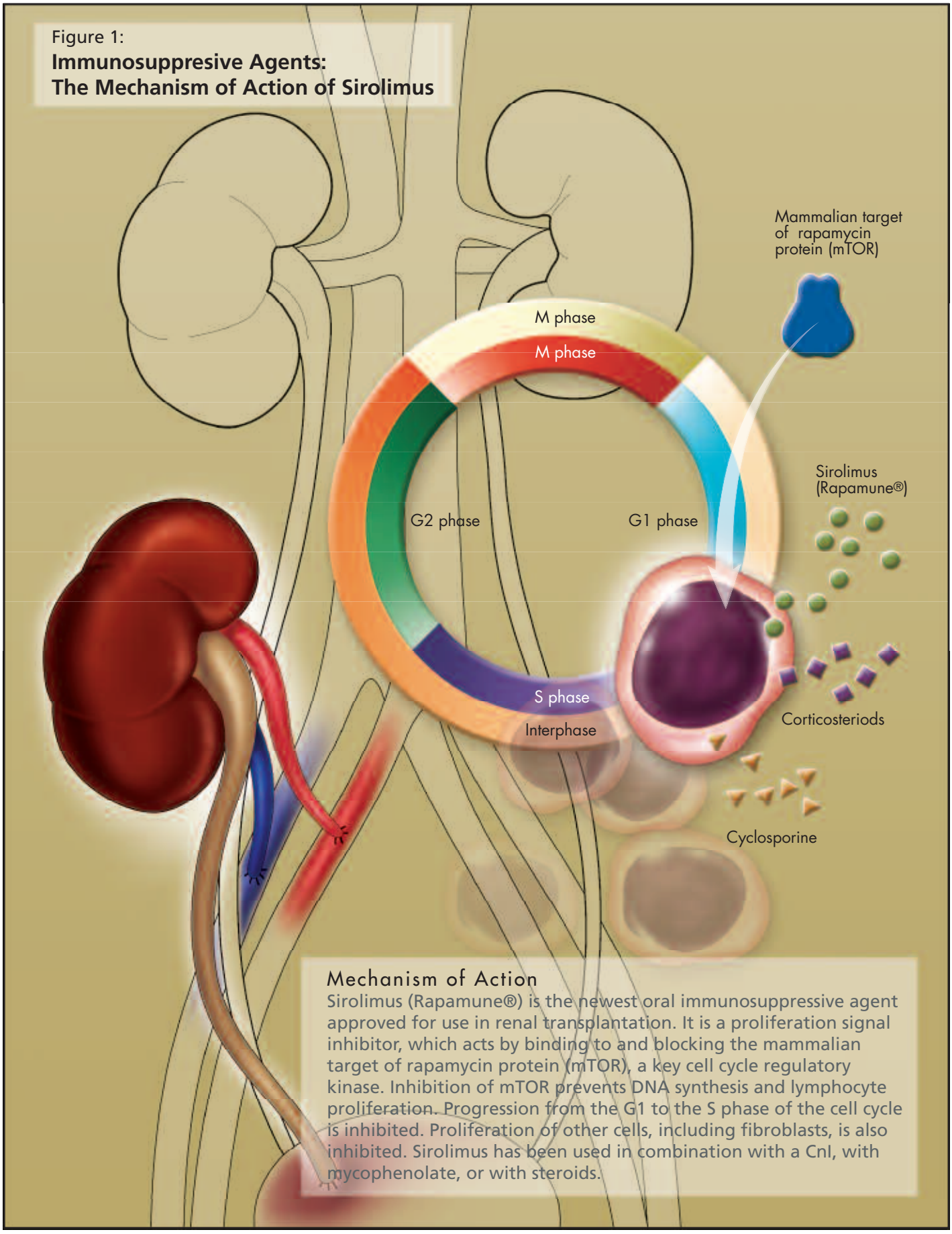
Transplant recipients are at higher risk for cancer compared to both the general and dialysis populations.[21] The overall risk of cancer after transplantation is increased two-fold. The relative risk is even higher for several cancers. In addition, cancers after transplantation can be more aggressive among transplant recipients than in the general population.

Women should have annual Pap smears if they are older than 18 and sexually active. Mammography with or without clinical breast examination are recommended for women over the age of 50, and may begin at 40 years of age. Testing for colon cancer, either by fecal occult blood testing, barium enema, sigmoidoscopy, or colonoscopy should be started at the age of 50. Screening for prostate cancer is recommended for men older than 50, but the evidence in favour of this is weak. Screening for skin cancer, melanoma, and Kaposi's sarcoma is also suggested, with monthly self-examinations by the patient and annual examinations by a physician.[22]

Vaccinations

Live vaccines should be avoided after transplantation. This includes the varicella, the measles, mumps, rubella vaccine, and the bacille Calmette-Guérin vaccine. Inactivated vaccines can be safely administered to transplant recipients. This includes the influenza, pneumococcus, Hepatitis A and B, and tetanus vaccines. However, Dukoral, an oral, inactivated vaccine against *E. coli*, and *V. cholerae* is contraindicated. Immunization should not be

Figure 1:
Immunosuppresive Agents:
The Mechanism of Action of Sirolimus



Mechanism of Action

Sirolimus (Rapamune®) is the newest oral immunosuppressive agent approved for use in renal transplantation. It is a proliferation signal inhibitor, which acts by binding to and blocking the mammalian target of rapamycin protein (mTOR), a key cell cycle regulatory kinase. Inhibition of mTOR prevents DNA synthesis and lymphocyte proliferation. Progression from the G1 to the S phase of the cell cycle is inhibited. Proliferation of other cells, including fibroblasts, is also inhibited. Sirolimus has been used in combination with a CnI, with mycophenolate, or with steroids.

Key Points

- Cardiovascular disease is the leading cause of death among transplant recipients.
- Target blood pressure for most patients is <130/80, while lipid targets are the same as for patients with established coronary disease.
- Interaction with immunosuppressive medications should be checked before prescribing new medications. Dosages may need to be adjusted for impaired renal function.
- Management of diabetes and screening for malignancy should be the same as for the nontransplant population; bone disease is also managed similarly among those with transplants and without.
- Live vaccines should be avoided among transplant recipients.

done in the first 6 months post-transplant, as the higher levels of immunosuppression may prevent an immune response. Close contacts and other family members should be advised to receive the influenza vaccine annually.[23]

Infections

Renal transplant recipients are at an increased risk of developing infections. Common infections include urinary tract infections, pneumonias, cellulitis and, among individuals with diabetes, diabetic foot infections.

The presentation is usually similar to that of the nontransplant populations, as are the infecting organisms. However, urinary tract infections frequently ascend to the renal transplant, causing pain over the graft and a rise in serum creatinine, which responds to antibiotic treatment.

Patients who are not severely ill can usually be managed without an adjustment in their immunosuppression and most patients will not need "stress-dose" steroids. If a patient is severely ill, has graft dysfunction, or is not responding to therapy, the transplant centre should be contacted.

Bone Disease

Renal transplant recipients have multiple risk factors for bone disease, including hyperparathyroidism, hypophosphatemia, and steroid use. Osteopenia and osteoporosis, as well as renal osteodystrophy, may be seen post-transplant. As such, transplant recipients are at an increased risk for fracture post-transplant.[24]

Treatment with a vitamin D sterol, calcitonin or bisphosphonates may prevent fractures post-transplant. Whether one treatment is superior to the others is unknown.[25] Given this, it appears to be reasonable to measure bone density and institute treatment if osteopenia or osteoporosis is present. Bone density should be first measured around 3 months post-transplant. Bisphosphonates may need to be given at a reduced dose or avoided among patients with severe graft dysfunction.

Other Considerations

Asymptomatic hyperuricemia should not be treated. Symptomatic gout can be treated with colchicine but NSAIDs should be avoided. Allopurinol can be used as prophylactic therapy, but only in consultation with the transplant centre. Since allopurinol inhibits the metabolism of azathioprine, there is the potential for severe neutropenia when it is introduced. Reduction of the azathioprine dose and monitoring of the white blood cell count are essential. Mycophenolate mofetil does not need to be adjusted for allopurinol.

Transplant recipients are at an increased risk for contrast-induced nephropathy. If intravenous contrast is required, a low or iso-osmolar contrast agent should be used. Patients should also receive intravenous hydration with bicarbonate and prophylactic administration of *N*-acetylcysteine if possible.

Because of their immunosuppression, transplant recipients are advised to use endocarditis prophylaxis for dental work. This includes routine cleanings.

Most renal transplant recipients do not have normal renal function, but instead meet the criteria for chronic kidney disease, with a decreased glomerular filtration rate,[7] therefore, because of this, doses of antibiotics and other medications may need to be adjusted for renal function.

Conclusion

Most renal transplant recipients have good and stable graft function. Many of their comorbidities are ones that primary care physicians routinely manage. In general, these problems can be managed by a family physician without endangering either the patient or their graft. If there is any concern, virtually every transplant centre will be more than happy to assist with advice over the telephone, or a transfer of care when necessary.

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