Primary Care of the Transplant Patient

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ABSTRACT

A total of 153,245 patients are living with a solid organ transplant in the US. In addition, patients are experiencing high 5-year survival rates after transplantation. Thus, primary care physicians will be caring for transplanted patients. The aim of this review is to update primary care physicians on chronic diseases, screening for malignancy, immunizations, and contraception in the transplant patient. Several studies on the treatment of hypertension and hyperlipidemia demonstrate that most agents used to treat the general population also can be used to treat transplant recipients. Little information exists on the medical management of diabetes in the transplant population, but experts in the area believe that the treatment of diabetes should be similar. Transplant recipients are at increased risk for all malignancies. Aggressive screening should be employed for all cancers with a proven screening benefit. Killed immunizations are safe for the transplant population, but live virus vaccines should be avoided. Women of childbearing age should be counseled about the impact of immunosuppressants on the efficacy and side effects of contraception.

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KEYWORDS: General internal medicine; Primary care; Transplantation

The 2006 annual report of the Scientific Registry of Transplant Recipients shows that by the end of 2004 there were 153,245 individuals living with a transplant in the US. In 2005, 16,072 individuals received a kidney transplant and 6000 received a liver transplant. Over 2000 individuals received a heart and 1400 received a lung transplant in the same year. As of 2005, there were over 89,000 individuals waiting for transplantation. The survival rate for transplant recipients is high. Unadjusted 5-year survival rates for living donor renal and liver transplant recipients are 90% and 77%, respectively, while heart recipients' 5-year survival is 74%. Because so many transplant recipients survive beyond the initial postoperative period, they are presenting to primary care offices in increasing numbers. Primary care physicians need to be prepared to evaluate and treat transplant recipients.

The primary care physician has the potential to play a major role in the prevention of illness and death for the transplant population. Among transplant recipients who have survived for at least 3 years after transplant, the cause of death is malignancy for 24% and complications of cardiovascular disease for 21%. A large component of the primary care physician's activities revolve around early detection of malignancy and prevention of cardiovascular disorders. Thus, primary care physicians need to be experts in the special attributes of malignancy and vascular disease in transplant patients.

The goal of this review is to assist the general internist or family physician to provide primary care for transplant recipients. Initially, the immunosuppressants commonly used in transplant medicine are reviewed. The care of hypertension, hyperlipidemia, and diabetes is then discussed. Lastly, screening for malignancies, contraception care, and proper immunization practices are reviewed.

THE IMMUNOSUPPRESSANTS

Primary care physicians should have a working knowledge of the common immunosuppressants employed for the solid organ transplant population. These medicines have the potential for multiple side effects as well as interactions with medicines commonly prescribed in a primary care practice.
The immunosuppressants used in transplant medicine include corticosteroids, cyclosporine, tacrolimus (FK506), sirolimus, azathioprine, and mycophenolate mofetil. A thorough discussion of the impact of corticosteroids on primary care practice is beyond the scope of this article and has been addressed previously.\textsuperscript{3−7} Cyclosporine and tacrolimus are the most common immunosuppressants used in transplant medicine.\textsuperscript{8−10} These calcineurin inhibitors and sirolimus are metabolized through the cytochrome P450 system, causing interactions with many medications employed in primary care. Medications that are metabolized through the same system (Tables 1, 2) can accelerate or decelerate the metabolism of these immunosuppressants, leading to either toxic or sub-therapeutic levels. Azathioprine and the newer immunosuppressant mycophenolate mofetil are purine synthesis inhibitors. They are not metabolized through the cytochrome P450 system and do not have as many problems with interactions.\textsuperscript{11}

**CLINICAL SIGNIFICANCE**

- Primary care physicians provide long-term care for organ transplant recipients.
- Most antihypertensive and lipid-lowering therapies can be used in the transplant recipient.
- Aggressive screening should be employed for all cancers with a proven screening benefit.
- Live virus vaccines should be avoided, but killed vaccines are safe.
- Women of child-bearing age should be counseled that immunosuppressants affect contraception.

**HYPERTENSION**

The prevalence of hypertension is increased in transplant recipients compared, with the general population. Among liver transplant recipients, the prevalence is 55%−85%. Renal recipients and heart recipients have a prevalence of up to 90% and 100%, respectively.\textsuperscript{12−14}

The pathophysiology of hypertension in transplant recipients is not fully understood, but is mediated through the use of immunosuppressants. Calcineurin inhibitors are known to increase the release of endothelin, leading to constriction of the afferent renal arteriole and a decrease in the glomerular filtration rate. This results in an expansion of the intra-vascular volume and an associated elevation in systolic blood pressure.\textsuperscript{13}

The National Kidney Foundation Kidney Disease Quality Outcomes Initiative and the American Society of Transplantation have published guidelines for assessment and management of hypertension in patients who are transplant recipients. The appropriate target for blood pressure control in renal and liver transplant recipients is <130/<80 mm Hg.\textsuperscript{12,15}

Several randomized controlled studies address treatment of hypertension in the transplant recipient.\textsuperscript{14,16−25} The following classes of antihypertensives have been shown to be effective in this population: calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and diuretics. No single class of drugs has been shown to be more effective. Primary care physicians should consider the following in choosing an antihypertensive regimen. First, one should consider the transplant recipient’s comorbid conditions in choosing an antihypertensive regimen. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are preferred in the presence of microalbuminuria or diabetes. Second, the pathophysiology of hypertension in transplant recipients should be considered. Theoretically, calcium channel blockers would be an appropriate agent for this group of patients because of their ability to counteract afferent arteriolar vasoconstriction. Diuretics would help to reduce volume expansion. Lastly, primary care physicians should consider drugs that reduce the cost of immunosuppressants. When calcium channel blockers such as diltiazem are used, cyclosporine, tacrolimus, and sirolimus levels increase, allowing for less costly lower doses of the medications.

**HYPERLIPIDEMIA**

Hyperlipidemia is a common problem among transplant patients. Six to 12 months after liver transplantation, total cholesterol increases by 20%−43%, triglycerides increase by 38%−56%, and high-density lipoprotein is reduced by 50%.\textsuperscript{26−29} The prevalence of hyperlipidemia for renal and heart transplant recipients is 90%\textsuperscript{30−33} and 64%, respectively.\textsuperscript{34}

The pathophysiology of hyperlipidemia in transplant recipients is multifactorial. Major factors include pretransplant lipid levels, weight gain that commonly occurs after transplantation, diabetes mellitus, and hypothyroidism. Immunosuppressants and medications used to treat hypertension also contribute to
Table 2  Medicines that Increase the Risk of Toxicity in Transplant Recipients on Calcineurin Inhibitors

<table>
<thead>
<tr>
<th>Antimicrobials</th>
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<tr>
<td>Fluconazole</td>
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<tr>
<td>Itraconazole</td>
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<td>Ketoconazole</td>
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<td>Erythromycin</td>
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<td>Clarithromycin</td>
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<td>Rifampin</td>
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<td>Antihypertensives</td>
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<tr>
<td>Diltiazem</td>
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<td>Verapamil</td>
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<tr>
<td>Nicardipine</td>
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<tr>
<td>Immunosuppressants</td>
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<tr>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Foods</td>
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<tr>
<td>Grapefruit</td>
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the development of hyperlipidemia. Corticosteroids increase appetite and increase secretion of very low-density lipoprotein by the liver. Cyclosporine A inhibits bile acid hydroxylase, decreasing bile acid synthesis from cholesterol and increasing circulating low-density lipoprotein levels.36-29

Treatment decisions in the transplant population are influenced by the increased risk of metabolic syndrome caused by immunosuppressant medicines, and the increased risk of side effects and interactions with the calcineurin inhibitors. The National Kidney Foundation Kidney Disease Quality Outcomes Initiative has published guidelines on targets for lipid lowering in the renal transplant population. In these guidelines, transplanted patients are included in the highest risk category. The guidelines recommend that evaluation for dyslipidemia should occur at initial presentation and then annually thereafter. Drug therapy is recommended for a low-density lipoprotein remaining over 100 mg/dL after 3 months of lifestyle interventions.35 In the absence of guidelines for heart and liver transplant recipients, primary care physicians should consider placing these patients in the high risk category, and following the guidelines for renal transplant recipients.

Recommendations for lifestyle interventions for the renal transplant recipient do not differ from interventions for the general population.35-38 Again, in the absence of guidelines about lifestyle interventions, primary care physicians should adopt recommendations made for the renal transplant population. Patients should be counseled to decrease portion sizes and to exercise to control weight and diabetes. Transplant recipients also should avoid alcohol, tobacco, and high-dose oral contraceptives, as well as drugs that increase low-density lipoproteins.

Initial drug therapy for transplant patients with an elevated low-density lipoprotein should be a statin.35 The impact of hydroxyl-methylglutaryl (HMG) Coa reductase inhibitors on cholesterol levels in solid organ transplant recipients has been studied in numerous small studies of short duration.39-58 These studies demonstrate that the following statins: lovastatin, pravastatin, simvastatin, cerivastatin, and atorvastatin, are tolerated well and that they are effective, even at low doses, in lowering cholesterol levels. Two studies of heart transplant recipients have further demonstrated a decreased mortality rate when statin medication is compared with placebo.59,60 One study of renal transplant recipients demonstrated that fluvastatin is effective at reducing cardiac deaths and nonfatal myocardial infarctions, but did not reduce the rates of interventional coronary procedures or overall mortality.61

No long-term studies of other classes of lipid-lowering therapies have been performed, however, small prospective studies have demonstrated modest effectiveness for gemfibrozil,37,56 nicotinic acid,56 and fish oil supplements.55 One retrospective analysis of ezetimibe has demonstrated it to be safe and effective in the renal transplant population.62 One study comparing cholestryramine with gemfibrozil and simvastatin in heart recipients demonstrated that these agents had similar efficacy, however, most patients randomized to cholestryramine had dropped out by the end of the study due to gastrointestinal side effects.48

Side effects of statins are similar for transplant recipients compared with the general population. Because cyclosporine A causes elevated levels of almost all statins, the primary risk in patients taking this immunosuppressant is myopathy and rhabdomyolysis.63 Of the HMG Coa reductase inhibitors, only fluvastatin has had no reported cases of rhabdomyolysis. Doses up to 80 mg daily have been shown to be safe. Fluvastatin has much less of an interaction with cyclosporine A and is metabolized primarily through the cytochrome P 2C9 system, which could account for this difference. Primary care physicians should start other statins at lower doses to avoid muscular toxicity, and dose adjustments should be performed while carefully monitoring for symptoms of muscle weakness or pain. Creatinine phosphokinase levels should be checked before and after initiation or adjustment of statin therapy. Fibric acid derivatives also are associated with a greater risk of myositis and thus, a similar monitoring strategy should be employed. Bile acid derivatives have been shown to interfere with the absorption of immunosuppressant medicine. Thus, careful monitoring of immunosuppressant levels should be performed for patients who are treated with these agents. Nicotinic acid has an increased risk of hepatotoxicity in the transplant population and is associated with an additional increased risk of diabetes, gout, and gastrointestinal discomfort, as well as flushing and itching. Thus, transplant patients on these agents should undergo close monitoring of fasting glucose and transaminase levels.63

**DIABETES**

The prevalence of diabetes increases to 53% after liver transplantation, compared with the general population.64-66
and to 22%\textsuperscript{67} after renal and 30%\textsuperscript{68} after heart transplantation.

In the postoperative period, factors that increase the risk of diabetes include increased stress levels, the use of steroids and calcineurin inhibitors, infection, and parenteral nutrition. Obesity that develops after transplantation causes increased tissue resistance, also contributing to an increased risk of developing diabetes.\textsuperscript{61}

There are no published guidelines addressing how to translate diabetes treatment to the transplant population. The 2009 American Diabetes Association guidelines do not include specific recommendations for this group of patients.\textsuperscript{69} For the general diabetic population, the American Diabetes Association recommends initial treatment with metformin for obese patients. For diabetics of normal weight, a sulfonylurea is recommended. Second-line therapy is insulin. The thiazolidinedione and incretin agents are reserved for third-line therapy.\textsuperscript{69} There are no studies on the use of these agents in the transplant population. However, the metabolism of biguanides, sulfonylureas, and insulin would not be expected to affect levels of immunosuppressants. Thus, in the absence of data, experts state that, "The management of diabetes in transplant recipients is not substantially different from its management in non-transplant patients."\textsuperscript{65} This should include lifestyle modification such as portion control, weight loss, avoidance of simple carbohydrates, regular exercise, and avoidance of high doses of steroids and calcineurin inhibitors. New research in this area addresses the downward adjustment of calcineurin inhibitors to avoid diabetes while preventing rejection of the transplanted organ.\textsuperscript{70}

**IMMUNIZATIONS**

Transplant recipients are at increased risk of infectious diseases in the immediate postoperative period\textsuperscript{91} and for as long as they are on immunosuppressants. There is little information available on the safety and efficacy of immunizations in the transplant population. Although killed virus vaccines are safe for transplant recipients, live virus vaccines are contraindicated. These include vaccines against herpes zoster, measles, mumps, rubella, intra-nasal influenza, oral polio, and the yellow fever vaccines. Transplant recipients should avoid prolonged contact with family members who have been immunized with these vaccines for 2 weeks after receiving these immunizations. Killed virus vaccines that are safe for transplant recipients include vaccines against influenza, *Streptococcus pneumoniae*, tetanus, diphtheria, pertussis, and hepatitis A and B.

Although killed virus vaccines are safe for transplant recipients, the efficacy of these vaccinations is unclear. Patients receiving the trivalent influenza vaccine have been shown to sero-convert up to 50%-95% of the time.\textsuperscript{92-94} Hepatitis A virus immunization is associated with seroconversion rates of 97% initially, that decrease precipitously after 2 years.\textsuperscript{95,96} Recombinant Hepatitis B titers also fall 2 years after immunization.\textsuperscript{97} and Pneumovax immunoglobulin A and immunoglobulin M levels rapidly decrease 6 months after immunization.\textsuperscript{98,99}

Because antibody titer response to immunization is reduced and of shorter duration, booster shots are under study for the transplant population. Heart transplant recipients who have been immunized before transplantation have been shown to have a better immunoglobulin G response to pneumococcal vaccination than those who receive their first pneumococcal vaccination after transplant.\textsuperscript{100} Similarly, a booster immunization strategy of liver transplant patients increased the percentage with therapeutic titers against influenza.\textsuperscript{94}

Primary care physicians should ensure that patients preparing for transplantation should receive all immunizations before surgery. Booster immunizations for the flu vaccine should be considered each year, and patients should be counseled to avoid family members who are ill or who have received a live virus immunization.

**EARLY DETECTION OF MALIGNANCY**

Screening for malignancy is a central activity of primary care providers. Multiple organizations, including the United States Preventive Services Task Force, the Canadian Medical Association, and the American Cancer Society, have published guidelines on cancer screening for the general population.\textsuperscript{71-73} These publications do not include guidelines for screening transplant populations.

Recent studies have addressed the increased risk of malignancy in the solid organ transplant population.\textsuperscript{74-89} The entire renal transplant population of Australia was compared with patients who had chronic renal insufficiency both before and after dialysis.\textsuperscript{84} Almost all cancers had an increased incidence after transplantation. The highest ratio of observed to expected cancer events were in cancers of the lip, eye, penis, vulva, lymphoma, and Kaposi’s sarcoma. Colon, lung, breast, cervix, and ovarian cancers also were disproportionately elevated after transplantation.

Because of the increased risk of malignancy in transplant patients, it would be advisable to screen for malignancies with reliable screening strategies. In the absence of guidelines, primary care physicians should consider maintaining an aggressive screening strategy for transplant recipients.
CONTRACEPTION
Fertility is restored in the majority of women of childbearing age after transplantation.\textsuperscript{101,102} Despite the return to fertility, only 49\% of women were counseled about contraception, and 93\% of pregnancies in one Brazilian renal transplant cohort were unplanned.\textsuperscript{103} Compared with the general population of women in Iran, renal transplant recipients were less likely to use oral contraceptive agents.\textsuperscript{104}

One small study of liver transplant recipients has demonstrated the safety and efficacy of low-dose hormonal contraception. In this study of 15 women who were followed for 12 months after liver transplantation, no cases of pregnancy or graft rejection occurred.\textsuperscript{105}

Primary care physicians should apply similar contraindications for oral contraceptive agents to the transplant population as are applied to the general population, including a history of thromboembolism, smokers over the age of 35 years, and those with known cardiovascular disease. Transplant recipients who have hypertension or diabetes have a relative contraindication for hormonal therapy. Low-dose oral contraceptives should be considered for this group. Barrier methods such as the diaphragm are effective but have failure rates of 18\%. The increased risk of urinary tract infections associated with the diaphragm may pose a greater risk for immunocompromised women.\textsuperscript{106} Intrauterine devices also might be associated with an increased risk of infection, and the efficacy might be impaired due to the need for an intact immune system for full contraceptive function. Decreased efficacy of the intrauterine device has been reported in this population.\textsuperscript{107}

CONCLUSION
Primary care physicians are called upon to care for an increasing number of transplant recipients. The role of the primary care physician is critically important to the survival of this population. Attention to meticulous chronic disease management, careful screening and immunization practices can serve to reduce morbidity and mortality. Immunosuppressants affect every aspect of this care. Physicians should be aware of the impact that immunosuppressants have on primary care. A summary of the recommendations for primary care physicians is shown in Table 3. There is a tremendous need for increasing knowledge that will help primary care physicians to care for the transplant population. Future studies are needed to address the safety and efficacy of medical treatments for chronic diseases, as well

<table>
<thead>
<tr>
<th>Table 3: Summary Recommendations for the Primary Care of Solid Organ Transplant Recipients</th>
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<tbody>
<tr>
<td><strong>Medications</strong></td>
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<tr>
<td>1. Check for possible drug interactions of all new medications prescribed.</td>
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<tr>
<td>2. Check immunosuppressant levels 48 to 72 hours after initiation of any new medication expected to affect levels.</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
</tr>
<tr>
<td>1. Target blood pressure is $&lt;130/&lt;80$ mm Hg for renal and liver transplant recipients and for other transplant recipients with renal disease or other cardiac risk equivalents.</td>
</tr>
<tr>
<td>2. The choice of blood pressure agents should be influenced by comorbid conditions, the pathophysiology of hypertension in transplant recipients, and drug effects on immunosuppressant levels.</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
</tr>
<tr>
<td>1. The target LDL is $&lt;100$ mg/dL for renal transplant recipients.</td>
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<tr>
<td>2. In the absence of data, PCPs should consider treating other transplant recipients to a target LDL of $&lt;100$ mg/dL.</td>
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<tr>
<td>3. Statins should be used as first-line therapy.</td>
</tr>
<tr>
<td>4. Special attention should be paid to the increased risk of myopathy associated with statin use in the transplant population.</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td>1. Recommendations of the American Diabetic Association should be applied to the transplant population.</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
</tr>
<tr>
<td>1. Transplant recipients should be considered at high risk for all malignancies.</td>
</tr>
<tr>
<td>2. PCPs should consider shorter screening intervals.</td>
</tr>
<tr>
<td>3. Annual dermatological examinations should screen for skin malignancies.</td>
</tr>
<tr>
<td>4. Sunblock with an SPF of 60 or greater should be applied daily to sun-exposed skin surfaces.</td>
</tr>
<tr>
<td>5. Patients with newly diagnosed malignancy should be considered for a reduction in immunosuppressants.</td>
</tr>
<tr>
<td><strong>Immunizations</strong></td>
</tr>
<tr>
<td>1. All patients preparing for transplantation should receive immunizations against tetanus, diphtheria, pertussis, Streptococcus pneumoniae, hepatitis A and hepatitis B.</td>
</tr>
<tr>
<td>2. After transplantation, booster immunization should be provided for influenza, tetanus, diphtheria, Streptococcus pneumoniae, and hepatitis A and B.</td>
</tr>
<tr>
<td><strong>Contraception</strong></td>
</tr>
<tr>
<td>1. Women of child-bearing age should be counseled about the need for contraception after transplantation.</td>
</tr>
<tr>
<td>2. Low-dose oral contraceptive agents should be considered for women who have diabetes, hypertension, or hyperlipidemia and do not have contraindications for their use.</td>
</tr>
<tr>
<td>3. Women should be counseled about the decrease in contraceptive efficacy of intrauterine devices after transplantation.</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein; PCP = primary care physician.
as to address cancer screening, early detection strategies, contraception, and immunization protocols for the transplant population.

References


73. American Cancer Society guidelines for early detection of cancer. Available at [http://www.cancer.org/docroot/bed/content/bed_2_3x_acscancer_detection_guidelines_36.asp](http://www.cancer.org/docroot/bed/content/bed_2_3x_acscancer_detection_guidelines_36.asp).


