

Review article

Considerations for a Primary Care Physician Assistant in Treating Kidney Transplant Recipients

Ryan Aston, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Allison Durkin, BS, BA, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Kristen Harris, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Amanda Mace, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Sierra Moore, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Brittany Smith, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Eric Soult, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Mara Wright, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Dustin Yothers, BS, PA-S

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Derrick L. Latos, MD

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Joseph Horzempa, PhD

Department of Graduate Health Sciences, West Liberty University, West Liberty, USA

Department of Natural Sciences and Mathematics, West Liberty University, West Liberty, USA

ABSTRACT

The escalating amount of kidney transplant recipients (KTRs) represents a significant dilemma for primary care providers. As the number of physician assistants (PAs) has been steadily increasing in primary care in the United States, the utilization of these healthcare professionals presents a solution for the care of post-kidney transplant recipients. A physician assistant (PA) is a state licensed healthcare professional who practices medicine under physician supervision and can alleviate some of the increasing demands for primary patient care. Here we provide an outline of the crucial components and considerations for PAs caring for kidney transplant recipients. These include renal function and routine screenings, drug monitoring (both immunosuppressive and therapeutic), pre-existing and co-existing conditions, immunizations, nutrition, physical activity, infection, cancer, and the patient's emotional well-being. PAs should routinely monitor renal function and blood chemistry of KTRs. Drug monitoring of KTRs is a crucial responsibility of the PA because of the possible side-effects and potential drug-drug interactions. Therefore, PAs should obtain a careful and detailed patient history from KTRs. PAs

should be aware of pre- and co-existing conditions of KTRs as this impacts treatment decisions. Regarding immunization, PAs should avoid administering vaccines containing live or attenuated viruses to KTRs. Because obesity following kidney transplantation is associated with decreased allograft survival, PAs should encourage KTRs to maintain a balanced diet with limited sugar. In addition, KTRs should be urged to gradually increase their levels of physical activity over subsequent years following surgery. PAs should be aware that immunosuppressive medications diminish immune defenses and make KTRs more susceptible to bacterial, viral, and fungal infections. Moreover, KTRs should be screened routinely for cancer due to the higher risk of development from immunosuppressive therapy. PAs must remain cognizant of the emotional well-being of the KTR, as many transplant patients struggle with fear, frustration, and acceptance.

Keywords: physician assistant, kidney transplant, nephrology, renal transplant, primary care, post-transplant kidney care, nephrologist

Introduction

The need for post-kidney transplant care in the United States is increasing. In 2011, 17,671 patients received kidney transplants and 181,000 people were living with a transplanted kidney.¹ The rising demand for care required by kidney transplant recipients (KTRs) and the decreasing availability of nephrologists poses a dilemma. The growing number of physician assistants (PAs) offers a valid solution. A physician assistant (PA) is a mid-level state licensed healthcare professional who practices medicine under the supervision of a physician. PAs practice medicine in many countries including the United States, Puerto Rico, Canada, the United Kingdom, the Netherlands, Germany, and Saudi Arabia. Of the 93,098 PAs in the United States, 32% practice in primary care.² While transplant centers assume the complex care of patients before and immediately following transplantation, primary care PAs can offer healthcare maintenance throughout the remainder of the patient's life. This review provides PAs essential elements to consider when providing care for the growing population of KTRs.

Main Text

Renal Function and Routine Screenings

Primary care PAs should monitor water and electrolyte balances in KTRs. Diarrhea is prevalent in 11.5% of KTRs the first year, 17.5% the second year, and 22.6% in the third year post-transplantation.³ Diarrhea leads to malabsorption, dehydration, and immunosuppression; all of these factors can lead to re-hospitalization and increase the likelihood of graft loss and death. These outcomes are exacerbated (2-fold increase) if the diarrhea is noninfectious.³

Closely monitoring mineral levels is imperative in KTRs. Abnormalities in calcium, phosphorus, and magnesium levels associated with transplants can lead to osteoporosis and bone fractures.⁴ Thirty percent of patients evaluated one year after transplantation and 12% of patients evaluated 5 years after transplantation were hypercalcemic (total serum calcium >2.62 mmol/L).⁴ Hypophosphatemia (total serum phosphorus <2.5 mg/dL) is observed more frequently after renal transplantation and decreases osteoblast function, making bones more fragile.⁴ Hypomagnesemia can occur in the first few weeks after transplantation and has been associated with a faster rate of decline in renal function, which leads to graft loss.⁴

An important indicator of kidney functionality is the measurement of protein in the urine. Patients with proteinuria levels >0.5 g/day had only a 70% chance of 5-year graft survival

(compared to 83% 5-year survival with 0.2-0.5g/day and 97.1% 5-year survival with <0.2g/day).⁵ Analyzing the glomerular filtration rate (GFR) in KTRs is also crucial for understanding the efficiency of the transplanted kidney. Patients with an estimated GFR (eGFR) of <40ml/min between year 1 and 2.5 accounted for 41% of graft failures.⁶ Those with lower eGFR also have higher levels of proteinuria.⁶

Immunosuppressive/Therapeutic Drug Monitoring

Calcineurin inhibitors comprise the majority of current immunosuppressive drugs for post-transplant kidney care. Blocking the action of calcineurin, results in T cell suppression, thereby antagonizing allograft rejection. Currently, cyclosporine (Neoral), tacrolimus, mycophenolate, prednisone, sirolimus, and azathioprine are commonly used immunosuppressive drugs.⁷

Immunosuppressive drugs can produce undesired side-effects in patients (Table 1). A recent study showed a high correlation between calcineurin inhibitors and new onset diabetes mellitus.⁸ Clearly, drug-drug interactions need monitored closely with immunosuppressive therapy (Table 2).⁹ Choosing the appropriate drug for the patient requires a careful and detailed history.

PAs should be made aware of the immunosuppressive therapy regimen of the KTR by reviewing the medical records and patient history. PAs should consult with their supervising physician regarding renal dosing of any medication recommended to the KTRs.¹⁰⁻¹⁵

Pre-existing/Co-existing Conditions

Cardiovascular disease, peripheral vascular disease, hypertension, new-onset diabetes mellitus, hyperlipidemia, gout, bone disorders, anemia, and sexual dysfunction are the most common pre-existing and co-existing conditions seen in KTRs (Table 3). These conditions impact treatment decisions (Table 3).

Immunizations

Immunizations play an important role in the preventive health of KTRs, though some are unsafe when combined with immunosuppressive drugs (Table 4).¹⁶ The standard of care is to avoid vaccines containing live or attenuated viruses.¹⁶ The influenza vaccine can be administered one-month post-transplant, prior to the onset of the annual influenza season, regardless of the status of immunosuppression.¹⁶ Depending on the level of immunosuppression and risk of infection, other vaccinations can be administered beginning three to six months post-transplant.¹⁷ By this time, most patients have commenced their baseline

Table 1: Common immunosuppressive drugs and side effects ⁹.

Immunosuppressive Drug	Common Side-Effects
Cyclosporine	Headache, high blood pressure, hyperlipidemia, and diabetes
Tacrolimus	Headache, insomnia and high blood pressure
Mycophenolate	Nausea, low WBC count, and abdominal pain
Prednisone	Cataracts, bone disease, irritability, mood swings, thrush
Sirolimus	High cholesterol, anemia, and joint pain
Azathioprine	Low WBC count, anemia, and hair loss
Beletacept	Agitation, abdominal pain, and black stools

Table 2: Immunosuppressive drug-drug interactions ¹⁰.

Immunosuppressive Drug	Antibiotics	Antifungal	Anticonvulsants	Other
Calcineurin Inhibitors (drugs listed decrease CNI concentration)	Nafcillin, rifampin	Caspofungin, terbinafine	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Octreotide, St John's wart, Echinacea
Mycophenolic Acid (drugs listed decrease MPA concentration)	Norfloxacin, Ciprofloxacin, Amoxicillin with Clavulanic acid, rifampin	N/A	N/A	Albumin-Magnesium Antacids, Sevelamer, Proton Pump Inhibitors
Glucocorticoids	Macrolides (erythromycin, clarithromycin) inhibit glucocorticoid metabolism	Ketoconazole, Isoniazid inhibit glucocorticoid metabolism	Phenytoin, Phenobarbital, carbamazepine induce glucocorticoid metabolism	Cholestyramine, antacids decrease steroid absorption

Table 3: Pre-existing and co-existing conditions. ^{11,12,13,14}

Condition	Consideration
Cardiovascular Disease	Consider length of dialysis prior to transplant. Have patient keep a cardiovascular risk profile data sheet and track blood pressure.
Peripheral vascular disease	Be aware that some dyes used in angiography are nephrotoxic. To reduce the risk of contrast-induced nephropathy, withhold ACE inhibitors, ARBs, and calcineurin inhibitors for 12 hours prior to the angiogram.
Hypertension	Anti-rejection drugs, obesity, and organ rejection may cause hypertension in a kidney transplant patient. Target BP is 130/80 for KTRs.
New-onset Diabetes Mellitus	Seen in 16% of KTRs. Be sure to monitor blood glucose and hemoglobin A1C levels.
Hyperlipidemia	Can be caused by weight gain, poor diet, anti-rejection medications, lack of exercise, or family history after transplant.
Gout	Anti-rejection drugs can cause kidney difficulty filtering uric acid.
Bone disorders	Monitor minerals and increase bone strength with weight bearing exercises.
Anemia	Could be a sign of organ rejection or medication side effects. Watch hemoglobin and hematocrit.
Sexual dysfunction	Typically returns back to normal after transplant, if prior problem existed.

maintenance immunosuppression therapy.¹⁷ Patients should be informed to avoid children and adults who have recently been administered a live or attenuated vaccine.¹⁷ For example, no direct contact should be made for three weeks with those who have received the oral polio vaccine or the attenuated varicella vaccine.¹⁷ KTRs should additionally avoid contact with those who have received live virus nasal sprays for influenza for seven days.¹⁷ If a KTR plans to travel out of the country, the transplant center or an infectious disease specialist should be consulted to determine a need to receive certain vaccines to prevent diseases that are common to the destination.¹⁶

Nutrition

Most weight gain occurs during the first year after a kidney transplant, which averages between 5 to 10 kg (11 to 22 lbs).¹⁸ Several variables contribute to weight gain such as

immunosuppressant drug side-effects and lessening of dietary restrictions previously maintained on the pre-transplant dialysis diet.^{19, 20} KTRs should limit foods that are high in fat and calories.²¹ Other food safety suggestions can also decrease the likelihood of infection (Table 5).

A balanced diet that includes high-fiber foods, such as fruits, vegetables, whole grain breads and pasta should be encouraged.¹⁹ In addition, PAs should ensure patients are consuming recommended levels of macronutrients and minerals to support graft function. Although dietary recommendations should be individualized to fit each patient's circumstances, general guidelines and instructions should be provided to each KTR.

Sodium: To avoid fluid retention and blood pressure imbalance, most KTRs need to have salt restrictions. Sodium should be limited to about three grams per day.²¹ Patients should

Table 4: Recommended immunizations of transplant patients. ^{16,17}

Immunizations	
Recommended Immunizations Post-Transplant	Contraindicated Immunizations Post-Transplant
Influenza type A and B (annually, at least 1 month post-transplant)	Varicella zoster
Pneumovax	Bacillus Calmette-Guérin (BCG)
Hepatitis A*	Smallpox
Hepatitis B (3 doses)	Intranasal influenza
Diphtheria-pertussis-tetanus	Live oral typhoid Ty21a and other newer vaccines
Inactivated polio	Measles (except during an outbreak)
<i>Haemophilus influenzae</i> B	Mumps
Meningococcus (if patient is at high risk)	Rubella
HPV (females up to age 26, males up to age 21, 3 doses)	Oral polio
Typhoid Vi	Live Japanese B encephalitis vaccine
For travel, occupational or other specific risk, and endemic regions	Yellow fever
Consider providing booster polysaccharide pneumococcal vaccine every 3-5 years	

avoid adding salt to food, and eating food high in sodium such as pickles, processed meat, canned soup, snack foods like potato chips, and highly processed packaged foods.²¹

Phosphorus: Post-transplant bone mass restoration increases phosphorus demand. KTRs should consume foods rich in phosphorus (e.g. low-fat dairy products, cheese, dried peas and beans). Monitor phosphorus levels and consider phosphorus supplements.^{19, 20}

Cholesterol: Immunosuppressant drugs can lead to elevated cholesterol levels.²¹ Recommendations to reduce lipid levels include: limiting total fat intake (use cooking oils and soft tub

margarine in place of butter and shortening), eliminating fried foods, limiting weight gain by exercising regularly, eating more high-fiber foods, and reducing consumption of high-fat dairy products.²¹

Protein: KTRs should consume between 5-6 ounces of protein per day.²² Quality sources of protein should be encouraged such as fish, chicken, turkey, eggs, lean red meats and low-fat dairy products two months post-transplant. When cooking, bake, grill or roast instead of frying.²¹

Sugar: Limiting intake of refined sugar can help reduce weight gain and prevent Cushing's syndrome due to high

Table 5: Food safety reminders for kidney transplant recipients to avoid infection. ^{18, 19}

Avoid	Food Safety
Fresh sprouts (bean and alfalfa)	Other Tips
Sushi, raw seafood, shellfish	Wash hands with soap and water before cooking
Salad bars and buffets	Wash all fresh fruits and vegetables before eating
Undercooked (rare) meats or eggs	Use a separate cutting board only for chicken
	Limit restaurant meals

Table 6: Clinically relevant dietary substances that alter drug pharmacokinetics. ²³

Dietary Supplement	Effect
St. John's wort	Increases hepatic and intestinal expression and activity Reduces systemic exposure of drugs like cyclosporine and tacrolimus
Grapefruit juice	Increases or decreases systemic exposure of numerous drugs like amiodarone, buspirone, felodipine, simvastatin, cyclosporine, aliskiren, and fexofenadine
Apple juice and orange juice	Inhibits intestinal organic anion transporting polypeptide
Green Tea	Inhibits intestinal organic anion transporting polypeptide

doses of corticosteroids.²¹ Calorie intake recommendations vary between age, sex, and physical activity levels.²² Patients whose blood glucose levels are controlled can consume sugar in moderation.

Hydration: Attention should be paid to adequate fluid intake. In general, about one-two quarts of fluids should be consumed each day. Water is highly recommended while high-sugar beverages such as regular soda and sweet tea should be limited. Sport/energy beverages should not be consumed unless advised by the transplant team or a dietitian.²¹

Herbal and Other Diet-Derived Products: About 20% of chronic kidney disease patients acknowledge the use of these products, though herbal product use is likely underreported.²³ Educating patients on dietary supplement-drug interactions is crucial (Table 6). Of special concern is grapefruit or grapefruit juice, because consuming these can increase or decrease the systemic exposure of numerous drugs.^{21, 23} More than 40 drug package inserts carry cautionary statements for grapefruit juice.²³

Integration of care with a dietitian may be beneficial to some patients even after one year post-transplant. If a dietitian is not available, refer to <http://www.choosemyplate.gov/> for further recommendations and nutritional guidance.²²

Physical Activity

Obesity prior to and following kidney transplantation is associated with poor patient outcomes, including decreased allograft survival.¹² The sedentary lifestyle often associated with obesity habitually continues following kidney transplantation. This lack of physical activity can diminish allograft function.²⁴ Patients are more likely to exercise when they have a greater self-efficacy for physical activity, especially when recognizing that such activity is associated with positive allograft outcomes.²⁴ Consequently, patient education is a crucial component of increasing physical activity among KTRs. Primary care PAs should focus on designing an exercise regimen with the patient in conjunction with a physical therapist, with consideration to that individual's co-morbidities and level of physical activity prior to transplantation.²⁵ Patients' levels of activity should increase gradually over subsequent years after surgery.²⁵

Infection

Infection is a major cause of mortality in KTRs.²⁶ Although immunosuppressive medications prevent graft rejection, these medications diminish the body's immune defenses. Within the first three years after transplant, infections are common, occurring in 45 out of 100 patients.²⁷ Due to immunosuppressive medications, patients are also vulnerable to respiratory infections and urinary tract infections.¹³ Bacterial infections occur most commonly, followed by viral and fungal infections respectively.²⁷ Bacterial infections include wound infections, which can occur at the surgical site. Candidiasis is the most common mycosis associated with KTRs. The infection typically presents in the mouth and throat, but can also be found at the incision site, eyes, respiratory tract, and urinary tract.²⁷ Cytomegalovirus (CMV) is the most common viral infection in KTRs, occurring in 8% of patients.²⁶ CMV infection symptoms include headaches, fatigue, arthralgia, fever, and pneumonia.

CMV can be transmitted from the donor by either blood transfusion or the transplanted kidney.²⁶ Herpes-simplex virus type I and II as well as herpes zoster infections are also linked to kidney transplants.²⁷ Herpes zoster infections can present with disseminated disease and more extensive skin involvement than in typical patients.²⁸ PAs should recommend the standard therapy for infections in KTRs except when contraindicated (See Table 2 for commonly contraindicated therapies; consult with the supervising physician to avoid prescribing drugs that could have deleterious effects on the KTR).

Cancer

Cancer development after kidney transplant is more likely, primarily due to the regimen of immunosuppressive drugs.²⁹ KTRs with a history of cancer should be monitored for malignancies following transplant.²⁹ Non-melanoma skin cancers and oral cancers have a 10-fold greater incidence in transplant patients, while Kaposi's sarcoma is 50-times more likely in KTRs.²⁹ Basal and squamous cell carcinomas are also likely to develop post-transplant.²⁹ Additionally, transplant patients under the age of 65 have a 15%-30% greater likelihood of developing cancer than those over 65.²⁹ KTRs diagnosed with cancer have significantly worsened prognoses.²⁹

Efficient screening techniques exclude donors with a history of kidney disease; however, many donors with a history of cancer and healthy kidneys are still eligible donors. As a result, KTRs may also acquire cancer from the transplanted kidney.²⁹ KTRs should also be educated on the importance of self-screening for cancers by regularly performing breast and testicular exams and identifying dysplastic or cancerous nevi.

Emotional Well-Being

PAs must remain cognizant of a KTR's emotional well-being. A major concern of many transplant patients relates to a fear of deterioration.³⁰ Constant thoughts that the new kidney may decline in function or the underlying disease may return weaken the patient's emotional well-being.³⁰

In addition, many KTRs experience extreme frustration stemming from unrealistic expectations such as restoration of a lifestyle similar to before renal insufficiency.³⁰ Disappointment ensues when patients realize the complications of post-transplant life.

Changes in self-perception pose an issue for many KTRs, especially females.³⁰ Factors experienced after transplant surgery, such as weight gain, hair growth, abdominal enlargement, and tremors, diminish self-esteem.³⁰ Patients also struggle with accepting the new kidney as their own, which causes patients to establish a new sense of self-perception.³⁰

KTRs struggle not only with self-relationships, but also in relationships with others.³⁰ Oftentimes, patients experience a lack of empathy following transplant surgery, which threatens aspects of their social relationships. Patients appreciate guidance in the maintenance of relationships to family and friends. Frequently, patients also desire assistance in connecting with their donor. A PA can effectively assist KTRs with adapting and maintaining relationships in order to promote a more manageable recovery. The PA can accomplish this by creating a

supportive environment and connecting them with resources to help manage stress and anxiety.

Conclusion

As outlined here, post-transplant kidney care is detailed and life-long. The best recommendation is to remember that transplant patients are often more knowledgeable about their condition than their primary care providers. Setting aside adequate time to talk with the patient will often lead to the most effective assessment and plan for care. Complications associated with transplanted organs are nearly inevitable, but properly trained PAs can reduce the number and severity while easing the workload of nephrologists. Though these elements provide a concise overview, PAs caring for kidney transplant patients should take time to consult with supervising physicians or nephrologists, especially when complications arise.

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Considerations for a Primary Care Physician Assistant in Treating Kidney Transplant Recipients

Summary:

- The kidney transplant recipient (KTR) is usually well-informed regarding their condition. Consider their suspicions and ideas when determining your assessment and plan.

Renal function and routine screenings:

- Monitor patients for dehydration/malabsorption
- Serum calcium < 2.62 mmol/L* decreases osteoporosis and bone fractures
- Blood phosphorus > 2.5 mg/dL* decreases osteoporosis and bone fractures
- Low magnesium is associated with graft loss
- Proteinuria < 0.2 g/day* increases 5-year survival rate to 97.1%
- GFR > 40 mL/min* decreases graft failure

* Lab values may vary between transplant centers

Immunosuppressive/therapeutic drug monitoring:

- Common immunosuppressive drug therapies include calcineurin inhibitors, mycophenolic acid, and glucocorticoids. Because of the possible side-effects (Table 1) and drug-drug interactions (Table 2), a careful patient history is vital.

Pre-existing/co-existing conditions:

- Pre-existing and co-existing conditions impact treatment of KTRs (Table 3).

Immunizations:

- Avoid vaccines containing live or attenuated viruses (Table 4).
- The influenza vaccine can be given one month-post transplant while others can be administered beginning three to six months post-transplant.

Nutrition:

- Encourage adequate hydration and a balanced diet with limited sugar and dietary cholesterol.
- Food safety is crucial to avoid infection (Table 5).
- Be aware of drug interactions with dietary and herbal supplements (Table 6).

Physical activity:

- Obesity following kidney transplantation is associated with decreased allograft survival.
- KTRs should increase levels of physical activity gradually over subsequent years following surgery.

Infection:

- Immunosuppressive medications diminish immune defenses and make KTRs more susceptible to bacterial, viral, and fungal infections.
- Bacterial infections are most common.

Cancer:

- KTRs should be screened routinely for cancer due to the higher risk of development from immunosuppressive therapy.
- Patients should be educated on detecting cancerous nevi.

Emotional well-being:

- PAs must remain cognizant of a post-kidney transplant patient's emotional well-being, as many transplant patients struggle with fear, frustration, and acceptance.

ADDRESS FOR CORRESPONDENCE

Joseph Horzempa, PhD, Department of Graduate Health Sciences, West Liberty University, West Liberty, USA 207 Arnett Hall, CUB 139, 208 University Drive, West Liberty, WV 26074, Tel: Fax: 304-336-8266, e-mail: joseph.horzempa@westliberty.edu