Case Study #3: Care of the Transplant Recipient in the Primary Care Setting

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Martha, a 40-year-old Caucasian female, presents to your clinic for a prevention visit. She had a kidney transplant at age 32 for a congenital renal anomaly. She is taking Prograf (Tacrolimus) 3 mg bid and Cellcept (mycophenalate mofetil) 250 mg bid. She was on Prednisone for 4 years, which was discontinued 4 years ago. She recently saw her nephrologist and her medications and condition are stable. She has no known additional risk factors.

1. What are the near-term risks for transplant recipients (1st year post-transplant)?

In the immediate post-transplant period, the transplant recipient is especially vulnerable to infection and perfusion failure (Lai, 2009). The patient's hemodynamic status is critical to maintaining perfusion to the transplanted organ, so fluid balance and glomerular filtration rate (GFR) must be strictly monitored, and any signs of edema or peripheral vasoconstriction must be acted on immediately (McPhee & Fronek, 2012). Immunosuppression therapy will be initiated to prevent transplant rejection; regimens vary, but typically include:

- Mycophenolate mofentil (MMF) or azathioprine. These are antiproliferatives that inhibit nucleotide synthesis (McPhee & Fronek, 2012).
- Corticosteroids, typically about 20mg daily and tapered as the patient's condition permits (Lai, 2009).
- Tacrolimus or cyclosporine. These calcineurin inhibitors act by inhibiting the activation of T-cells (Lai, 2009).
- Sirolimus and everolimus are new medications sometimes used in place of calcineurin inhibitors but have a less favorable adverse effect profile. They also act to inhibit leukocyte proliferation, but through a different pathway. Their role in immunosuppression is still under debate (McPhee & Fronek, 2012).

- Induction agents, a supplement to immunosuppression therapy that target specific immune cells, are frequently also used in the United States (Lai, 2009). In the absence of complications, the hospital stay is typically one week (McPhee & Fronek, 2012).
- Post-hospital, the focus is on maintaining the health of the donated organ and the prevention of complications. The immunosuppressive therapy puts patients at great risk for infection, so the following prophylaxis regimen is recommended during the first year:
  - Treatment with co-trimoxazole for pneumocystic pneumonia,
  - Valacyclovir for cytomegalovirus (CMV),
  - Isoniazid for tuberculosis,
  - Proton pump inhibitors to reduce risk of peptic ulceration (Lai, 2009).

Patients who do not have hepatitis B should have received the vaccine prior to transplantation, but carriers should receive lamivudine (McPhee & Fronek, 2012). Patients should also be vaccinated for herpes zoster prior to surgery (Lai, 2009). Immunosuppressive therapy can also make weight gain a problem for patients; hypertension and hyperlipidemia frequently develop post-transplant, and statins are recommended (Lai, 2009). A particular problem for renal transplant patients is the polyoma BK virus, which is common in adults and usually asymptomatic. However, in transplant recipients it can be nephrotoxic and is associated with a high risk of transplant failure (Lai, 2009). Diagnosis is usually made on plasma BK PCR and transplant biopsy with symptomatic patients; however, more centers are moving toward surveillance strategies and checking BK PCR at predetermined intervals (Obhrai et al., 2010).

Measured reduction in immunosuppression remains the cornerstone treatment for BK infection; however, there is always the risk of rejection with a decrease in immunosuppression. Coexisting BK infection and rejection presents a therapeutic challenge as one requires lowering

immunosuppressive therapy and the other requires intensifying immunosuppressive therapy (Obhrai et al., 2010).

Also, because transplant recipients often have multiple medical issues, it's important to monitor for pharmacokinetic and pharmacodynamics drug interactions (Obhrai et al., 2010). For example, tacrolimus and cyclosporine are metabolized via cytochrome P450. Cyclosporine is an inhibitor of the P450 and may affect plasma concentrations of antifungal drugs, macrolides, calcium channel blockers, protease inhibitors and statins (Obhrai et al., 2010).

Labs for GFR, creatinine, and immunosuppressive drug concentrations will be monitored throughout the first year, as often as three times weekly immediately after discharge (McPhee & Fronek, 2012). Patients should be educated to be vigilant about weight gain, reduced urine output, and fever, as these can all be signs of graft rejection or possibly infection (Lai, 2009). It is essential that patients adhere with treatment and be protective of their own health. A study conducted by Prihodova et al. (2014) showed that "poor adherence in the first year post-transplantation was associated with increased risk of poor future graft and patient outcomes in the following 12 years."

2. What are the long-term risks for transplant recipients (>1 yr)?

There are many risk factors for a transplant recipient after the first year. In fact, although short-term (1- year post-transplant) survival has improved, long-term survival has stagnated. An Australian research article describes the risk of death of a transplant recipient as being equivalent to that of an average person who is 30 years older (Chapman, 2013). Some of the most common reasons for chronic allograft dysfunction after the 1st year post-transplantation include: chronic allograft nephropathy (CAN), CNI nephrotoxicity, chronic and/or de novo glomerular disease, polyoma (BK) infections, and late acute rejection (Djamali et al., 2006). Monitoring serum levels

of immunosuppressant drugs is critical. CNI toxicity can damage the transplanted kidney. Excessive immunosuppression can result in infection with polyoma BK virus, which is also nephrotoxic, so regular urine testing for characteristic "decoy" cells (Lai, 2009) or BK PCR is recommended (Obhrai et al., 2010).

The leading causes of death in patients with a functioning allograft are cardiovascular disease, infection and malignancy (Djamali et al., 2006). 80% of patients develop hypertension after renal transplant, thought to be related to the use of CNIs and steroids (Lai, 2009). As cardiovascular disease is such a common cause of death, this is a key area for intervention. ACE inhibitors are strongly recommended because of their beneficial effects on proteinuria, preservation of renal function and cardiac function (Lai, 2009). Other long-term complications include new-onset diabetes, anemia, and increased risk for fracture (Schaefer, 2012).

3. What prevention activities should she receive at this time?

As Martha's PCM our goals are the same as for every patient - maximizing wellness, preventing disease, and encouraging healthy lifestyle behaviors. However, it is essential to have a knowledge of the specific risk factors a kidney transplant recipient faces, as well as evidence-based guidelines for screening and follow up. Increasing numbers of kidney transplant recipients are presenting to primary care physicians (PCP) post-transplant for routine medical care, but often a lack of protocols and guidelines makes the task of managing these patients difficult (Gupta et al., 2010). PCPs play a crucial role in improving long-term survival by taking an active part in the management of these high-risk patients.

Studies have shown that the average half-life of an allograft kidney is around 8 years, and allograft function can decrease significantly after that time (Djamali et al., 2006). Complications related to CVD, diabetes, and infections have been shown to significantly accelerate graft loss

(Gupta et al., 2010). Cardiovascular disease and infections are the first and second most common causes of death post-transplant (Djamali et al., 2006). Post-transplant the risk of lung, prostate, breast, and colon cancer can increase 2-3 times, and there is a 100-fold increase in skin cancer risk (Djamali et al., 2006). Around 60% of kidney transplant recipients also have some level of osteoporosis (Djamali et al., 2006).

Even with a transplant, these patients are still cared for as patients with chronic kidney disease. A thorough history and detailed physical exam with special focus on cardiovascular, GI, and GU/renal is essential. Education should be provided at each visit on lifestyle modifications - including weight management, healthy diet (DASH), regular aerobic and weight bearing exercise, daily sunscreen use, early infection treatment, and smoking cessation (Djamali et al., 2006). Blood pressure/vital signs and BMI should be monitored at every visit with appropriate counseling. Blood pressure control has been shown to prolong allograft survival, and JNC 7 recommendations are to maintain BP less than 130/80 in this population (Djamali et al., 2006). ACE inhibitors or ARB's are the first line treatment for hypertension (Bia et al., 2010). Kidney function (metabolic panel with creatinine/BUN, eGFR) and transplant medication levels should be monitored every 2-3 months (Djamali et al., 2006). Annually a CBC, UA, urine protein:creatinine ratio, lipid panel, fasting glucose/CMP, and HgA1C should be assessed as well as periodic renal ultrasounds (Bia et al., 2010). Dyslipidemia should be treated aggressively with statins (Djamali et al., 2006). DEXA screening for osteoporosis should be done periodically (Djamali, et al., 2006) and calcium/vitamin D supplements prescribed if needed. Immunizations should be updated including annual flu vaccine and pneumovax (live virus vaccines are contraindicated). The patient should have annual clinical breast exams and begin annual mammography now that she is 40. She should have PAP screening per guidelines (3-5 years) and

have annual fecal occult blood rectal exams or consider scheduling first colonoscopy due to increased cancer risks (Bia et al., 2010). Bi-annual skin checks, in concert with dermatology, are essential to detect skin cancers (Bia et al., 2010). Finally, pre-conceptual counseling is a topic that is a priority to discuss as pregnancy places increased strain on the kidneys. Additionally, her current medication includes Cellcept, which is a category D. Adequate birth control counseling is a priority.

4. Who is responsible for ensuring prevention in transplant recipients?

With the increasing survival rates of transplant patients, "it is imperative…that the primary care provider have an understanding of the complex and interacting medical issues these patients face" (Schaefer, 2012). As these patients age, they will end-up with many of the same health issues as their peer group and will therefore have medical needs that cannot be managed by the constraints of the transplant centers. For example, even with a successful kidney transplant, the patient's life can be significantly shortened by cardiovascular disease and the annual risk of CVD-associated death for these patients is a 50-fold increase over the general population (Schaefer, 2012). Close coordination by the PCM, along with a partnership with the nephrologist and transplant center, is essential to ensure all preventative and therapeutic interventions are being met, and can significantly improve length and quality of life for this patient population.

Primary care providers must have an in-depth knowledge of immunosuppressive agents as they have associated effects on hypertension, dyslipidemia, and diabetes; the three most prevalent CVD risk factors in the kidney transplant patient (Schaefer, 2012). Therefore, it is the primary care provider that will work with the patient in implementing lifestyle modifications to include weight loss, dietary sodium restrictions, and physical exercise to achieve optimum blood

pressure, serum cholesterol levels and Hgb A1C, in addition to managing any related medications.

5. Which immunizations should the transplant recipient receive, which should they not? Is there a different schedule for transplant recipients?

Immunization recommendations for kidney and general solid organ transplant patients are similar. If a patient was immunized before transplantation, a vaccine-specific immune response was generated in the absence of immunosuppressive drugs. As immunosuppressive drugs (Prograf/Cellcept) affect both the generation of de novo immunity as well as the maintenance of memory responses, clinicians might expect an accelerated decrease in preexisting vaccine-specific immune responses after transplantation (Sester et al., 2008). Although antibody titers toward some antigens may show an accelerated loss after initiation of immunosuppression, protective immunity is not overtly lost. Because a preexisting immunity may be boosted more efficiently compared with primary vaccination post transplantation, it is favor of complete vaccine coverage before transplantation (Sester et al., 2008).

Because these patients develop some type of immunologic response, it is worthwhile to vaccinate for transplant recipients population (Kotton, 2011). The first few months after transplant are likely to result in a reduced optimal response to vaccination. If booster immunizations or primary vaccinations are applied after transplantation, they should be started at approximately 6 months post transplantation to increase efficacy (Sester et al., 2008). Clinicians should consider giving more frequent booster doses of vaccines for immunocompromised patients, and initiation of immunosuppressive drug therapy because their immunity wanes more rapidly (Kotton, 2011).

In general, although live attenuated vaccines should be deferred in this population, including intranasal influenza, varicella, zoster, measles, mumps, rubella, yellow fever, Bacille Calmette Guerin (BCG), and oral Salmonella typhi. Most other routine vaccines are recommended (Kotton, 2011). However, According to Sester et al. (2008) compared to other live vaccines, no contraindication exists for MMR or VZV vaccines, as a transmission of the vaccine strains has not been reported for MMR or is extremely rare in case of the VZV vaccine. All inactivated vaccines may be safely administered in transplant recipients, whereas most live vaccines are strictly contraindicated or should only be administered after a careful risk benefit assessment (Sester et al., 2008).

Additional recommendations range from yearly influenza vaccination for all contacts older than 6 months as well as a booster vaccination toward pertussis, hepatitis A and B, and further receive MMR and varicella vaccination unless already immune (Sester et al., 2008). Recipients also should avoid intimate contact with individuals who have received live vaccines.

> This includes avoiding close contact with children who have received oral polio vaccine for 3 weeks and may include close contact with adults receiving the attenuated varicella vaccine to prevent zoster. Immunosuppressed individuals are advised to avoid contact for 7 days with individuals who have received live virus nasal sprays for influenza. We concur with the recommendation for flu vaccine, but common practice in the United States is to wait 3-6 months after transplant before it is administered. (Bia et al., 2010)

PICOT Questions

Beatty: In renal transplant recipients with hypertension who are placed on ACE-inhibitors compared to those on calcium channel blockers, what is the incidence of allograft rejection at 10 years post-transplant?

Fiandt: In adults with renal transplants, what is the effect of therapeutic lifestyle coaching compared with standard of care on hypertension and GFR one year post-transplant?

Kim: Organ transplant patients with recommended immunizations longer term survival rate compare to the patient without recommended immunizations?

Negard: When blood pressure is well-controlled, is there a difference in preeclampsisa rates when comparing renal transplant patients who are more than one year but within ten years post-transplant with those who are more than ten years post-transplant?

Torres: Are kidney transplant recipients with a history of diabetes before transplant at an increased risk for appendicular skeletal fractures compared with kidney transplant recipients with new-onset diabetes?

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