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CLINICAL UPDATE

Pearls for the Internist Taking Care of the Patient with a Solid Organ Transplant

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Is the miraculous becoming routine? There are now nearly 30,000 solid organ transplant (SOT) recipients per year in the United States.[1] For conditions such as end-stage kidney disease, transplantation is the standard of care—with survival far exceeding that of hemodialysis. Patients with a SOT emerge from the transplantation specialist's domain and arrive at your primary care office or inpatient ward. What do we need to be aware of as we care for these patients? Consider the following three situations.

Table 1. Rejection Syndromes in Solid Organ Transplant Recipients

Transplanted organ	Symptoms	Exam findings	Testing
Heart	Symptoms of heart failure	Tachycardia, signs of heart failure	Reduced ejection fraction (EF), biopsy (gold standard)
Lung	Shortness of breath, cough	Hypoxia (if severe)	Reduction in spirometry, biopsy
Liver	Jaundice, right upper quadrant (RUQ) pain (if severe or acute)	Jaundice, RUQ tenderness (if severe), signs of liver failure	Transaminases and tests for synthetic function, liver biopsy
Kidney	May have none if mild or symptoms of renal failure	Tenderness of graft site if severe	Elevated creatinine, renal biopsy

The SOT Recipient with an Acute Problem

Picture the patient you are called to admit in the Emergency Department or who presents to your clinic with an acute problem.

The first question to ask is: "Is the presenting concern related to the patient's transplant?"

If there is dysfunction of the transplanted organ, consider rejection. Rejection syndromes vary (Table 1)—they may be chronic or acute. Evaluate the transplanted organ for symptoms and signs of dysfunction if clinically relevant. While acute rejection may cause clinically evident symptoms, milder forms and chronic rejection may be more readily apparent by laboratory monitoring or testing.

However, not all complications in a transplanted organ are related to rejection. For example, heart transplant patients can develop coronary artery disease either from atherosclerosis or cardiac allograft vasculopathy; liver transplant recipients may develop recurrent hepatitis C; and kidney transplant patients can develop BK virus nephropathy. In almost all cases, solid organ transplant dysfunction merits consultation with the appropriate specialist.

Be wary of infection. Greeted by ever-more inflammatory and autoimmune conditions, an internist is no stranger to patients receiving immunosuppression. When a SOT recipient presents with potentially infectious symptoms, we need to consider whether there is an opportunistic infection. Knowing the time course and the degree of immunosuppression is essential.[2] For the first month post transplantation, the patient is typically under the close care of the transplant team. During this period, nosocomial, donor-derived, and recipient colonization infections are common. At one to six months, patients still have high levels of immunosuppression and are at risk for—and usually receive prophylaxis against—viral infections (e.g. cytomegalovirus (CMV)) and fungal infections (e.g. *Pneumocystis jurevecii*). This time period is also when patients may return to the primary care setting. After six months, community-acquired infections predominate, and opportunistic infections are less common. However, there are three important considerations: First, even community-acquired infections may present differently in immunosuppressed patients; second, if a patient has had episodes of rejection treated with additional immunosuppression, this may "reset the clock" with regard to infections the patient is at risk for; and third, CMV infection can occur even in this later period.

Watch for cancer—it will most likely present to the generalist. SOT recipients are at increased risk for cancer from both immunosuppression as well as other risk factors that led to the transplant in the first place, such as smoking and alcohol. Similar to the patient with HIV, non-melanoma skin cancers are common.

Post-transplant lymphopro-liferative disorder (PTLD) is particularly important to consider. PTLD is a type of lymphoma associated with immunosuppression, particularly calcineurin inhibitors (e.g. cyclosporine, tacrolimus) that may present in various organs. It

continued on page 2

continued from page 1

often presents late after transplantation, when a patient may be primarily seen by generalists, and its symptoms may be specific to the organ involved. For example, it may present with cough if it arises in the lung, gastrointestinal (GI) bleeding if in the GI tract, neurologic symptoms or headache if in the central nervous system. There are not always localizing symptoms, and therefore a high level of suspicion is critical.

Be wary of drug interactions with the patient's immunosuppressant regimen. As you proceed with workup and treatment of the other conditions—whether in the hospital or in primary care—it is good practice to pause and check for drug interactions whenever you prescribe a new medication, as drug interactions can severely affect the SOT recipient. Common offenders include azoles, clarithromycin (e.g. as used in *H. pylori* therapy), trimethoprim-sulfa, statins, amiodarone, and non-dihydropyridine calcium channel blockers.

For inpatients, consult with the transplant specialist for immunosuppressive management. Immunosuppressive medications are generally continued even in the presence of infection, unless it is truly life threatening. Consider supplemental dose ("stress dose") steroids if the patient is on chronic moderate or high-dose glucocorticoids. Daily levels of immunosuppressive medications do not always need to be monitored in the inpatient setting; it depends on the clinical situation and likelihood of fluctuation. Change in renal/hepatic function, drug interactions, and NPO status can all affect drug levels. Acute kidney injury is common in admitted patients, and calcineurin inhibitors (e.g. tacrolimus, cyclosporine) often require adjustment. Overall, decisions on immunosuppresive medication choice and dosing should only be made by, or in consultation with, the transplant team.

Routine Assessment (example)
Transplant: Liver August 2013 for alcoholic cirrhosis
CMV: Donor positive, recipient negative
Last biopsy: August 2015 normal; last labs (date) AST, ALT normal, INR 1.0, platelets 140; lab tests every three months
Complications: CMV colitis January 2014, mild CKD Cr 1.3
Rejection: Acute rejection November 2013, treated with corticosteroids
Medications: Prednisone 5 mg daily, tacrolimus 1 mg bid, goal level ___
Alcohol: Attends AA, no relapse
Hepatologist: Dr. _____

Routine History and Assessment

Consider the patient who returns to your clinic for scheduled follow up or the hospitalized patient whom you are treating for a separate condition. We still need to make sure all is well with the transplant.

How did we get where we are? Why did the patient receive a transplant? When? Have there already been complications post transplantation (especially *infection* and *rejection*)? What is the patient's and donor's CMV status?

Where are we now? How is the organ doing—is it functioning well? How are we monitoring it (e.g. lab tests, symptoms, biopsies, imaging)? Is the patient taking his/her medications appropriately or having side effects (Table 2)? Who is on the care team if we need consultation?

Most patients receive a combination of a calcineurin inhibitor (e.g. tacrolimus, cyclosporine), an antimetabolite (e.g. mycophenolate, azathioprine), and a glucocorticoid, although the exact regimen varies by transplant center protocol, type of organ transplant, and a patient's history of rejection or toxicities.

Obtaining this basic information and having it well organized will be of benefit to other providers as well

continued on page 3

Table 2. Partial List of Side Effects of Immunosuppressants Used in SOT Recipients*

Immunosuppressant	Side Effect
Calcineurin inhibitors (cyclosporine, tacrolimus)	Renal insufficiency, tremor, hyperuricemia, hypertension, diabetes, gingival hyperplasia (cyclosporine), hirsutism
Mycophenolate	Diarrhea, leukopenia
Azathioprine	Leukopenia, hepatotoxicity
Sirolimus	Poor wound healing, pulmonary edema

**Glucocorticoid side effects are well known and not listed here.*

continued from page 2

as the patient who will not need to relate this to each new provider.

Primary Care

Finally, consider the SOT recipient in your primary care clinic—these patients need monitoring and prevention, with some key differences.

Screen for and treat metabolic illnesses. Chronic kidney disease is very common, often caused by calcineurin inhibitors used for immunosuppression. Hypertension, hyperlipidemia, gout, and diabetes all may be caused or worsened by immunosuppressive medications. Osteoporosis is more common depending on how much glucocorticoid exposure the patient has received—most patients should have a DEXA scan at one year post-transplant with subsequent re-testing depending on the initial results.

Assess the risk of the organ-killing disease coming back. Some patients may be completely cured by transplantation (e.g. lung transplantation for idiopathic pulmonary fibrosis), while others are not so fortunate. Will the lupus that led to renal failure become active again? Is the liver transplant recipient at risk to resume drinking alcohol? Hepatitis C nearly always returns to the liver transplant recipient, but fortunately now there are effective (albeit expensive) treatments.

Don't forget routine preventive health. SOT recipients still need routine care. There are several key differences to be aware of. While vaccinations should be emphasized, patients should not receive live vaccines due to immunosuppression. They should continue to have routine cancer screening. Some guidelines advocate more frequent cervical cancer screening, and most recommend yearly skin cancer screening in SOT recipients.

In addition to these brief pearls, your patients will no doubt teach you about their care. SOT recipients are a rewarding population to care for. They are at the forefront of medicine, and they require all of our skills and training as internists to weave the miraculous with the meticulous and coax clarity from complexity.

References

1. Wong CJ, Pagalilauan G. Primary care of the solid organ transplant recipient. Med Clin North Am 2015; 99(5):1075-103.
2. Pagalilauan GL, Limaye AP. Infections in transplant patients. Med Clin North Am 2013; 97(4):581-600.

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