



A Streamlined Approach to the Solid Organ Transplant Recipient with an Infection

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Abstract: Addressing these three simple questions can assist any physician in making the best-informed decision about diagnostic tests and treatments in regard to a solid organ transplant recipient with an infection. This article serves as a preliminary guide to finding the simplest approach to what is typically a complicated patient and the course of the disease.

Keywords: solid organ transplant; infection

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A 63-year-old man with a past medical history of hypertension, diabetes, history of living donor renal transplant, presents to the hospital with 2 days of fevers, crampy abdominal pain, and diarrhea. The emergency room requests an infectious disease consultation.

Analogous to the notorious fever of unknown origin consultation, the request for a post-transplantation infectious disease consultation strikes the core of the community infectious disease physician with anxiety or with enthusiasm. Rarely is there an indifferent response to the ID transplant consultation. Those who are in the depths of the transplant ecosphere may examine this patient as a thought-provoking challenge, whereas those who are farther removed from transplant centers tend to approach this patient with hesitation. The innumerable potential causes of infection in a transplant recipient can be formidable without an organized approach. Under ideal circumstances, these patients are best served at the institutions where they were transplanted and where their transplantation course is best understood. However, serious infections do not always deliver the convenience of time and place of a patients choosing. It is often in the community where these patients are initially evaluated, and preliminary diagnostic and treatment decisions are made.

Addressing these patients with an organized systematic method can alleviate the uncertainty that comes with assessing the infection in the transplant recipient. This article will address the simplest approach to the post solid organ transplant patient with a potential infection. There are three main

questions that should guide the evaluation of the solid organ transplant recipient. Addressing these three questions will assist any physician in making the best-informed decision about initial diagnostic tests and treatments.

The first and possibly the most imperative question is what is the timing of the infection in relation to the transplant? There are three separate time frames that define the types of infections most likely to predictably occur: the first month post transplantation, the second through the sixth month post transplantation, and the late post-transplant period (beyond the sixth month post transplantation).

Most infections during the first month post transplantation are related to donor-derived infections or infectious complications of surgery and hospitalization. Donor-derived infections are less common, depending on the national standard of donor screening but can include West Nile, *Mycobacterium tuberculosis*, *Candida*, and *Aspergillus* species, herpes simplex virus (HSV), and human herpesvirus 8 (HHV-8), lymphocytic choriomeningitis virus, rabies, *Trypanosoma cruzi*, human immunodeficiency virus (HIV), and hepatitis C virus (HCV) [1]. Rarely, bloodstream infections can occur if the donors have active bacteremia or fungal infection at the time of procurement that adheres to anastomotic sites, including multidrug-resistant bacteria [2]. The typical standard of care is to provide proof of adequate therapy for these types of infections prior to accepting the organ for transplantation. The risk of donor-derived infections is mitigated by careful risk stratification from obtaining the donor's medical and social history, careful physical assessment of the donor and the donor organs, and laboratory screening of the donor for infection. Variation in national screening can depend on available resources, technologies, and local epidemiology. Donor-derived infectious diseases are involved in approximately 0.2% of deceased organ donor transplants [3].

During the first month post transplantation, post-surgical infections are far more common than donor-derived infections and can include bacterial and candida wound infections, pneumonia, urinary tract infections, or technical or anatomical problems related to the allograft [4]. Solid organ transplant recipients are uniquely at risk for superinfection of graft tissue, ischemia of graft tissue, and development of post-surgical fluid collections such as hematomas, lymphoceles, and urinomas, as well as leaks from anastomotic sites. Duration of the actual operation correlates to the mean number of episodes of infection per patient [5]. Noninfectious complications such as thrombosis of critical vasculature, for example, hepatic artery thrombosis post liver transplant, can mimic infectious signs and symptoms and are important to consider in the differential. Surgical complications such as vesicoureteral reflux after kidney transplantation and mediastinal bleeding requiring reexploration in thoracic organ transplantation increase the risk of developing allograft pyelonephritis [6] and mediastinitis [7], respectively. Typical nosocomial infections related to prolonged ventilatory support, indwelling foley catheters, and longstanding intravenous catheters are also common during this first month post transplantation.

If our first patient presented with fevers and abdominal pain a week or two post transplantation, common surgical complications such as ileus, post-surgical abdominal abscess, or ischemia, and hospital-acquired infections such as *C. difficile* would be far more common than opportunistic infections seen in the later post-transplant period. Understanding the post-surgical course is critical during this early time period; it should also be kept in mind that although donor-derived infections are rare, they are possible. Access to the donor infectious disease markers is typically available at the time of transplantation, and they are important to review during this early post-transplant period.

If the patient presents within the second to sixth month post transplantation, this time period is when typical classic post-transplant opportunistic pathogens present such as cytomegalovirus (CMV), *Pneumocystis jirovecii*, *Aspergillus* spp., *Nocardia* spp., *T. gondii*, EBV, HHV-6 and 8, hepatitis B virus (HBV), HCV, *strongyloides*, *T. cruzi*, and *Listeria monocytogenes*. This time period is traditionally the interval and when the effect of immunosuppression is the greatest. The types of opportunistic infections that can develop during this time period vary widely based on local epidemiology, type of immunosuppression, and type of antimicrobial prophylaxis used during this post-transplant period. Major infections during this early post-transplant period would include *Pneumocystis jirovecii* (depending on type and presence of antimicrobial prophylaxis), viral pathogens such as CMV, EBV,

HHV-6, reactivation HBV and HCV, and BK polyomavirus (in kidney transplant recipients), latent infections such as strongyloidiasis, toxoplasmosis, and Chagas disease, endemic fungal mycoses, and TB.

If our initial patient presented during this time frame, consideration of specific immunotherapy as well as disease entity clinical presentation is important. This will be reviewed in further detail below. If our patient with diarrhea and abdominal pain presented 3 months post transplantation while on higher dosages of prednisone, mycophenolate, and tacrolimus, we would now more strongly consider typical opportunistic infections such as CMV, reactivation hepatitis, and Strongyloides—opportunistic disease entities that can present with fever, abdominal pain, or diarrhea.

During this time period, it is also important to take into consideration what type of prophylaxis the patient is taking. If the patient is on letermovir or prophylactic dose valganciclovir, reactivation CMV is less likely. Similarly, if the patient is taking trimethoprim–sulfamethoxazole for pneumocystis prophylaxis or valacyclovir for antiviral prophylaxis, the likelihood of breakthrough infections is far less likely with these pathogens.

After 6 to 12 months post solid organ transplantation, most patients are receiving stable or reduced levels of immunosuppression. Late post transplantation, the transplant recipient will present with similar infections that other patients in the community are most predisposed to, such as community-acquired pneumonia. In patients who are on higher amounts of immunosuppression 6 months post transplantation, they may continue to be at risk for opportunistic infections such as *Pneumocystis*, cryptococcus, *Nocardia*, or virus-associated malignancies such as post-transplant lymphoproliferative disorders.

The second question to address when assessing the transplant recipient with an infection is what is their net state of immunosuppression? The time post transplantation can provide an initial lead, but looking at the type, dose, and duration of immunosuppression can be clues to the types of infections the patient is susceptible to (see Table 1). Antilymphocyte antibodies such as alemtuzumab (Campath 1-H) severely depletes T cells and essentially predisposes the patient to the same opportunistic infections that would affect a patient with end-stage AIDS, such as disseminated *Mycobacterium avium complex* (MAC), *Cryptococcus neoformans*, *Pneumocystis jirovicii*, and *toxoplasmosis*. Alemtuzumab itself also commonly causes a cytokine release syndrome; it is also not uncommon to see fevers, rigors, and hypotension during therapy [8]. Glucocorticoids can increase the risk of developing *Pneumocystis pneumonia*, reactivation of HBV and HCV, and bacterial infections. Mycophenolate can cause B cell depression and may have a role in late-onset CMV. Cyclosporine/tacrolimus increases the risk of intracellular pathogens (i.e., *Listeria*, *Chlamydia* spp.). Assessing the patients overall condition, age, and other comorbidities should also be part of the calculation in the net state of immunosuppression, as well as other host factors affecting immune function, such as neutropenia or hypogammaglobulinemia. Typically, bacterial and fungal pathogens are more important to consider during neutropenia, whereas viral infections and intracellular pathogens should be strongly considered with T cell immune deficiencies. There are important viral pathogens that present with classic clinical presentations in the transplant recipient. BK polyomavirus in renal transplant patients can cause hemorrhagic cystitis, ureteric obstruction, elevated creatinine function, and asymptomatic viruria [9]. Adenovirus classically causes a syndrome of hemorrhagic cystitis, hepatitis, and/or pneumonia in transplantation recipients. HHV-8 is associated with Kaposi sarcoma and the estimated incidence post renal transplant ranges from 0.5 to 5.3%, depending on geographical location [10]. Parvovirus B19 can present with pancytopenia, myocarditis, and hepatitis, and in particular, refractory anemia [11]. Consider these specific clinical syndromes especially if the patient is presenting within the first year post transplantation or if the patient remains on higher doses of immunosuppression because of graft rejection.

The last question that should come naturally to all infectious disease physicians is what are the patients epidemiologic exposures? This requires a detailed history of potential encounters and a review of latent pathogens present in the host and donor that could be reactivated. Consider typical community pathogens and likely exposures during the assessment. For example, in 2020, the primary

circulating respiratory virus was SARS-CoV-2 and influenza was rarely seen [12]. In the Midwest, endemic mycoses such as *Histoplasma capsulatum* and *Blastomyces* would be considered. In the southwest, *Coccidioides* would also be included, whereas, in the Pacific Northwest, *Cryptococcus gattii* would be important to consider. Traveling to any of these geographic areas provides ideas for the differential diagnosis. Consider the donor and recipients CMV baseline serostatus, and if the donor and recipient could have been exposed to West Nile, Chagas disease, or *Strongyloides*.

Table 1: Type of immunosuppression and infection.

Type of Immunosuppression	Mechanism of Action	Risk of Opportunistic Infection
Prednisone	Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability. Suppresses the immune system by reducing activity and volume of the lymphatic system	Pneumocystis jirovicii, reactivation HBV and HCV, reactivation CMV, bacteria
Antimetabolite (azathioprine, mycophenolate)	Causes a reduction in intracellular purine synthesis, resulting in decreased number of circulating B and T lymphocytes [13], reduced immunoglobulin synthesis, and decreased IL-2 secretion [14]	Leukopenia, neutropenia. Viral infections, particularly reactivation VZV and reactivation HBV, HCV. Possible role in late-onset CMV
Calcineurin inhibitor (cyclosporine or tacrolimus)	Selectively inhibit calcineurin, impairing transcription of IL-2, TNF-alpha, IL-3, IL-4, CD40L, granulocyte-macrophage colony-stimulating factor, and interferon-gamma	Viral (particularly reactivation CMV), intracellular bacterial (listeria, chlamydia)
Mammalian target of rapamycin (mTOR) inhibitor (belatacept)	Selective T cell costimulation Blocker	Bacterial, fungal, HSV, CMV
Alemtuzumab (Campath 1-H)	Binds to CD52, a nonmodulating antigen present on the surface of B and T lymphocytes, majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes	Can be associated with fevers, hypotension, cytokine release syndrome (CRS). Prolonged lymphopenia for up to 3 years [15]. Risk of opportunistic infections with low CD4 counts: cryptococcosis, MAC, toxoplasmosis, Pneumocystis jirovici

Returning back to the original patient, now consider if our patient presented 3 years post transplantation and is on low dosages of mycophenolate and prednisone and presented with acute onset of fevers, crampy abdominal pain, diarrhea, hyponatremia, a lobar infiltrate, and altered mental status, and is from a skilled nursing facility where three other patients have been diagnosed with similar symptoms. *Legionella pneumophila* would be top on the differential because this patient is farther out from his transplantation, and epidemiologically, he has likely been exposed to the same contaminated water source as the other residents in his living facility who also presented with a classic clinical syndrome consistent with Legionnaires disease.

Starting with these three simple questions will help guide preliminary diagnostic and therapeutic decisions. Instead of being overwhelmed by the broader differential in an immunocompromised patient, use these three questions to guide you to what the most probable cause of infection is

based on timing relative to the actual transplant, net immunosuppression (paying attention to specific agents and their immunologic effects), and epidemiologic exposures. The management becomes far simpler as the patient is farther out from his or her actual transplant date and as immunosuppression is reduced. The post-transplant patient with an infection can be a complex domain to understand, but addressing the patient in a systematic way using these tips will help simplify and organize the approach.

Conflicts of Interest: The author declares no conflict of interest.

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