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With the increased longevity of solid organ transplant patients, the complications of chronic maintenance immunosuppression are emerging. Infection remains a significant concern in this setting. The spectrum of infectious complications is different, however, in the long-term well transplant patient compared to the recently transplanted patient. This article reviews the important spectrum of pathogens to consider in the late transplant period (>6 months after transplantation). The prevention of infectious complications through minimizing environmental exposures and vaccination are reviewed, particularly in light of the nature of the impaired host defenses. The importance of certain infections in the development of malignancies is highlighted.

CHRONIC N'ER DO WELL:

A patient who is >6 months post transplantation and who is not doing well, e.g., remaining on a high level immunosuppression, multiple episodes of rejection, or malnutrition.

Infection and rejection have been the two main barriers to successful organ transplantation. Since the first successful organ transplant on December 23, 1954 by Dr. Murray, of a kidney between identical twins, significant advances in immunosuppressive medications have been developed (mercaptopurine in 1953, azathioprine in 1960, and cyclosporin in 1983) thus allowing improved graft and patient survival. Despite improvements in immunosuppression, infection remains one of the most important complications in this population, occurring in approximately one-third to half of all patients.

Infectious disease complications in the solid organ transplant (SOT) patient can be divided into three time periods, as seen in Figure 1: early (less than 1 month post-transplantation), intermediate (1-6 months post-transplantation), and late (greater than 6 months post-transplantation).[1] The early transplant period is typically characterized by procedure related complications either technical (e.g., suture lines) or supportive care in origin (e.g., catheters). The predominant organisms involved are usually the typical nosocomial pathogens: bacterial (Gram-negatives, MRSA, VRE, *C difficile*) or fungal (*Candida* species). The intermediate period is characterized by opportunistic pathogens (related to the high level of immunosuppression), such as: CMV, HSV, HCV, HBV, *Listeria*, *M. tuberculosis*, *Nocardia*, PCP, *Aspergillus*, *Cryptococcus*, and *Strongyloides*. The late transplant period, the focus of this article, is characterized by an increased susceptibility to community pathogens and certain opportunistic organisms.[1-5]

Principles

To minimize infectious complications, several principles must be kept in mind when caring for a SOT patient.

Net State of Immunosuppression. This is a critical but complex concept and is influenced by more than the immunosuppressive regimen (dose, duration, and sequence of medications). It is a function of the immunosuppressive regimen, allograft rejection, leukopenia, mucosal integrity, metabolic abnormalities (e.g., protein-calorie malnutrition, uremia), and infection with immunomodulating viruses (e.g., CMV, EBV, HHV-6, HBV, HCV, HIV). Increased immunosuppression leads to impaired cell-mediated immunity and an increased risk of infectious complications. Thus certain chronic viral infections create a vicious cycle of disease: augmenting immunosuppression which further increases viral replication.

The majority (approximately 80%) of SOT patients will have a relatively uncomplicated post-transplant course and will be maintained on chronic low level immunosuppression by 6-12 months after transplantation. In contrast, a minority (approximately 20%) of patients will have complications that impair their net state of immunosuppression, with

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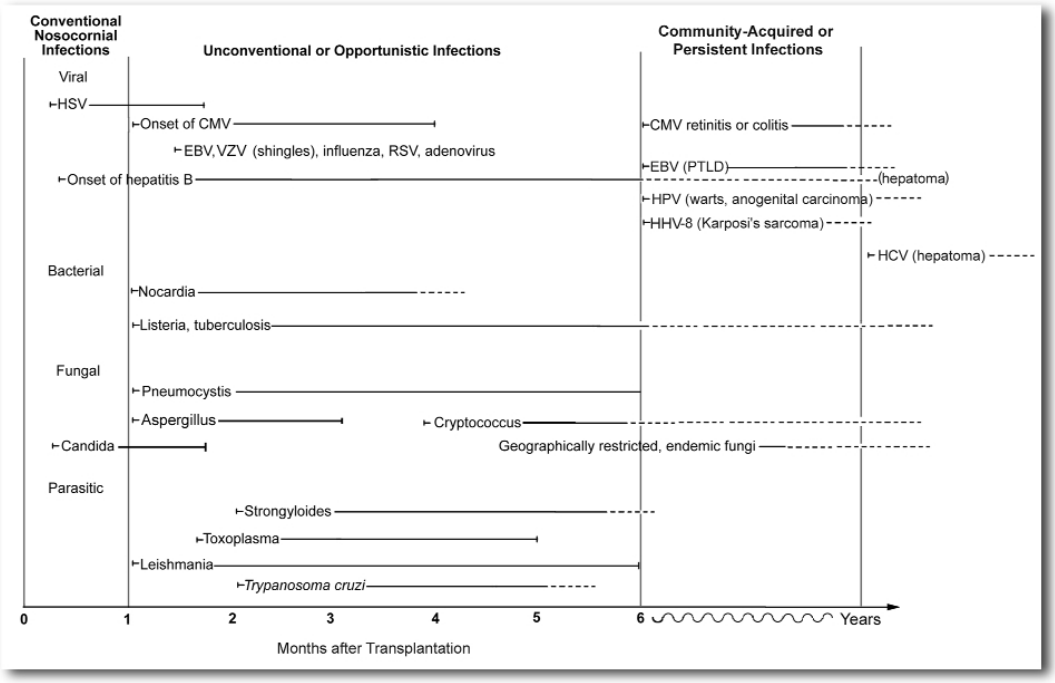

Figure 1. The typical sequence of infection after organ transplantation. HSV–herpes simplex virus; CMV–cytomegalovirus; EBV–Epstein-Barr virus; VZV–varicella-zoster virus; RSV–respiratory syncytial virus; PTLD–post-transplantation lymphoproliferative disease; HPV–human papilloma virus; HBV–hepatitis B virus; HCV–hepatitis C virus; HHV-8–human herpes 8 virus. Adapted from ref. 1 and 70.

NET STATE OF IMMUNOSUPPRESSION:

The sum total effect, in a given patient, of the various immune-suppressing forces, including: immunosuppressive medications, allograft rejection, leukopenia, mucosal integrity, metabolic abnormalities, and immunomodulating viruses.

chronic viral infections and augmented immunosuppression for allograft rejection being the most important. These patients have been aptly characterized by Rubin, as "chronic n'er do wells".[1,5] This patient group, despite being greater then 6 months from their transplant, remains at risk for pathogens typically associated with the intermediate post-transplant period (1-6 month post-transplant).[1,4-6]

Finally, when therapy for acute rejection is given, the risk for opportunistic infections typically seen in the intermediate period rises substantially. Prophylaxis for these pathogens, such as CMV and PCP, should be revisited.

Epidemiologic Exposures. Epidemiologic exposures are of two varieties: reactivation or new acquisition. Reactivation of quiescent or latent pathogens is typically associated with heightened immunosuppression. The organisms which typically present via this mechanism include viruses (HSV, CMV, VZV, HHV-6, HBV, HCV, JC/BK), bacteria (*M. tuberculosis*), fungae (coccidiomycosis, histoplasmosis) and parasites (*Strongyloides*, *Toxoplasma*, *Trypanosoma cruzi*). Patients not previously exposed to these pathogens are certainly at risk for infection when exposed. A primary infection in the setting of multiple immunosuppression is typically more severe than reactivation or primary infection in the immunocompetent host. For example, primary varicella infection in the SOT patient often leads to severe complications such as pneumonia, hepatitis and encephalitis, and may be lethal in these patients.

New acquisition of a pathogen depends on the nature of organisms present in the local environment and the inoculum of exposure. As a general rule, SOT patients require less exposure time and lower inoculi than immunocompetent individuals for an infection to occur. Proper assessment of risk requires an understanding of geographic diseases (e.g., endemic mycoses, parasitic diseases), animal flora (e.g., birds, reptiles, cats), dietary habits (e.g., water supply, exotic foods), occupation, hobbies (e.g., gardening), and sexual habits. Overall, the most important organisms to consider include: PCP, *Nocardia*, *Cryptococcus*, *Aspergillus*, *Legionella*, *Salmonella*, *Cryptosporidium*, and respiratory viruses.[3]

LATENT INFECTION:

A pathogen which is dormant in an immunologically normal host but has the potential to reactivate and cause disease when immunosuppression occurs (e.g., herpes viruses, M tuberculosis, endemic mycoses).

Diminished Clinical Signs and Symptoms. An inevitable consequence of immunosuppression is to diminish the inflammatory response. Therefore it is not uncommon for a patient on steroids or multiple immunosuppressive medications to lack the typical signs and symptoms of an active infection. A high index of suspicion must be maintained when new symptoms develop, as these patients often do not present to medical attention until the advanced stages of an infectious process.

Types of Infectious Complications. Infectious agents may affect the transplant patient in four ways:

1. directly by causing tissue damage,
2. indirectly by augmenting immunosuppression,
3. augmenting allograft injury, and lastly
4. by oncogenesis.

CMV and recently HHV-6 have been most clearly associated with augmenting immunosuppression and allograft injury. EBV and HPV have been associated with the development of malignancies, post-transplant lymphoproliferative disorder and cervical/anal carcinoma respectively. Therefore treatment of these viruses must be carefully directed at the disease process of concern.

Types of Therapeutic Intervention. Therapy should be deployed in one of three ways:

1. treatment,
2. prophylaxis, and
3. preemptive therapy.

Treatment is directed against a known focus of infection. Prophylaxis is directed at a group as a whole (e.g., vaccination, *Pneumocystis carinii* prevention with trimethoprim-sulfamethoxazole after SOT). Pre-emptive therapy is directed at an at risk group when evidence of increased risk is manifest (e.g., utilizing CMV viral load to determine when to institute ganciclovir prior to clinical symptoms developing).

Pre-emptive therapy is frequently used in the transplant patient to diminish infections during high-risk periods. Two important principles need to be kept in mind: first, this strategy usually diminishes the overall occurrence of the infection, and second, this strategy typically delays the incubation period 1-4 months after the prophylaxis has been discontinued (e.g., CMV is most likely to occur during the 1-4 months after ganciclovir prophylaxis has been discontinued).

Drug Interactions and Toxicities. The therapies used to treat or pre-empt infections often pose significant drug interactions and toxicities. Given calcineurin inhibitors are metabolized via the cytochrome P-450-IIIA (CYP3A) pathway, other medications which modulate this enzyme system (and CYP1A) should be used cautiously. Medications which upregulate the metabolism of calcineurin inhibitors thus increasing the risk for rejection, include rifampin, isoniazid, nafcillin, phenytoin, phenobarbital and carbamazepine. Medications which downregulate the metabolism of calcineurin inhibitors therefore increasing the risk of nephrotoxicity and over immunosuppression, include: macrolides (clarithromycin, erythromycin), azole antifungal agents (fluconazole, itraconazole), calcium channel blockers (diltiazem, nicardipine, verapamil) and metoclopramide. A third type of medication interaction is important to consider, synergistic nephrotoxicity, which has been seen when aminoglycosides, fluoroquinolones, amphotericin, or trimethoprim-sulfamethoxazole have been used in conjunction with cyclosporine or tacrolimus.

Prevention. It is significantly easier to prevent an infectious complication then to treat. Therefore thorough pre-transplant evaluation and treatment is warranted (e.g., vaccinations, secondary prophylaxis for TB, *Strongyloides* assessment). In the post-transplant setting it is prudent to augment immunity by minimizing immunosuppression and vaccinating when possible, optimally pre-empt latent disease (e.g., CMV) and prophylax for common exposures (e.g., PCP) particularly during high-risk periods (e.g., OKT3 therapy for rejection), and minimize environmental exposures.

Type of Transplant. There are several important issues raised by the different types of SOTs which should be considered. First, there is an immunologic difference, with some degree of HLA matching in renal transplantation but not for other organs. This manifests itself in the high level of maintenance immunosuppression lung and cardiac transplant patients require. Second, certain organs, such as lung and livers, are transplanted into contaminated environments: airways and biliary tree without a sphincter, respectively. Third, artificial organ replacement therapy is available for renal failure but not for other types of organ dysfunction (to a limited extent in hepatic failure with hepatic dialysis

and cardiac failure with left ventricular assist device). This severely limits treatment options for heart, lung and liver transplant recipients in the setting of a severe infection where it might otherwise be appropriate to sacrifice a renal allograft to treat a life threatening infection such as invasive aspergillosis. Fourth, the allograft is subject to particular infectious complications: UTIs in renal allografts, pneumonia and bronchial anastomotic disruption in pulmonary allografts, biliary infection and hepatitis in liver allografts, and myocarditis in cardiac allografts.[7]

Syndromes

The primary infectious disease concerns for transplant patients who are doing well (excellent allograft function, on baseline immunosuppression and no chronic viral infection) are related to pathogens circulating in the community, particularly respiratory and enteric pathogens. Central nervous system infection, though not as common, may be particularly severe, thus are important to consider. When a new infection is acquired and there is no increase in immunosuppression then a significant environmental exposure should be considered. The SOT patient is often the first in the community to become clinically ill during an epidemic, such as with influenza, thus altering public health officials to the transmission of a given infectious agent. As noted above, the altered anatomy and immunology of the transplanted organ specifically predisposes to a high rate of graft related infections (e.g., urinary tract infections in the setting of a renal transplant). When a local graft related infection occurs appropriate diagnostics to guide therapy are warranted.

PREEMPTIVE THERAPY:

An intervention directed at a group who is at high risk for a disease, typically identified by an epidemiologic or biochemical marker (e.g., CMV viral load).

Respiratory. The well transplant patient is not immune to common community infections. As respiratory infections are highly prevalent in the general population, so they are in transplant patients. The most common pathogens reflect what is circulating in the community and include Influenza A and B, *Pneumococcus*, and *Leigonella*. Depending on the local epidemiology other pathogens to consider include respiratory syncytial virus (RSV), parainfluenza, adenovirus, rhinovirus, *Haemophillus influenzae*, Mycoplasma, and Chlamydia.

SOT patients are more likely to be symptomatic when infected, have more severe disease, and have prolonged viral shedding (when infected with a virus) even after symptomatic recovery. Prolonged viral infections predispose to bacterial superinfections with, such organisms as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Hemophilus influenzae*, and Gram-negative *bacilli*. Therefore when URI symptoms develop a prompt diagnosis is warranted, such as nasal washings for viruses, and early antiviral therapy for Influenza (amantadine, rimantadine, zanamivir, oseltamivir) and RSV (aerosolized ribavirin, RSV-IG, palivizumab) may be beneficial.

Lung transplant recipients are at highest risk for respiratory infections and complications given the impaired local immunity (HLA mismatching), pre-existing anatomical abnormalities (such as bronchiectasis in single lung transplant patients, which predisposes to colonization with *Aspergillus*, *Mycobacterium avium*, *Pseudomonas*, and *Burkholderia*), and chronic colonization with resistant organisms (either due to anatomical abnormalities and/or multiple prior courses of antibiotics). Thus when a viral process further impairs host defenses the possibility of a bacterial superinfection is increased. This situation is further complicated by the concern for rejection, which may present as a respiratory syndrome.

Potential epidemiologic exposures to respiratory pathogens must be carefully assessed as SOT are at particular risk for organisms which require intact cell-mediated immunity. Most immunosuppressive agents used in SOT significantly impair cell-mediated immunity, even at lower maintenance doses years out from the transplant. Common pathogens which may flourish under these conditions include *Cryptococcus*, *Nocardia*, *Aspergillus*, *Pneumocystis carinii* (PCP), endemic mycoses, *Mycobacterium tuberculosis*, and *Leigonella sp*. Certain types of these pathogens are geographically restricted such as the endemic mycoses (*Histoplasma*, *Blastomycosis*, *Coccidioidomycosis*, and *P. marnefii*), therefore a careful exposure history should be obtained. Understanding the natural reservoir for certain organisms is essential to proper counseling and risk reduction for example, *Cryptococcus*/birds, *Nocardia*/soil and *Aspergillus*/soil (Table 1).

With the advent of trimethoprim-sufamethoxazole prophylaxis the 10-15% occurrence of PCP pneumonia during the first 6 months after transplantation has been reduced to near zero.[8] However, in the well transplant patient off prophylaxis, who develops a need for significantly increased immunosuppression, resumption of prophylaxis should not

Table 1 | **Important Infectious Pathogens in the SOT Patient and the Associated Vector(s)**

Common Vector	Pathogen(s)
Animals	
Cats	Toxoplasma
Birds	Cryptococcus, Chlamydia
Reptiles	Salmonella
Aquarium/Fish	Mycobacteria marinum
Bats	Rabies
Environmental Exposures	
Soil/Gardening	Aspergillus, Nocardia, Fusarium
Spelunking	Histoplasma
Geographically restricted	Histoplasma, Blastomycosis, Coccidioidomycosis, Strongyloides
Construction/Damp Basement	Aspergillus
Day care	Respiratory and enteric viruses
Food	
Poultry, Eggs	Shigella, Campylobacter, HAV, Salmonella
Deli meats, cold slaw	Listeria
Undercooked meat	Toxoplasma
Unpasteurized dairy	M. TB, Salmonella, Brucella, M. bovis
Poorly washed produce	Cyclospora, Cryptosporidium, Giardia, E. Coli
Contaminated water	Leigonella, Cryptosporidium, Aeromonas, Giardia, Microsporidium
Person to person	M. TB, measles, VZV, HSV, EBV, respiratory viruses (RSV, parainfluenza, influenza, adenovirus), enteric viruses (rotavirus, norwalk virus, adenovirus)
Sexual activity, IVDU, or blood products	HIV, HCV, HBV, CMV, HSV, HPV, *T. cruzi*
Reactivation of latent infection	HIV, HBV, HCV, Herpes viruses (CMV,EBV, HSV I + II, VZV, HHV-6, HHV-8), HPV, *T. cruzi*, Histoplasma, M. TB, Coccidiomycosis, Melioidosis

HAV–hepatitis A virus; M. TB–mycobacterium tuberculosis; M. bovis–mycobacterium bovis; VZV–varicella-zoster virus; HSV–herpes simplex virus; EBV–Epstein-Barr virus; RSV–respiratory syncytial virus; CMV–cytomegalovirus; HDV–human immunodeficiency virus; HCV–hepatitis C virus; HBV–hepatitis B virus; HHV-6–human herpes virus 6; HHV-8–human herpes virus 8; T. cruzi–Trypanosoma cruzi.

be forgotten. Certain viral infections such as CMV increase the risk for fungal infections, such as *Aspergillus* and PCP, likely due to augmented local immunosuppression.[9,10] Therefore settings which increase CMV viral turnover, such as rejection treated with OKT3, the increased risk for other infections should be taken into consideration.[10-12]

Given the global prevalence and the public health considerations, *M. tuberculosis* requires special consideration. Developing tuberculosis after SOT has been estimated to occur in 0.35-15% of patients, of which approximately 35% occur within 6 months of transplantation, 22% between 6-12 months, and 43% greater than 12 months.[13] Active infection has been correlated with endemic tuberculosis infection rate of the patient, non-renal transplantation, rejection within 6 months of illness, and intensity of immunosuppression. Approximately half of the cases are pulmonary disease, thus raising important infection control concerns, and one third will have disseminated disease, with OKT3 and anti-T cell antibodies being the most important predictors.[13] The GI tract is the most frequent site for extrapulmonary reactivation. Mortality is high, approximately 29%, in SOT who develop active tuberculosis infection. Thus it is important to consider chemoprophylaxis in patients at risk for having latent infection, and to diagnose early those patients with active disease.[13]

PROPHYLACTIC THERAPY:

An intervention directed at a group as a whole (e.g., PCP prophylaxis for all SOT patients).

Enteric. Immunosuppressive therapy, such as corticosteroids for SOT, may blunt the abdominal pain and other manifestations of GI infections. Even diverticulitis or appendicitis with perforation or cholecystitis may present with few signs or symptoms until advanced illness has occurred. This is compounded by the immune defects related to immunosuppression, thus facilitating an infectious process to progress more rapidly. A high index of suspicion for common abdominal ailments must be maintained and early diagnostic evaluation pursued. Management of gastrointestinal symptoms is challenging, as GI intolerance is a common side effect of commonly used medications, notably mycophenolate mofetil.

When an infectious gastrointestinal illness develops in a patient on chronic immunosuppression, a broad range of pathogens should be considered. Depending on epidemiologic exposures, these include bacteria (*Listeria*, *Salmonella*, *Mycobacteria*), viruses (HSV, VZV, CMV), parasites (*Cryptosporidium*, *Isospora*, *Cyclospora*, *Giardia*, *Strongyloides*, *Leishmania*), and fungi (*Aspergillus*, *Histoplasma*, *Cryptococcus*, *P. marnefii*).

Intracellular bacteria, mainly *Salmonella* and *Listeria*, may cause particularly serious consequences and have been associated with conditions that impair cell-mediated immunity such as corticosteroid use, DM, SOT, hematologic malignancy and collagen vascular disease. Immunocompromised hosts experience more severe GI illness as well as an increased risk for extraintestinal dissemination compared with immunologically normal individuals.[14-16] In one study of renal transplant patients, 2.3% of patients with gastroenteritis had a positive culture for *Listeria*, and 5.6% of patients were found to have *Listeria* isolates over the course of a year.[17] Asymptomatic carriage was most common during July and August. The risk of dissemination beyond the GI tract (particularly to the CNS), prolonged GI shedding, and relapsing disease is particularly increased in patients on corticosteroids.[18,19] In one series of salmonella infections, the rate of extraintestinal dissemination was 20% compared to <1% in non-immunocompromised individuals and is associated with increased mortality.[20] Sites of dissemination include the meninges, arterial vasculature, bone and urinary tract. Renal transplant patients infected with *Salmonella* have relapsed with the same strain 15 years after initial infection. The arterial vasculature and reticuloendothelial system are thought to be the likely reservoirs for relapsing illness. Trimethoprim-sulfamethoxazole prophylaxis for PCP has likely decreased the occurrence of *Listeria* and *Salmonella* infections, however, as alternative prophylactic agents such as atovaquone, which lack activity against these organisms, are adopted we may see an increase in this infection. With the prolific use of antibiotics globally, trimethoprim-sulfamethoxazole resistance is becoming increasingly common in some *Salmonella* species. Shigellosis and campylobacter infection have also been found to have a higher rate of extraintestinal dissemination in this patient population. For all bacterial agents of enteritis in immunocompromised persons, masking of symptoms, increased risk for bacteremia and metastatic infection mandate a high index of suspicion and prompt initiation of diagnostic studies and antibacterial therapy.

Many parasites have been reported to cause illness in immunocompromised patients, typically in the outpatient setting, including *Cryptosporidia*, *Cyclospora*, *Giardia*, *Strongyloides*, *Microsporidia*, *Isospora*, *Blastocystis hominis* and *Leishmania*.[21] Typically infection with these pathogens represents a significant epidemiologic exposure in the setting of impaired host defenses. In areas of the world, such as Egypt, 23% of immunocompromised hosts were found to have an opportunistic parasite in their GI tract.[22] *Strongyloides* is of particular importance as it is able to complete its life cycle in the human intestines, thus individuals infected can maintain the organism for decades, and in the setting of corticosteroid use infection may become clinically apparent with a 'hyperinfection' syndrome, which can be fatal. An eosinophilia and a careful travel history may be the only early clues to infection. If *Strongyloides* is suspected, stool for O+P (preferably the Baermann method) and a serology are important to obtain, prior to initiating immunosuppression.[23]

As we discover and are able to diagnose new pathogens such as intestinal protozoa, their importance in human disease is increasingly appreciated. For example, *Cryptosporidium* has the potential for explosive outbreaks as a recent epidemic of over 400,000 cases from a contaminated water supply in Milwaukee demonstrated. Recurrent and prolonged cryptosporidial diarrhea was common in individuals in this outbreak and an increased mortality was found in immunosuppressed patients.[24] Diagnosis of intestinal protozoal (*Cryptosporidia*, *Cyclospora*, *Microsporidia*, and *Isospora*) infection requires careful

evaluation of a wet stool preparation and modified acid-fast and trichrome stains. Multiple stool samples should be examined, as the sensitivity of a single sample is low. It is important to note that normal healthy individuals infected with one of these organisms rarely requires antibiotic therapy, while immunocompromised patients may require lifelong therapy.[25,26]

There are several principles worth highlighting. It is important to note that in this patient population the presentation of GI infection and its complications, such as intestinal perforation, may be subtle until the patient is quite ill. These patients are at greater risk for dissemination of the offending pathogen (e.g., *Listeria* and *Salmonella*) with potential visceral seeding. In addition, it is important to consider a history of epidemiologic exposures, geographic or local epidemic, when patients present with GI illness. When an infection is ultimately identified, eradication of the organism is usually more difficult in the SOT patient, therefore, early institution of appropriate antibiotic therapy is essential. Finally, these patients usually require prolonged therapy. Follow-up cultures must be obtained after completion of therapy, as relapses are common, especially in the setting of life long suppressive therapy. When an enteric bacterial pathogen is suspected we recommend early antibiotic therapy with a quinolone; however, if antibiotic resistance is probable, as with *Listeria* or DT104 strain of *Salmonella*, then therapy should be adjusted accordingly.

Central Nervous System. There are four patterns of central nervous system disease which occurs in SOT patients:

1. acute/subacute meningitis typically caused by *Listeria monocytogenes*,
2. subacute/chronic meningitis which presents with indolent headache, fever and diminished consciousness and is typically due to *Cryptococcus neoformans*, *Mycobacteria tuberculosis*, and *Coccidioides immitis*,
3. focal brain infection often presenting with focal neurologic defects and a mass on imaging, the typical pathogens to consider include *Listeria monocytogenes*, *Toxoplasma gondii*, *Cryptococcus neoformans*, *Nocardia sp*, and *Aspergillus sp*, and
4. progressive dementia typically presenting with slow loss of cognitive function and usually caused by polyomavirus JK (PML: progressive multifocal leukoencephalopathy).

Despite the varied pathogens which may be encountered, over three-fourths of CNS infections in the SOT patient are due to *Listeria*, *Cryptococcus*, and *Aspergillus*. Trimethoprim-sulfamethoxazole prophylaxis likely is effective in preventing *Listeria*, *Nocardia*, and *Toxoplasma* infections. It is important to note that immunosuppression may significantly blunt the inflammatory response when meningitis is present (e.g., lack of meningismus) thus a low index of suspicion to perform an LP or CNS imaging is required when a SOT patient presents with fever and headache or focal neurologic deficits. Important considerations in diagnosis and management of these patients are the development of cryptococcal antigen testing and the antibiotic resistance profile of *Listeria*.

Chronic Viral Infections

CMV. CMV donor positive, recipient negative transplant patients are at the highest risk for developing CMV infection. CMV may present remotely from the date of transplantation when the prophylaxis is terminated or the immunosuppression has been adjusted, usually in the setting of rejection and the use of anti-T cell antibodies. Symptomatic CMV infection typically occurs in 50-60% of seronegative recipients of a seropositive organ and 10-20% of seropositive recipients.[27] In the absence of prophylaxis, symptomatic illness occurs 1-4 months post-transplant. With the advent of successful prophylactic therapy the overall incidence of CMV disease has decreased and the incubation period for those who develop disease has increased as well (to 1-4 months after prophylaxis is discontinued). The incidence of CMV disease is approximately 10-15%, when antilymphocyte antibody therapy is used there is a 65% incidence of CMV disease (which varies with the type of antibody therapy: OKT3 = ALG >Thymoglobulin >basilixamab). When pre-emptive antiviral therapy with ganciclovir is used during antibody therapy, the incidence of CMV disease is diminished to <1%.[28] The role of newer agents with more favorable oral pharmacokinetics, such as valganciclovir, remains to be determined.

CMV may cause a variety of clinical syndromes, fever, leukopenia, hepatitis, pneumonia, retinitis and gastrointestinal disease. The last two are the more common CMV complications remotely from transplantation. Diagnosis requires evidence of increased CMV viral turnover (such as CMV viral load or antigenemia assays) or identification of typical

PTLD:

Post-transplant lymphoproliferative disorder, typically associated with increased EBV replication in the setting of immunosuppression.

CMV inclusions on histopathology. Of note, serum markers are unreliable in the setting of gastrointestinal disease. There are three other important disease associations with increased CMV turnover which should be considered: acute and chronic rejection, malignancy (with 7- to 10-fold increased risk for PTLD) and increased risk of superinfection due to augmented immunosuppression (e.g., *Aspergillus*).[29] Given the high incidence of CMV disease after SOT, various prophylactic strategies have been developed depending on the organ transplanted, donor/recipient CMV status, and intensity of the immunosuppression. It is beyond the scope of this article to review the various pre-emptive strategies for CMV prophylaxis in SOT patients, suffice it to say that CMV is a latent virus and the risk of reactivation persists, therefore when anti-rejection therapy is required, an approach to minimize the complications from reactivating CMV should be developed.[27,28]

TYPES OF INFECTIOUS COMPLICATIONS:

There are several ways infections can cause injury: direct tissue damage, augmenting immunosuppression, augmenting allograft injury, and oncogenesis.

VZV. Approximately 10% of SOT patients will develop zoster at some point post-transplant (typically within 2-36 months). This typically presents as a dermatomal or multi-dermatomal disease. Visceral dissemination is uncommon. With the widespread use of acyclovir and ganciclovir the incidence of zoster has decreased, however, when it does occur, it is typically 1-4 months after prophylaxis is discontinued. Famciclovir and valacyclovir will hasten the resolution of skin lesions.[30]

Primary varicella infection can be a very aggressive infection presenting with severe pneumonia, rash, encephalitis, hepatitis and death.[31] If diagnosed early then high dose acyclovir (10 mg/kg IV every 8 hours) should be given. If a seronegative transplant patient is exposed to varicella then prophylaxis with VZIG (varicella immune globulin) is warranted. It is imperative to assess varicella immunity prior to transplantation, as administration of the varicella vaccine can be safely given at that time. In the post-transplant setting, carefully weighing of the risk benefit ration of administering the varicella vaccine, once the patient is on basal immunosuppression, is required (risk of a live attenuated virus given in a controlled setting vs. the severity of wild type varicella).[32,33]

Human Herpes Virus-6. The spectrum of illness due to HHV-6 is still being delineated. However, it is likely similar to CMV with a mononucleosis syndrome, pneumonitis, hepatitis, bone marrow suppression and encephalitis. Like CMV it likely plays a role in rejection, oncogenesis and facilitating opportunistic infections. As diagnostic assays for this pathogen improve, we will better delineate the extent of disease caused by this pathogen and how to deploy prophylaxis.[34-37]

Hepatitis B Virus. For the first two years post-transplant, HBV has little impact on the post-transplant course. After two years post-transplant the effects of progressive liver disease may be seen. By 8-10 years post-transplant, increased mortality from chronic liver disease, sepsis and hepatocellular carcinoma have been reported. Up to 38% of HBV-infected renal transplant patients develop chronic progressive hepatitis, 42% cirrhosis, and half may die from liver failure.[38-40] As HBV viral replication is steroid responsive, newer steroid sparing immunosuppressive regimens may lead to less HBV-associated morbidity. Monitoring in $HBsAg^+$ patients should include LFTs, HBeAg and HBV DNA levels. In patients who develop high level HBV replication and organ injury, minimizing immunosuppression (in certain cases sacrificing the allograft may be necessary), antiviral therapy (lamivudine, famciclovir) and immune therapy (anti-HBs immune globulin) should be considered. The role of alpha-interferon is controversial given the potential to precipitate allograft rejection.[41]

Hepatitis C Virus. HCV disease rarely manifests before 3-5 years post-transplantation. Increased mortality in HCV infected transplant patients does not manifest itself until the second decade post-transplantation (83.7% vs. 88.9% survival at 10 years, 63.9% and 87.9% survival at 20 years in HCV positive vs. negative patients respectively). HCV is less virulent than HBV. However given the significantly greater number of patients who are HCV positive, it accounts for more illness. Dual infection with HCV and HBV leads to synergistic liver disease.[41] It is imperative to review the vaccination status, with respect to hepatitis A and B, of all transplant patients but particularly those with a chronic infection with a hepatitis virus as a significant mortality has been associated with acute hepatitis A infection in the setting of chronic HCV infection.[42] Minimizing concomitant hepatotoxic insults, such as alcohol use, is important as accelerated liver disease occurs in this setting.[43] Monitoring should include LFTs and possibly HCV viral load.[44] If persistently elevated then a liver biopsy should be performed.

The role of alpha-interferon and ribavirin remains controversial given the potential to induce allograft rejection.

Malignancy

The transplant patient is at increased risk for several malignancies such as skin cancer (predominantly squamous cell), renal cell carcinoma, cervical carcinoma, anal carcinoma, lymphoma, and hepatoma. Several factors contribute to this increased risk including: impaired immune surveillance from immunosuppression, toxicities of immunosuppressive medications, chronic viral infections, and increased sensitivity to environmental exposures. The chronic viral infections clearly linked to the development of malignancy are: HBV/HCV with hepatoma, human papilloma virus with anal/cervical carcinoma, HHV-8 with Kaposi's sarcoma (KS), and EBV with post-transplant lymphoproliferative disease (PTLD).[45,46] The impact of the hepatitis viruses has already been discussed.

RISK OF INFECTION:

A function of host susceptibility and environmental exposure.

Human Papilloma Virus. The increased risk for anogenital neoplasia has been estimated to be 20-fold more common in renal transplant patients than the general population. Twenty-seven of 133 three renal allograft recipients, in one study, were found to develop an anal neoplasia. The serotype most highly associated with the development of neoplastic lesions is HPV-16. Cervical carcinoma is also increased in this population. Early diagnosis, by physical exam and PAP smear is essential for successful treatment.[47,48] Common skin warts are prevalent and may be disfiguring thus requiring repeated local measures for control. The increased incidence of these malignancies in SOT recipients makes annual screening for cervical and anorectal neoplasia mandatory.

Human Herpes Virus-8. The risk ratio for developing Kaposi's sarcoma (KS) has been estimated to be 224 times that of the general population.[46] Approximately 8% of renal transplant patients are seropositive for HHV-8 with 1-2% acquiring infection at the time of transplantation. The incidence parallels the seroprevalence of KS in the host population: 0.5% in US, 1.6% in Italy, 2.4% in Israel, 4% in South Africa, and 5.3% in Saudi Arabia. Twenty-eight percent of HHV-8 positive patients developed KS over the first 3 years after transplantation.[49] Risk factors associated with developing KS post-transplant include African or Middle East descent, anti-lymphocyte therapy, and presence of HHV-8 antibodies. The most common site of involvement is the skin, appearing as violaceous nodules. Other sites of involvement include: gastrointestinal tract, lungs and bladder. Diagnosis is made by biopsy; however, viral load determination by PCR assay from peripheral blood leukocytes is under development. Treatment is to minimize immunosuppression and possible antiviral therapy with ganciclovir, foscarnet or cidofovir.[49-51]

Epstein-Barr Virus. The transplant patient has a 7-fold increased risk of developing post-transplant lymphoproliferative disorder (PTLD), typically an EBV-mediated lymphoma, compared with the general population. PTLD accounts for approximately 20% of malignancies in this population and occurs in approximately 1-2% of renal allograft recipients and 6% of liver transplant patients.[45,52,53] There are several important characteristics of PTLD in this population worth noting: the majority are non-Hodgkin's lymphoma (over 90%), they typically present with extranodal involvement, and CNS involvement is not uncommon. Fever, adenopathy, constitutional symptoms, GI bleeding, diarrhea, abdominal pain, and focal neurologic defects are common presenting features.

The development of PTLD is closely linked to the degree of immunosuppression with cytolytic therapy such as OKT3 and the number of rejection episodes being important risk factors.[54,55] Diagnosis requires biopsy and histopathology, although clinical suspicion can be heightened with a positive EBV PCR test and a markedly elevated serum lactate dehydrogenase (LDH) (>1200 mg/dL). In addition, 70% of SOT transplant recipients will have a lymphomatous mass within the transplanted organ. Therefore, a CT scan with intravenous contrast of the chest, abdomen and pelvis can be quite helpful in localizing areas to biopsy and increasing the likelihood of the diagnosis.

The majority of PTLD occur early in the transplant course (within a few years of transplantation) and are typically EBV-associated. PTLD which occur late after transplantation (usually >4 years post-transplantation) usually are not EBV associated. The pathogenesis of early PTLD is related to increased EBV viral replication leading to polyclonal B-cell activation in conjunction with decreased cytotoxic T-cell surveillance due to immunosuppression. Thus early in the post-transplant course, PTLD is

often polyclonal and typically responds to decreased immunosuppression. Later in the evolution of PTLD, a monoclonal population of cells develop, and this rarely responds to decreased immunosuppression.[56,57] The role of monitoring the level of EBV viral replication for the development of PTLD is under active investigation as well as the use of antiviral therapy (e.g., acyclovir or ganciclovir) particularly during high risk periods (e.g., OKT3 treatment for rejection).[58,59] Primary EBV infection increases the risk for the development of PTLD given the high replication of EBV and the large number of infected cells in the setting of an impaired immune system.

Treatment options when PTLD develops include minimizing immunosuppression, chemotherapy, antivirals, and anti-B cell monoclonal antibodies (e.g., anti-CD20). Most early, polyclonal PTLD can be treated completely by lowering immunosuppression. Monoclonal PTLD tends to be much more aggressive, and generally must be treated with systemic chemotherapy. The use of antiviral therapy (e.g., acyclovir, ganciclovir, foscarnet) may be beneficial by decreasing the EBV B-cell stimulation. A promising new therapy for PTLD is the anti-CD20 monoclonal antibody rituximab, which has been shown to eradicate PTLD in a large percentage of SOT patients.[60-63]

Prophylaxis

Treatment of infections is always easier in the setting of an intact immune system, therefore issues to consider prior to SOT include, assessing for the risk of *M. tuberculosis*, *Strongyloides*, endemic mycoses, and herpes viruses. If the patient has a positive skin test for *M. tuberculosis*, then secondary prophylaxis is almost always warranted. However, the timing should be modified based on other care issues, e.g., concomitant hepatotoxic medications. Short course prophylaxis with rifampin and pyrazinamide is appealing in this population, however, the medication interactions need to be carefully considered, e.g., rifampin upregulating the P-450 system. If *Strongyloides* is identified then an appropriate course of therapy is warranted, especially prior to the initiation of corticosteroids. If *Histoplasma* or *Coccidioides* are identified, close surveillance and early azole therapy post-transplantation should be considered.

Preventing infection is always easier then treating. Therefore it is imperative to understand what each patient is at risk for, both from the standpoint of latent viral disease as well as environmental exposure (geographic, occupational, hobbies, sexual practices, etc.).[64] Careful review of a patient's serologic status and appropriate counseling are essential. For example, a CMV seronegative patient with a seronegative transplant should be thoroughly instructed in how to avoid acquiring CMV, with review of sexual and blood transfusion risks. Updating vaccinations and counseling how to avoid environmental hazards are also critical. Table 1 outlines the common vectors for common infections in this population.

Vaccination is an important part of any infection prevention strategy (Table 2). Several principles need to be considered:

1. immunizations typically produce less of a response in immunocompromised hosts both in terms of the rate of seroconversion and the height of the protective titer,
2. live attenuated vaccines (varicella, measles, mumps, rubella, oral polio) pose a risk of disseminated disease and household members may spread vaccine virus to their contacts,
3. the immune activation (via increased cytokines may precipitate rejection. This last concern remains controversial.[5,65,66]

Given the above concerns, ensuring up to date vaccinations prior to transplant (>1 month) are essential. Oral poliovirus should be avoided in immunocompromised patients as vaccine-associated paralysis has been documented. When polio vaccination is required, IPV should be used. The risk of disseminated infection with other live attenuated viral vaccines needs to be carefully weighed against the benefits. As varicella, measles and mumps infection can be quite severe in the transplant patient and limited experience suggests these live attenuated vaccines have not been shown to cause significant illness in immunocompromised recipients, vaccinating the at risk individuals may be appropriate. Follow-up serology post-vaccination is warranted as it will impact post-exposure prophylaxis with VZIG (varicella immune globulin, which should be used in a non-immune individual within 96 hours of an exposure) and MIG (measles immune globulin, which should be used within 6 days of an exposure in a non-immune individual). Household contacts may be a vector of infection to the transplant patient either through community or vaccine exposures. Therefore it is prudent to ensure that

Table 2 | **Approach to Vaccination**

Vaccine	Pre-Tx	Post-Tx	Special Circumstance	Assess Immunity	Comments
Live Attenuated					
Varicella	Y	N		Y	Consider post-transplantation with caution
Measles	Y	N		Y	Consider post-transplantation with caution
Mumps	Y	N		N	Consider post-transplantation with caution
Rubella	Y	N		Y	Consider post-transplantation with caution
Oral Polio	Y	N		N	Do not use in household contacts
Inactivated					
dT	Y	Y		N	Revaccinate every 5-10 years
Pneumococcal	Y	Y		N	Consider re-vaccination 3-5 years
Menningococcal	Y		Y	N	In college students
Influenza	Y	Y		N	Consider annual re-vaccination
Hepatitis B	Y	Y		Y	Consider re-immunizing if no seroconversion
Hepatitis A	Y	Y		Y	
IPV	Y	Y		N	
Rabies			Y		High risk occupations or post-exposure
Lyme			Y		Consider vaccinating if in a highly endemic area

It is important to assess immunity after vaccination for varicella, measles, and hepatitis B as this may influence post-exposure prophylaxis. Rubella seroconversion is important for reproductive considerations. Household contacts should have their IPV, varicella, measles, and influenza vaccinations up to date. Travel-related vaccines are not discussed here. Adapted from reference 67.

household contacts have their vaccinations up to date (particularly for influenza, measles, and varicella) however, the oral polio virus vaccine should be avoided as vaccine-associated infections have been documented in immunocompromised patients from household transmission.[67] The converse should also be considered, if a patient has chronic active hepatitis B infection then household contacts should be vaccinated against hepatitis B for their own protection.

Prevention of GI illness in this patient population should occur prior to, as well as, after immunosuppression. The CDC, Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation have recently published guidelines addressing the prevention of opportunistic infections in BMT patients.[68] The principles expressed in this careful review provide guidance as to how best to minimize exposure to potential pathogens for SOT patients as well. Table 3 illustrates their recommendations to minimize epidemiologic exposure to GI pathogens. Careful attention to water supply and food handling and preparation are warranted. Exposure to fresh water swimming should be minimized, specifically swallowing water. Immunocompromised patients who wish to travel require special counseling concerning the risk of acquiring gastrointestinal infections and the role of prophylactic antibiotics should be discussed, such as ciprofloxacin or trimethoprim-sulfamethoxazole for the duration of travel.[68]

The splenectomized patient (e.g., post-liver transplantation) has an increased risk for severe infection with encapsulated organisms (e.g., *S. pneumoniae*, *H influenza* type B, and *N. meningococcus*). Therefore these patients should be vaccinated for these pathogens. In addition, antibiotics such as amoxicillin ± levofloxacin (due to increasing pneumococcal resistance) should be given to the patient to take in the event of an infection developing when medical care is not readily available, analogous to an epi-pen for a patient at risk for anaphylaxis.

Table 3 | **Foods That Pose a High Risk for Hematopoietic Stem Cells Transplant (HSCT) Recipients and Safer Substitutions**

Foods That Pose a High Risk	Safer Substitutions
Raw and undercooked eggs* and foods containing them (e.g., french toast, omelettes, salad dressings, egg nog, and puddings)	Pasteurized or hard boiled eggs
Unpasteurized dairy products (e.g., milk, cheese, cream, butter and yogurt)	Pasteurized dairy products
Fresh-squeezed, unpasteurized fruit and vegetable juices	Pasteurized juices
Unpasteurized cheeses or cheeses containing molds	Pasteurized cheeses
Undercooked or raw poultry, meats, fish, and seafood	Cooked poultry, well-done meats, cooked fish and seafood
Vegetable sprouts (e.g., alfalfa, bean, and other seed sprouts) †	Should be avoided
Raw fruits with a rough texture (e.g., raspberries)§	Should be avoided
Smooth raw fruits	Should be washed under running water, peeled and cooked
Unwashed raw vegetables ¶	Should be washed under running water, peeled and cooked
Undercooked or raw tofu	Cooked tofu (i.e., cut into 1-inch cubes and boiled for 5 minutes 5 minutes in water or broth before eating or using in recipes)
Raw or unpasteurized honey	Should be avoided
Deli meats, hot dogs, and processed meats**	Should be avoided unless further cooked
Raw, uncooked grain products	Cooked grain products including bread, cooked and ready-to-eat cold cereal, pretzels, popcorn, potato chips, corn chips, tortilla chips, cooked pasta and rice
All moldy and outdated food products	Should be avoided
Unpasteurized beer (e.g., home-brewed and certain bottled or canned, or draft beer	Pasteurized beer (i.e., retail microbrewery beer) that has been pasteurized after fermentation)
Raw, uncooked brewers yeast	Should be avoided; HSCT recipients should avoid any contact with with raw yeast (e.g., they should not make bread products themselves)
Unroasted raw nuts	Cooked nuts
Roasted nuts in the shell	Canned or bottled roasted nuts or nuts in baked products

*Source: CDC. Outbreaks of *Salmonella* serotype enteritidis infection associated with consumption of raw shell eggs—United States, 1994–1995. MMWR 1996; 45(34):737–42.
†Source: Taormina PJ, Beuchat LR, Slutsker L. Infections associated with eating seed sprouts: An international concern. Emerg Infect Dis 1999;5(5):626–34.
§Source: Herwaldt BL, Ackers ML. Outbreak in 1996 of cyclosporiasis associated with imported raspberries. New Engl J Med 1997;336(22):1548–56.
¶Source: CDC. Foodborne outbreak of cryptosporidiosis—Spokane, Washington, 1997. MMWR 1998;47(27):565–7.
**Source: CDC. Update: multistate outbreak of listeriosis—United States, 1998–1999. MMWR 1999;47(51):1117–8.
Recently published IDSA/CDC/ASH guidelines on how to minimize food borne illness in bone marrow transplant recipients. The principles espoused here provide guidance on how to improve the food safety for SOT patients. Adapted from reference 68.

The immune dysfunction induced by transplantation does not engender any special need for endocarditis prophylaxis, thus prophylaxis should be utilized as outlined in the published guidelines.[69] The only exception to this is how best to handle cardiac transplant patients and, clinical practice varies between centers. The issue of how to handle pets, hobbies, occupation and other environmental exposures will forever be challenging and need to be managed on a case by case basis. Table 1 lists various pathogens and their associated reservoirs. Careful analysis of each situation and counseling concerning how to reduce risk of acquiring various agents is mandatory.

Conclusion

The optimal care of the well transplant patient is a moving target as our patients continue to do better and live longer, in large part due to improved immunosuppressive regimens. Central to minimizing infectious complications is a careful evaluation of the net state of immunosuppression and epidemiologic risks. Continued re-evaluation of infection prophylaxis and pre-emptive strategies is essential.

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