Prevention and Management of Infections in Solid Organ Transplantation

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Cover Illustration by Kathryn K. Johnson
INTRODUCTION

Infection is a feared complication of solid organ transplantation and the source of significant posttransplant morbidity and mortality. Transplant patients are at risk for not only community-acquired and health care–associated infections but also reactivation of opportunistic latent and endemic infections. The risk for infection in solid organ transplant recipients depends on the time of presentation, pathogen exposure, and the intensity of immunosuppression. The net state of immunosuppression is based on a combination of factors that include the immunosuppressant medications, underlying chronic and immunocompromising conditions, and infections with immunomodulatory viruses such as cytomegalovirus (CMV).

PRETRANSPLANT CONSIDERATIONS

RECIPIENT

Transplant candidates warrant assessment for occult and latent infections prior to organ transplantation (Table).1,2 A thorough pretransplant evaluation can prevent some potentially serious complications after transplant. All potential recipients should be tested for latent tuberculosis, HIV, syphilis, hepatitis A virus, hepatitis B virus (HBV), and hepatitis C virus (HCV). Heart transplant candidates should receive serologic evaluation for prior Toxoplasma infection. Serologic testing for latent infection with herpes simplex virus (HSV), Epstein-Barr virus (EBV), and CMV is necessary to determine the risk for primary or reactivated infection after transplantation. Potential recipients who have resided in endemic areas can be screened for latent infections with Strongyloides stercoralis, Trypanosoma cruzi, and endemic fungi (eg, Coccidioides immitis).

Prior to transplantation, candidates can be assessed for immunity to vaccine-preventable infections and should receive the appropriate immunizations (eg, pneumococcal polysaccharide vaccine; trivalent inactivated influenza vaccine; tetanus, diphtheria, and pertussis [Td or Tdap] vaccination; and hepatitis A and hepatitis B vaccination in seronegative individuals).3,5 Live vaccines (eg, measles, mumps, rubella, varicella and herpes zoster) should be administered as early as possible prior to transplantation but should be avoided if transplantation is anticipated in the next 4 to 8 weeks and are presently contraindicated after transplantation due to the possible risk of reactivation in the setting of immunosuppression.

Treatment and clinical resolution of bacterial, fungal, and parasitic infections in potential recipients is recommended prior to transplantation. Latent tuberculosis, strongyloidiasis, and Chagas’ disease should be treated before transplantation when practical and feasible since these infections can present with fulminant disease in the setting of potent immunosuppression.6 Strongyloides hyperinfection syndrome has been well described in the setting of recent transplantation and in the setting of increased immunosuppression for graft rejection in untreated latent carriers of Strongyloides stercoralis.7-9 Empiric therapy with ivermectin prior to transplantation and during periods of intensified immunosuppression may be warranted in appropriate patients. There are no consensus guidelines in the treatment of solid organ transplant candidates with laboratory evidence or clinical history of infection with endemic fungi such as Histoplasma capsulatum or Coccidioides immitis. In the case of latent Coccidioides infection, clinical practice is institution-specific in endemic areas and ranges from universal lifelong prophylaxis with fluconazole to targeted prophylaxis for a defined period of time posttransplant and during periods of increased immunosuppression.10,11

DONOR

Living donors can be easily screened for the presence of infections that could be transmitted with the allograft. Screening in cadaveric donors is somewhat more challenging due to time constraints and potentially
insensitive screening tests that may not detect acute or recent infections. In recent years, transmission of lymphocytic choriomeningitis virus, rabies virus, West Nile virus, and HIV from donors with unrecognized active infection has been described.\textsuperscript{12-15} Signs and symptoms of viral meningitis, encephalitis, meningoencephalitis, or unexplained altered sensorium in donors preclude organ donation. Potential recipients need to be counseled about the risks of acquiring infections from high-risk donors when screening tests may not detect acute or recent infection or when expeditious screening tests may not exist.\textsuperscript{16}

Rarely, donor infection or bacterial or fungal contamination of the graft preservation media can seed vascular suture lines and increase the risk for mycotic aneurysms and loss of integrity at the anastomotic site.\textsuperscript{17,18} Allografts from bacteremic cadaveric donors can still be considered, as retrospective studies have demonstrated that donor transmission of bacterial pathogens is rare.\textsuperscript{19-21} It is likely prudent to treat recipients with antimicrobial therapy targeting the donor pathogen (for approximately 5–7 days) particularly in the setting of multidrug resistant or vasculotropic pathogens such as \textit{Staphylococcus aureus} and \textit{Pseudomonas aeruginosa}.\textsuperscript{22} With the exception of bacterial meningitis and bacteremia, there is no convincing evidence that treatment of the recipient is necessary for donor bacterial infections isolated from sites other than the transplanted organ.\textsuperscript{23-25}

Testing for hepatitis B surface antigen in prospective donors is recommended to prevent transmission of HBV to transplant recipients. Active HBV infection precludes organ donation. The use of organs from hepatitis C antibody–positive deceased donors is controversial. The risk of transmitting HCV to the recipient is nearly 100%, but the risks of developing cirrhosis need to be weighed against the risks of organ failure. There is evidence that heart transplant recipients, regardless of their HCV status, may have increased mortality in the setting of receiving allografts from HCV antibody–positive donors.\textsuperscript{26} HCV recurrence appears to be universal in HCV-infected liver transplant recipients. Time to graft failure may be accelerated in the setting of HCV–positive recipients receiving livers from HCV–positive donors,\textsuperscript{27} although other studies have demonstrated that recipient seropositivity was more predictive of future graft failure than donor seropositivity.\textsuperscript{28,29} Due to the ongoing shortage of organs, allografts from HCV antibody–positive donors have been used in recipients with a personal history of HCV or with adequate counseling in the setting of urgent need for transplantation or older age.

**Table.** Pretransplant Screening in Solid Organ Transplantation

<table>
<thead>
<tr>
<th>Recipients and donors</th>
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<tbody>
<tr>
<td>HIV-1 and HIV-2 antibodies</td>
<td>Herpes simplex virus IgG</td>
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<tr>
<td>Cytomegalovirus IgG</td>
<td>Epstein-Barr virus IgG</td>
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<tr>
<td>Varicella zoster virus IgG</td>
<td>Hepatitis C antibody</td>
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<td>Hepatitis B surface antigen</td>
<td>Hepatitis B surface antibody</td>
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<tr>
<td>Hepatitis B core IgM and IgG (in persons with an isolated HBcAb it may be prudent to check circulating DNA levels)</td>
<td>Syphilis (RPR)</td>
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<tr>
<td>Toxoplasma antibody (recommended in heart transplant candidates)</td>
<td>Trypanosoma cruzi serology (for both donors and recipients residing or with a history of residence in an endemic area)</td>
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<th>Recipients</th>
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<tr>
<td>Tuberculin skin testing or quantiferon-gold</td>
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<tr>
<td>Strongyloides serology and/or stool ova and parasite examination (in the setting of residence or previous residence in an endemic area or in the setting of unexplained serum eosinophilia)</td>
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<td>Coccidioides serology (in the setting of residence or previous residence in an endemic area)</td>
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<th>Donors</th>
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<tr>
<td>HTLV type 1 and 2</td>
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<td>HBCAb = hepatitis B core antibody; HTLV = human T-lymphotropic virus; RPR = rapid plasma reagin.</td>
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Infection with HIV or human T-lymphotropic virus (HTLV) is presently a contraindication to organ donation.

**SOLID ORGAN TRANSPLANTATION AND HIV**

With improved outcomes since the advent of highly active antiretroviral therapy, HIV–infected patients are now potential transplant candidates. Liver and kidney transplantation in HIV–infected individuals is gaining acceptance and is currently being investigated in the United States in a multicenter NIH-sponsored trial.\textsuperscript{30} Interactions with protease inhibitors require significant dose reduction of calcineurin inhibitors (eg, tacrolimus) and TOR inhibitors (eg, sirolimus) and diligent monitoring of drug levels.\textsuperscript{31} Recurrence of HCV in liver transplant recipients coinfected with HIV is often aggressive.\textsuperscript{32} Promising results have been observed in HBV-HIV coinfected liver transplant recipients and in HIV–infected kidney allograft recipients.\textsuperscript{33}
Most infectious complications typically occur during the first year after transplantation, which is traditionally divided into the first month posttransplant (early period), 2 to 6 months posttransplant (intermediate period), and over 6 months posttransplant (late period). The risk for specific infections in solid organ transplantation is primarily based on timing, exposures, degree of immunosuppression, and duration and mode of prophylaxis after transplantation (Figure).

The overwhelming majority of infections in the first month after transplantation are health care–associated bacterial infections. Like immunocompetent surgical patients, transplant recipients are at risk for typical postsurgical infections such as surgical site infections, health care–associated or ventilator-associated pneumonia, catheter-associated bloodstream and urinary tract infections, and *Clostridium difficile* colitis. Factors that influence the occurrence of these infections include the duration and complexity of the operation (eg, estimated blood loss and/or the presence of fluid collections or hematomas requiring surgical reexploration) and the presence and duration of vascular, drainage, and urinary catheters. The diagnosis of these infections is rarely a challenge; however, management is frequently limited by antimicrobial resistance and refractory surgical complications.

Perioperative antibacterial prophylaxis is guided by the transplanted organ and institutional epidemiology. Although evidence is lacking, prior recipient and donor culture information may be helpful in individualizing the perioperative prophylactic regimen. For example, in a recipient with a history of nasal carriage of methicillin-resistant *Staphylococcus aureus* and a history of peritonitis with an extended-spectrum β-lactamase–producing *Klebsiella pneumoniae*, it may be appropriate to use vancomycin and a carbapenem for perioperative prophylaxis.

Rarely, donor-derived infections can present during this early time period as well. Although donor screening largely eliminates this risk, unrecognized donor infection can occasionally be transmitted to the recipient. It is important to notify the organ procurement organization (OPO) of the possibility of a donor-derived infection in the setting of an unexplained febrile illness in the early posttransplant period or the presence of any other symptoms that may suggest a potential donor-derived infection.
unexpectedly early or unusual opportunistic infection. The OPO will investigate for donor transmission by notifying the centers with recipients of other organs from the same donor.

Opportunistic infections such as *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), *Nocardia, Aspergillus, Cryptococcus*, CMV, and tuberculosis classically occur 1 to 6 months after transplantation when cell-mediated immunity is at its nadir (Figure). Recognition and treatment of latent infections prior to transplantation and use of prophylaxis has pushed some of these diseases to present later posttransplant. When opportunistic infections occur in the first month after transplantation, evaluation for an environmental source of infection or donor-derived infection should be pursued.

After 6 months, transplant recipients with functioning grafts are at less risk for opportunistic infection but remain at increased risk for community-acquired bacterial and viral infections. Clinicians should be aware that the risk for opportunistic infections may persist with augmented immunosuppression specifically in the setting of rejection. Furthermore, the routine use of prophylaxis may delay the onset of infections such as CMV. Like other immunocompromised host populations, transplant recipients are at increased risk for malignancies, notably EBV-associated posttransplant lymphoproliferative disease (PTLD) and skin and anogenital carcinomas due to papillomaviruses. In the management of most infections, decreasing immunosuppression in addition to appropriate antimicrobial therapy should be considered when possible.

**Fungal Pathogens**

*Candida, Aspergillus, Cryptococcus, and Pneumocystis* are the major fungal pathogens causing disease in transplant recipients. In specific regions and in travelers or previous long-term residents of those regions, endemic fungi like *Coccidioides* or *Histoplasma* can cause clinically significant primary infection or reactivated disease. Infections with other non-*Aspergillus* filamentous fungi (eg, zygomycetes, *Fusarium*, and *Scedosporium*) are rare but can pose management dilemmas due to inherent antifungal resistance. The risk of reactivation of latent fungal diseases appears to decrease as patients are maintained on lower doses of immunosuppressants but is present throughout the late posttransplant period. The appropriate clinical scenario should trigger diagnostic evaluation for these pathogens.

Treatment of fungal infections in transplant recipients is especially challenging due to toxicities and drug-drug interactions. It should be noted that amphotericin B and its lipid formulations are associated with nephrotoxicity that may be augmented with concomitant receipt of calcineurin and TOR inhibitors. Azoles can increase levels of both calcineurin and TOR inhibitors, and doses of these immunosuppressants should be reduced and levels monitored closely when patients are receiving azole therapy.

**Candida**

*Candida* is the most common fungal pathogen associated with infection early after transplantation and typically occurs in the first month posttransplant. In the setting of prolonged and complicated hospitalizations, the risk for invasive candidiasis may extend beyond the early posttransplant period. Most infections are catheter-related bloodstream infections or intra-abdominal infections. Due to favorable safety profiles lipid formulations of amphotericin B, echinocandins, and azoles are preferred over conventional amphotericin B, which was previously the mainstay of therapy for invasive candidiasis. Echinocandins are effective and very well tolerated first-line agents in the treatment of invasive candidal infections and have demonstrated activity against azole-resistant *Candida* isolates (eg, *Candida krusei* and azole-resistant *Candida glabrata*).

Institutional epidemiology and patient history should guide empiric antifungal choices in the setting of suspected or documented candidiasis. Once clinical stability has been established and identification of *Candida* species and possibly antifungal susceptibility testing results are known, step-down therapy to an oral azole can be considered.

Targeted antifungal prophylaxis in high-risk liver transplant recipients has decreased the incidence of posttransplant invasive candidiasis. Established risk factors for invasive candidiasis in liver transplant recipients include fulminant hepatic failure, retransplantation, renal insufficiency, prolonged operative time, excessive blood loss, and receipt of spontaneous bacterial peritonitis prophylaxis. Most institutions will administer targeted prophylactic fluconazole in high-risk liver transplant recipients based on a randomized controlled study that demonstrated efficacy. Pancreatic and intestinal transplant recipients are also at increased risk of postoperative invasive candidal infections and may benefit from prophylaxis. Fluconazole prophylaxis, however, may also increase the risk for azole-resistant candidiasis and care should be taken to note the institution-specific isolation rates of azole-resistant *Candida* species.

**Aspergillus**

*Aspergillus* infections are most commonly diagnosed within the first year after solid organ transplantation and are associated with significant morbidity and mortality.
Lung transplant patients are at the highest risk of developing invasive aspergillosis and it is an important cause of posttransplant morbidity in this population. Although most disease is clinically apparent during the first 6 months after transplant, patients remain at increased risk for disease any time during their posttransplant course.

*Aspergillus* infection can present in a variety of forms including invasive pulmonary disease, aspergilloma, rhinosinusitis, and brain abscesses. Invasive pulmonary disease remains the most common form of aspergillosis. Nearly half of all lung transplant recipients are noted to be colonized with *Aspergillus* after transplantation. Although colonization does not always indicate underlying invasive disease, lung transplant recipients with evidence of colonization within the first 6 months posttransplant may be at higher risk for developing locally invasive or disseminated disease. Other risk factors for the development of invasive aspergillosis include CMV disease, rejection, intensive immunosuppression, and renal dysfunction.

*Aspergillus* tracheobronchitis can be a disconcerting finding in lung transplant recipients. It has a tendency to involve the anastomotic site, potentially placing the suture line at risk for dehiscence. Often the disease is diagnosed in asymptomatic patients with surveillance bronchoscopy. Patients may also present with symptoms such as cough, wheezing, or even hemoptysis suggesting endobronchial disease. The spectrum of clinical disease ranges from irritation and mild bronchitis to the formation of pseudomembranes, ulcers, and even dehiscence and bronchopleural fistula formation.

The treatment of choice for both primary invasive aspergillosis and tracheobronchitis is voriconazole. It should be noted that due to the risk of significant toxicity, doses of calcineurin and TOR inhibitors should be reduced and monitored closely in the setting of concomitant voriconazole therapy. Conventional amphotericin B is also approved for the treatment of invasive aspergillosis but is now considered a second-line agent mainly due to toxicity. Although only approved as salvage therapy for aspergillosis, lipid formulations of amphotericin B are also effective in treating *Aspergillus* infections. Vigilant monitoring for both electrolyte disturbances and renal function is necessary for patients receiving conventional amphotericin B or its lipid formulations particularly in association with calcineurin inhibitors. Surgical débridement can be an essential adjunct to therapy and should be pursued when feasible. Caspofungin is approved by the U.S. Food and Drug Administration (FDA) for salvage therapy in the setting of invasive *A. fumigatus*. Posaconazole and micafungin have been used anecdotally for salvage in transplant recipients but their use is currently not FDA-approved for this indication.

Antifungal prophylaxis with aerosolized amphotericin B and/or systemic voriconazole in lung transplant recipients is based on observational data demonstrating lower rates of invasive aspergillosis. Antifungal prophylactic strategies in lung transplantation, however, are not standardized as demonstrated by a recent survey, and further studies are needed to determine whether universal or targeted prophylaxis is optimal.

The incidence of aspergillosis in non-lung organ transplants is low but has been reported. After liver transplantation, recipients are at highest risk for invasive aspergillosis. The incidence of invasive aspergillosis has been reported in up to 8% of liver transplant recipients with most cases historically occurring within the first 100 days posttransplantation. Cited risk factors for the development of invasive aspergillosis in this population include environmental exposures, fulminant hepatic failure, renal dysfunction requiring dialysis, rejection, and retransplantation. In more recent years, late-onset aspergillosis has been associated with increased immunosuppression especially in the setting of CMV disease. Treatment of aspergillosis in this population is the same as that for lung transplant recipients.

**Cryptococcus**

Infection with *Cryptococcus neoformans* usually presents several months posttransplant. It can present as a subacute or chronic infection and primarily manifests as pulmonary disease with or without involvement of the central nervous system (eg, meningitis or cryptococcoma). Other less common presentations include involvement of the skin, joints, and genitourinary system. In 1 series, the incidence of cryptococcal disease after solid organ transplantation was close to approximately 2.8% and the associated mortality approached 42%. Disseminated cryptococcosis appears to occur at the highest frequency in liver allograft recipients. Culture or visualization of the organism remains the gold standard in terms of diagnosis, but a positive serum cryptococcal antigen has a high positive predictive value for cryptococcal infection and may be indicative of extensive pulmonary disease or extrapulmonary disease. Lumbar puncture should be performed to exclude concurrent central nervous system disease, and it is important to note that the serum cryptococcal antigen may be negative in the setting of isolated pulmonary disease.

Amphotericin B, with or without adjunctive fluconosine, remains the mainstay of therapy for severe cryptococcal disease. The preferred regimen includes 2-week induction therapy with lipid formulations of amphotericin B and fluconosine followed by consolidation therapy with high-dose fluconazole for an additional
8 weeks. Fluconazole-based therapy has been used anecdotally with success in the setting of less severe isolated extraneural disease. After completing induction therapy, patients should be maintained on low-dose fluconazole for at least 6 to 12 months.

**Pneumocystis jiroveci**

Due to the routine use of trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis in transplant recipients, the incidence of *Pneumocystis jiroveci* pneumonia (PCP) has decreased. Prior to universal prophylaxis, the incidence of PCP approached 14% in the solid organ transplant recipient and occurred primarily 6 to 8 weeks after transplant. In patients with a history of sulfonamide allergy, atovaquone and dapsone can be considered as alternative prophylactic agents. Dapsone should be avoided in patients with severe sulfonamide allergies and in patients with serologic evidence of glucose-6-phosphate dehydrogenase deficiency. It is important to note there is an increased risk for PCP in the setting of increased immunosuppression to treat rejection and in the setting of recent withdrawal of high-dose corticosteroids, PTLD, and CMV disease.

Diagnosis of PCP can be challenging in the transplant recipient. Clinical presentations can range from asymptomatic radiographic changes to acute onset of dyspnea requiring ventilatory support. Although bilateral ground-glass opacities on chest radiograph is a classic finding, transplant recipients can have nonspecific and even normal radiographic studies in the setting of *Pneumocystis*. Visualization of organisms in tissue or in bronchoalveolar lavage specimens is diagnostic. Rapid noninvasive tests such as direct fluorescent antibody (DFA) testing of induced sputum is less sensitive in transplant patients compared with HIV patients possibly due to a reduced organism burden. If there is a high clinical suspicion, a negative DFA test does not exclude the diagnosis. TMP-SMX and adjunctive corticosteroids is the treatment of choice, although the role of corticosteroids is less certain in the transplant population.

Although most institutions will use TMP-SMX prophylaxis for 3 to 6 months after transplantation, clinicians are encouraged to resume prophylaxis in the setting of intensified immunosuppression for rejection or in the setting of PTLD or active CMV disease. Lifelong prophylaxis should be considered in patients without side effects or toxicity, as TMP-SMX may also prevent infection with susceptible Enterobacteriaceae, *Nocardia* species, *Salmonella*, community-associated methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Legionella*, and a handful of parasitic diseases (e.g., toxoplasmosis, *Isospora belli*, and *Cyclospora cayetanensis*).

**VIRAL PATHOGENS**

**Cytomegalovirus**

CMV is a major pathogen in solid organ transplantation and responsible for significant posttransplant morbidity. It is associated with allograft rejection and predisposes patients to other serious infectious complications including EBV-associated PTLD and invasive fungal infections due to its immunomodulatory effects. The most important risk factor for CMV infection in transplant recipients is the serologic status of the recipient compared with that of the donor. Seronegative recipients are at the highest risk for developing CMV disease when receiving an organ from a seropositive donor (D+/R-). Seropositive recipients are also at risk for reactivation of latent CMV irrespective of donor serologic status. CMV can reactivate and cause disease in the setting of increased immunosuppression, particularly in the setting of T-cell depleting agents like antilymphocyte antibodies. The risk for CMV disease also depends on organ type, with the highest rates reported in lung transplantation and the lowest rates in kidney transplantation. CMV disease generally refers to CMV infection with associated symptoms.

The spectrum of CMV disease spans from a non-specific mono-like or flu-like illness to tissue-invasive disease. Clinical manifestations often include a constellation of constitutional symptoms such as fever, malaise, headaches, and diarrhea. Commonly identified laboratory derangements include leukopenia, thrombocytopenia, atypical lymphocytosis, and mild elevation of liver enzymes. Gastrointestinal involvement including colitis, oral ulcers, and esophagitis is the most common manifestation of tissue-invasive disease. Other tissue-invasive manifestations include hepatitis, pneumonitis, nephritis, and encephalitis. For unknown reasons, CMV chorioretinitis is uncommon in solid organ transplant recipients. The diagnosis of tissue-invasive disease typically requires histopathology that demonstrates intranuclear viral inclusions or positive CMV immunostaining. While serum DNA polymerase chain reaction (PCR) is frequently positive in the setting of CMV disease, negative results can be seen in the setting of isolated gastrointestinal disease.

CMV infection is also associated with indirect clinical effects, many of which are unique to the transplanted organ. For example, CMV has been associated with bronchiolitis obliterans in lung transplant recipients, vanishing bile duct syndrome in liver transplant recipients, and accelerated coronary atherosclerosis in the setting of heart transplantation. Other indirect effects include an increased risk for bacterial, fungal, and other viral infections due to the immunomodulating effects of CMV and an association with an increased risk for rejection.
There are 2 commonly used strategies in the prevention of CMV disease. With the preemptive approach, patients undergo weekly surveillance with either pp65 antigenemia or serum DNA PCR, and antiviral therapy is only administered when viral replication is demonstrated. With universal prophylaxis, all recipients at risk for CMV receive intravenous ganciclovir or more typically oral valganciclovir for at least 3 months.73 Meta-analyses have demonstrated that both approaches are effective for reducing CMV disease.74,75 For seronegative recipients receiving organs from seronegative donors (D−/R−), the risk for CMV disease is generally low and valacyclovir prophylaxis is appropriate to prevent HSV and varicella zoster virus in these patients.

Treatment of CMV disease has traditionally required intravenous administration of ganciclovir for at least 2 weeks.72,76 There is an increasing body of literature suggesting that oral valganciclovir in treatment doses can be used as induction therapy in the setting of mild CMV disease or asymptomatic viremia, although the current standard of care remains initial therapy with intravenous ganciclovir for clinical CMV disease.1,77-80 However, a recent prospective controlled study has demonstrated that primary therapy with oral valganciclovir may be as effective as intravenous ganciclovir particularly in kidney transplant recipients.79 Duration of therapy is not standardized and should be individualized to clinical response. Accordingly, therapy should not be discontinued until viremia has been eradicated and clinical signs and symptoms have resolved. The need for maintenance or prophylactic therapy following induction therapy remains unsettled and requires further investigation. Older studies suggested a risk for relapse after 2 to 3 weeks of therapy. However, recent data demonstrate that viremia will be eradicated in fewer than 50% of patients after 21 days of therapy.79 Therefore, it is not known if a significant risk for relapse exists if therapy is discontinued after viremia has been eradicated.

Ganciclovir-resistant CMV requires therapy with foscarnet or cidofovir. Risk factors for ganciclovir resistance include D+/R− status, prolonged exposure to ganciclovir, rejection, and increased immunosuppression with corticosteroids or antilymphocyte preparations.81,82 Mutations in UL97, the CMV phosphotransferase required to convert ganciclovir into its active form, confer low-level resistance to ganciclovir and is considered the most common mechanism for ganciclovir-resistant virus. Mutations in UL54, the CMV polymerase, are associated with high-level resistance and cross-resistance with both foscarnet and cidofovir. In vitro susceptibility testing remains the gold standard for determining true ganciclovir resistance. The possibility of resistance should be considered and addressed in patients with increasing serum viral load or refractory symptoms despite treatment with intravenous ganciclovir.

Late-onset CMV disease is becoming a clinically significant entity in the setting of universal prophylaxis.83,84 Risk factors for the development of late-onset CMV disease includes D+/R− serologic status and rejection.

**BK Virus**

BK virus is a polyoma virus that predominantly causes disease in kidney transplant recipients. Subclinical infection with BK virus often occurs in childhood and most adults demonstrate serologic evidence of previous infection. The virus is tropic to the genitourinary epithelium where it remains latent in immunocompetent individuals. In the setting of increased immunosuppression, however, it can be associated with allograft injury in renal transplant recipients. In renal transplant recipients, tubulointerstitial nephritis and ureteral stenosis associated with BK virus is a significant concern and associated with allograft loss in this population.85

The clinical presentation of BK nephropathy resembles acute rejection and usually presents as asymptomatic increase in serum creatinine. Urine cytology can demonstrate decy cells, which are uroepithelial cells with enlarged nuclei and basophilic intranuclear inclusions. Presence of decy cells in the urine is suggestive of BK nephropathy but lacks sensitivity. The absence of BK viremia essentially rules out BK nephropathy. When BK viremia is detected, biopsy is required because histopathology remains the gold standard for diagnosis. The cornerstone of treatment is reduction in immunosuppression although observational data have suggested better outcomes with adjunctive low-dose cidofovir.86 The roles of intravenous immunoglobulin, ciprofloxacina, and leflunomide remain unclear.87-89

A preemptive strategy with serial monitoring of serum BK virus PCR and reduction of immunosuppression when BK virus is detected can successfully prevent BK virus nephropathy without an increased risk of rejection.90-92

**MISCELLANEOUS PATHOGENS**

**Toxoplasmosis**

Toxoplasmosis is primarily a complication following heart transplantation but is uncommon in the setting of universal TMP-SMX (or pyrimethamine) prophylaxis.93 Seronegative heart transplant recipients who acquire organs from seropositive donors are at high risk for primary toxoplasmosis, which can be prevented with
prophylaxis. Toxoplasma can encyst and lie dormant within the myocardium and can reactivate in the setting of immunosuppression. The clinical manifestations of primary toxoplasmosis include myocarditis, cardiomyopathy, brain abscess, and disseminated infection. Biopsy of the myocardium is recommended to distinguish primary toxoplasmosis from acute rejection. Treatment with pyrimethamine and sulfadiazine is recommended.

Nocardia

Nocardiosis is another infection that is infrequently seen in the solid organ transplant population due to routine use of TMP-SMX prophylaxis, although breakthrough infections have been described. Nocardia is a branching gram-positive saprophytic organism ubiquitous in the environment and inhalation is the most common mode of acquisition. Risk factors for Nocardia infection include high-dose immunosuppression and CMV disease. Pulmonary infection is the most common presentation of nocardiosis and is primarily caused by N. asteroides. Nocardia also has a predilection for the central nervous system and magnetic resonance imaging of the brain should be considered in patients with pulmonary Nocardia infection to assess for CNS infection. TMP-SMX is the mainstay of therapy.

Tuberculosis

Infection with Mycobacterium tuberculosis is a potential source of morbidity and mortality in the solid organ transplant population. In contrast to the general population, transplant recipients are much more likely to develop reactivated tuberculosis and present with disseminated disease rather than isolated pulmonary tuberculosis. Although lower in North America and Western Europe, rates have been reported to be as high as 15% in endemic regions.

Screening for and treatment of latent tuberculosis infection (LTBI) may be effective in preventing reactivation of disease in transplant recipients. The risk of hepatotoxicity with isoniazid is of concern particularly in liver transplant candidates but patients with compensated cirrhosis can be safely treated with frequent monitoring of hepatic enzymes. In recipients of nonhepatic allografts, treatment for LTBI can be initiated at any time with monitoring of hepatic enzymes. In untreated liver transplant recipients with LTBI, therapy can be considered once liver function has stabilized with close laboratory and clinical monitoring.

The treatment of tuberculosis in transplant recipients is similar to that for the general population with special attention to drug-drug interactions. Rifampin and rifabutin can decrease serum levels of calcineurin inhibitors and diligent monitoring of calcineurin and TOR inhibitor levels and subsequent dose adjustments are necessary to maintain appropriate levels. When management proves too complex or difficult, therapy without rifampin or rifabutin can be administered but requires longer treatment.

Epstein-Barr Virus

Primary infection with EBV following solid organ transplantation is the major risk factor for the development of PTLD. Suspicion for PTLD is highest in seronegative individuals who acquire organs from seropositive donors. PTLD is more of a concern in pediatric solid organ transplant recipients who are frequently seronegative but acquire organs from seropositive adult donors compared with adult transplant recipients who have already acquired immunity to EBV. Intestinal transplant recipients are at the greatest risk for the development of PTLD. Other risk factors for the development of PTLD include the duration and intensity of immunosuppression, the presence of CMV serologic mismatch or active CMV disease, and the receipt of antilymphocyte antibodies.

PTLD encompasses a heterogeneous group of disorders associated with B-lymphocyte proliferation ranging from benign polyclonal proliferation to malignancy resembling non-Hodgkin’s lymphoma. Clinical manifestations may mimic infection and include fever, lymphadenopathy, and weight loss. Pediatric patients may have nonspecific symptoms such as tonsillitis. Intestinal transplant patients can present with peritonitis in the setting of bowel perforation. Most often patients present with extranodal disease. Involvement of the central nervous system may occur and can be the only focus of disease in a small group of patients. PTLD can also present as allograft dysfunction, and biopsy is necessary to distinguish it from rejection since the treatment of these entities is entirely different.

Diagnosis of PTLD is made by histopathology including immunostaining. It is unclear if the EBV viral load or serology is helpful in diagnosing PTLD or screening for PTLD but low or undetectable circulating EBV viral load has a negative predictive value of nearly 100%. Reduction of immunosuppression is the mainstay of therapy and spontaneous regression of PTLD has been noted in up to 50% of cases. When reduction in immunosuppression is not a therapeutic option due to rejection or in the setting of refractory disease, B-cell monoclonal antibody therapy with rituximab (anti-CD20) can be considered often in combination with chemotherapy.
CONTINUING CARE OF THE TRANSPLANT RECIPIENT

Advances in immunosuppression, prophylactic strategies, and early recognition of surgical and infectious complications have contributed to increasing long-term allograft and patient survival. As previously noted, transplant recipients remain at risk for both common and opportunistic pathogens. Early recognition and active prevention remain important in this group of patients.

Transplant recipients should be implored to practice hand hygiene and appropriate food and water safety both at home and abroad. Their immunosuppressed state places them at increased risk for waterborne infections, including parasitic infections (eg, cryptosporidium and giardiasis) as well as food borne illnesses (eg, listeriosis and enterohaemorrhagic Escherichia coli). Influenza vaccination should be updated annually, and vaccination with the pneumococcal polysaccharide vaccine is recommended every 5 years. Patients should undergo all screening examinations recommended for persons of their age (eg, mammogram, routine gynecologic examination, and colonoscopy as indicated).

Pretravel evaluation for both vaccinations and appropriate prophylaxis should be completed several weeks prior to the anticipated travel date. Environmental exposures to potential opportunistic pathogens (eg, construction sites, gardening) should be avoided if at all possible. Transplant recipients should always make an effort to avoid close contact with persons with respiratory infections or mononucleosis-like syndromes. Employment of safe sexual practices is also strongly encouraged.

As with all infectious diseases evaluations, an astute history that includes a detailed social and travel history will help make these complex patients a little less complicated to assess and treat.

REFERENCES

Infectious Diseases Volume 11, Part 5


TEST YOURSELF WITH SELF-ASSESSMENT QUESTIONS

Questions for self-assessment in selected specialties are available on Hospital Physician’s Web site. Go to www.turner-white.com, click on Hospital Physician, then click on “Self-Assessment Questions.”