

## CHAPTER 95

# Management of Infection in Patients With Kidney Transplant

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## OBJECTIVES

This chapter will:

1. Recognize risk for and manifestations of common opportunistic infections in renal transplant recipients admitted to the intensive care unit.
2. Describe appropriate evaluation and treatment for infections in renal transplant recipients admitted to the intensive care unit.

Chronic kidney disease (CKD) is pervasive throughout the world, resulting in increased need for renal transplantation. Unfortunately, current donor pools (live or cadaveric) cannot meet the increasing need of potential recipients.<sup>1</sup> Given the favorable survival rates of patients receiving a renal transplant as compared with those on dialysis, the need is expected to continue to rise.<sup>1</sup> Improved surgical techniques, pre- and posttransplant care, and the evolution of immunosuppressive regimens aid in graft survival and function; however, the immunosuppressants also result in increased risk of posttransplant complications, particularly infections.<sup>1-3</sup> Infections are paramount because they continue

to portend significant morbidity and mortality among transplant recipients.<sup>2-4</sup>

## General Risk Factors for Infection

Sources of infection among renal transplant recipients (RTRs) include reactivation of latent infection in recipients, donor-derived infections, and de novo posttransplant infections, which can include immediate postoperative, nosocomial, and community-acquired infections.<sup>1</sup> Underlying comorbidities such as malnutrition, diabetes, obesity, or cirrhosis also may increase the overall risk of infection.<sup>5</sup> Factors directly related to the transplant, including the hospitalization, surgical procedure, and need for supportive equipment such as urinary catheters, endotracheal tubes, and central lines, provide further potential sources of infection. Postoperatively, intensive immunosuppressive therapy is used to prevent acute rejection and preserve renal graft function. The level and duration of immunosuppression correlates with increased risk of developing opportunistic infections.<sup>6-8</sup> Thus, despite advances in management of immunosuppression, a fine balance exists between the quantity of immunosuppression needed to prevent

rejection and the superimposed risk of infection. Infection in immunocompromised hosts carries a broad spectrum of potential pathogens and atypical presentations of infection compared with the general population.

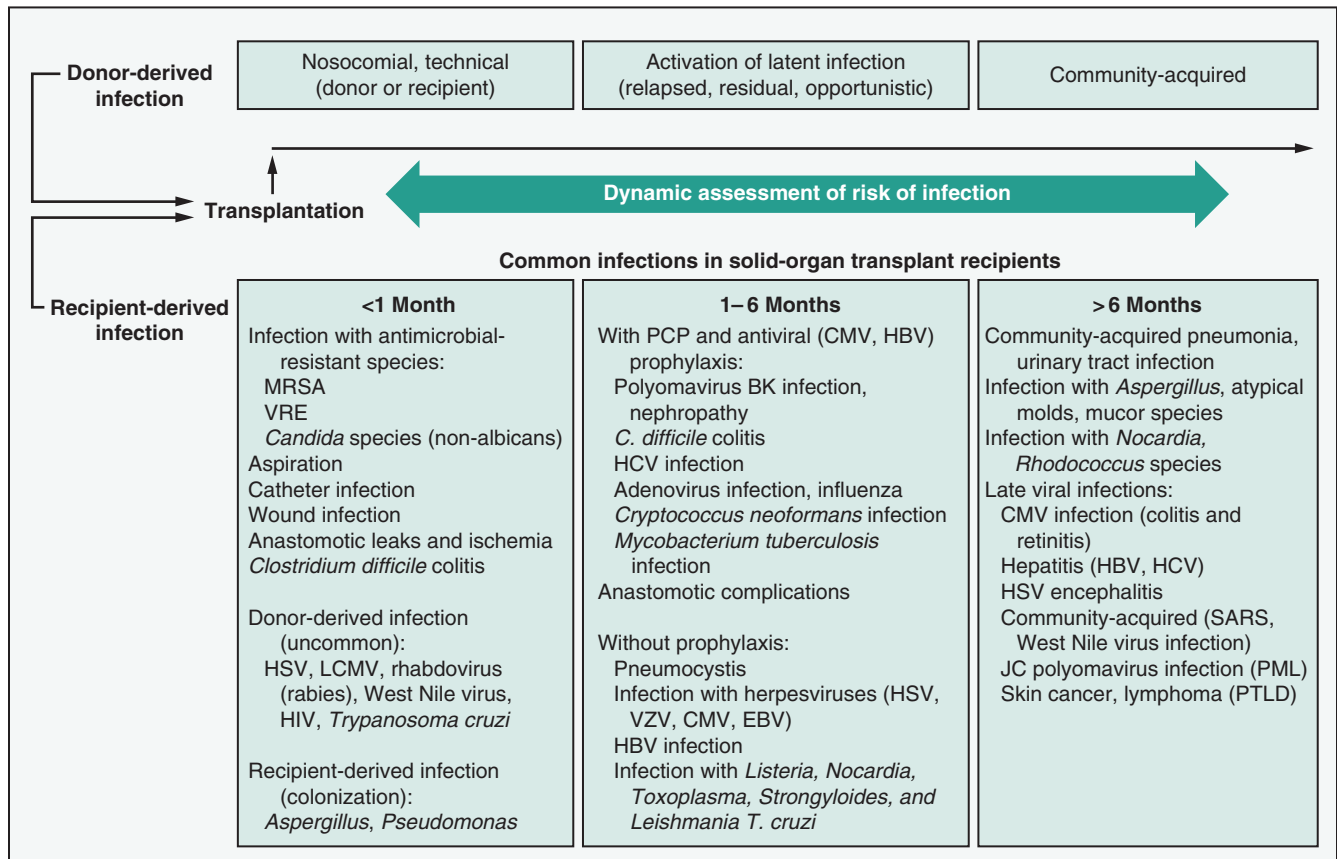
### Pretransplant Evaluation

Because of the infectious risks of transplantation and the resultant immunosuppression, pretransplant evaluations for donors and recipients are completed to minimize these risks. Pretransplant evaluations and management may vary across transplant centers. A thorough medical history including travel, prior infections, environmental exposures, and immunization history should be obtained. Common testing includes serology for cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), Human T-Cell Lymphotropic Virus (HTLV) 1 and 2, Rapid Plasma Reagin/ Venereal Disease Research Laboratory (RPR/VDRL), hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).<sup>3</sup> Further screening and treatment may be completed based on exposure risks for latent tuberculosis, *Strongyloides* spp., *Trypanosoma*

*cruzi*, *Coccidioides* spp., *Histoplasma* spp., and West Nile virus.<sup>3,6,9,10</sup> Pretransplant vaccinations may reduce morbidity and mortality because of these pathogens and often include pneumococcal; seasonal influenza; combined tetanus, diphtheria, and pertussis; varicella and zoster viruses; measles, mumps, and rubella; human papillomavirus (age dependent); and hepatitis A and B.<sup>11</sup>

### TIMELINE OF INFECTION AFTER KIDNEY TRANSPLANTATION

Infectious complications posttransplantation typically are categorized based on their temporal relation to the transplantation (Fig. 95.1). Because risk of acute cellular rejection is highest in the first several months after transplantation, patients are given induction immunosuppression perioperatively and subsequently placed on long-term maintenance immunosuppression. The effects of the induction immunosuppression often last 3 to 6 months or more and, depending on graft function and occurrence of rejection,



**FIGURE 95.1** Changing timeline of infection after organ transplantation. Infections occur in a generally predictable pattern after solid-organ transplantation. The development of infection is delayed by prophylaxis and accelerated by intensified immunosuppression, drug toxic effects that may cause leukopenia, or immunomodulatory viral infections such as infection with cytomegalovirus (CMV), hepatitis C virus (HCV), or Epstein-Barr virus (EBV). At the time of transplantation, a patient's short-term and long-term risk of infection can be stratified according to donor and recipient screening, the technical outcome of surgery, and the intensity of immunosuppression required to prevent graft rejection. Subsequently, an ongoing assessment of the risk of infection is used to adjust prophylaxis and immunosuppressive therapy. *HBV*, Hepatitis B virus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus, *LCMV*, lymphocytic choriomeningitis virus; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *PCP*, *Pneumocystis carinii* pneumonia; *PML*, progressive multifocal leukoencephalopathy; *PTLD*, posttransplantation lymphoproliferative disorder; *SARS*, severe acute respiratory syndrome; *VRE*, vancomycin-resistant *Enterococcus faecalis*; *VZV*, varicella zoster virus. (Modified from Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med.* 1998;338(24):1741-1751 and Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med.* 2007;357(25):2601-2614.)

the maintenance immunosuppression is weaned over time (however, rarely is stopped unless allograft fails and is removed). If the course is complicated by rejection, patients often require augmented immunosuppression. Prolonged and intensive immunosuppression increases risk for opportunistic infections and in an effort to reduce risk of the most common infections, antimicrobial prophylaxis often is used.<sup>12</sup>

### Early Period (During the First Month)

Infections occurring during the first month after transplantation usually are related to the transplant.<sup>13</sup> Complications resulting from the surgery, including prolonged ischemic time and leakage or strictures of urinary and vascular anastomoses, increase risk for superficial and deep surgical site infections with nosocomial pathogens. The most common infections after kidney transplant are urinary tract infections and can occur shortly after the procedure.<sup>14</sup> Urine cultures from donor and recipient are obtained immediately before the transplantation, and typically the recipient receives a course of antibiotics directed at these pathogens guided by susceptibility testing. Other nosocomial infections, including pneumonia, central venous catheter–related infections, and *Clostridium difficile* infection can be seen during this time. Reactivation of herpes simplex or varicella zoster viruses (HSV or VZV) also may manifest during this early period in the absence of antiviral prophylaxis because of the effects of the stress of the transplantation and immunosuppression. Unusual donor-derived infections, including free-living amoeba, lymphocytic choriomeningitis virus (LCMV), rabies virus, and West Nile virus, have been reported during this period or shortly thereafter, and should be considered if the patient develops unexplained signs, symptoms, or laboratory findings concerning for these processes.<sup>15</sup>

### Middle Period (Between 1 and 6 Months)

Opportunistic infections occur commonly between months 1 and 6 after transplantation and often are caused by reactivation of latent infections. Most centers use trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis jiroveci*, which also offers protection against infections resulting from *Listeria* spp., *Nocardia* spp., *Toxoplasma* spp., and some urinary and gastrointestinal pathogens. However, if this is not prescribed or taken, all of the aforementioned infections can be seen. Viral infections are also common, and most patients receive antiviral prophylaxis to prevent reactivation of HSV and VZV, but cytomegalovirus (CMV) infection can be problematic in at-risk patients. Other viral infections, including BK virus, adenovirus, and EBV also can occur during this time. Reactivation of tuberculosis or endemic/dimorphic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*) also should be considered in patients with the appropriate clinical scenario and exposure.<sup>3,12,16</sup>

### Late (After 6 Months)

Patients who require treatment for rejection continue to be at risk for opportunistic infections while they require intensive immunosuppression.<sup>13</sup> In the absence of rejection, infections occurring 6 months or more posttransplantation are, for the most part, similar to those seen in the general

community. Depending on donor and recipient serostatus and duration of antiviral prophylaxis, delayed infections resulting from herpesviruses also can occur, primarily because of reactivation of latent infection in recipient or primary infection transmitted via the allograft.<sup>12</sup>

## SPECIFIC INFECTIONS: PRESENTATION AND TREATMENT

### Bacterial Infections

Bacterial infections account for a large proportion of post-transplant complications and include but are not limited to upper and lower urinary tract infection (UTI), bloodstream infection, pneumonia, meningitis, and deep and superficial wound infections. Because of deceased donors or pending recipients may have been hospitalized preceding donation, drug-resistant organisms (methicillin resistant staphylococcus aureus (MRSA), vancomycin resistant enterococci (VRE)) must be considered for any bacterial infection.<sup>1</sup> **Treatment for bacterial infections should be guided by drug penetration of the site of infection, local antibiograms, and susceptibility testing.** Duration of therapy depends on source control, presence of concurrent infections (e.g., bloodstream infection), and clinical response.

### Urinary Tract Infection

UTIs are the most common bacterial infection in renal transplant recipients, present in approximately one third of patients, and make up 50% to 75% of posttransplant infections.<sup>1,3,4,17–19</sup> Infection can range from simple cystitis to ascending infection with renal abscess, lobar nephronia, and pyelonephritis with concurrent bloodstream infection. Recurrent infections may indicate anatomic complications or retained nidus of infection.<sup>1</sup> Symptoms may be similar to those in the general population, with hematuria, dysuria, suprapubic, or low back pain.<sup>1</sup> However, the allograft often is located in the pelvis; thus pain in the lower abdomen may indicate upper tract infection involving the allograft, which occurs more readily in this population because of the shortened ureter. Female gender, advanced age, preceding time on dialysis, urinary tract abnormalities (anatomic, catheter, and stent presence), cadaveric donor kidney, comorbidities such as diabetes, graft function, graft rejection, and other infections may increase the risk for posttransplant UTI.<sup>3,4,17,18</sup>

Common bacterial urinary pathogens in RTRs include the Enterobacteriaceae flora of the recipient (*Escherichia coli*, *Proteus* spp., *Klebsiella* spp.). *Pseudomonas aeruginosa* and other nosocomial pathogens such as *Enterococcus* species are also common.<sup>1,18,19</sup> Controversy remains in the literature regarding whether UTIs result in increased risk for allograft dysfunction or rejection.<sup>19</sup> Asymptomatic bacteruria is common, and persistent bacteruria has been associated with allograft infection and acute rejection in some, but not all, studies.<sup>1,3,19</sup> However, demonstrable reduction in symptomatic UTIs via treatment of asymptomatic bacteruria is lacking in the literature.<sup>4,19</sup> Because of the controversies remaining in the literature, consensus on treatment of asymptomatic bacteruria has not been reached, but some transplant programs use this practice.<sup>3</sup> Patients receiving TMP-SMZ for *Pneumocystis jiroveci* prophylaxis may have lower risk of asymptomatic bacteruria and UTI.<sup>17</sup>

## Bacterial Pneumonia

Bacterial pneumonia may arise from a diverse spectrum of pathogens from community and nosocomial exposures. Clinical manifestations of pneumonia may be subtler initially and require clinicians to maintain a high level of suspicion. Diagnostic workup should consist of respiratory samples (sputum, nasal swab for viral pathogens, tracheal secretions, and/or bronchoalveolar lavage [BAL]). Urine streptococcal and legionella antigens are also appropriate. Blood cultures should be drawn in the setting of sepsis to ascertain concomitant bloodstream infection and possible metastatic sites of infection, because this may alter antimicrobial choices and duration of therapy. *S. aureus*, *Pseudomonas*, and the enteric gram-negative bacilli account for the majority of cases in the nosocomial setting, and these organisms should be covered empirically in patients with pneumonia until culture data is available. *S. pneumoniae* is the most common community-acquired bacterial respiratory pathogen in patients greater than 6 months from transplantation, with no augmented immunosuppression for rejection.<sup>1</sup> *Legionella* remains a potential sporadic and epidemic pathogen, and clinicians must recognize the need for atypical coverage with macrolide or quinolone. Empiric antimicrobial therapy should be based on exposure risks, antibiograms, and individual patient issues (allergies, drug interactions, comorbidities) and tailored appropriately on susceptibilities. Please refer to published guidelines for further detail.<sup>20,21</sup>

## Surgical Site Infection

In the United States, approximately 4% to 7% of patients undergoing renal transplant develop a surgical site infection (SSI).<sup>5</sup> SSIs are among early potential infectious sources. SSIs are categorized by depth of infection: superficial/incisional, deep-incisional, and organ space.<sup>5</sup> Depending on depth, SSIs may require aggressive management with and debridement of infected tissue and antimicrobial therapy. Assessment of source control with imaging to rule out abscess in more superficial infections may be of value also in this setting. As with previously mentioned infections, pathogens here include nosocomial exposures (MRSA, VRE, *Pseudomonas*), skin flora, and Enterobacteriaceae among the most common pathogens for SSI; thus empiric coverage should reflect this.

## *Clostridium difficile* Infection

*Clostridium difficile* infection (CDI) remains the most common cause of nosocomial infectious diarrhea, and transplant patients have many risk factors for acquisition of and increased severity of CDI. Antimicrobial use is common given the risk of posttransplant infections and is the primary modifiable risk factor. Further, recent surgical procedures and immunosuppression also increased the overall risk.<sup>22</sup> Although diarrhea may be common in this population, clinicians should have a low threshold to test for CDI and initiate empiric therapy while awaiting results given the increased risk of severe disease.<sup>1</sup> If testing for CDI is negative, further evaluation for infections resulting from bacteria, viruses, and parasites should be considered.

## Tuberculosis

*Mycobacterium tuberculosis* (TB) is endemic in many areas of the world, and its prevalence among transplant recipients

correlates with that of the home country. Active infection with tuberculosis does portend an increased morbidity and mortality to transplant patients.<sup>3</sup> Pretransplant screening may be falsely negative because of anergic response in the setting of end-stage renal disease (ESRD), but if the recipient is diagnosed with or suspected to have latent TB, treatment with isoniazid typically would be initiated before transplant.<sup>3,23</sup> Patients may undergo renal transplantation while receiving isoniazid for latent tuberculosis.<sup>3</sup> Classic presentations of active TB include cough, fever, malaise, night sweats, and weight loss.

However, in the setting of the immunosuppression, patients may have extrapulmonary symptoms/sites of infection.<sup>23</sup> A diverse spectrum of clinical and radiologic findings including cavitory and noncavitory lesions can be seen. Consideration of active infection should prompt respiratory isolation in a negatively pressured, externally vented single room to avoid patient-to-patient spread. Tuberculin skin tests and interferon gamma release assays are intended for assessment of latent tuberculosis, not active infection; therefore culture, nucleic acid testing, or tissue specimen with staining for acid-fast bacilli should be obtained for a confirmed diagnosis and drug susceptibility testing.<sup>3</sup> Combination treatment should be initiated with the assistance of the infectious diseases and the transplant team because of regimen adjustments required based on drug-drug interactions and side effect profiles.<sup>1,23</sup> Nontuberculous mycobacterial infections are possible and may occur atypically, including with dissemination, among transplant recipients. Specific testing, including acid-fast staining and mycobacterial culture media, should be requested if these organisms are being considered in the differential diagnosis.

## *Nocardia* Species

Nocardiosis is a relatively rare opportunistic infection among RTRs and may occur with localized infection or systemic disease, including multiple cavitory or mass-like pulmonary lesions with or without associated hematogenous spread to skin, central nervous system, or other viscera.<sup>24</sup> Clinical manifestations of organ involvement may be subtle or absent.<sup>24</sup> If nocardiosis is diagnosed, brain imaging should be performed to evaluate for central nervous system involvement, because this infection has a predilection for spreading to the brain and may be present with minimal to no symptoms. Therapy may include decreased immunosuppression, surgery, and antimicrobials. Empiric treatment should include at least two to three agents with potential efficacy against *Nocardia* strains, taking into account sites of infection (CNS penetration may be necessary). Antimicrobial therapy is usually a prolonged course (6 to 12 months) based on antimicrobial susceptibility. The incidence of nocardiosis has fallen, possibly secondary to improved immunosuppression practices and/or the standard use of TMP-SMX prophylaxis for *Pneumocystis jirovecii*.<sup>24</sup>

## Viral Infections

Viral infections in renal transplant patients have a wide range of presentations with potential short-term and long-term sequelae, such as susceptibility to other infections, allograft dysfunction, rejection, and malignancy. Exposure to viruses may constitute a “primary” infection if the recipient has no prior viral-specific immunity or may represent a “secondary” infection, whereby a dormant strain

from a prior exposure reactivates as a result of immunosuppression. Suggested tests for each viral pathogen are discussed in their individual sections. The herpesvirus family includes herpes simplex viruses 1 and 2 (HSV-1, HSV-2), cytomegalovirus (CMV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and human herpesviruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8). These viruses establish latency after initial infection and can reactivate during periods of immunosuppression. Other important viral pathogens are the polyoma JC/BK viruses, parvovirus B-19, adenovirus, rotavirus, norovirus, respiratory viruses, and the viral hepatitis.

### Cytomegalovirus

CMV is the most common and significant viral infection in RTRs.<sup>3</sup> The spectrum of illness ranges from asymptomatic viremia to CMV syndrome and tissue-invasive disease.<sup>25</sup> Asymptomatic viremia is defined as a virus detected in blood by nucleic acid testing (NAT) without associated clinical or laboratory manifestations.<sup>26</sup> Depending on the quantitative viral load and timing posttransplantation, patients with asymptomatic viremia often require either antiviral therapy or close monitoring to ensure the infection does not progress to disease. CMV syndrome occurs when patients have constitutional symptoms (fever, malaise, myalgia) and/or laboratory findings (leukopenia, thrombocytopenia) in the setting of viremia. CMV tissue-invasive disease is characterized by focal tissue inflammation caused by viral invasion with biopsies demonstrating the cytopathic effect of the virus with intranuclear inclusions. Patients with CMV disease usually also have higher viral loads, and if biopsy cannot be performed, patients sometimes are treated empirically in the setting of characteristic symptoms, radiographic findings, and CMV viremia.<sup>25</sup> The most common organ system involved is the gastrointestinal tract, but pneumonitis, hepatitis, retinitis, and nephritis also can occur. The most severe presentation is CMV pneumonitis, and patients are often severely ill.

Diagnosis and treatment of CMV disease often is undertaken with the input of an infectious diseases specialist. In addition to the direct effects mentioned above, CMV infection is associated with numerous “indirect” effects. CMV is an immunomodulatory virus that can increase susceptibility to various coinfections.<sup>27</sup> CMV infection also can lead to acute and/or chronic allograft dysfunction and has been associated with increased mortality.<sup>3,27</sup> Based upon pretransplant serology, recipients who are seronegative (R–) and receive an organ from a donor-positive donor (D+) are at highest risk for CMV infection and progression to CMV disease; this is referred to as *CMV mismatch*. Recipients who have positive antibodies (IgG) for CMV before transplant (CMV D-/R+ or CMV D+/R+) are considered to be intermediate-risk recipients for CMV infection.<sup>25</sup> Cases in which donor and recipient are seronegative (D–/R–) are at lowest risk for CMV infection, and it is important that they receive CMV-negative or leukocyte-depleted blood products to avoid iatrogenic transmission.<sup>25</sup> Patients who are at high or intermediate risk for CMV infection and receive induction therapy or treatment of acute rejection with antilymphocyte agents are at increased risk for CMV infection during the subsequent 3 to 6 months. In an effort to reduce CMV infection and disease as well as its indirect effects, several prevention strategies have been implemented. One option is to provide antiviral prophylaxis (intravenous ganciclovir or oral valganciclovir) to at-risk individuals during high-risk periods. Another option is preemptive monitoring, which entails periodic monitoring with NAT, and if patients are

found to have a threshold load of viral DNA or rising level on serial testing, treatment is initiated to prevent progression to CMV syndrome or tissue-invasive disease.<sup>3,25</sup>

First-line treatment for CMV infection typically includes reducing immunosuppression when possible and antiviral therapy with intravenous ganciclovir or oral valganciclovir, depending on severity of illness.<sup>25</sup> CMV disease usually is treated initially with intravenous ganciclovir and in some cases may transition to oral valganciclovir, pending clinical improvement and ability to absorb oral medications. Both agents require dose adjustments in the setting of renal dysfunction, and valganciclovir should not be used in patients requiring hemodialysis. Both agents can cause myelosuppression heralded by leukopenia and/or thrombocytopenia. Depending on the severity, these cases may necessitate using granulocyte colony-stimulating factor (G-CSF) or switching to another antiviral, but the dose should never be reduced for this indication because of the risk of resistance. Treatment for CMV disease is generally at least 3 weeks and should be continued until the viral load is negative. The viral load may continue to rise for the first 7 to 10 days after starting antiviral treatment, but occasionally the virus can develop resistance. In patients with rising viral loads despite more than 14 days of treatment with appropriately dosed ganciclovir or valganciclovir, testing for antiviral resistance and initiation of alternative therapy may be indicated.<sup>3,26</sup> Approved second-line therapy for CMV infections include foscarnet and cidofovir, but both agents have potential to cause nephrotoxicity as well as other adverse effects.

### Epstein-Barr Virus

Like CMV, EBV infections in RTRs can be donor derived or a reactivation of latent infection in the recipient and can be asymptomatic or cause a mononucleosis-like illness (malaise, fever, headache, and sore throat). This virus establishes latency in B cells and is associated with posttransplantation lymphoproliferative disease (PTLD), which is an unchecked proliferative of B lymphocytes with the potential for malignant transformation.<sup>3,28</sup> Not all patients with EBV infection develop PTLD, but risk factors include high viral loads, EBV and CMV sero-mismatch, and T cell-depleting agents. Compared with other organ types, kidney transplant recipients are at relatively low risk for PTLD, which occurs in about 1% to 2% of patients.<sup>28</sup> PTLD may manifest in nodal tissue, extranodal viscera, including the allograft, or both. Treatment depends on the pathologic diagnosis and extent of disease but may include a reduction in immunosuppression, surgical resection, anti-CD20 antibody (rituximab), or even cytotoxic chemotherapy. The use of antiviral agents such as acyclovir or ganciclovir and/or immunoglobulin is controversial but may be considered as an adjunctive therapy.<sup>28</sup> Treatment for PTLD requires a multidisciplinary approach with input from specialists in transplant nephrology, surgery, oncology, and infectious diseases.

### Herpes Simplex Virus

Herpes simplex virus (HSV) 1 and 2 have a seroprevalence in the United States adult population of approximately 80% and 26%, respectively. Reactivation may occur in seropositive, immunocompetent patients. Reactivation in RTR occurs more commonly in the absence of antiviral prophylaxis and has been seen as early as 1 month

posttransplantation. Presentation may range from mucocutaneous lesions of the oropharynx or genital regions to dissemination throughout multiple organ systems (hepatitis, pneumonitis, esophagitis) or the CNS. Diagnosis of mucocutaneous HSV infection is clinical, with direct observation of the characteristic lesions, but unroofing a vesicular lesion and swabbing for confirmatory testing with either polymerase chain reaction (PCR) or direct fluorescent antibody (DFA) may be helpful. Diagnosis and treatment of HSV keratitis or retinitis requires referral to an ophthalmologist. For disseminated or other organ disease, DNA detected by PCR on affected fluid or tissue is often the preferred diagnostic test. Obtaining cells or tissue for cyto- or histopathology with intranuclear inclusions and staining HSV antigens helps to confirm diagnosis but is not always feasible.<sup>29</sup>

Treatment for mucocutaneous HSV infections is typically with oral acyclovir, famciclovir, or valacyclovir for a 7- to 10-day course. In disseminated HSV, hepatitis, or meningoencephalitis, immunosuppression ideally should be reduced, and intravenous acyclovir 5 to 10 mg/kg (10 mg/kg for CNS dosing or severe visceral disease) every 8 hours should be administered. The dose should be adjusted based on renal function. Prophylaxis against HSV and VZV (discussed later) with oral acyclovir, famciclovir, or valacyclovir often is given posttransplant and during periods of augmented immunosuppression. Ganciclovir and valganciclovir for treatment or prevention of CMV also have activity against HSV and VZV. Although antiviral resistance is less common in HSV than in CMV, it can occur and should be considered in patients who fail to respond to treatment. Genotypic testing for resistance and alternate therapy is available.<sup>29</sup>

### **Varicella-Zoster Virus**

Varicella-zoster virus (VZV) is responsible for chickenpox and is spread via direct contact droplet inhalation. After primary infection, such as HSV, the virus also established latency in the nerve root and can reactivate in immunocompetent and immunocompromised individuals. Most US adults had the virus in childhood, but the varicella vaccine was introduced for use in the United States in 1995, so some young adults have seropositivity as a result of the vaccine. VZV IgG testing is performed as part of the transplant workup, and vaccination in those who are nonimmune generally is recommended if not contraindicated (at least 4 weeks before transplantation). Reactivation of VZV in RTRs can occur as single or multiple dermatome skin eruptions, disseminated infection, or visceral or CNS involvement.<sup>30</sup> The diagnosis is usually clinical but often is confirmed using VZV PCR or DFA. For disseminated, CNS, or visceral disease, DNA detected by PCR on affected fluid or tissue is the preferred diagnostic test. Obtaining cells or tissue for cyto- or histopathology with intranuclear inclusions and immunocytochemistry helps to confirm diagnosis but is not always feasible. In the absence of disseminated disease, oral antiviral treatment with acyclovir, valacyclovir, or famciclovir is likely adequate. If there is concern for disseminated infection, CNS, or other organ involvement or disseminated infection, VZV requires intravenous acyclovir for 7 to 14 days.<sup>30</sup>

### **Other Herpesviruses**

HHV-6, HHV-7, and HHV-8 also establish latency after initial infection and can reactivate. HHV-6 and HHV-7 may have

immunomodulatory properties and may be a marker for increased risk of coinfections.<sup>31</sup> HHV-6 has been reported infrequently to cause graft dysfunction, bone marrow suppression, encephalitis, pneumonitis, and hepatitis.<sup>32</sup> HHV-8 is associated with Kaposi sarcoma, a vascular endothelial tumor that can cause a cutaneous mucosal or visceral disease, and is particularly common in transplant recipients of African, Mediterranean, or Middle Eastern origin. Seroprevalence in the United States is only about 5%.<sup>31</sup> Transmission of HHV-8 has been shown to occur via the renal allograft.<sup>33</sup> HHV-8 also is known to cause primary effusion lymphoma (PEL) and multicentric Castleman disease, both of which are lymphoproliferative processes seen most commonly in the HIV population.

### **BK Polyomavirus**

Serologic studies demonstrate that up to 90% of adults are seropositive for BK virus (BKV). The route of transmission is thought to be via the respiratory or GI tract followed by asymptomatic viremia. The virus then establishes latency in the urinary tract and can have asymptomatic viral shedding in the normal population. This virus has a unique pathogenesis in renal transplant and hematopoietic stem cell transplant (HSCT) recipients and can result in two disease processes in this population: polyoma-virus associated nephropathy (PyVAN) and polyomavirus-associated hemorrhagic cystitis (PyVHC). PyVHC occurs much more frequently in the HSCT population but has been observed in RTRs as well; this process is heralded by dysuria and hematuria, sometimes causing urinary obstruction resulting from blood clots.

PyVAN is the most common disease presentation in RTRs and occurs as a result of high-level viral replication in the urine progressing to viremia.<sup>34</sup> Diagnosis should be suspected in any RTRs with declining allograft dysfunction in patients with high-level viruria, decoy cell shedding, and BKV viremia. Because rejection also is included in this differential and requires very different management, renal biopsy usually is undertaken to differentiate between the two and to stage the severity. If the diagnosis of PyVAN is confirmed, reduction of immunosuppression is the first and most important intervention. The use of immunoglobulin and antiviral agents is controversial because there are no definitive data that they provide any benefit, and some have associated toxicities.<sup>13</sup> Previously studied antiviral agents include cidofovir, leflunomide, and fluoroquinolones.<sup>34</sup>

### **Adenovirus**

Adenoviruses are classified into seven subgroups (A to G) and encompass more than 50 viral serotypes. Some serotypes are capable of establishing latent infections and can reactivate or be transmitted via allograft.<sup>35</sup> The virus can be transmitted in a variety of modes, including via aerosols or bodily fluids and causes symptomatic disease in the immunocompetent and immunocompromised but has a much higher likelihood of causing disseminated disease in the immunocompromised. Adenovirus can cause a wide variety of illnesses, including upper and lower respiratory tract infections, conjunctivitis, enteritis, and hepatitis. Adenovirus is another cause of hemorrhagic cystitis and allograft dysfunction (similar presentation to BKV) and also can be associated with rejection.<sup>36</sup> Risk factors include younger age, given lower likelihood of immunity, and treatment with lymphocyte-depleting agents.<sup>35</sup> Because of

the variable presentation, diagnosis may be a challenge and usually is based on molecular detection (PCR) or histopathology.<sup>37</sup> Management of infection usually includes reduction of immunosuppression. Antiviral agents, specifically cidofovir and its lipid conjugate, brincidofovir (CMX001), have been used for treatment of significant infections, but currently there are no approved drugs for this indication (brincidofovir is not commercially available at the time of writing).

### **Influenza and Other Community-Acquired Respiratory Viruses**

Important community-acquired respiratory virus infections in immunocompromised hosts include influenza virus types A and B, respiratory syncytial virus (RSV), parainfluenza viruses (PIV), coronavirus, rhinovirus, and human metapneumovirus (hMPV). These viruses are transmitted by direct contact and respiratory droplets from infected individuals and typically follow a seasonal pattern. The clinical presentation may include upper respiratory tract infection, tracheobronchitis, influenza-like illness, bronchiolitis, or pneumonia. In the immunocompromised host, viral shedding may persist for months. It can be difficult to distinguish between these infections based on clinical presentation, and therefore to make a definitive diagnosis, multiplex PCR assays for respiratory specimens now are being used. Viral antigen testing for influenza and RSV also can be performed, but sensitivity is lower. Influenza is typically the most severe of the aforementioned viral infections, and treatment with a neuraminidase inhibitor such as oseltamivir or zanamivir usually is indicated, because it may shorten the duration of symptoms and prevent progression to more severe illness. Newer agents, such as intravenous peramivir, are not used routinely in critically ill or immunocompromised patients. Treatment recommendations should be reviewed yearly for updates in recommendations and management. Seasonal influenza vaccination is recommended. The treatment for the rest of the aforementioned viral infections is usually supportive in the renal transplant population. Antiviral therapy with ribavirin has been used to treat RSV, hMPV, and PIV in the lung transplant or HSCT population, but it is reserved for severe infections and should be administered under the direction of an infectious diseases specialist.<sup>38</sup>

### **Viral Hepatitis**

Pretransplant management of viral hepatitis is imperative, because these infections affect morbidity and mortality in the transplant setting. Hepatitis C is of particular concern because it further blunts the immune system if not treated before transplant. Further, HCV infection and secondary cryoglobulinemia may affect negatively graft function post-transplant.<sup>1,3</sup> HBV and HCV can reactivate with immunosuppression. For those who receive infected donor organs, development of active infection is variable in presentation but can be very rapid in clinical progression. Further, in the setting of immunosuppression, antibodies may not form for seroconversion, thus nucleic acid testing should be used to assess for infection.<sup>3,6</sup>

### **Fungal Infections**

Among all solid organ transplant recipients, RTRs have the lowest rates of invasive fungal infection (IFI), accounting

for approximately 5% of infections in this population.<sup>16</sup> As a result, prophylaxis against fungal pathogens is not recommended routinely in RTRs. However, the case-fatality rate is the highest for fungal infections compared with other pathogen categories, and therefore, if infections occur, prompt recognition and treatment is important. Most fungal infections occur within the first 6 months after transplantation, although a longer period of risk may occur in more heavily immunosuppressed recipients.

### **Yeast**

Infections resulting from *Candida* species represent the most common fungal infection in RTRs. Older age, central venous catheters, surgical drains, urinary catheters, diabetes mellitus, use of corticosteroids or broad-spectrum antibiotics, and length of hospital and intensive care unit stay are important risk factors for the development of *Candida* infection in transplant recipients.<sup>39</sup>

Candidiasis can be categorized as either superficial or deep. Commonly involved superficial sites are the oral cavity, esophagus, and bladder. Oral candidiasis manifests as single or multiple, white, raised, plaque-like lesions over the palate and oropharyngeal mucous membranes and often can be treated with topical agents. Oral candidiasis can progress distally and can lead to esophageal involvement with symptoms ranging from asymptomatic to odynophagia/dysphagia. Esophageal candidiasis, if untreated, can lead to esophageal bleeding, perforation, and disseminated candidiasis. In most cases *Candida* spp. isolated from sputum or BAL cultures is thought to be a colonization or contaminant and usually does not require treatment. Candiduria may represent asymptomatic colonization in renal recipients with indwelling bladder catheters versus lower or upper tract infection. Candiduria in a RTR theoretically can lead to ascending infection with involvement of the ureteral anastomosis or allograft, so a clinical bias to treat even asymptomatic candiduria in the recent renal recipient is rational. Therapeutic options include azoles, or amphotericin B bladder irrigation; echinocandins have poor urinary penetration and therefore are not recommended to treat UTIs.

Deep-seated candidiasis can manifest with persistent fever or sepsis in patients who are receiving antibacterial therapy or have other risk factors for candidiasis. Definitive diagnosis of invasive candidiasis is based on isolation of the organism from sterile source (e.g., blood, ascites), but sensitivity of blood cultures for candidemia is only about 70%. Therefore isolation of *Candida* from one or more blood cultures always should be considered to represent a true pathogen. Candidemia may be the result of deep tissue-invasive candidiasis or catheter-related infection, in which case, line removal is recommended strongly. In the RTR, candidemia can lead to metastatic infection at the renal vascular anastomosis or in the renal parenchyma. Other signs of dissemination include skin lesions or new ocular symptoms, including eye pain, photophobia, and visual loss, which may signify *Candida* endophthalmitis and should prompt an ophthalmology evaluation with dilated eye exam. Treatment for deep-seated *Candida* infections or candidemia requires a systemic antifungal agent and options include azoles, echinocandins, and liposomal amphotericin B. In patients with severe infections or those at risk for resistance *Candida* spp., first-line treatment is usually an echinocandin; if the patient is stable and has not had significant exposure to azoles, fluconazole is a reasonable option. Once the species has been identified, treatment can be guided by likely susceptibility profile.<sup>39</sup> *Cryptococcus neoformans* is a ubiquitous encapsulated yeast

found in the soil and in pigeon feces. Although the main portal of entry is the respiratory tract, *Cryptococcus* pneumonia is seen relatively infrequently. More concerning, this infection can disseminate hematogenously and spread to the central nervous system and lead to subacute meningitis. Diagnosis requires the detection of *Cryptococcus* in the cerebrospinal fluid by India ink staining, identification of cryptococcal antigen, or culture. Treatment requires combination therapy with amphotericin B or lipid formulation amphotericin B and 5-flucytosine for several weeks, followed by fluconazole once cerebrospinal fluid (CSF) cultures are negative.

## Dimorphics

The endemic mycoses (histoplasmosis, coccidiomycosis, and blastomycosis) should be considered in enigmatic pulmonary, cutaneous, or complex disseminated presentations in patients who are native or have traveled to one of the classic geographic areas where the prevalence of such fungi is more common. They are termed dimorphic because they grow as yeast at warmer temperature (body) and as mycelial forms at cooler temperature (lab) and therefore appear as yeast on histopathology but grow as molds in culture. Serology, fungal antigen (e.g., urine, serum, BAL fluid), stain with culture and nucleic acid testing are possible methods of achieving the diagnosis. For severe disease, liposomal amphotericin is the preferred initial drug with eventual transition to an azole pending organ involvement and clinical course. These infections can reactivate from latent infections, be donor derived, or occur de novo posttransplantation.

## Molds

Infections resulting from filamentous fungi (also known as molds) are the least common of the IFI in RTRs. *Aspergillus* infections are acquired by airborne transmission of spores to the sinuses or respiratory tract, and outbreaks have been reported among patients in proximity to hospital construction sites. In a recent publication 51 cases were identified over 13 years at 19 institutions, and risk factors include chronic obstructive pulmonary disease (COPD), graft dysfunctions, rejection, and occurrence of other infections.<sup>40</sup> The most common species are *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus terreus*. The lungs are the most common initial site of infection, which may manifest as solitary or multiple nodules or cavitory lesions and may invade pulmonary vasculature. Hematogenous dissemination to organs, including the brain, infrequently occurs but has very high mortality rates.

Voriconazole, with or without a second active agent (echinocandin, lipid amphotericin B), has emerged as the first-line treatment for aspergillosis, coupled with reduction of immunosuppression and occasionally with surgical resection of isolated lung or brain lesions. Treatment duration depends on clinical and radiographic improvement as well as ability to reduce immunosuppression or surgically resection. Other, less common mycelial fungi of clinical importance include those causing zygomycosis (*Mucor*, *Rhizomucor*), *Pseudallescheria boydii*, dematiaceous (pigmented molds), *Fusarium*, and others.

## Special Considerations: *Pneumocystis jiroveci*

*Pneumocystis jiroveci* (PJP, formerly called *Pneumocystis carinii*, or PCP) can cause severe pneumonia after

transplantation and carries an approximately 30% to 50% mortality rate for RTRs.<sup>3</sup> Infection with this pathogen has decreased among this population because of the universal use of chemoprophylaxis among transplant centers for the first several months posttransplant with TMP-SMX as the preferred agent.<sup>3</sup> Alternative options include atovaquone, dapsone, and inhaled pentamidine, but these agents are less effective and breakthrough infections can occur. Symptoms of PJP include fever, dyspnea, and nonproductive cough with hypoxia that is more severe than expected. Imaging with radiograph or computed tomography (CT) scan often reveals the presence of interstitial infiltrates, often characterized as “ground glass” in appearance. Diagnosis is dependent on identifying the organism via respiratory secretions (sputum, BAL, or tissue specimen) and usually is made via appropriate staining (Silver or Giemsa) or molecular techniques (PCR). Therapy consists of 14 to 21 days of high-dose intravenous TMP-SMX (dosage adjusted according to kidney function) or, in case of sulfa hypersensitivity, intravenous pentamidine, atovaquone, clindamycin, and pyrimethamine or TMP plus dapsone (G6PD deficiency must be tested before administration of this medication). In addition, corticosteroids should be considered for those with significant hypoxia (partial pressure of oxygen in the alveoli of <70 mm Hg on room air).<sup>3</sup> Further, *P. jiroveci* pneumonia, like most other severe infections, requires reduction of immunosuppression.

## CENTRAL NERVOUS SYSTEM SYNDROMES

Central nervous system (CNS) infections are not common, but in the general population, can be fatal. Clinicians must maintain a high level of suspicion for CNS infections in transplant recipients, because immunosuppressive therapy may result in more subtle presentations of typical infections.<sup>1</sup> Further, opportunistic pathogens also may result in varying clinical presentations. Fever and headache remain among the most reliable presenting symptoms.<sup>1</sup> Examples of potential infections include community-acquired meningitis, mass lesions such as bacterial brain abscesses, invasive aspergillosis, nocardiosis, toxoplasmosis, and cryptococcus.<sup>1</sup> Viral infections may result in syndromes of meningitis/meningoencephalitis, including many of the herpesviruses (e.g., HSV, VZV). JC virus rarely can result in progressive multifocal leuko encephalopathy (PML) in transplant patients. Any of these may experience headache, fever, nuchal rigidity, impaired consciousness, or change in cognitive function. Finally, noninfectious causes of CNS syndrome also must be considered, including drug toxicity and posterior reversible encephalopathy syndrome (PRES).

There should be a low threshold for lumbar puncture with spinal fluid analysis with any fever and neurologic symptoms. Focal neurologic symptoms require imaging, and magnetic resonance imaging (MRI) particularly, may provide important diagnostic clues. Empiric management for presumed meningitis/encephalitis often includes vancomycin, a third- or fourth-generation cephalosporin or carbapenem, ampicillin (for possible *Listeria* infection) and intravenous, high-dose acyclovir while awaiting CSF analysis.

## HUMAN IMMUNODEFICIENCY VIRUS AND RENAL TRANSPLANT

Renal transplantation is performed in patients with HIV or, less commonly, may be acquired posttransplant in patients



with high-risk behaviors.<sup>3</sup> Because of the availability of molecular testing for HIV, the incidence of donor-derived HIV infection is extremely low. A full discussion of HIV and the resultant implications on transplant is out of the scope of this chapter. However, clinicians must recognize the importance of continuing antiretroviral therapy, monitoring for drug interactions, and changing regimens only with the assistance of a multidisciplinary team, including the transplant team, HIV specialist, and pharmacy.<sup>3</sup> Furthermore, there are increased risks of certain infections and malignancies in the setting of immunologic impairment from HIV and immunosuppressants, and these will have to be factored into differential diagnoses and management.

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### Key Points

1. Infections after kidney transplant vary by time from transplantation.
2. Type and depth of immunosuppression affect infectious risk and types of infection.

3. Posttransplant, there are many infections of concern, but CMV, EBV, and BK virus are of particular risk in regard to acute and long-term complications of the patient and of the allograft.
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