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Chapter 90

Prevention and Treatment of Infection in Kidney Transplant Recipients

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CHAPTER CONTENTS

Despite advances in immunosuppression, surgical techniques, and donor and recipient screening that have increased the life expectancy of renal transplant recipients, infectious complications remain a significant cause of morbidity and mortality among renal transplant recipients.[1] A recent analysis of the U.S. Renal Data System database found that for patients who received a tranplant between 1991 and 1998, 51% had a hospital discharge diagnosis that included infection during the first year after transplantation.[2] Unfortunately, the incidence of infection in the post-transplant period seems to be increasing; total infection-related hospital discharge diagnoses have increased each year since 1999.[3]

For the clinician, the challenge lies in both the prevention of and the early diagnosis and treatment of infection in this population. This is hampered by the lack of standardized diagnostic testing for many pathogens and the often atypical presentation of infectious diseases in immunocompromised patients. Additionally, many of the more commonly used antimicrobials have significant drug interactions with immunosuppressive medications, putting the patient at risk for allograft rejection or toxic adverse effects.[4] Some drug-drug interactions of importance are listed in Table 90-1; however, the clinician should always check for drug interactions before prescribing any antimicrobial, preferably with the input of a clinical pharmacist, if available.

Although the list of pathogens that may cause disease in the transplant recipient continues to increase, each broad class of infection contains several "typical" organisms with which the practitioner should be familiar. One helpful method of thinking about infection in the transplant patient is to consider how much time has elapsed since the transplant occurred, because some infections tend to manifest during certain time windows after surgery. This finding has been summarized in chart form by Fishman[5] (Fig. 90-1). In the first month post-transplant, nosocomial infections tend to predominate, including wound and catheter-related bacterial and fungal infections, and flares of prior latent or allograft-transmitted viruses if no prophylaxis is given (i.e., herpes simplex virus [HSV], hepatitis B, hepatitis C). During the following 5 months, viral infections predominate, including reactivation or primary infection with varicella-zoster virus (VZV), Epstein-Barr virus (EBV), or cytomegalovirus (CMV), although if the patient is receiving antiviral prophylaxis, disease may be delayed until prophylaxis is discontinued. Patients are also increasingly susceptible to community-acquired respiratory viruses, environmental fungi, and parasites as they begin to travel and congregate with others outside the healthcare setting. After 6 months, the risk of opportunistic infections declines as the period of maximum immunosuppression passes, and community-acquired pathogens and post-transplant lymphoproliferative disease (PTLD) tend to be more common.

The use of vaccines before transplantation and selected prophylaxis regimens after transplantation, along with good infection control practices and common sense guidelines for the recipient to minimize high-risk exposures after discharge, will greatly reduce the risk of infectious complications.[6,7] However, there are still many pathogens for which there are no vaccines or effective prevention strategies. This chapter discusses the more common infections encountered in the transplant setting; however, an exhaustive review of infectious diseases is beyond the scope of this chapter. An excellent resource containing comprehensive guidelines for the majority of infectious diseases encountered by the clinician is available in a recent supplement to the *American Journal of Transplantation*.[8]

Table 90-1 Important Drug-Drug Interactions

	Drugs By Class	Cyclosporine Interaction	Tacrolimus Interaction	Nephrotoxic?
Antifungals	Amphotericin B/lipid amphotericin B	—	—	Yes
	Caspofungin	*	↓	
	Fluconazole/itraconazole	↑↑	↑↑	
	Ketoconazole	↑↑↑	↑↑↑†	
	Voriconazole	↑↑↑	↑↑↑†	
Antibacterials	Erythromycin/clarithromycin	↑↑↑	↑↑↑	
	Nafcillin	↓↓	—	Yes
	Aminoglycosides	—	—	Yes
	Rifampin	↓↓↓	↓↓↓	
	Trimethoprim/sulfamethoxazole	—	—	Yes
	Dapsone	—	↑	
	Chloramphenicol	↑↑	↑↑	
	Quinupristin/dalfopristin	↑↑	—	
	Metronidazole	↑↑	↑↑	
Antivirals	Foscarnet	—	—	Yes
	Cidofovir	—	—	Yes
	Protease inhibitors	↑↑	↑↑	
	Tenofovir	—	—	Yes

*Combination may increase caspofungin levels and induce hepatotoxicity.
†Use with sirolimus contraindicated.
Adapted from Immunosuppressive drug interactions with anti-infective agents. Am J Transplant 2004;4(Suppl 10):164–166.

VIRAL INFECTIONS

Cytomegalovirus

Cytomegalovirus is the most important viral infection that develops after solid organ transplant and is associated with significant morbidity and mortality.[9] CMV is a member of the Betaherpesvirus family; its seroprevalence in the general adult population ranges from 50% to 80% by age 40, and the virus establishes lifelong latency in the host.[10] Primary infection with CMV in the immunocompetent host may be asymptomatic or may manifest as fever, malaise, and a mononucleosis-type syndrome. After primary infection, the virus typically remains latent with no systemic signs or symptoms of reactivation. However, in the transplant recipient, the effects of CMV are myriad, including a *viral syndrome* with fever, leukopenia, and thrombocytopenia that may be compounded by immunosuppressive medications, and also tissue-invasive disease, potentially involving the transplanted organ as well as the lungs, liver, gastrointestinal tract and, rarely, the retina.[11] CMV also has been associated with several indirect effects in solid organ tranplant patients, including increased risk of rejection, reduced long-term survival, increased risk of other opportunistic infections, bacterial infections, and allograft dysfunction.[12]

Prior to the widespread use of antiviral prophylaxis, most CMV disease occurred in the first 3 months after solid organ transplantation, with donor-seropositive/recipient-seronegative patients at the highest risk for disease. In addition to donor seropositivity, other major risk factors for CMV infection and disease include the degree of immunosuppression, including the use of antilymphocyte and OKT3 monoclonal antibody therapy for induction or treatment of rejection, rejection itself, and other concurrent viral infections (e.g., human herpesvirus 6 [HHV-6] infection).[9] Primary CMV infection via the transplanted organ in the seronegative recipient, reactivation of latent disease in the seropositive recipient, and superinfection of donor virus in the seropositive recipient can all cause symptomatic disease. Two strategies have been used for CMV prevention in at-risk patients: universal prophylaxis and preemptive therapy.

Universal CMV prophylaxis involves giving antiviral therapy to all "at-risk" patients (i.e., those with either a CMV-seropositive donor or recipient) at the time of transplantation or immediately afterward for a specified period with the goal of preventing CMV disease during the period of maximum immunosuppression. This approach may be preferable in patients in whom close monitoring for CMV disease is not possible or practical. Although numerous approaches (including acyclovir, valacyclovir, and CMV immunoglobulin) have been associated with a reduction in CMV disease, ganciclovir has been the mainstay of both CMV treatment and prophylaxis in solid organ transplant recipients after studies showed improved efficacy over acyclovir in this population.[13–15] The

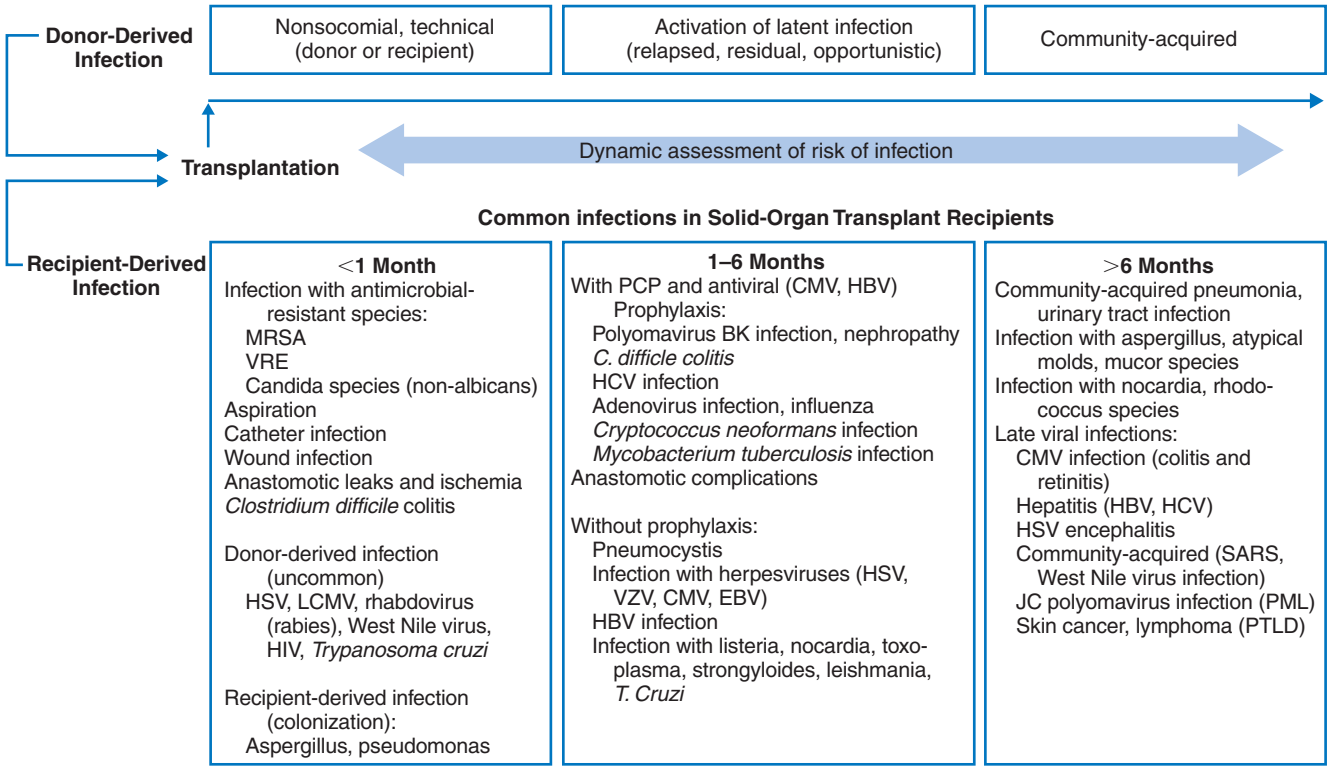

Figure 90-1 Timeline of infection after solid organ transplantation, summarizing typical donor-derived and recipient-derived infections. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis carinii* pneumonia; PML, progressive multifocal leukoencephalopathy; PTLD, post-transplant lymphoproliferative disorder; SARS, severe acute respiratory syndrome; VRE, vancomycin-resistant *Enterococcus faecalis*; VZV, varicella-zoster virus. (From Fishman JA: Infection in solid-organ transplant recipients. N Engl J Med 2007;357:2601–2614.)

intravenous form of ganciclovir has given way to oral formulations at many centers due to ease of administration. Oral ganciclovir has a significantly lower bioavailability than the intravenous form, but at doses of 1 gram three times a day it has proven efficacy in reducing the incidence of CMV disease.[16] The valine ester prodrug of ganciclovir, valganciclovir, has improved bioavailability compared to oral ganciclovir, and at doses of 900 mg daily has been shown to be equally efficacious in renal transplant patients,[17] with a slightly increased incidence of neutropenia compared to ganciclovir (8.2% vs. 3.2%). Valganciclovir is not indicated for patients undergoing combined liver and kidney transplantation due to reports of breakthrough CMV disease in liver transplant recipients receiving valganciclovir prophylaxis.[18]

Preemptive therapy requires close monitoring of patients for signs of CMV reactivation or primary infection, with prompt initiation of anti-CMV therapy to prevent progression to CMV disease. Blood CMV DNA or RNA levels or CMV antigenemia assays can be utilized at weekly intervals for the initial post-transplantation phase, and then at longer intervals as immunosuppression is reduced. Culture techniques, including shell vials, have fallen out of favor due to long turnaround times or poor sensitivity. A randomized trial of prophylactic or preemptive oral valganciclovir was published in 2006, comparing prophyloctic valganciclavir 900 mg daily for 100 days posttransplant and preemptive valganciclovir 900 mg twice a day for 21 days; the trial measured whether CMV DNA levels rose above 2000 copies/mL in blood samples assessed weekly for the first 16 weeks and then at 5, 6, 9, and 12 months post-transplant. There were no significant differences in efficacy in the prevention of CMV disease, and a cost-sensitivity analysis was similar for both approaches.[19]

The optimal duration of CMV prophylaxis remains unclear. Now that many centers use prophylaxis for the first 3 months after transplant, CMV disease typically occurs later after transplantation, most often at a median of 5 months post-transplant in donor-seropositive/recipient-seronegative patients.[20,21] Unfortunately, extension of prophylaxis beyond 3 months raises concerns of drug toxicity or the development of drug resistance, although a study of 301 high-risk solid organ transplant patients who received 100 days of valganciclovir prophylaxis failed to show the development of drug resistance.[22] Monitoring immune markers of CMV also does not appear to be predictive of the development of CMV disease, as a recent study by LaRosa and colleagues[23] suggests. This study examined interferon gamma release from T cells at biweekly intervals between 4 and 6 months after transplant. No association was found between presence or absence of T-cell response and development of CMV disease.[23] However, the failure to develop IgG antibodies at 6 months' post-transplant in patients seronegative at the time of transplant may be predictive of late-onset CMV disease (10% developed disease vs. 1.3% of patients with CMV IgG by 6 months).[24]

Standard treatment of CMV disease uses intravenous ganciclovir, 5 mg/kg twice daily (with dose adjustments for renal

insufficiency) and reduction of immunosuppression until resolution of symptoms and CMV viremia. Unfortunately, ganciclovir-resistant CMV has emerged as an uncommon but growing problem in the solid organ transplant population, perhaps due to prolonged use of oral ganciclovir prophylaxis and more potent immunosuppression regimens.[25] Although this has not been commonly reported in recipients of kidney transplants alone, it may occur more frequently in pancreas transplant recipients; a major risk factor for this is prolonged exposure to low-dose ganciclovir during periods of asymptomatic infection. Resistance can be detected via phenotypic or genotypic testing, but usually requires additional time. Failure to respond to adequate dosing of ganciclovir should raise a suspicion of ganciclovir resistance, and substitution of another antiviral agent may be warranted. Options for the treatment of resistant CMV include foscarnet with or without ganciclovir and cidofovir, both of which may be highly nephrotoxic, especially when used in the context of calcineurin inhibitors. Adjunctive intravenous immunoglobulin (CMV specific or nonspecific) has been used for treatment of refractory CMV disease, although there are no large-scale trials or specific guidelines for its use.[11]

Epstein-Barr Virus

Similar to CMV, EBV is a ubiquitous herpesvirus that also establishes latent infection in the host. EBV is a member of the Gammaherpesvirus family along with human herpesvirus 8 (HHV-8)/Kaposi's sarcoma-associated herpesvirus (KSHV). EBV infection in the immunocompetent host may be asymptomatic if acquired during childhood or may result in infectious mononucleosis in young adults. More than 90% of the population is seropositive by adulthood. In the transplant recipient, EBV is associated with PTLD, a group of disorders involving varying degrees of abnormal B-cell and T-cell proliferation. Patients at highest risk for PTLD are seronegative recipients who acquire primary infection after transplantation, making pediatric patients especially vulnerable. The virus is efficiently transmitted via saliva and other body fluids, but may also be transmitted by lymphocytes in the transplanted allograft. The risk of PTLD varies by the organ transplanted, with small-bowel transplant recipients at highest risk; lung, heart, pancreas, and liver patients at moderate risk; and renal transplant recipients at lowest risk (approximately 1%).[26–28] Other risk factors include the type and duration of immunosuppression, including OKT3 and polyclonal antibody use. A recent analysis of the French Registry of PTLD in renal transplant recipients demonstrated an incidence of 1.18% after 5 years, with a 61% survival rate at 5 years after diagnosis.[29] Infection with hepatitis B or C was also noted to be a risk factor for patient death, in addition to the more commonly recognized risk factors.

The diagnosis of PTLD initially requires clinical suspicion, because the presentation may be variable, ranging from an infectious mononucleosis-like syndrome to localized or diffuse lymphatic tissue involvement or even isolated allograft involvement. The standard test for diagnosis is biopsy of the involved site with examination of cellular phenotype and clonality, as well as examination for the presence of EBV gene products, such as EBER, via in situ hybridization. Staging should be performed with special attention paid to allograft involvement, the presence of multifocal disease, including involvement of the central nervous system, and the category of PTLD (i.e., monomorphic vs. polymorphic, B cell vs. T cell). EBV viral load testing has not yet been established as an accepted diagnostic test for PTLD because viremia is variable and does not correlate specifically with the presence or absence of PTLD. A low viral load has good negative predictive value, but a high viral load is nonspecific, and certain subtypes of PTLD are EBV-negative.[30,31] Studies are currently underway examining different EBV antigens as markers for patients at risk for developing PTLD and possibly also as surrogate markers for global immunosuppression levels.

Prevention strategies for PTLD are limited, because systematic study of various modalities is lacking. Identification of high-risk recipients is recommended, specifically EBV-seronegative recipients and those at risk for CMV disease. Avoidance of overzealous immunosuppression should be encouraged as well, because this has been shown to be a risk factor for development of PTLD. The benefit of antiviral prophylaxis specifically targeted toward EBV has not been established, but CMV prophylaxis regimens may have some benefit in reducing the risk for PTLD. The use of prophylactic CMV intravenous immunoglobulin (IVIG) did not prove efficacious in a small clinical trial.[32]

Treatment of early PTLD begins with reduction of immunosuppression, which may result in spontaneous regression in 23% to 50% of cases. In renal transplant patients, confirmed PTLD should prompt cessation of immunosuppression, even at the expense of rejection of the allograft. Retransplantation after recovery from PTLD is possible, with a recent OPTN/UNOS database study showing retransplantation patient survival of 100% and graft survival of 88.9% at a mean follow-up of 742 ± 107 days.[33] Other treatment modalities include surgical debulking of the tumor or explant of the allograft, if involved; referral to an oncologist for monoclonal B-cell antibody therapy (rituximab) if the tumor cells are CD20+; and cytotoxic chemotherapy for refractory disease. A variety of other treatment modalities are under investigation, including anti-interleukin-6, interferon alfa, and adoptive immunotherapy using the patient's own lymphocytes activated ex vivo.[27] Late-onset or EBV-negative PTLD typically does not respond as well to reduction of immunosuppression and thus requires more aggressive therapeutic measures, so early consultation with an oncologist is prudent in these patients.

Herpes Simplex Viruses 1 and 2 and Varicella-Zoster Virus

Herpes simplex virus-1, HSV-2, and VZV are members of the Alphaherpesvirus family and, like other herpesviruses, establish lifelong latency after primary infection. Seroprevalence of HSV-1, the common etiological agent for orolabial lesions, is >60% in the United States, whereas seroprevalence of HSV-2 (genital ulcer disease) exceeds 20%.[34] Antibodies to VZV, the cause of chickenpox and zoster/shingles, are present in more than 90% of adults, although the epidemiology of this virus may change in the future due to the adoption of universal vaccination of children in the United States in 1995. Most disease caused by these viruses is secondary to reactivation of latent infection; however, in seronegative patients primary infection may be acquired rarely via transmission from the allograft or more commonly from community spread, usually early in the post-transplant course if prophylaxis is not given.

Reactivation of HSV-1 and HSV-2 may present as localized orolabial or genital ulcers, but disseminated disease may occur, causing pneumonitis and hepatitis. Similarly, VZV may reactivate as dermatomal zoster, but can also cause more generalized skin disease as well as invasive disease involving the lungs, gastrointestinal tract, and central nervous system.

Most centers use oral acyclovir 400 to 800 mg orally bid to tid[35] or valacylovir 500 mg daily as prophylaxis against HSV-1, HSV-2, and VZV in patients who are not receiving prophylaxis for CMV; regimens for CMV prophylaxis using ganciclovir or valganciclovir are also effective.[34] The VZV serostatus of prospective transplant recipients should be assessed early in the evaluation process so the live, attenuated varicella vaccine can be administered well before transplantation occurs. In the previously infected, immunocompetent host, varicella vaccine has been shown to reduce the incidence of zoster.[36] Whether varicella vaccine is safe and effective for the prevention of zoster after transplantation is unknown.

Human Herpesviruses 6 and 7

The Betaherpesviruses HHV-6 and HHV-7 were identified in 1986 and 1990, respectively. Both tend to cause primary infection in childhood, such as roseola infantum, exanthema subitum, or other nonspecific febrile illnesses, and then establish latency in adults, with 90% of adults demonstrating seropositivity for the viruses.[34] The role of reactivation of these viruses in the post-transplantation period is still under investigation, but it appears that they may have immunomodulatory effects either independently or in combination, especially in that reactivation of HHV-6 and HHV-7 is often found in the context of CMV disease. Primary disease caused by HHV-6 has been reported to include bone marrow suppression, encephalitis, hepatitis, colitis, pneumonitis, and fatal hemophagocytic syndromes,[34,37–39] whereas primary HHV-7 syndromes have been less well-described. In a prospective study of Betaherpesvirus viremia after renal transplantation, CMV was the most commonly detected virus, occurring in 58% of patients; HHV-7 occurred earliest (in 47%) of patients, and HHV-6 occurred in 23% of patients.[40] Interestingly, the authors found a correlation between HHV-7 viremia and increased number of rejection episodes in an analysis restricted only to patients with rejection (overall there was no association between presence of Betaherpesvirus viremia and occurrence of rejection), and there was an increased incidence of CMV disease in patients who demonstrated infection with both CMV and HHV-7.[40]

Detection of HHV-6 and HHV-7 can be accomplished by nucleic acid testing, but prevention strategies remain undefined. Ganciclovir may be effective for HHV-6 prophylaxis, but variability of susceptibility to this agent may exist between the A and B variants of the virus. HHV-7 does not appear to be affected by ganciclovir prophylaxis,[41] and both viruses appear to be resistant to acyclovir. Optimal treatment of these viruses is clouded by frequent coinfection with CMV. Ganciclovir, foscarnet, and cidofovir appear to reduce HHV-6 and HHV-7 viremia when used for coincident CMV disease, but it is unclear if this reduction is due to clearance of CMV and resolution of its immunomodulatory effects, or direct antiviral effects on HHV-6 or HHV-7. Individual case reports of reduction of immunosuppression and ganciclovir treatment for HHV-6 infection have been published.[37]

Human Herpesvirus 8/Kaposi's Sarcoma–Associated Herpesvirus

Human herpesvirus 8 is a Gammaherpesvirus related to EBV that similarly establishes latency after primary infection, and is the cause of Kaposi's sarcoma (KS), primary effusion lymphoma, and some forms of multicentric Castleman's disease. Seropositivity for HHV-8 is more geographically restricted than for other herpesviruses, with highest prevalence rates in Africa and the Middle East. In the United States, seroprevalence is estimated to be less than 5%, although in certain populations (i.e., men who have sex with men) the rates may be higher.[42] Seroconversion post-transplant appears to depend on the donor status and perhaps the geographical location of the recipient, although a study of 100 solid organ transplant recipients in Pittsburgh showed seropositivity rose from 5.3% to 15.8% after transplantation with presumed donor-negative organs (90% documented as negative via serum sample), regardless of patient age or type of organ received.[43] Incidence of KS has been estimated to be up to 500 times higher in solid organ transplant recipients as compared to the general population,[44] and rates in the United States have been reported to be from 0.5% to 6%. Most U.S. patients present with cutaneous KS, and disease occurs a median of 30 months after transplantation.[34]

Detection of HHV-8 antibodies is useful for establishing seroconversion, and an assay for the detection of serum nucleic acid is available for detection of viremia. No guidelines exist for prevention of disease, although the replicating virus appears to be susceptible in vitro to ganciclovir, foscarnet, and cidofovir.[34] Treatment of post-transplantation KS depends on the extent of disease (i.e., cutaneous or visceral involvement), but typically begins with reduction of immunosuppression; if necessary radiotherapy and chemotherapy may be added for more extensive disease. Recently a series of 15 renal transplant recipients with post-transplantation KS were successfully treated with discontinuation of cyclosporine and mycophenolate mofetil and addition of sirolimus.[45] Sirolimus, an immunosuppressive medication that targets mTOR and prevents interleukin-2-induced proliferation of T cells, inhibits the growth of several tumor cell lines in vitro, and inhibits Akt, a protein kinase in the mTOR signaling pathway that has been implicated in KS pathogenesis. Sirolimus trough levels were maintained between 6 and 10 ng/mL, and no episodes of rejection occurred in any of the patients.[45]

Respiratory Viruses (Adenovirus, Respiratory Syncytial Virus, Influenza, Parainfluenza)

Recipients of renal transplants are at risk of contracting common community-acquired respiratory viruses from household contacts and others. In many cases, these viruses may be seasonal (e.g., respiratory syncytial virus [RSV], parainfluenza, and influenza), and the impact on the patient varies with the proximity to the transplant and the degree of immunosuppression of the recipient. Polymerase chain reaction (PCR) techniques have made the rapid diagnosis of most of these pathogens possible (fluorescent antibody detection is also available in many centers), but prevention strategies and treatment are limited for many of these viruses. Infection control practices to prevent nosocomial spread and hand hygiene in and outside of

the hospital are the primary means of prevention of these viruses, along with yearly influenza vaccination for all transplant recipients, household contacts, and healthcare workers.

Adenovirus can cause symptomatic and invasive disease (i.e., hemorrhagic cystitis, gastroenteritis, pneumonitis) that can occasionally be fatal in transplant recipients, more commonly in pediatric patients. No vaccine or prophylaxis is currently available against adenovirus, and definitive treatment recommendations have not been established. Several case reports suggest that cidofovir may be efficacious in treating hematopoetic stem cell transplant patients, although dosing recommendations are unclear.[46] Dosing of cidofovir at 5 mg/kg every 1 to 2 weeks may cause nephrotoxicity, but dosing at 1 mg/kg three times per week may cause breakthrough CMV or HSV infections.[46,47] Ribavirin has also been used for treatment of tissue-invasive adenoviral disease, but its antiviral activity is limited to certain serotypes of adenovirus, there are significant toxicities associated with its use, and convincing efficacy data has not been shown to warrant recommendation of its use.[46,47] Ganciclovir has in vitro activity against adenovirus, but there is no definitive data supporting its use for treatment of adenoviral disease, and conflicting data exist regarding prophylactic benefits. Insufficient evidence exists for the use of other agents, such as zalcitabine and vidarabine, for treatment.[47] Reduction of immunosuppression should be attempted in all cases along with supportive care.

RSV is a common pediatric pathogen that causes seasonal disease in the winter months, usually among children age 2 and younger. It appears that immunity to the virus is not lifelong, and transplant recipients may manifest more severe disease than immunocompetent hosts. Manifestations are typically pulmonary, and the development of lower respiratory tract disease portends a worse prognosis.[48] The benefit of prophylaxis with palivizumab or RSV-IVIG in adult transplant recipients has not been proven. Data are limited for treatment of established RSV disease in solid organ transplant patients, but some benefit may exist for the use of aerosolized ribavirin in combination with palivizumab or RSV-IVIG early in lower tract disease.[48]

The mainstay of prevention of influenza A and B is the yearly vaccination of the transplant recipient and their close contacts.[6,49] The preferred vaccine is a combination of inactivated antigens from strains of influenza A and B that are predicted via epidemiological studies to circulate for a given year; thus, the composition may change on a yearly basis. Although the response of transplant patients is lower than that of healthy immunocompetent individuals, sufficient levels of protection are likely to occur in most individuals. Early concerns about an increased risk of graft rejection as a result of the immune response to vaccination have not been supported by the literature, and a recent multicenter retrospective analysis of rejection in more than 3000 heart transplant recipients found no association between influenza vaccination and episodes of rejection.[50] If infection is suspected, rapid treatment should be initiated within 48 hours of symptom development concurrently with a diagnostic test such as nucleic acid detection. Neuraminidase inhibitors (oseltamivir, zanamivir) have become the mainstay of therapy because they are efficacious against both A and B strains of influenza; however, studies specifically evaluating their efficacy in transplant recipients have yet to be conducted.[48] Treatment dosing of oseltamivir is 75 mg orally twice a day for 5 days (zanamivir is only available as an inhaled agent). Prophylaxis with oseltamivir may also be beneficial within 48 hours in cases of known or suspected exposure to influenza at a dose of 75 mg orally once a day for a minimum of 10 days. The use of amantidine or rimantidine has fallen out of favor due to the lack of efficacy against influenza B and the recent reports of resistance of influenza A during the 2006 influenza season.[51]

Parainfluenza viruses 1 and 2 tend to circulate in the fall and winter months, and typically produce nonspecific upper respiratory tract symptoms. There is currently no vaccine, prophylaxis, or accepted treatment regimens for these viruses.[48]

Hepatitis B

The incidence of new acquisition of hepatitis B during the hemodialysis period has been markedly reduced since the adoption of improved infection control practices in 1977. Widespread use of the hepatitis B vaccine was adopted in 1982, further reducing the incidence of hepatitis B acquisition.[52] Vaccination of all patients with compensated renal disease well in advance of dialysis dependence should be encouraged using a four-dose vaccine schedule (0, 1, 2, and 6 months), and yearly monitoring of HBsAb titers should be conducted, with booster vaccination given as needed.[53] Currently the prevalence among hemodialysis patients is approximately 1.6%. Among dialysis patients who seroconvert, 80% may develop chronic hepatitis B, and a subset of patients who undergo transplantation after becoming HBsAg-negative will reactivate after the transplant.[54] Patients who receive a transplant when HBsAg-positive have a poorer prognosis with high rates of chronic hepatitis by 10 years (85%) and also an increased likelihood of sepsis and hepatocellular carcinoma in the posttransplant period.[54] A high risk of HBV transmission exists when grafting an HBsAg-positive organ into a seronegative recipient, so this circumstance should be avoided. Transplantation of a hepatitis BsAg-negative/cAb-positive kidney may be undertaken in a seronegative recipient if the recipient is fully vaccinated and the donor is HBV DNA-negative; although the recipient may seroconvert based on the presence of new HBcAb, this did not affect patient survival or graft function.[55] Close follow-up of these recipients with monitoring for transmission of hepatitis B is important; the use of hepatitis B immunoglobulin and pharmacotherapy may be warranted in this situation.

For recipients with hepatitis B, close monitoring of viral load and HBeAg is warranted, and a liver biopsy before transplantation to assess the extent of hepatitis or cirrhosis should be performed, because the more extensive the liver disease present before transplantation, the higher the liver-associated mortality after transplantation.[54] Treatment of these patients may include use of the nucleoside analogs lamivudine, adefovir, entecavir, and telbivudine, and nucleotide analogs such as tenofovir. Treatment with lamivudine typically results in a large reduction in HBV DNA, but resistance may develop with prolonged use of the drug (>1 to 2 years).[56] This approach is advocated before transplantation to suppress the viral load and should be continued after transplantation in nonhepatic recipients with chronic hepatitis B. Tenofovir and adefovir have both been associated with nephrotoxicity in patients who are not transplant recipients, raising concerns about their safety in renal transplant recipients. Recent data regarding the use of long-term (up to 5 years) adefovir in chronic hepatitis B patients was recently published, suggesting that this agent is well tolerated, with a small risk of renal insufficiency at 1 to 3 years and a low risk of development of resistance after 5 years.[57] A smaller analysis of renal

transplant recipients with chronic hepatitis B resistant to lamivudine was reported that showed a significant reduction in hepatitis B DNA with no evidence of adefovir-related renal toxicity after a median of 15 months of treatment, although several patients required phosphorus supplementation.[58] Pretransplant treatment with interferon-alfa to reduce viral load and promote seroconversion has been investigated in renal transplant recipients, but specific guidelines regarding its use have not been published; this approach is not currently recommended.

Hepatitis C

Infection with hepatitis C leads to chronic infection in 85% of exposed individuals, and cirrhosis develops after approximately 20 years in 10% to 30% of these individuals.[54] Fortunately, the rates of HCV infection in the hemodialysis population have declined due to improved infection control measures and screening of blood products.[52] However, de novo infection still occurs in the dialysis setting, with a seroconversion rate of 2.5% per 100 person-years in a recent prevalence study.[59] Screening of potential renal transplant recipients and donors is critical, because discovery of chronic infection with HCV has implications for treatment and surveillance.

Hepatitis C can be efficiently transferred via the transplanted organ, with seroconversion occurring in 67% of recipients of an HCV-positive organ and detection of HCV RNA in 96% of recipients.[60] This result underscores the difficulty of relying solely on serological testing in transplant recipients, and nucleic acid testing for HCV is required for the immunocompromised host, including both dialysis patients and transplant recipients. Because transmission of the virus occurs frequently, HCV-seropositive donors now are considered extended-criteria donors and are typically reserved for HCV-positive recipients or other special circumstances. Nucleic acid testing for hepatitis C RNA in antibody-positive renal donors can help identify those donors who are viremic and therefore likely to transmit hepatitis C.[61]

The effects of HCV positivity on graft and patient survival have been variable. In a cohort of patients on a renal transplant waiting list, HCV-positive patients had a higher risk of death compared to HCV-negative patients regardless of whether they remained on dialysis or underwent transplantation.[62] However, HCV-positive recipients who underwent transplantation or seronegative recipients who received a HCV-positive kidney had improved long-term survival compared to patients who remained on dialysis after 6 months.[60,63–65] HCV infection in the post-transplant period is associated with increased chance of new-onset diabetes mellitus, sepsis, and HCV-related glomerulonephropathy; long-term mortality; and graft failure.[54,66–69] Recent studies have suggested that hepatitis C infection in renal transplant patients may not necessarily predispose recipients to rapid progression of liver disease.[70] Increased variability of the hypervariable region (HVR-1) of HCV E_2 glycoprotein may be a predictor of lack of progression of fibrosis.[70,71]

Because of the implications of chronic hepatitis C infection in the post-transplant period, efforts should be made to stage the extent of disease in transplant candidates. Serum transaminases do not reflect the extent of liver fibrosis or cirrhosis, so a liver biopsy should be performed during the transplant evaluation to determine the extent of liver damage. Treatment of hepatitis C in the pretransplant period should also be considered in an effort to eradicate the virus.[66] Ribavirin and PEG-interferon-alfa combinations are the treatments of choice, but adverse effects such as anemia prevent the use of ribavirin in this population. After transplantation, interferon-alfa has been associated with an increased risk of renal failure and possible graft rejection, so it is generally not recommended for use after renal transplantation.[54,72,73]

BK Virus

The BK virus is a double-stranded DNA polyoma virus that infects up to 90% of the adult population and appears to be primarily asymptomatic in the immunocompetent host, although upper respiratory symptoms and cystitis have been reported.[74] In the renal transplant recipient, BK virus can be transmitted by the transplanted organ or can reactivate from latency in seropositive recipients. Typically the virus causes asymptomatic viruria in this population, but in some patients nephropathy with allograft dysfunction or ureteral stenosis or stricture develops as a result of BK disease. The risk factors for development of BK viremia or viruria are unclear, but the extent of immunosuppression appears critical, as does antirejection treatment.[75]

The methods and screening intervals used for the diagnosis of BK virus infection are not well-defined, but include frequent urine cytological examination looking for abnormal epithelial *decoy cells* and more sensitive PCR methods of detection of both urine and blood specimens.[76] Nucleic acid techniques also can provide a quantitative assessment of viral load and are able to differentiate between BK virus infection and other viruses that may produce a similar cytological appearance of epithelial cells (i.e., JC virus). Plasma viral loads greater than 10^4 copies/mL and urine viral loads greater than 10^7 copies/mL are suggestive of underlying BK virus nephropathy (BKVN).[77] The diagnosis and staging of BKVN requires renal biopsy, and the incidence of BKVN appears to range between 1% and 10% of renal transplant recipients. Recent research has examined the utility of nucleic acid-based detection techniques as screening tools for the development of BK viruria, viremia, and nephropathy.[78] Both the level of BK viremia and the presence of recurrent viremia have been correlated with the presence of BKVN.[75,79]

Treatment and prevention of BK virus is still evolving. Reduction of immunosuppression remains the mainstay of prevention and therapy of BK viruria, viremia, and nephropathy. Antiviral agents have not been uniformly efficacious in the prevention or treatment of BK viruria, but several have been anecdotally reported, including cidofovir and leflunomide. Unfortunately, no randomized, controlled clinical trials have been performed with either of these agents, but their use may be warranted in patients who have severe BKVN with concurrent rejection that may limit reduction of immunosuppresion.[80] Cidofovir has activity against polyoma viruses in vitro, but its nephrotoxicity has led to reduced dosing in renal transplant patients for treatment of BK virus infection (0.25–1 mg/kg given intravenously every 1–3 weeks), and clinical results remain mixed.[80] Of 26 patients with BKVN treated with cidofovir at the University of Pittsburgh, viremia cleared in 25 patients, and 15% lost the graft, compared to a historical graft loss rate of 45% without cidofovir.[81]

Leflunomide, a drug used for the treatment of rheumatoid arthritis, also has antiviral activity against BK virus in vitro, and a limited amount of data is available regarding its clinical utility.

A series of 17 patients with biopsy-proven BKVN was treated with leflunomide at a loading dose of 100 mg/day for 5 days and then 20 to 60 mg per day titrated to maintain blood levels higher than 40 μg/mL.[82] Those patients who achieved blood levels greater than 40 μg/mL had reduction or clearance of the virus in the urine and blood by 6 months, with persistence of response beyond that time.[78] However, the pharmacokinetics of leflunomide are unpredictable, making uniform dosing recommendations difficult and serum drug level monitoring necessary.

Quinolones and IVIG have also been explored for the treatment of BK virus infection, but limited clinical data is available on efficacy, and no recommendations can be made about these agents until further studies are performed.[80,81]

Retransplantation after BKVN is feasible, with a low risk of recurrence of BKVN, regardless of transplant nephrectomy before retransplantation or the presence of active BKVN and viremia.[83,84]

FUNGAL INFECTIONS

The morbidity and mortality of fungal infections in transplant recipients remains high despite recent advances in antifungal medications and diagnostic testing. Compared with other transplant recipients, renal transplant patients are at lower risk for fungal infections unless they are receiving a simultaneous pancreas transplant.[85] Despite this reduced risk, clinicians need to remain vigilant for unexplained fever, respiratory symptoms, or skin lesions as possible manifestations of fungal disease. The unpredictability of the clinical signs and symptoms of fungal infections, the difficulty of interpreting radiological studies and biopsies, and the limited number of laboratory-based markers of fungal infection often result in the dissemination and invasion of fungal disease before proper treatment can be initiated. The added difficulties of managing the interactions between immunosuppressive medications and many antifungal medications increase the complexity of treating these infections.

Fungal infections in the early transplant period (<1 month) typically involve *Candida* species or, in rare instances, nosocomial transmission of other environmental fungal pathogens, such as *Cryptococcus neoformans* or *Aspergillus* species.[9,85] A variety of risk factors have been associated with early invasive fungal infections after transplant, including simultaneous pancreas transplant or pancreas transplant after kidney transplant, enteric or bladder drainage procedures, primary allograft dysfunction, prolonged transplantation surgery, high intraoperative blood loss, prolonged intensive care unit stay, chronic graft dysfunction/rejection, presence of immunomodulating viruses, prolonged use of antibiotics, artificial stents, donor fungemia, and prior or concurrent fungal infection in the recipient.[85] Care must be taken to identify the species of *Candida* isolated for therapeutic reasons, because *Candida albicans* remains susceptible to fluconazole, but other *Candida* species are becoming more frequent pathogens and are not uniformly susceptible to fluconazole (i.e., *Candida glabrata* may be resistant or have dose-dependent susceptibility, *Candida kruseii* is intrinsically resistant). The choice of empirical therapy for life-threatening candidal infections depends on the epidemiology of isolates at an individual institution and may include high-dose fluconazole, voriconazole or an echinocandin.

In the later post-transplant period, patients are at risk for environmental pathogens and endemic mycoses, both via primary exposure and reactivation of latent disease.[9,85] *Aspergillus* and *Cryptococcus neoformans* infections are the most commonly encountered fungal pathogens during this period. Risk factors for fungal infection include diabetes, prolonged pretransplant dialysis, use of tacrolimus, and treatment for rejection.[86] A careful history, including travel, workplace and home exposures (i.e., construction or remodeling, pets), and hobbies such as gardening or spelunking should be elicited, and a careful review of systems performed. Radiological studies may be warranted, and any suspicious skin lesions should be biopsied. Suggested diagnostic testing and treatment regimens for *Candida, Aspergillus,* and *Cryptococcus* are summarized in Table 90-2.

PNEUMOCYSTIS JIROVECI INFECTIONS

Pneumocystis jiroveci (formerly *Pneumocystis carinii*) remains an important cause of respiratory disease in transplant recipients despite excellent prophylaxis regimens. The use of more potent immunosuppression and the ultimate cessation of prophylaxis at approximately 6 months post-transplant require the physician to consider *Pneumocystis* infection in any transplant recipient with flulike symptoms and persistent respiratory complaints, including dry cough and dyspnea. Radiographic findings may be atypical in transplant recipients and can manifest as diffuse ground-glass infiltrates, more focal consolidation, or pneumothorax.[87]

Prophylaxis with trimethoprim-sulfamethoxazole for the first 6 months after transplant is strongly recommended, because it also reduces the risk of other opportunistic infections, such as toxoplasmosis, listeriosis, and nocardiosis, as well as bacterial urinary tract infections (UTIs). If the patient cannot tolerate trimethoprim-sulfamethoxazole, other agents can be used, such as aerosolized pentamidine, atovaquone, and dapsone, but care must be taken to monitor for compliance and adverse effects of the medications.[87] Treatment of *Pneumocystis* disease should be with trimethoprim-sulfamethoxazole 15 to 20 mg/kg daily in four divided doses, with corticosteroids given if hypoxia with a PO_2 lower than 70 mm Hg by arterial blood gas is documented. A minimum 14-day course of trimethoprim-sulfamethoxazole is often sufficient if immunosuppression can be reduced, and 40 to 60 mg of prednisone for 5 to 7 days followed by a taper is recommended for concomitant hypoxemia.

BACTERIAL URINARY TRACT INFECTIONS

Urinary tract infections, especially involving the transplanted kidney, are the most commonly encountered bacterial infections in renal transplant recipients. The incidence of UTI in this population has been estimated to be between 35% and 79%, and this infection is the most common source of gram-negative bacteremias.[88] The high rate of infection is likely due to several factors, including surgical factors (e.g., refluxing vs. nonrefluxing anastomosis of the ureters, ureteral stent placement, impaired bladder emptying), presence and duration of bladder catheters, and immunosuppression.[88,89] Of increasing concern is the number of highly resistant gram-negative

Table 90-2 Suggested Diagnostic Testing and Treatment Regimens for *Candida, Aspergillus,* and *Cryptococcus*

Pathogen	Prophylaxis	Diagnosis	Treatment of Invasive Disease	Special Considerations
Candida species	Candiduria: fluconazole 400 mg/day until eradication SPK: fluconazole 400 mg/day or liposomal amphotericin B 3–5 mg/kg/day for ≥4 wks until risk factors resolved	Smear/culture of blood or sterile site Nucleic acid detection (not universally accepted) Radiology: CT of viscera, MRI of brain Histopathology	Fluconazole 200–800 mg/day depending on site and isolate MIC, renal function Amphotericin B lipid formulations: 1–5 mg/kg/day Amphotericin B: 0.5–1.5 mg/kg/day Echinocandins: caspofungin 75 mg × 1 loading dose then 50 mg/day, dose reduction for liver disease Anidulafungin 200 mg × 1 loading dose, then 100 mg/day Triazoles: voriconazole 6 mg/kg IV q12h × 2 doses, then 4 mg/kg q12h; 400 mg PO q12h × 2 doses, then 200 mg q12h for patients >40 kg; dose reduction for liver disease; itraconazole 200 mg PO or IV q12–24h Other options not yet FDA approved for this indication: micafungin, posaconazole	*C. glabrata* MICs/resistance increasing to fluconazole, *C. kruseii* intrinsically resistant *C. lusitaniae* intrinsically resistant; monitor renal function and electrolytes Monitor renal function and electrolytes May be hepatotoxic if given with cyclosporine; may decrease tacrolimus levels IV form not recommended if renal impairment, significant drug interactions. including contraindication of voriconazole use with sirolimus; reduce dose of tacrolimus by two thirds and reduce cyclosporine by one half; monitor levels
Aspergillus species	None recommended	Culture of sterile site Antigen detection: galactomannin assay not universally accepted, false postives with concurrent piperacillin use Radiology: CT of viscera with nodules, cavities; halo sign, crescent sign may be seen/MRI of brain Histopathology	Voriconazole: dosed as above Liposomal amphotericin B: 5 mg/kg/day Amphotericin B: 1–1.5 mg/kg/day Caspofungin: dosed as above Role of combination therapy unclear Other options not yet FDA approved for this indication: micafungin, posaconazole	As above As above As above As above
Cryptococcus neoformans	None recommended (fluconazole may provide some protection)	Smear/culture of blood, CSF, sterile site (transplant patients *must* have CSF evaluation, may have elevated opening pressure) India ink preparation of CSF Antigen detection in CSF, blood (false-negatives if nonencapsulated strain, prozone effect) Nucleic acid detection (not universally accepted) Radiology: CT of viscera, MRI of brain Histopathology	Liposomal amphotericin B: 5 mg/kg/day OR Amphotericin B: 0.5–1 mg/kg/day PLUS 5-flucytosine 100 mg/kg/day divided q6h; renal dosing required × 14 days THEN Fluconazole 400 mg/day, duration unknown	As above As above Monitoring serum creatinine and 5-flucytosine levels suggested, goal 30–80 μg/mL 2 hr after dose

CSF, cerebrospinal fluid; CT, computed tomography; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; SPK, simultaneous pancreas-kidney transplantation.
Adapted from Fungal infections. Am J Transplant 2004;4(Suppl 10):110–134, Tables 3 and 4.

organisms isolated from these patients and the limited number of antimicrobial options for treatment.

The impact of early UTI in renal transplant recipients has been associated with pyelonephritis, bacteremia/septicemia, and increased mortality compared to the general population[88–91]; late UTI may also be associated with increased mortality,[92] although most tend to mimic UTIs in the immunocompetent host. Most centers provide prophylaxis against early UTI using either trimethoprim-sulfamethoxazole or a quinolone for the first 6 to 12 months after transplant.[93–95] Use of trimethoprim-sulfamethoxazole is not only inexpensive, but also provides prophylaxis against *Pneumocystis,* toxoplasmosis, listeriosis, and nocardiosis, although quinolones may be better tolerated.[93] Most centers use low-dose trimethoprim-sulfamethoxazole daily, but some studies have suggested that higher doses (320 mg/1600 mg) may be more efficacious in the prevention of UTI during the first month after transplant.[95,96] Whether higher doses may be associated with increased toxicity is unknown.

Treatment of UTI in this population requires that close attention be paid to the susceptibilities of the isolate, because rates of highly resistant gram-negative pathogens appear to be increasing.[97,98] Most centers use a longer duration of treatment in transplant recipients, typically 14 days.[88] Candidal UTIs in this population are also problematic because they may lead to the formation of fungal balls and resultant urinary obstruction, so the finding of yeast in a sterile urine specimen should prompt further investigation.

TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIA

Although tuberculosis (TB) remains a relatively rare disease after renal transplantation, the complexities of treatment and high associated mortality require vigilance of the provider during both the pretransplant and posttransplant periods. The incidence of TB after renal transplantation in the United States is estimated to be less than 1%, but the mortality rate in these patients approaches 25% to 30%.[99,100] Most patients develop symptomatic disease within the first year after transplantation.

Evaluation of the transplant recipient should include a detailed history of prior TB, possible exposure to the disease, or travel to endemic areas. Tuberculin skin testing is recommended for all potential recipients, and should be interpreted as positive if greater than 5 mm of induration is detected.[101] If no prior prophylaxis has been given, or if the patient's response to the test has recently converted to positive, the patient should be treated as having latent TB infection. Unfortunately many patients with severe renal disease may be anergic, rendering the test unreliable if negative. The recent release of a blood test for interferon-gamma release from patient's sensitized lymphocytes after exposure to purified protein derivative (QuantiFERON test) is promising, but as yet is not indicated for use in immunosuppressed individuals.[102] Chest radiographs may be useful for finding evidence of prior or active disease that would warrant further evaluation, especially if no prior treatment or prophylaxis was given. In patients in whom latent TB infection is suggested, treatment with 300 mg of isoniazid daily for 9 months is recommended after evaluation for underlying liver disease. Ideally, prophylaxis should be completed before transplantation and the onset of more severe immunosuppression; however, if the donor had risk factors for latent TB infection, the recipient should receive prophylaxis after transplantation to reduce the risk of transmission of disease.[101] Liver function tests should be monitored every 2 weeks for the first 6 weeks of therapy, then monthly, looking for elevations of transaminases greater than 4 times normal.

Diagnosis and treatment of active tuberculosis after transplantation is complex; the involvement of an infectious diseases specialist is recommended, as well as involvement of local public health departments. Patients are likely to present in the first year after transplantation and are more likely to present with disseminated disease than immunocompetent patients, although pulmonary disease remains the most common manifestation.[99,100] Diagnosis may require extensive imaging and multiple specimens from suspicious areas for microbiological culture and susceptibility testing. The use of the QuantiFERON test has not been validated for diagnosis of active infection in immunosuppressed patients.[103] The standard four-drug regimen typically initiated at diagnosis of TB (isoniazid, rifampin, pyrazinamide, and ethambutol) is problematic in the transplant recipient due to the interaction between rifampin and calcineurin inhibitors that induces the metabolism of these agents. Substitution with rifabutin or a quinolone such as levofloxacin is a common approach to eliminate this problem, although rifabutin is still associated with significant drug interactions.[101] Once susceptibility of the isolate to isoniazid and rifampin is confirmed, therapy should continue for a minimum of 6 months, if isoniazid and rifampin or rifabutin are used, and longer with other regimens or more severe disease.

Nontuberculous mycobacterial infections in transplant recipients are rare and not well-studied. Many of these organisms are environmental contaminants and can cause disease as a result of nosocomial transmission or exposure in the community. Again, a high index of suspicion must be maintained, and early involvement of an infectious diseases specialist is helpful, because many of these organisms require special growth conditions in the microbiology laboratory and do not have uniform susceptibilities to antimicrobial agents. More detailed recommendations can be found in recently published guidelines.[104,105]

HUMAN IMMUNODEFICIENCY VIRUS AND RENAL TRANSPLANTATION

The widespread use of highly active antiretroviral therapy (HAART) has changed the prognosis for patients with human immunodeficiency virus (HIV) infection, allowing these patients to be considered for renal transplantation.[106] Prior to the widespread use of HAART, a retrospective analysis of HIV-positive renal transplant recipients suggested a slightly worse 3-year survival compared to HIV-negative patients during the same 10-year period (83% vs. 88%).[107] More recently, several case series have reported encouraging results after renal transplantation in HIV-positive patients, showing similar graft survival and mortality at 1 year compared to controls from the UNOS database.[108,109] Unfortunately, graft rejection rates appear to be higher in the HIV-positive groups. Currently a prospective, multicenter trial is underway to study HIV-positive renal and liver transplant recipients to study the

effects of immunosuppressive medications on patient survival and how HIV infection and HAART affect graft survival.

Ideally, HIV-positive patients being considered for transplantation should have $CD4^+$ cell counts greater than 200 cells/μL and an undetectable viral load for 3 months on stable antiretroviral therapy.[110] Comorbid conditions should be assessed, including the presence of other viral infections (i.e., HBV, HCV) that may have accelerated courses in the presence of both HIV and immunosuppression, and history of opportunistic infections that may reactivate post-transplantation. After transplantation, these patients require close monitoring, because the pharmacokinetics and drug interactions of antiretroviral medications and immunosuppressive medications may be complex; notably, there are significant drug interactions between calcineurin inhibitors and antiretroviral agents, including both protease inhibitors and nonnucleoside reverse transcriptase inhibitors.[108,111] Frequent assessment of serum drug levels of the calcineurin inhibitors is therefore mandatory for patients on protease inhibitor-based HAART. More comprehensive guidelines have been established by the Cooperative Clinical Trials in Adult Transplantation group and include specific recommendations regarding inclusion and exclusion criteria and pharmacological considerations for HAART, immunosuppression, and prophylaxis regimens.[111]

Management of infectious disease complications continues to pose a challenge for physicians treating transplant recipients. As the use of newer, more potent immunosuppressive regimens becomes more common, the risk for opportunistic pathogens and more severe manifestations of both community-acquired and nosocomial pathogens increases. Continued attention to improved preventive, diagnostic, and treatment strategies to minimize the impact of infections on outcomes is required.

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