7-1-2006

Infectious Complications in Renal Transplant Recipients

Ravi Parasuraman
Henry Ford Health

Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

Vanji Karthikeyan
Henry Ford Health, vkarthi1@hfhs.org

Ramon del Busto
Henry Ford Health

Recommended Citation
Parasuraman R, Yee J, Karthikeyan V, del Busto R. Infectious Complications in Renal Transplant Recipients. Advances in Chronic Kidney Disease 2006; 13(3):280-294.

Infectious Complications in Renal Transplant Recipients

Ravi Parasuraman, Jerry Yee, Vanji Karthikeyan, and Ramon del Busto

Post–kidney transplant infection is the most common life-threatening complication of long-term immunosuppressive therapy. Optimal immunosuppression, in which a balance is maintained between prevention of rejection and avoidance of infection, is the most challenging aspect of posttransplantation care. The study of infectious complications in immunologically compromised recipients is changing rapidly, particularly in the fields of prophylactic and preemptive strategies, molecular diagnostic methods, and antimicrobial agents. In addition, emerging pathogens such as BK polyomavirus and West Nile flavivirus infections and the introduction of newer immunosuppressive agents that constantly change the risk profiles for opportunistic infections has added layers of complexity to this burgeoning field. Although remarkable progress has been made in these disciplines, comprehensive understanding of the clinical manifestations of infections remains limited, and the standardization of prophylaxis, diagnosis, and treatment of most infections is yet inadequately defined. The long-term goal for optimal care of transplant recipients, with respect to infection, is the prevention and/or early recognition and treatment of infections while avoiding drug-related toxicities.

Index Words: Transplantation; Infections; Immune Suppression

Kidney transplantation is considered the treatment of choice for patients with end-stage renal disease, and, presently, 1-year patient and graft survival rates are 95% to 97% and 89% to 95%, respectively.[1] Despite such success, transplant recipients remain vulnerable to several infectious complications that are largely determined by the net state of immunosuppression, environmental exposures, and breaches in mucocutaneous barriers. Optimal immunosuppression, whereby balance is maintained between rejection and infection, is the most challenging aspect of posttransplantation care.

We contend that a facile appreciation of the key concepts delineated hereafter is essential to optimizing the management of infectious complications in transplant recipients:

1. The first step is identification and eradication of infections before transplantation.[2,3]
2. Adequate screening of the donors for transmissible infections is important because reactivation of infection(s) under the influence of induction immunosuppression is a major problem.
3. Evaluation for and provision of prophylaxis against particular infections in high-risk situations (eg, seropositive cytomegalovirus [CMV] donor with a seronegative recipient) can prevent serious infection and complications.
4. Defining other high-risk situations in which infections produce substantial morbidity, in order that prospective monitoring or preemptive/prophylactic therapy can be initiated (eg, lymphocyte-depleting antibody therapies [Thymoglobulin, Sang-Stat Medical Corp, Fermont, Calif], intravenous immunoglobulins, plasma exchange, and anti-CD 20 [Rituximab, Genentech Inc, San Francisco, Calif]) antibody therapy is critical.
5. Acknowledgement of the potential for insidious clinical manifestations of active infection in immunocompromised recipients, which may present explosively and leave an abbreviated period for effective management. Such situations require aggressive management with broad spectrum coverage for various infections.
6. Transplant recipients with serious infections require careful review and analysis of their immunosuppressants, with possi-

From the Divisions of Nephrology and Hypertension, and Infectious Disease, Henry Ford Health Systems, Detroit, MI

Address correspondence to Raviprasenna Parasuraman, MD, Henry Ford Health Systems, Division of Nephrology and Hypertension, 2799 West Grand Blvd, CFP-2, Detroit, MI 48202.

1548-5595/06/1303-0011$32.00/0

doi:10.1053/j.ackd.2006.04.008

ble reduction or discontinuation in life-threatening situations.

7. Detailed knowledge of pharmacokinetic and pharmacodynamic interactions between immunosuppressive and antimicrobial agents is required to prevent deleterious drug interactions and to appropriately recommend drug dose adjustments.

In addition to these 7 general concepts, knowledge of 2 specific areas, the "net state of immunosuppression" and a "timetable of infections posttransplantation" is crucial for optimal management of infections.

Net State of Immunosuppression

The net state of immunosuppression (NSI) of a recipient can be determined from the analysis of several factors.[3] The most important factor is the nature of the immunosuppressive regimen, including doses of agents, durations of their employment, and the temporal sequence of drugs used, including induction therapy. Other variables that may contribute to NSI include prolonged neutropenia, breach in mucocutaneous barriers, and the presence of uncontrolled metabolic abnormalities (eg, diabetes, uremia, and malnutrition). Infections with immunomodulating viruses such as CMV, human herpesvirus 6 (HHV-6), and human immunodeficiency virus (HIV) are highly significant in terms of their ability to mitigate native immune responses (ie, down-regulation). Notably, nearly 90% of infections, especially opportunistic fungal infections, occur in the presence of immunomodulatory viral replication. Finally, the age of the recipients also adds to the NSI that may significantly affect the outcome in elderly patients.

Timetable of Infection Posttransplantation

The posttransplantation interval is the next important area critical to evaluation of infections because different infections prevail at different times after transplantation. Although the introduction of newer immunosuppressants and antimicrobial prophylaxis has altered the timetable of infections, opportunistic infections are still rare during the first month after transplantation, despite induction therapies and greater levels of immunosuppression. This observation implies that ongoing immunosuppression (net state of immunosuppression) is the most important factor that fosters opportunistic infections.

Three categories of infection occur during the initial posttransplantation month. The first is largely related to technical problems, including surgical wound infections, urinary tract infections, vascular access infections, and pneumonia.[4,5] The second category constitutes a priori recipient infections, which are exacerbated by immunosuppression. The last and relatively rare category is represented by donor-transmitted infections. Infections stemming from immunomodulatory viruses, including CMV, Epstein Barr virus (EBV), HHV-6, hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV generally proceed 1 to 6 months posttransplantation. As described, such infections may significantly contribute to the net state of immunosuppression and invite opportunistic infection, even in the absence of significant environmental exposure. Beyond 6 months, approximately 80% of recipients are treated by low maintenance doses of immunosuppression and are primarily at risk for various community-acquired infections.

Remaining transplant recipients have chronic viral infections or remain at substantial risk for opportunistic infections because of overimmunosuppression. These individuals may require antimicrobial prophylaxis indefinitely.[2,5]

Urinary Tract Infections

Urinary tract infection (UTI) is the most common bacterial infection in kidney transplant recipients, with an incidence of 35% to 79% in the absence of antibiotic prophylaxis.[6,7] With widespread use of prophylaxis, the incidence of UTI has decreased significantly.[8–10] Most UTIs occur within the first 3 months after transplantation, and the major risk factor is the presence of a urethral catheter. Other risk factors include a protracted duration of dialysis before transplantation, female gender, duration of catheterization, vesicoureteral reflux, polycystic kidney disease with recurrent

UTIs, diabetes mellitus, chronic viral infections, and increased urinary aluminum excretion.[11] In addition, many centers routinely implant vesicoureteral stents that facilitate the risk of infection.

The causative organisms are similar to those causing UTI in the general population, but resistant pathogens such as extended-spectrum β-lactamase–producing *Klebsiella*, vancomycin-resistant *Enterococcus spp*, *Pseudomonas aeruginosa*, and *Candida spp* have all emerged as significant pathogens. In addition, opportunistic infections caused by BK polyomavirus, CMV, *Mycoplasma hominis*, *Corynebacterium urealyticum*, and *Microsporidium* can also occur. UTI is an important cause of bacteremia in the kidney transplant recipient, and 60% of bacteremias originated from foci of infection in and around the revised urinary tract.[12] Half of bacteremic UTIs are associated with technical complications related to surgery such as ureteral leak, stricture, or perinephric hematoma.

More recently, Abbott et al[13] in a review of 33,479 kidney transplant recipients in the United States Renal Data System database showed that the urinary tract was the source of infection in one third of patients hospitalized with septicemia. In contrast to UTIs that occur within the first 3 months, UTIs that occur after 6 months posttransplantation have a lower rate of pyelonephritis, bacteremia or relapses and respond well to conventional 10- to 14-day courses of antimicrobial treatment.[4,7,14] UTIs that appear in this late time period in association with bacteremia or recurrent infections warrant investigation for anatomic and/or functional abnormalities.

Treatment of active UTI should be guided by results of antimicrobial susceptibility testing. The most frequently used antimicrobials are trimethoprim-sulfamethoxazole (TMP-SMX) and ciprofloxacin, and aminoglycosides should be avoided if feasible because of their synergistic nephrotoxicity with tacrolimus and cyclosporine. The duration of therapy is controversial and principally based on expert opinion.[15] UTIs occurring in the first 4 to 6 months require prolonged antibiotic therapy for up to 6 weeks,[7] but others advocate standard courses of therapy (10-14 days), reserving prolonged therapy for patients with relapsing infection or when prostatitis is suspected.[7,14,16] Late infections because of their "benign" nature can usually be treated for 10 to 14 days. The efficacy of short-course therapy (single dose or 3 days) has not been studied rigorously in kidney transplant recipients and is not recommended.[16] The management of asymptomatic UTI remains controversial and is considered largely unsuccessful.[16–18] Others posit treatment for asymptomatic infections only during the first month after transplantation. Lastly, asymptomatic candiduria may be the only microbiological manifestation of disseminated candidiasis and generally requires treatment.[19]

Although some parties recommend antimicrobial prophylaxis for UTI, no discernible impact on overall graft or patient survival has been shown,[15,16] and the exact duration of treatment, optimal agent(s), and antimicrobial dosing have not been determined. TMP-SMX remains the most frequently used drug for prophylaxis and is associated with fewer febrile hospital days and a reduction of UTIs and other bacterial infections compared with placebo.[9] In addition, TMP-SMX utilization has virtually eliminated pneumocystis pneumonia (PCP) and reduced the infection rate from *Nocardia*, *Listeria*, and *Toxoplasma*. In patients with TMP-SMX intolerance, an alternative agent is ciprofloxacin, which is better tolerated and at least as effective as TMP-SMX for UTI prevention.[10] In our center, we use TMP-SMX prophylactic therapy for 6 to 12 months after transplantation. Lastly, in patients with recurrent UTIs, anatomic abnormalities, or neurogenic bladder, an indefinite course of therapy has been advised.

Skin and Soft-Tissue Infections

Skin and soft-tissue infections (SSTIs) in the kidney transplant recipient are frequently caused by unusual pathogens and may herald serious systemic infection. Although pyogenic bacteria such as *Streptococcus pyogenes* or *Staphylococcus aureus* cause most SSTIs, almost any organism may be causative. Infections caused by opportunistic pathogens have been reported, including fungi (*Cryptococcus*, *Scedosporium*, *Aspergillus*, zygomycetes, dermatophytes and dematiaceous fungi), herpes sim-

plex virus, varicella-zoster, papilloma virus, nontuberculous mycobacteria (*M cheloneae* and *M abscessus*), *Nocardia spp*, and even algae such as *Prototheca*.[20] It is important, therefore, to obtain biopsies of skin lesions for appropriate staining and cultures, especially in patients unresponsive to conventional antibacterial therapy.

Surgical Wound Infections

Improvement in surgical techniques and the use of antibiotic prophylaxis has reduced the incidence of wound infections to just 1% to 2% after kidney transplantation.[20] The most common etiology of SSTIs is *S aureus*, but *S epidermis*, gram-negative bacilli, *Candida spp*, and *Mycoplasma hominis* are also pathogenic.[20] Wound infections can be a serious problem, especially if these involve the perinephric space.[20] The risk profile includes urinary leak, hematoma, obesity, diabetes, reoperation through a previous incision, prolonged bladder catheterization, prior peritoneal dialysis, and the use of mycophenolate mofetil in comparison to azathioprine.[21] In an evaluation of 2,013 kidney transplant recipients, obesity was found to be the most important risk factor for deep infections, and reduced graft survival was associated with the presence of wound infections.[22]

Pneumonia

Pneumonia occurring within the first 30 days of transplantation is usually nosocomially acquired and caused by gram-negative bacteria or *S aureus*. Pneumonias attributable to opportunistic pathogens such as CMV, PCP, and *Nocardia* occur 1 to 6 months posttransplantation; however, more recent implementations of prophylactic therapy have substantively reduced the frequencies of these infections. Conventional pathogens such as *Streptococcus pneumoniae*, *Legionella*, *Hemophilus influenzae*, and bacteria associated with aspiration have become relatively more common, and these typically manifest more than 6 months after transplantation. In addition, community-associated viral pneumonia caused by influenza, parainfluenza, respiratory syncytial virus, and adenovirus have become more frequently recognized pathogens.[20]

The risk of active tuberculosis in transplant recipients is relatively greater than in the general population and must always be considered in the differential diagnosis of pneumonia in transplant recipients. Occasionally, interstitial pneumonia is manifested as a drug side effect and has been associated with rapamycin. Kidney transplant recipients with pneumonia require early and aggressive diagnostic studies such as computerized chest tomography, bronchoalveolar lavage, and lung biopsy, with the institution of specific therapy to reduce morbidity and mortality.

Central Nervous System Infections

Central nervous system (CNS) infections in kidney transplant recipients are frequently caused by opportunistic pathogens such as *Cryptococcus neoformans*, *Listeria monocytogenes*, *Nocardia asteroides*, and the herpes group of viruses (CMV, herpes simplex virus 1 and 2, varicella-zoster virus, and HHV-6).[20] With the use of prophylactic TMP-SMX, the incidence of *Nocardia*, *Listeria*, and *Toxoplasma* infections has decreased significantly. The highest risk for CNS infection occurs between 1 to 6 months after tranplantation, with the exception of cryptococcal disease, which frequently occurs after the sixth month posttransplantation. In addition to acute, subacute, and chronic meningitis or encephalitis, CNS infections may manifest as an intracranial mass lesion or as progressive dementia.[5]

Acute meningitis is usually caused by *Listeria monocytogenes*, whereas subacute and chronic meningitis is usually the product of *Cryptococcus neoformans* infection and less frequently of an *M tuberculosis*, *Nocardia*, *Listeria*, *Histoplasma*, or *Coccidioides* infection. Space-occupying brain lesions may be caused by *Nocardia*, *Aspergillus*, zygomycetes, and *Toxoplasma*. Progressive dementia with or without other neurologic deficits may be related to progressive multifocal leukoencephalopathy because of patient's virus or infections from herpes simplex virus, CMV, EBV, and, occasionally, as a side effect of cyclosporine or tacrolimus therapy.[5] It must be emphasized that clinical presentations of CNS infection in

transplant recipients are often quite different from those of nonimmunosuppressed individuals.[5] Frequently, there are fewer signs of meningeal inflammation, and the changes in the level of consciousness may be subtle.[5] Any unexplained fever and headache should prompt a neurologic evaluation by brain computed tomography scan or magnetic resonance imaging and lumbar puncture.[5]

CMV Infection

Antiviral prophylaxis has led to a significant decrease in the incidence of CMV infection and disease in kidney transplant recipients. However, CMV continues to be an important pathogen. In addition to the characteristic infectious syndromes and direct tissue damage caused by CMV (pneumonia, colitis, esophagitis, nephritis, and so on), the indirect effects are just as important and include an increase in the net state of immunosuppression that leads to opportunistic infections, allograft dysfunction and rejection, EBV-associated posttransplantation lymphoproliferative disorder, and β-Herpes virus interactions.[5,23] The most important risk factors for CMV disease include primary infection from serological mismatch (donor-positive and recipient-negative CMV status) and use of antilymphocyte antibodies (ORTHOCLONE OKT3 [Ortho Biotech Products, Bridgewater, NJ] and antilymphocyte globulin). Other risk factors include the type of organ transplanted (lung > liver, heart, kidney-pancreas > kidney); reactivation of HHV-6, HHV-7, and hepatitis C virus; treatment of acute rejection; stressors associated with critical illness; and intraoperative hypothermia.[23] Until recently, the available techniques for diagnosing CMV were based on histopathology, viral culture, and serology.[24] However, diagnosis of tissue-invasive disease requires recognition of cytomegalic inclusion bodies, immunohistochemistry, or DNA hybridization techniques[14,24,25] and an invasive procedure to obtain samples. Currently, polymerase chain reaction (PCR) is the most frequently used test for the diagnosis of CMV, but results must be critically interpreted in the context of the clinical situation.[24]

A significant decrement in the frequency of CMV infection and disease has been achieved with different preventive antiviral therapies such as universal prophylaxis, selective prophylaxis, and preemptive therapy.[5,23,26] Universal prophylaxis involves the treatment of all patients before the detection of active CMV infection. A variant of the universal approach, "selective prophylaxis," denotes administration of antiviral therapy to patients at very high risk of reactivation attributable to heightened levels of immunosuppresion, especially during utilization of antilymphocyte globulin and OKT3. Preemptive therapy is given only to asymptomatic patients in whom active CMV is detected by the CMV viral load. Naturally, there are advantages and disadvantages to the aforementioned approaches.[26,27] Universal prophylaxis has the advantage of not requiring routine laboratory testing to define risk, and it may also prevent reactivation of other herpesviruses. However, prolonged antiviral therapy may induce drug toxicity and drug resistance, although the risk of either is low. Preemptive therapy and selective prophylaxis are advantageous because they reduce exposure to antiviral drugs and reduce drug costs, toxicity, and possibly emergence of drug resistance.[27,28] Even so, preemptive therapy is logistically demanding and difficult and requires costly surveillance testing. Moreover, in the setting of rapid viral replication as occurs in serologically mismatched patients (donor CMV positive, recipient CMV negative), CMV disease may occur before identification of risk (ie, positive CMV PCR). Nonetheless, it must be emphasized that prophylaxis and preemptive therapy are both effective for preventing CMV disease.[29]

The American Society of Transplantation and the Canadian Society of Transplantation have recently published guidelines for the prevention of CMV infection and disease in solid organ transplantation[28,30] (Table 1). In the seronegative recipient with a CMV-positive donor, universal prophylaxis is the preferred methodology because the rapid rise in viral load renders preemptive strategies logistically difficult. For the CMV-seropositive recipient, prophylaxis or preemptive therapy is acceptable.

The antiviral agents most commonly used for prophylaxis include oral or intravenous ganciclovir and oral valganciclovir, a ganci-

Table 1. Antimicrobial Prophylaxis in Kidney Transplant Recipients [9,10,25,28,30,75]

Infection	*Prophylaxis**	*Comments*
UTI	TMP-SMX (TMP 80 mg/ SMX 400 mg) oral, daily. Alternative: ciprofloxacin 250 mg oral twice a day	Duration of therapy not well defined. Usually 6–12 months
Pneumocystis jiroveci (formerly P. carinii)	TMP-SMX as above Alternatives: Dapsone 100 mg oral qd or aerosolized pentamidine 300 mg once a month or atovaquone 1500 mg oral qd	Duration of therapy not well defined. Usually 6–12 months. Prophylaxis following treatment of rejection is also recommended
CMV D-/R-	None	Consider monitoring PCR or pp 65 antigen monthly for 3 months and treat preemptively if positive. Recipient should receive CMV negative blood or leukodepleted blood products
CMV D+/R-	Valganciclovir 900 mg oral everyday for 3 months. Alternative: ganciclovir oral (3g/d) or IV (5 mg/kg/d)	Universal prophylaxis preferred over preemptive therapy. Selective prophylaxis (valganciclovir 900 mg bid or IV ganciclovir 5mg/kg every 12 hours) is recommended in patients receiving ALG /OKT3 therapy for rejection
D+/R+ or D-/R+	Universal prophylaxis: Valganciclovir 450–900 mg oral everyday for 3 months. Alternatives: ganciclovir oral (3 g/d) or IV 5 mg/kg/day	Preemptive therapy: Valganciclovir 900 mg oral twice a day. Alternative IV ganciclovir 5 mg/kg every 12 hours. Duration for at least 1 week after CMV viral load is undetectable. Selective prophylaxis (valganciclovir 900 mg twice a day or IV ganciclovir 5mg/kg every 12 hours) is recommended for patients receiving ALG /OKT3 therapy for rejection

Abbreviations: UTI, urinary tract infection; TMP-SMX, trimethoprim sulfamethoxazole,; D, donor; R, recipient; PCR, polymerase chain reaction; OKT3, muromonab-CD3; ALG, antilymphocyte globulins.
*All doses are for normal renal function.

clovir prodrug that has significantly better bioavailability than ganciclovir by the oral route. The agents used in the treatment of established CMV disease include intravenous ganciclovir, valganciclovir, foscarnet, and cidofovir. The largest clinical experience is with ganciclovir, and because of the significant nephrotoxicity of foscarnet and cidofovir, ganciclovir is the preferred antiviral agent for this indication. The recommended dose of intravenous ganciclovir is 5 mg/kg every 12 hours, with dosage modifications for renal impairment. Neither oral ganciclovir nor acyclovir is recommended for treatment of established infection. Based on pharmacokinetics studies, valganciclovir can be used as an alternative to intravenous ganciclovir, but further studies are warranted to validate this

approach. Treatment should be continued for at least 1 week after the CMV viral load becomes undetectable. Some experts recommend the use of CMV immune globulin in cases of severe CMV disease or when hypogammaglobulinemia is present. In addition to antiviral therapy, immunosuppression should be reduced if possible. Alternative drugs for ganciclovir-resistant CMV or ganciclovir-intolerant patients include foscarnet or, less frequently, cidofovir. Foscarnet has been used alone in full dose or at a reduced dose in conjunction with reduced dose intravenous ganciclovir. In patients suspected to have drug resistance, genotypic testing is recommended.

Hepatitis B and C

Infection control measures and vaccination of patients have resulted in a reduced incidence of hepatitis B among kidney transplant recipients, and, currently, most viral hepatitis is attributable to HCV.[31,32] The safety and efficacy of kidney transplantation in hepatitis B surface antigen (HBsAg)-positive patients remains controversial.[14] Increased mortality from liver disease showed in some but not in all studies, and when it occurred, it was generally after 10 years or more after transplantation.[14] Fornairon et al[33] studied a cohort of 151 HBsAg-positive kidney transplant recipients with a median follow-up of 125 months and revealed a high rate of persistent viral replication (50%) and reactivation (30%). Serial biopsies in the same study disclosed histological progression (85%) and cirrhosis (28%), with 23% of cirrhotic patients developing hepatocellular carcinoma. Co-infection with hepatitis C was significantly associated with histological worsening, and liver disease was the leading cause of death in that cohort.

Mathurin et al[34] compared patient and graft survival rates in HBV and HCV-infected kidney transplant recipients with noninfected recipients and determined that infection with HBV or HCV significantly reduced patient and graft survival. The patient survival 10 years after transplant for uninfected, anti–HCV-positive and HBsAg-positive recipients was 80%, 65%, and 55%. Graft survivals were 63%, 49%, and 36%, respectively. In patients with a pretransplantation diagnosis of cirrhosis, 10-year recipient survival was just 26%. The authors concluded that biopsy-proven cirrhosis is a contraindication for kidney-only transplantation. In such circumstances, combined liver-kidney transplantation should be considered.[35]

The treatment of hepatitis B in kidney transplant recipients is not well defined, and interferon-α is contraindicated because of the risk of graft rejection.[35] Lamivudine appears to be safe and effective before and after transplantation, although resistance is a frequent problem. Preemptive or prophylactic treatment with lamivudine before transplantation may be more beneficial than salvage treatment after hepatic dysfunction ensues after transplantation.[36] In cases of lamivudine resistance, antiviral agents such as adefovir, tenofovir, or entecovir may be considered, although clinical experience with these drugs is limited. Most importantly, all nonimmune patients should be immunized against hepatitis B before transplantation.

Hepatitis C is the leading cause of posttransplantation chronic liver disease, and the prevalence of anti-HCV antibodies in kidney transplant recipients ranges from 11% to 49%.[31,37] Anti-HCV antibodies may occasionally be negative in transplant recipients with positive HCV RNA, and all patients with liver disease after transplantation should be tested for HCV RNA, despite an absence of anti-HCV antibodies.[31]

The impact of HCV infection on the outcome of kidney transplantation is not well defined. The patient and graft survival rates are lower in HCV-infected versus noninfected individuals, with the difference becoming apparent 10 years after transplantation.[31,34] Knoll et al[38] showed that at 2 years after transplantation, HCV-positive recipients had a better survival rate than HCV-positive patients awaiting transplantation, which implies that chronic HCV infection should not be considered a contraindication to kidney transplantation.[35] In a 1993 survey, 89% of transplant centers in the United States accepted HCV-positive patients for kidney transplantation, and 37% required histological absence of progressive liver disease.[39] The presence of cirrhosis and advanced age are associated

with poorer outcomes and transplantation should be discouraged in these scenarios.[34,35] In such patients, combined liver and kidney transplantation may be considered. In view of the supply and demand crisis in kidney transplantation, it is considered acceptable to transplant organs from HCV-positive donors into HCV-positive recipients.[31]

The antiviral therapy of hepatitis C before and after kidney transplantation remains problematic. In patients with end-stage renal disease, ribavirin is contraindicated because reduced renal clearance of the agent may induce hemolysis.[40] Patients with chronic hepatitis, but without cirrhosis, should be considered for interferon monotherapy, preferably as its pegylated form, before transplantation.[40] However, interferon is not recommended after transplantation because of the onset of graft rejection that occurs with a frequency of nearly 50%.[31] Lastly, even though ribavirin monotherapy reduces hepatic enzyme elevations in HCV RNA-positive recipients after 1 year of therapy, there is no significant alteration of viremia or hepatic histopathology.[41]

HIV

Before the highly active antitetroviral therapy (HAART) era, HIV-infected patients were excluded from solid organ transplantation because of poor prognosis (ie, 3-year patient and graft survival rates were significantly lower in HIV-seropositive patients [83% and 53%] compared with seronegative [88% and 73%], respectively[42]). The introduction of HAART in the mid-1990s has substantially improved the survival of HIV-infected patients, and a recent evaluation of United States Renal Data System data discovered that HIV-infected recipients had improved survival compared with HIV-uninfected recipients; the difference was not statistically significant.[43] A multicenter study of 23 HIV-infected kidney transplant recipients with the following eligibility criteria: pretransplantation CD4 + T-cell counts greater than 200 mL, undetectable HIV RNA, absence of opportunistic infections, and 6 months or more of HAART[44] disclosed 1-year recipient and graft survival rates similar to HIV-negative recipients. Consequently, the authors contended that kidney transplantation should be offered to selected HIV-infected patients. One important concern in the management of HIV-infected transplant recipients is the pharmacokinetic interactions between immunosuppressive agents and antiretrovirals, emphasizing the importance of a well-coordinated multidisciplinary team with expertise in transplantation, HIV medicine, and pharmacology.[45]

Polyomavirus Infection

BK virus (BKV), a polyomavirus infection in adults, is seen with seroprevalence rates as high as 60% to 80%.[46–48] The infection rates in kidney transplant recipients varies between 10% and 60%, and most of these infections result from reactivation of latent virus from renal tubular epithelial cells, although they remain asymptomatic in nearly 90% of patients.[49–51] The clinical manifestation of BKV disease may include interstitial nephritis, cystitis, and/or ureteral stenosis, and the reported prevalence of BKV-induced nephropathy is 1% to 8%.[52–54]

The median time to develop BKV disease is approximately 9 to 14 months, and the most common clinical manifestation is allograft dysfunction.[55–57] The definitive diagnosis of BKV disease requires kidney biopsy, showing viral inclusions with little inflammation in the early stages and mononuclear cell infiltrates with tubulitis at later stages. Infected epithelial cells show enlarged nuclei, with basophilic or amphophilic intranuclear viral inclusions.[58] Experience with DNA PCR screening of either urine or plasma is limited; however, quantitative rather than qualitative DNA is more likely to be clinically useful. Because there is no definitive treatment available at present, the optimal management of BKV disease appears to be judicious reduction in immune suppression with possible elimination of calcineurin inhibitors, in conjunction with active surveillance for rejection. Although the antiviral agent cidofovir has shown some promise when combined with lowered immunosuppression in small studies, its nephrotoxic side effect may limit its overall utility.[54] Some have reported limited success with the use of leflunomide. Overall, the prognosis for graft survival is poor, and several institutions have

reported a 1% to 4% graft loss related to BKV disease.[52] Successful retransplantation after graft loss from BKV disease has been reported, usually after a 6- to 12-month hiatus from immunosuppression.[59]

EBV Infection

EBV infection is quite common in the general population, and most individuals remain asymptomatic. Primary EBV infection induces a mononucleosis-type syndrome with lymphocytosis, pharyngitis, or lymphadenopathy. The clinical syndromes of EBV infection can range from a benign polyclonal B-cell infectious mononucleosis-like syndrome to malignant monoclonal lymphoma. Because the virus replicates readily in the oropharyngeal epithelium, it is commonly transmitted through saliva. Primary infection can also occur through organ transplantation. EBV infection of B lymphocytes frequently results in a latent infectious state that may manifest as overt B-lymphocyte proliferation.[60–62] EBV plays a central role in the pathogenesis of posttransplantation lymphoproliferative disease (PTLD), and its incidence ranges from 1% to 3%.[2] The most clearly defined risk factors for PTLD are primary EBV infection (donor positive/recipient negative) that increases the risk for PTLD by 10- to 76-fold, increases the net state of immunosuppression, and enhances the risk for coinfection by other immunomodulatory viruses.[63] The clinical management of PTLD depends on disease stage, and immune reconstitution is universally favored for these patients. Thus, the first step in the management of PTLD is reduction of patients' immunosuppression as much as feasible. Other therapeutic options, including anti–B-cell therapy (anti-CD20 antibodies; Rituximab), chemotherapy, and irradiation are required, depending on the clinical situation, particularly for the most malignant forms of monoclonal B-cell lymphoma.

Human Herpes Virus Infections (HHV-6, HHV-7, and HHV-8)

HHV-6 and HHV-7 are homologus to CMV, and seropositivity is observed in more than 90% of adults. However, the role of these viral infections is ill defined. HHV-6 has been associated with many clinical syndromes including myelosuppression, encephalitis, hepatitis, and interstitial pneumonitis. Coinfection by HHV-6 and CMV viruses is common and postulated to promote symptomatic CMV disease. These immunomodulatory viruses may also increase a recipient's susceptibility to opportunistic infections.[64–66]

Diagnosis of HHV-6 and HHV-7 infections is based on qualitative and quantitative molecular assays, immunohistochemistry, and by mononuclear cell culture, whereas the mainstay of treatment is reduction in immunosuppression. Antivirals such as ganciclovir and cidofovir have been shown to be effective in some observations. HHV-8 is associated with Kaposi sarcoma and transplantation-associated Kaposi sarcoma occurs in 0.2% to 5% of kidney transplant recipients, depending on ethnicity and the net state of immunosuppression. Treatment characteristically involves immunosuppression reduction in addition to chemotherapy.

West Nile Virus Infection

The West Nile Virus (WNV) was recently shown to transmit through organ transplantation, in which a single donor was responsible for infection in 4 recipients.[67] It appears that when exposed to this infection, transplant recipients are at higher risk than the general population for meningoencephalitis. Diagnosis of WNV infection requires a high index of clinical suspicion and subsequent confirmation by serological or molecular testing. Reduction in immunosuppression is the only treatment option at present, and all donors from endemic areas should be tested for WNV.

Fungal Infections

Kidney transplant recipients have the lowest rate of fungal infection among solid organ transplant recipients. Acknowledged risk factors for fungal infections include exposure to pathogens, the net state of immunosuppression, glucocorticoid steroid usage, the presence of immunomodulatory viral infections, prolonged antimicrobial courses of therapy,

metabolic derangements favoring fungal growth (uncontrolled diabetes), interruption of host barriers (eg, intravenous catheters), indwelling urinary catheters, and longer dialysis vintage antedating transplantation.[68–70] Among the fungal infections, *Candida* and *Aspergillus* are the most common. *Candida* infection is quite common and usually manifests from the time of immediate posttransplantation up to 6 months later, whereas *Aspergillus* infections present themselves somewhat later. With the exception of crytococcosis, fungal infections occurring 6 months after transplantation are rare, unless immunosuppression was intensified to prevent allograft rejection and/or significant environmental exposure to a pathogen has taken place.

Candida species account for 90% to 95% of all invasive fungal infections in kidney transplant recipients. Typical clinical manifestations of *Candida* species include infections related to vascular accesses, the urinary tree, and deep wound infections. Disseminated infections account for less than 5%[70,71] of these infections. Treatment options for candidemia include fluconazole, which is the most frequently used anitmicrobial, amphotericin B plus fluconazole, and the echinocandins (eg, caspofungin or micafungin). The treatment success rate is significantly higher with a combination of amphotericin B and fluconazole, in comparison to fluconazole alone (69% *v* 56%).[72] Caspofungin is considered to be as effective as amphoericin B with fewer drug-related adverse events.[73]

The angioinvasive *Aspergillus* species and their spores are ubiquitous. This fungus is frequently isolated from hospital ventilation systems, especially during periods of construction or renovation. However, community environmental exposures also occur. Spore inhalation is the principal mode of infection acquisition, with lung and upper respiratory tract being the most common sites of infection. Pulmonary involvement is seen in up to 90% of solid organ transplant recipients with invasive aspergillosis, and central nervous system involvement is not uncommon. However, if the organism breaches the confines of the respiratory tract and invades the vasculature, tissue infarction, hemorrhage, and dissemination will ensue. CMV prevention strategies and induction protocols with antilymphocyte antibodies may significantly raise the incidence of *Aspergillus* infections. The treatment of choice for invasive aspergillosis is voriconazole. Alternative antifungals consist of amphotericin B, itraconazole, and caspofungin. A consensus for the duration of therapy does not exist, and so patients often receive long-term maintenance therapy.

Cryptococcal species can cause subacute and chronic meningitis, and disseminated disease involving skin or osteoarticular tissues are not uncommon. Recently, the incidence of emergent fungal infections that includes scedosporium, zygomycosis (*Absidia*, *Mucor*, and *Rhizopus*), and *Fusarium* are increasing and account for more than 10% of all opportunistic fungal infections. Like *Aspergillus* species, the zygomycetes can invade blood vessels causing hemorrhagic necrosis, vascular thrombosis, and tissue infarction. Risk factors for infections by these organisms include treatment of rejections, especially with glucocorticosteroids, prolonged neutropenia, ketoacidosis, kidney failure, and the presence of foreign bodies. The common clinical manifestation is pulmonary zygomycosis, but extrapulmonary infections include rhinocerebral, CNS, genitourinary, musculoskeletal, gastrointestinal, and cutaneous infections. Molds such as *Aspergillus* species can be seen concomitantly in pulmonary cavitary lesions and may represent a reservoir of infection.

Fusarium, a teleomorphic/anamorphic filamentous fungi of which there are more than 20 species, can produce infection in neutropenic and immunocompromised recipients. The portals of entry are generally the respiratory tract and skin. Characteristic skin lesions are a clue to the diagnosis. Fusariosis syndromes include sinopulmonary infection, skin/soft-tissue infection, fungemia, and disseminated disease. *Fusarium* is more commonly isolated from blood cultures than *Aspergillus* species, which are rarely cultured from blood. Tissue biopsy procedures are strongly recommended to ascertain a diagnosis. Notably, the histological diagnosis may be confused with the hyphal elements of an *Aspergillus spp*.

Scedosporium apiospermum, a dimorphic asexual fungus, commonly manifests with

Table 2. Screening of Donors Before Kidney Transplantation[77]

Serologic Test	*Action/Comments*
CMV serology	Use to determine prophylaxis in conjunction with recipient serology
HIV-1, HIV-2 +	Exclude from organ donation
HTLV I/II +	Generally excluded from organ donation
Hepatitis C +	Usually reserve organ for HCV + recipient
HBsAg + or HBcAb IgM +	Exclude from organ donation
HBsAb +	Generally safe for organ donation
HBcAb IgG +	Small risk of transmission; used for vaccinated recipients or with HBV prophylaxis with HBIG and/or lamivudine
EBV +	Consider PCR monitoring if recipient seronegative (mismatch is a risk factor for PTLD)
Syphilis (RPR) +	Not a contraindication to donation. Treat recipient with benzathine penicillin
West Nile virus	Screening of live donors, blood products recommended

Abbreviations: CMV, cytomegalovirus; HIV, human immunodeficiency virus; HTLV, human T cell lymphotropic virus; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBIG, hepatitis B immune globulin; EBV, Epstein-Barr virus; RPR, rapid plasma reagin; PTLD, post-transplant lymphoproliferative disease; +, positive test.

skin lesions that later progress to invasive or nodular pulmonary disease. This infection is found in lung transplant recipients and has also been reported in kidney transplant recipients. It has even recurred during retransplantation. *S apiospermum* is resistant to most antifungal agents including amphotericin B; however, some success has been achieved with voriconazole.[74]

Coccidioides immitis and *Histoplasma capsulatum* are geographically restricted fungi—*Coccidioides* in the southwestern United States and *Histoplasma* in the central United States (ie, the Gulf Coast to the Great Lakes regions). New disease may be acquired while traveling through endemic areas or transmitted via organ donation. The clinical consequences of endemic mycoses include pneumonia and disseminated infections involving mucocutaneous, musculoskeletal, CNS, and gastrointestinal tract systems. All transplant recipients with evidence of remote granulomatous lesions on chest radiographs should be evaluated for mycobacterial and fungal infections. Patients with a history of either epidemiological exposure and/or with history of coccidioidomycosis or histoplasmosis should receive prophylaxis with an "azole" chronically. The diagnosis of coccidioidomycosis or histoplasmosis is generally guided by serologic testing and tissue demonstration of microorganisms. Lastly, all forms of the disease can result in allograft dysfunction and death.

Strategies for Prevention of Infections

Fortunately, many infectious complications after kidney transplantation are preventable. Preventive strategies include counseling of patient and family members regarding risk factors for infections,[75] donor and recipient screenings before transplantation, antimicrobial prophylaxis for recipients, and immunizations of patients, their household members, and health care workers. A complete history should be obtained focusing on prior infectious diseases and exposures, antibiotic allergies, immunizations, traveling or prior residence in areas endemic for specific infections (eg, mycoses [coccidioidomycosis and histoplasmosis] and/or parasitic diseases [malaria, strongyloidiasis, schistosomiasis]), use of illicit drugs, high-risk sexual behavior(s), and incarceration.[14] Antimicrobial prophylaxis of recipients and recommendations regarding the screening of donors and recipients before transplantation are summarized in Tables 1, 2, and 3. It should be emphasized that prophylaxis for PCP and CMV should be started immediately after transplantation and also whenever antilymphocyte antibodies are used for rejection. Children who are awaiting kidney transplantation should receive, in addition to the standard primary vaccine series, varicella vaccination, if not immune.[76] In the adult patient, every effort should be made to update immunizations before transplantation

Table 3. Screening of Recipient Before Kidney Transplantation[77]

Test	*Action/Comments*
CMV	Use to determine prophylaxis in conjunction with donor serology
HIV 1, HIV2 +	Selected patients may be considered for transplantation (see text)
Hepatitis C +	Consider for transplant unless advanced liver disease. Consider treatment with interferon before transplant. Combined liver and kidney transplantation should be considered in the presence of liver cirrhosis
Hepatitis B	If seronegative, vaccinate before transplant
VZV	If seronegative and exposed to VZV, prophylaxis with VZIG and acyclovir recommended. Consider immunization before transplant
PPD +	Treat for latent TB infection (INH+ Vitamin B6 for 9 months) Need to rule out active disease
Other serologic testing:	Test candidates from endemic areas for histoplasma, coccidioides, strongyloides, trypanosomal infections

Abbreviations: CMV cytomegalovirus; HIV, human immunodeficiency virus; VZV, varicella-zoster virus; VZIG, varicella-zoster immunoglobulin; PPD, purified protein derivative; +, positive test.

because the antibody titers achievable in transplant recipients are often suboptimal. In addition, because of the risk of disseminated disease, the use of live virus vaccines (measles-mumps-rubella and varicella) is contraindicated after transplantation. Recommendations on immunizations of adults awaiting kidney transplantation are summarized in Table 4.

References

1. Available at: www.ustransplant.org. Accessed February 15, 2006
2. Rubin RH: Infection in the organ transplant recipient, in Rubin RH, Young LS (eds): Clinical Approach to Infection in the Compromised Host (ed 4). New York, NY, Kluwer Academic/Plenum Publishers, 2002
3. Rubin RH, Ikonen T, Gummert JF, et al: The therapeutic prescription for the organ transplant recipient:

Table 4. Immunizations for Adults Awaiting Kidney Transplantation[25,76,78,79]

Vaccines Routinely Recommended	*Comments*
Hepatitis B	For all seronegative patients. Consider booster if HBsAb titers are low after immunization
Influenza virus	Yearly Vaccination prior to influenza season. Avoid live, inhaled vaccine
Pneumococcal, 23-valent polysaccharide	Repeat vaccination after 3–5 years
Diphtheria, tetanus, pertussis	Booster every 10 years
Polio, inactivated	Avoid live oral vaccine
Vaccines recommended in special situations	
Hepatitis A	Consider if patient has chronic liver disease
Meningococcal	Consider if patient lives in college dormitory, in patients with functional or anatomic asplenia, members of the military and travelers to high-risk areas
Vaccines not recommended after transplantation	
Measles-mumps- rubella, varicella	All are live vaccines. Consider immunization prior to transplantation as needed, per current guidelines. If exposure to varicella virus occurs in seronegative transplant recipient, administer varicella zoster immunoglobulin

The linkage of immunosuppression and antimicrobial strategies. Transpl Infect Dis 1:29-39, 1999
4. Rubin RH: Infectious disease complications of renal transplantation. Kidney Int 44:221-236, 1993
5. Fishman JA, Rubin RH: Infection in organ-transplant recipients. N Engl J Med 338:1741-1751, 1998
6. Rubin RH: Infectious disease complications of renal transplantation. Kidney Int 44:221-236, 1993
7. Tolkoff-Rubin NE, Rubin RH: Urinary tract infection in the immunocompromised host. Lessons from kidney transplantation and the AIDS epidemic. Infect Dis Clin North Am 11:707-717, 1997
8. Tolkoff-Rubin NE, Cosimi AB, Russell PS, et al. A controlled study of trimethoprim-sulfamethoxazole prophylaxis of urinary tract infection in renal transplant recipients. Rev Infect Dis 4:614-618, 1982
9. Fox BC, Sollinger HW, Belzer FO, et al : A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: Clinical efficacy, absorption of trimethoprim-sulfamethoxazole, effects on the microflora, and the cost-benefit of prophylaxis. Am J Med 89:255-274, 1990
10. Hibberd PL, Tolkoff-Rubin NE, Doran M, et al: Trimethoprim-sulfamethoxazole compared with ciprofloxacin for the prevention of urinary tact infection in renal transplant recipients: A double-blind, randomized, controlled study. Online J Curr Clin Trials August 11, (Doc No 15) 1992
11. Schmaldienst S, Dittrich E, Hörl WH: Urinary tract infections after renal transplantation. Curr Opin Urol 12:125-130, 2002
12. Myerowitz RL, Medeiros AA, O'Brien TF: Bacterial infection in renal homotransplant recipients: A study of fifty-three bacteremic episodes. Am J Med 53:308-314, 1972
13. Abbott KC, Oliver JD III, Hypolite I, et al: Hospitalizations for bacterial septicemia after renal transplantation in the United States. Am J Nephrol 21:120-127, 2001
14. Patel R: Infections in recipients of kidney transplants. Infect Dis Clin North Am 15:901-953, 2001
15. Brown PD: Urinary tract infections in renal transplant recipients. Curr Infect Dis 4:525-528, 2002
16. Muñoz P: Management of urinary tract infections and lymphocele in renal transplant recipients. Clin Infect Dis 33:553-557, 2001 (suppl 1)
17. Griffin PJA, Salaman JR: Urinary tract infections after renal transplantation: Do they matter? Br Med J 1:710-711, 1979
18. Moradi M, Abasi M, Moradi A: Effect of antibiotic therapy on the clinical course of asymptomatic bacteriuria in renal transplant recipients. BJU Int 94:43-44, 2004 (suppl 2)
19. Rex JH, Walsh TJ, Sobel JD: Practice guidelines for the treatment of candidiasis. Clin Infect Dis 30:662-678, 2000
20. Dummer JS, Ho M: Infections in solid organ transplant recipients, in Mandell GL, Bennett JE, Dolin R (eds): Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (ed 6). Philadelphia, Elsevier Churchill Livingstone, 2005, pp 3501-3512
21. Lapchik MS, Filho AC, Pestana J, et al: Risk factors for nosocomial urinary tract and post operative wound infections in renal transplant recipients: A matched-pair case control study. J Urol 147:944-948, 1992
22. Humar A, Ramcharan T, Denny R, et al: Are wound complications after a kidney transplant more common with modern immunosuppression? Transplantation 72:1920-1923, 2001
23. Paya CV, Razonable RR: Cytomegalovirus infection after solid organ transplantation, in Bowden RA, Ljungman P, Paya CV (eds): Transplant Infections (ed 2). Philadelphia, PA, Lippincott Williams and Wilkins, 2003, pp 298-325
24. Brennan DC: Cytomegalovirus in renal transplantation. J Am Soc Nephrol 12:848-855, 2001
25. Varon NF, Alangaden GJ: Emerging trends in infections among renal transplant recipients. Expert Rev Anti Infect Ther 2:95-109, 2004
26. Snydman DR: Counterpoint: Prevention of Cytomegalovirus (CMV) infection and CMV disease in recipients of solid organ transplants: The case for prophylaxis. Clin Infect Dis 40:709-712, 2005
27. Singh N: Late-onset cytomegalovirus diseases as a significant complication in solid organ transplant recipients receiving antiviral prophylaxis: A call to heed the mounting evidence. Clin Infect Dis 40:704-708, 2005
28. Preiksaitis JK, Brennan DC, Fishman J, et al : Canadian Society of Transplantation Consensus Workshop on Cytomegalovirus Management in Solid Organ Transplantation Final Report. Am J Transplant 5:218-227, 2005
29. Kalil AC, Levitsky J, Lyden E, et al: Preemptive therapy (PRE) and universal prophylaxis (PRO) for cytomegalovirus (CMV) in solid organ transplant recipients (SOT): A meta-analysis. Infectious Diseases Society of America, Boston, 42nd Meeting, page 167, abstract #639, September 2004
30. American Society of Transplantation: Infectious disease community of practice. Guidelines for the prevention and management of infectious complications of solid organ transplantation. Cytomegalovirus. Am J Transplant 4:51-58, 2004 (suppl 10)
31. Zacks SL, Fried MW: Hepatitis B and C and renal failure. Infect Dis Clin North Am 15:877-899, 2001
32. Koziel MJ, Siddiqui A: Hepatitis B virus and hepatitis delta virus, in Mandell GL, Bennett JE, Dolin R (eds): Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (ed 6). Philadelphia, Elsevier Churchill Livingstone, 2005, pp 1864-1890
33. Fornairon S, Pol S, Legendre C, et al: The long-term virologic and pathologic impact of renal transplantation on chronic hepatitis B virus infection. Transplantation 62:297-299, 1996
34. Mathurin P, Mouquet C, Poynard T, et al: Impact of hepatitis B and C on kidney transplantation outcome. Hepatology 29:257-263, 1999
35. Wright TL, Berenguer M: Hepatitis viruses after hemopoietic stem cell or solid organ transplantation, in Bowden RA, Ljungman P, Paya CV (eds): Transplant Infections (ed 2). Philadelphia, PA, Lippincott, Williams and Wilkins, 2003, pp 412-435

36. Han DJ, Kim TH, Park SK, et al: Results on preemptive or prophylactic treatment of lamivudine in HBsAg (+) renal allograft recipients: Comparison with salvage treatment after hepatic dysfunction with HBV recurrence. Transplantation 71:387-389, 2001
37. Pereira BJG: Hepatitis C infection and post–transplantation liver disease. Nephrol Dial Transplant 10:58-67, 1995 (suppl 1)
38. Knoll GA, Tankersley MR, Lee JY, et al: The impact of renal transplantation on survival in hepatitis C-positive end-stage renal disease patients. Am J Kidney Dis 29:608-614, 1997
39. Schweitzer EJ, Bartlett ST, Keay S, et al: Impact of hepatitis B or C infection on the practice of kidney transplantation in the United States. Transplant Proc 25:1456-1457, 1993
40. Gane E, Pilmore H: Management of chronic viral hepatitis before and after renal transplantation. Transplantation 74:427-437, 2002
41. Kamar N, Sandre-Saune K, Selves J, et al: Is there a place for ribavirin in the treatment for renal transplant patients infected by hepatitis C virus? Nephrologie 24:89-94, 2003
42. Swanson SJ, Kirk AD, Ko CW, et al: Impact of HIV seropositivity on graft and patient survival after cadaveric renal transplantation in the United States in the pre highly active antiretroviral therapy (HAART) era: An historical cohort analysis of the United States Renal Data System. Transpl Infect Dis 4:144-147, 2002
43. Abbott KC, Swanson SJ, Agodoa LYC, et al: Human immunodeficiency virus infection and kidney transplantation in the era of highly active antiretroviral therapy and modern immunosuppression. J Am Soc Nephrol 15:1633-1639, 2004
44. Murphy B, Carlson L, Rohal S, et al: Renal transplantation in HIV-infected recipients: Twenty three cases in the HAART era. J Am Soc Nephrol 13:11A, 2002 (abstr)
45. Roland ME, Stock PG: Review of solid organ transplantation in HIV-infected patients. Transplantation 75:425-429, 2003
46. Shah KV, Daniel RW, Warszawski RM: High prevalence of antibodies to BK virus, an SV40-related papovavirus, in residents of Maryland. J Infect Dis 128: 784-787, 1973
47. Flaegstad T, Ronne K, Filipe AR, et al: Prevalence of anti BK virus antibody in Portugal and Norway. Scand J Infect Dis. 21:145-147,1989
48. Gardner SD: Prevalence in England of antibody to human polyomavirus (BK). BMJ 1:77-78, 1973
49. Hogan TF, Borden EC, McBain JA, et al: Human polyomavirus infections with JC virus and BK virus in renal transplant patients. Ann Intern Med 92:373-378, 1980
50. Mylonakis E, Goes N, Rubin RH, et al: BK virus in solid organ transplant recipients: An emerging syndrome. Transplantation 72:1587-1592, 2001
51. Coleman DV, Gardner SD, Field AM: Human polyomavirus infection in renal allograft recipients. BMJ 3:371-375, 1973
52. Binet I, Nickeleit V, Hirsch HH, et al: Polyomavirus disease under new immunosuppressive drugs: A cause of renal graft dysfunction and graft loss. Transplantation 67:918-922, 1999
53. Hirsch HH, Knowles W, Dickenmann M, et al: Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 347:488-496, 2002
54. Trofe J, Gordon J, Roy-Chaudhury P, et al: Polyomavirus nephropathy in kidney transplantation. Prog Transplant 14:130-140, 2004
55. Nickeleit V, Hirsch HH, Binet IF, et al: Polyomavirus infection of renal allograft recipients: From latent infection to manifest disease. J Am Soc Nephrol 10: 1080-1089, 1999
56. Pappo O, Demetris AJ, Raikow RB, et al: Human polyoma virus infection of renal allografts: Histopathologic diagnosis, clinical significance, and literature review. Mod Pathol 9:105-109, 1996
57. Randhawa PS, Finkelstein S, Scantlebury V, et al: Human polyoma virus-associated interstitial nephritis in the allograft kidney. Transplantation 67:103-109, 1999
58. Sundsfjord A, Spein AR, Lucht E, et al: Detection of BK virus DNA in nasopharyngeal aspirates from children with respiratory infections but not in saliva from immunodeficient and immunocompetent adult patients. J Clin Microbiol 32:1390-1394, 1994
59. Ramos E, Vincenti F, Lu WX, et al: Retransplantation in patients with graft loss caused by polyoma virus nephropathy. Transplantation 77:131-133, 2004
60. Straus SE, Cohen JI, Tosato G, et al: Epstein-Barr virus infections: Biology, pathogenesis, and management. Ann Intern Med 118:45-58, 1993
61. Preiksaitis JK, Diaz-Mitoma F, Mirzayans F, et al: Quantitative oropharyngeal Epstein-Barr virus shedding in renal and cardiac transplant recipients: Relationship to immunosuppressive therapy, serologic responses, and the risk of posttransplant lymphoproliferative disorder. J Infect Dis 166:986-994, 1992
62. Paya CV, Fung JJ, Nalesnik MA, et al: Epstein-Barr virus–induced posttransplant lymphoproliferative disorders. ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. Transplantation 68:1517-1525, 1999
63. Walker RC, Marshall WF, Strickler JG, et al: Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis 20:1346-1353, 1995
64. Singh N: Human herpesviruses-6, -7 and -8 in organ transplant recipients. Clin Microbiol Infect 6:453-459, 2000
65. Mendez JC, Dockrell DH, Espy MJ, et al: Human beta-herpesvirus interactions in solid organ transplant recipients. J Infect Dis 183:179-184, 2001
66. Razonable RR, Brown RA, Hart GD, et al: Late onset cytomegalovirus (CMV) disease in solid organ transplant (SOT) recipients: Risk stratification based on serology, viral load and allograft status. Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract V-1288, September 14-17, 2003, Chicago, IL
67. Iwamoto M, Jernigan DB, Guasch A, et al: West Nile virus in transplant recipients investigation team.

Transmission of West Nile virus from an organ donor to four transplant recipients. N Engl J Med 348:2196-2203, 2003
68. Silkensen JR: Long–term complications in renal transplantation. J Am Soc Nephrol 11:582-588, 2000
69. Paya CV: Fungal infections in solid–organ transplantation. Clin Infect Dis 16:677-688, 1993
70. Singh N: Fungal infections in the recipients of solid organ transplantation. Infect Dis Clin North Am 17: 113-134, 2003
71. Hibberd PL, Rubin RH: Clinical aspects of fungal infection in organ transplant recipients. Clin Infect Dis 19:S33-S40, 1994 (suppl 1)
72. Rex JH, Pappas PG, Karchmer AW, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group: A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in non neutropenic subjects. Clin Infect Dis 36:1221-1228, 2003
73. Mora-Duarte J, Betts R, Rotstein C, et al; Caspofungin Invasive Candidiasis Study Group. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 347:2020-2029, 2002
74. Ahmed J, Ditmars DM, Sheppard T, et al: Recurrence of Scedosporium apiospermum infection following renal re-transplantation. Am J Transplant 4:1720-1724, 2004
75. Soave R: Prophylaxis strategies for solid-organ transplantation. Clin Infect Dis 33:S26-S31, 2001 (suppl 1)
76. Avery RK, Ljungman P: Prophylactic measures in the solid-organ recipient before transplantation. Clin Infect Dis 33:S15-S21, 2001 (suppl 1)
77. American Society of Transplantation: Infectious disease community of practice. Guidelines for the prevention and management of infectious complications of solid organ transplantation. Screening of donor and recipient prior to solid organ transplantation. Am J Transplant 4:10-20, 2004 (suppl 10)
78. Molrine DC, Hibberd PL: Vaccines for transplant recipients. Infect Dis Clin North Am 15:273-305, 2001
79. American Society of Transplantation. Infectious disease community of practice. Guidelines for the prevention and management of infectious complications of solid organ transplantation. Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant 4:160-163, 2004 (suppl 10)