ABSTRACT

Despite progress in preventing and controlling infectious complications of renal transplantation, posttransplantation viral infections remain a significant threat to patients’ health. Optimizing outcomes after renal transplantation depends on effective management of posttransplant infectious complications. This paper discusses manifestations, prevention, diagnosis, and treatment of common viral complications of renal transplantation. Preventive therapy and prompt diagnosis remain the cornerstones of effective control of viral infections in the renal transplant recipient. Measures to prevent and control posttransplantation viral infections include careful screening of recipients and donors for infectious disease, meticulous postoperative care, prophylactic antiviral therapy, judicious use of immunosuppression, efficient use of laboratory and other diagnostic tests for specific diagnosis, and treatment targeted at causative pathogens.


UPDATE ON PREVENTION, DETECTION, AND MANAGEMENT OF VIRAL INFECTIONS IN THE RENAL TRANSPLANT RECIPIENT

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ABSTRACT

Although infectious complications of renal transplantation are less common and cause less morbidity and mortality today than during the initial decades after the advent of renal transplantation, they remain a significant threat to the health of renal transplant recipients. Infections are associated with organ rejection1 and can be caused by viruses, bacteria, fungi, or protozoa. Of the infectious diseases, those caused by viruses cause significant morbidity and mortality in renal transplant recipients.2 These viruses are immunosuppressive as well as oncogenic, and they also may induce kidney graft dysfunction.

The renal transplant patient is vulnerable both to pathogens and—because of the patient’s immunosuppressed status—to viruses that typically would not cause disease in healthy individuals. Optimizing outcomes after renal transplantation depends on prevention, diagnosis, and effective management of transplantation-associated viral infections. This paper discusses manifestations, prevention, diagnosis, and management of common viral infectious complications of renal transplantation.

IMMUNOSUPPRESSIVE STATUS AND INFECTION AFTER RENAL TRANSPLANTATION

The immunosuppressed status of the renal transplant recipient increases the vulnerability to viral infection, including that caused by organisms that typically do not cause disease in healthy individuals. The degree of immunosuppression depends on numerous factors (Table 1).3

The main immunosuppressive therapies used in renal transplant recipients include corticosteroids, cal-
The inosine monophosphate dehydrogenase inhibitor mycophenolate mofetil, and mammalian target of rapamycin (mTOR) inhibitors. Few prospective studies on the association of individual immunosuppressive agents and infectious risk have been conducted, although as discussed later in this article, evidence suggests that immunosuppressive agents may differ in their association with risk for specific infections. In addition to type of immunosuppressive therapy, the dose, duration, and timing (including sequence) of immunosuppressive therapy are each important determinants of infectious risk in renal transplant recipients.

**Sources of Viral Infection in the Renal Transplant Recipient**

Sources of infection in the renal transplant recipient include donor tissue, latent infection, or colonization in the recipient, the hospital setting, and the community. Community-acquired infection can involve food- or water-borne illness in addition to person-to-person transmission. Nosocomial infections increasingly involve antimicrobial-resistant organisms. Donor-originating infections can arise from infections that were latent in the donor and become active in the renal transplant recipient or from active but undetected infection of the donor tissue. To reduce the risk of donor-originating infections, donors are screened with serologic tests and viral cultures for common infections including cytomegalovirus, Epstein-Barr virus, and hepatitis B and C viruses. Because of the risk of infection to the organ recipient, the following viral infections in donors are usually considered contraindications to organ donation: herpes simplex encephalitis; West Nile virus infection; rabies; human immunodeficiency virus (HIV) infection; and active hepatitis A, B, or C. Some active infections may not be detected by current routine screening methods. For example, in 1 investigation, 2 clusters of recipients of solid-organ transplants were found to be infected with lymphocytic choriomeningitis virus that was not detected in the organ donor. In 1 of the clusters, the donor had been exposed to a pet hamster infected with the viral strain identical to that in the organ recipients. No source of infection was identified for the second cluster.

Preexisting latent infection or colonization in the transplant recipient can become active infection in the context of immunosuppression. Examples of preexisting subclinical infections that can become active in immunosuppressed individuals include viral infections, such as hepatitis B and hepatitis C and HIV. Clues to the possible existence of a latent infection can come from review of vaccination history and a careful inventory of dietary habits.

**Timing of Infections After Renal Transplantation**

Risk factors for infections vary over time from the immediate posttransplant period through months to years after transplantation as the patient’s level of immunosuppression changes (Table 2). The pattern of infection and the most likely pathogens can be predicted to some extent based on this timeline, which is delineated by 3 periods: the first month after transplant, 1 to 6 months after transplant, and more than 6 months after transplant. This timeline is affected by numerous factors, including the changing pattern of use of immunosuppressive therapies and antimicrobial prophylaxis, antimicrobial resistance, and the increas-
The increasing frequent practice of transplantation in people infected with HIV and/or hepatitis C virus.3 During the first month after transplantation, immunosuppressive therapy is typically being titrated and has not yet reached maximum impact. The infectious risks to the renal transplant recipient during the perioperative period are similar to those for nonimmunosuppressed individuals. Infections are often caused by hospital pathogens and reflect surgical or postoperative complications. The main infectious complications during this period include bacterial or fungal wound infections, postoperative pneumonia, and catheter-related infections. Although perioperative infections in renal transplant recipients are often similar in type to those in nonimmunosuppressed individuals, they may be both less manifest and more severe given the immunosuppressed status of the transplant patient.

Besides surgical or postoperative complications, donor-originating infections or recipient-derived infections that were latent before surgery can occur during the perioperative period. However, the latter infections become more important 1 to 6 months after transplantation—during the time of most intensive immunosuppression. From 1 to 6 months after transplantation, viral infections from organisms, such as cytomegalovirus, herpes simplex virus, varicella zoster virus, Epstein-Barr virus, and hepatitis B and C virus, often transmitted from tissue of seropositive donors, pose a significant risk. Many of these viruses are themselves immunosuppressive. Opportunistic infections caused by bacteria and fungi are also common from approximately 1 to 6 months posttransplant. Many of these infections can increase the risk of viral infection and graft failure.

From approximately 6 months to 12 months post-transplantation, the level of immunosuppression is typically at a steady state and is less intense than that during the first 6 months after transplantation. Patients with good allograft function have an infectious risk profile similar to that of the general population. Community-acquired infections, particularly respiratory infections, such as influenza, constitute the greatest infectious risk. Patients whose level of immunosuppression is not reduced because of poor allograft function during this time continue to be at risk for opportunistic infections. Regardless of the level of immunosuppression, a minority of patients develops chronic viral infections, acquired earlier, that can cause malignancy or organ damage and increase risk of graft rejection. For example, Epstein-Barr virus infection can cause posttransplantation lymphoproliferative disease. BK polyomavirus infection can cause nephropathy.

### Table 2. Timing of Viral Infections After Transplantation

<table>
<thead>
<tr>
<th>Time After Transplant:</th>
<th>&lt;4 weeks</th>
<th>1–6 months</th>
<th>&gt;6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common source of infection</td>
<td>Recipient-derived</td>
<td>Recipient (opportunistic infection or activation of latent infection)</td>
<td>Community</td>
</tr>
<tr>
<td>Common pathogens</td>
<td>Herpes simplex virus</td>
<td>Herpes simplex virus, cytomegalovirus, hepatitis virus, or Epstein-Barr virus</td>
<td>Pathogens causing pneumonia or cytomegalovirus</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>Being titrated; submaximal immunosuppression</td>
<td>Maximum immunosuppression</td>
<td>Stable, submaximal immunosuppression</td>
</tr>
</tbody>
</table>

Data from Splendiani et al; Sia and Paya; and Fishman.7

### Viral Infections in the Renal Transplant Recipient: Prevention, Diagnosis, and Management

#### General Considerations

Prevention of infections in the renal transplant recipient begins with a thorough pretransplantation evaluation of the donor and the recipient. Elements of the pretransplantation evaluation include a comprehensive history, a complete physical examination, and diagnostic tests to assess for active and latent infectious disease. The history should include inventories of previous infectious diseases, vaccinations, and hobbies or travel that could result in exposure to pathogens. Pretransplantation laboratory tests include blood cell count and viral serology for HIV, varicella zoster virus, and others.
Epstein-Barr virus, herpes simplex virus, cytomegalovirus, and hepatitis viruses A, B, and C.

Prevention of transplantation-associated infections begins before transplantation by treating active infections identified during the pretransplant evaluation, vaccinating against the major posttransplantation pathogens, and avoiding exposure to pathogens during the perioperative period.1 Antimicrobial prophylaxis directed against the most likely and dangerous organisms can be particularly important during the early weeks and months after transplantation. The above-mentioned timeline for developing transplantation-associated infections can be used as a general guide in developing preventive strategies.

In the event that prophylactic efforts are not effective, early and precise diagnosis is crucial in identifying an appropriate course of therapy for posttransplantation infections. Infections in renal transplant recipients may be manifested by nonspecific, ill-defined signs and symptoms. Laboratory tests, imaging, and invasive diagnostic tools, such as biopsy, are often required for accurate and prompt diagnosis. Antimicrobial therapy is often initially broad spectrum and becomes more targeted as the causal pathogen(s) is identified. The risk of drug interactions and the impact on immune status (and therefore on risk of organ rejection and further infection) should be considered in selecting and dosing antimicrobial therapy. Clinically significant interactions between antimicrobials and the immunosuppressants tacrolimus and cyclosporine are common.

As infectious risk is directly related to intensity of immunosuppression, reduction in the amount of immunosuppression may be warranted among patients who are not at maximum level. This strategy might be particularly appropriate for patients whose infections appear to result from excessive immune suppression—for example, patients whose latent viral infections, such as cytomegalovirus or Epstein-Barr virus, become active in the context of immunosuppression. The risk of graft rejection must be carefully weighed against the possible benefit of reducing immunosuppression.

**COMMON VIRAL INFECTIONS IN THE RENAL TRANSPLANT RECIPIENT**

**Cytomegalovirus.** Cytomegalovirus is a frequent cause of infection in renal transplant recipients.6 Cytomegalovirus infection can be manifested by fever, neutropenia, and may manifest as organ involvement, such as pneumonitis, colitis, gastritis, ulcers, hepatitis, pancreatitis, and chorioretinitis. These manifestations, except chorioretinitis, are usually evident within 6 months after transplantation. Chorioretinitis, manifested by progressive blurring of vision, scotomata, and decreased visual acuity, occurs later during the posttransplant period. Cytomegalovirus infection markedly inhibits immune function and thereby renders the patient susceptible to secondary infections with organisms, such as *Pneumocystis*, *Candida*, and *Aspergillus*. Cytomegalovirus infection may play a direct or indirect role in the occurrence of acute and chronic allograft rejection in renal transplant recipients.7 Conversely, prevention of cytomegalovirus infection has been linked to a reduced risk of graft rejection.8,9

Transmission of cytomegalovirus occurs through primary infection, reactivation, or superinfection.10 Primary infection occurs in a seronegative organ recipient who receives a graft from a seropositive donor with a latent infection. The virusreactivates, disseminates, and manifests in immunosuppressed renal transplant recipients. Primary infection rarely can also occur through blood transfusion or community exposure. In reactivation, preexisting latent virus gets reactivated in a seropositive organ recipient. In superinfection, latent virus is reactivated in a seropositive organ recipient who also receives a graft from a seropositive donor.

Risk factors for cytomegalovirus disease include primary infection, intensive immunosuppressive therapy, and the use of antilymphocyte antibody preparation.7 Antiproliferative immunosuppressive agents, such as azathioprine, mycophenolate, and cyclophosphamide, appear to be more likely to reactivate latent cytomegalovirus than cyclosporine, tacrolimus, rapamycin, or maintenance prednisone.7 Regimens including cyclosporine have been associated with a higher incidence of symptomatic cytomegalovirus infection than regimens including tacrolimus.10,11 In addition, recent data suggest that tacrolimus may be associated with greater risk of cytomegalovirus infection than sirolimus.

In a 2007 report of a retrospective observational study of adult recipients of kidney transplants, inclusion of the mTOR inhibitor sirolimus in the immunosuppressive regimen during the early posttransplant period was associated with lower risk of infection with cytomegalovirus, diagnosed through pp65 antigenemia testing based on clinical suspicion, than inclusion of the calcineurin inhibitor tacrolimus.12 Both drugs were administered as part of a multidrug immunosuppressive
regimen, which also included mycophenolate mofetil with or without prednisone. These results may be attributed to varying prevalence of acute rejection and the need for antilymphocyte therapy for acute rejection rather than to immunosuppressive agents per se.

Strategies for preventing cytomegalovirus infection include universal prophylaxis and preemptive therapy. In universal prophylaxis, antiviral therapy is administered beginning immediately after the transplant to all patients at risk of infection. This strategy is typically adopted for seronegative recipients of an organ from a seropositive donor because of the high risk of invasive primary infection. Universal prophylaxis may help to prevent other viral diseases in addition to cytomegalovirus. In preemptive therapy, patients are assessed periodically after transplant for quantitative evidence of early disease and are administered antiviral therapy only in the presence of a positive assay. Antivirals, such as ganciclovir, are effective for cytomegalovirus prophylaxis.

Diagnosis of cytomegalovirus infection can often be accomplished noninvasively by molecular assays or an antigen detection assay. The antigen detection assay detects cytomegalovirus early antigen (pp65), which is present in circulating neutrophils and reflects total viral burden. The most common molecular assays are plasma-based polymerase chain reaction (PCR) tests to detect viral DNA. In individuals with neurologic and gastrointestinal disease, these assays may not be positive despite organ involvement. Hence, the diagnosis is frequently made with biopsy instead of blood assays. Viral cultures and serologic tests are not optimum tools for diagnosing cytomegalovirus infection in the renal transplant recipient. Cytomegalovirus cultures may take up to 1 week and lack sensitivity. Serologic tests are not generally reliable because immunosuppressed patients may or may not augment antibody with active infection and because of the difficulty in differentiating acute from latent infection.

Cytomegalovirus infection, whether invasive or noninvasive, is treated with intravenous (IV) ganciclovir. IV foscarnet and cidofovir also are effective for cytomegalovirus disease. These antivirals have significant nephrotoxicity and should be reserved for those resistant to ganciclovir. Risk of relapse is substantial in seronegative individuals.

**Epstein-Barr virus.** Epstein-Barr virus infection or relapse causes a mononucleosis syndrome with fever and B-cell lymphocytosis that may manifest as fever, lymphadenopathy, meningitis, hepatitis, and pancreatitis. This virus contributes to the development of posttransplantation lymphoproliferative disease, which is characterized by a mononucleosis-like syndrome, unexplained fever, gastrointestinal bleeding, abdominal lesions, liver or pancreatic dysfunction, and infiltrative disease of the allograft. Posttransplantation lymphoproliferative disease most commonly involves B cells but can also involve T cells, natural killer cells, and null cells. Primary infection with Epstein-Barr virus is the main risk factor for posttransplantation lymphoproliferative disease. The risk of posttransplantation lymphoproliferative disease is related to younger age, having a nonrenal transplant, and being a seronegative recipient receiving an organ from a positive donor. The risk of posttransplantation lymphoproliferative disease is further potentiated by the use of antilymphocyte antibody, intensive immunosuppression, and inclusion of tacrolimus in the immunosuppressive regimen.

Diagnosis of Epstein-Barr virus infection or posttransplantation lymphoproliferative disease relies on quantitative Epstein-Barr virus viral load testing. Serial longitudinal measurements are particularly useful in early detection of viral replication. Serial viral monitoring may be particularly important in pediatric transplant recipients and in seronegative recipients with seropositive donors. Quantitative viral loads were serially monitored in a study of 102 pediatric recipients of kidney transplants. The incidence of Epstein-Barr virus infection was 4%, but the incidence of subclinical viremia was 38.2% for Epstein-Barr virus and 6.9% for cytomegalovirus + Epstein-Barr virus. Subclinical viremia predicted poorer 3-year graft function, risk of acute rejection, hypertension, and graft loss. Risk factors for subclinical viremia were age younger than 5, lack of prophylaxis, and steroid use.

Ganciclovir prophylaxis for cytomegalovirus also may be effective in preventing Epstein-Barr virus infection and its sequelae. Epstein-Barr virus infection or posttransplantation lymphoproliferative disease is usually managed by reducing or stopping immunosuppressive therapy. Antiviral therapy can be useful in reducing viral load and counteracting the immunosuppressant effect of the virus. Ganciclovir and acyclovir have been shown to reduce the risk of posttransplant lymphoproliferative disorder in renal transplant recipients. Ganciclovir may be more potent in this regard than acyclovir. The anti-CD20 monoclonal antibody rituximab has shown promising...
results in treating posttransplant lymphoproliferative disorder.19 Newer less tested strategies include anti–B-cell monoclonal antibodies and adoptive immunotherapy.27 Epstein-Barr virus-specific cytotoxic T lymphocytes have been shown to improve Epstein-Barr virus-specific immune responses, reduce viral load in infected organ transplant recipients, and induce remission of posttransplantation lymphoproliferative disorder.24 This treatment potentially increases risk of acute rejection in renal transplant recipients. Reduction of immunosuppressive therapy remains a universal therapy and can potentially increase the chance of acute graft rejection.

**BK polyomavirus.** Polyomaviruses (nonenveloped viruses with double-stranded DNA genomes) occur as JC viruses, which cause demyelinating central nervous system disease, and BK viruses, which cause nephritis. The majority of the general population has antibodies to these polyomaviruses.29,30 JC virus infection and BK virus infection can occur in renal transplant recipients although JC virus infection, manifested as progressive multifocal leukoencephalopathy with seizures or focal neurologic deficits, is uncommon. However, BK virus is an increasing problem in renal transplant recipients in recent years. These viruses potentially can be introduced into the recipient from the donor, be recipient-derived, or both; however, the mode of acquisition of these viruses requires further assessment.

BK virus nephritis is primarily observed in renal transplant recipients; it is rare in recipients of transplants of other organs. For reasons unknown, the incidence of BK virus nephritis among transplant recipients has increased over the past decade in the United States.31,32 The increase has been attributed to the introduction and increasingly widespread use of the immunosuppressants mycophenolate mofetil and tacrolimus, the introduction of which coincided with acute rejection rates and a concomitant increase in incidence of BK virus nephritis. However, BK virus nephritis has also been observed in patients not using these immunosuppressive therapies.33 Risk factors for BK virus nephritis are use of mycophenolate mofetil with tacrolimus, prior acute rejection, donor seropositivity, and degree of HLA mismatches.

BK virus nephritis is manifested with or without renal dysfunction and sterile pyuria, sometimes accompanied by ureter obstruction manifesting as hydronephrosis, and/or hemorrhagic cystitis.33 In 33% to 66% of cases of BK virus nephritis, progressive renal failure occurs.34-36 Diagnosis of BK virus nephritis is usually made on the basis of renal histological evidence of a cytopathic effect of the virus with signs of inflammation.35 Typical findings include focal interstitial mononuclear inflammatory cell infiltrates (which cannot always be distinguished from that associated with acute organ rejection), presence of plasma cells, necrotic tubular epithelium, and homogeneous intranuclear inclusion bodies. Diagnosis and evaluation of clinical course can be aided by the findings of decoy cells in urine, viremia, viruria, and the presence of serum BK virus-specific antibody (Table 3).

Prevention of BK virus nephritis remains the cornerstone of management. Preventive strategies include monitoring plasma BK viral loads after transplant and preemptively reducing intensity of immunosuppressive therapy in patients with BK viremia or viruria. The practice of preemptively decreasing immunosuppression is supported by data suggesting that the presence of viruria predates viremia, which in turn predates the detection of clinical renal disease and histological evidence of BK virus nephritis.37,41 Higher prevalence of viruria than viremia and lack of good correlation with viruria have prompted investigators to use viremia as a better marker for preemptive reduction in immunosuppressive therapy. Vigorous posttransplant screening and preemptive reduction in immunosuppressive therapy for those with significant viremia has been shown to reduce the prevalence of nephritis.42 This strategy also resulted in earlier diagnosis of BK virus nephritis and improved graft survival among screened patients compared with a cohort of patients who did not have screening.

Treatment of BK virus nephritis involves reducing immunosuppression with or without antiviral treatment with agents, such as leflunomide, cidofovir, amantadine, or vidarabine. The goal in treating BK virus nephritis is to eliminate the virus while preserving renal function and preventing secondary acute or chronic rejection. Leflunomide with reduction in immunosuppressive therapy has been effective in eliminating circulating viremia.43 Similarly, cidofovir appears to be effective in treating this infection.44,45 However, the efficacy of leflunomide and cidofovir requires further elucidation as these agents have been used with reduction in immunosuppressive therapy, which may have played a role in clearing the virus. In some patients, renal function can be stabilized by reducing immunosuppression alone.46 For example,
in a retrospective analysis conducted by this author and his colleagues, the efficacy and safety of reducing immunosuppression without using antiviral therapy were evaluated for the treatment of BK viremia. The sample included 24 patients, of whom 16 had BK virus nephritis and 8 had viremia without nephritis. A progressive decline in BK viral load was observed within 15 to 30 days of reducing immunosuppressive therapy by halving both antimetabolites and calcineurin inhibitor doses. Viremia was eliminated over a mean period of 5.8 months. Three patients (13%) developed acute cellular rejection with reduction in immunosuppressive therapy and were treated successfully with IV bolus steroids. During the follow-up period, 1 patient had a relapse of BK virus nephritis during her pregnancy, and she lost her graft. The remaining 23 patients are alive with stable kidney function.

Herpes simplex viruses. Most herpes simplex infections in renal transplant recipients occur because of reactivation of the virus. Severe manifestations of orofacial and genital herpes are commonly observed during the initial weeks after transplantation. The diagnosis can be established by presenting symptoms, clinical examination findings, and cytology. Oral or IV antivirals including acyclovir and foscarnet are effective therapy. The risk of herpes simplex virus after transplantation can be significantly reduced with the use of acyclovir prophylaxis.

Varicella zoster virus. Like herpes simplex virus infections, varicella zoster virus infections primarily are reactivations. Primary varicella zoster virus infection can occur as chickenpox or as a potentially lethal infection with pneumonia, encephalitis, pancreatitis, and hepatitis. Diagnosis can be established with history, clinical examination, cytology, immunoglobulin (Ig) G-IgM seroconversion, and varicella zoster virus PCR quantification in vesicle contents.

Data from 1 study suggest that the prevalence of seronegativity to varicella zoster virus appears to be low (2%–3%) in renal transplant recipients in addition to patients waitlisted for kidney transplantation. Likewise, the incidence of varicella zoster virus infection in renal transplant recipients is relatively low;

### Table 3. Tests to Aid in Diagnosis of BK Virus Nephritis

<table>
<thead>
<tr>
<th>Test</th>
<th>Findings</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal histology</td>
<td>Inflammatory changes with viral cytopathic effects, positive immunoperoxidase reaction with SV40 stain, predominant CD20-positive lymphocytic infiltrates</td>
<td>Gold standard, invasive procedure</td>
</tr>
<tr>
<td>Urine cytology</td>
<td>Presence of decoy cells</td>
<td>Seen in approximately 50% of transplant recipients Positive predictive value ~20%</td>
</tr>
<tr>
<td>Viremia (plasma BK virus DNA)</td>
<td>Copies &gt;7000/mL plasma</td>
<td>Seen in 10%–20% of transplant recipients Positive predictive value ~60%</td>
</tr>
<tr>
<td>Viruria (urinary BK virus DNA)</td>
<td>Copies 100-fold higher than plasma values Positive predictive value ~40%</td>
<td>Seen in 30%–40% of transplant recipients</td>
</tr>
<tr>
<td>BK virus DNA in renal tissue</td>
<td>Detection of BK virus DNA in renal biopsy tissue</td>
<td>Negative predictive value ~100% Positive predictive value ~70%</td>
</tr>
<tr>
<td>Serum BK virus-specific antibodies</td>
<td>BK virus-specific antibodies</td>
<td>Seen in 80%–90% of the general population</td>
</tr>
</tbody>
</table>

however, it can cause significant morbidity and mortality when it does occur.\textsuperscript{56,57} In a study of herpes zoster infection following solid organ transplantation (ie, kidney, liver, lung, or heart), independent predictors of the posttransplant development of herpes zoster were induction therapy and antiviral treatment other than prolonged cytomegalovirus prophylaxis (which may be a marker for increased risk of latent herpesvirus reactivation).\textsuperscript{55} To prevent primary varicella zoster infection, seronegative patients should be administered a varicella vaccination before organ transplantation. Vaccination of seronegative patients waitlisted for kidney transplantation resulted in a positive serologic response in 7 of 11 patients in 1 study.\textsuperscript{58} Seronegative patients exposed to the virus can be administered zoster immune globulin to prevent serious disease. Antiviral medications effective for varicella zoster virus include acyclovir, valacyclovir, and famciclovir.

\textit{Hepatitis viruses A, B, and C}. Viral hepatitis in transplant recipients is usually caused by hepatitis C or hepatitis B—most often by hepatitis C.\textsuperscript{2} Both viruses suppress immune function and immunosuppressive therapy stimulates replication of these viruses. Individuals with a positive serologic test for the hepatitis B surface antigen should be vaccinated before transplantation. Infection attributed to hepatitis C is rarely acutely symptomatic in the renal transplant recipient, and progression of liver disease is slow.

Appropriate management of hepatitis infection before transplantation is critical for enhancing short- and long-term survival. Pretransplant evaluation and management of hepatitis virus infection continues to evolve with better diagnosis and treatment strategies. Hepatic enzymes are not particularly useful for pretransplant diagnosis of hepatitis. The correlation between hepatic enzyme elevation and degree of viral activity is poor. Hepatic enzymes may be elevated because of other conditions, such as liver congestion or alcohol and drug toxicity. In patients with end-stage renal disease, hepatic enzymes might not be elevated despite the presence of active infection. Hepatitis C antibody evaluations are the gold standards for evaluating hepatitis C status. The third-generation assay has become a routine screening test before transplantation for patients with end-stage renal disease. Third-generation hepatitis C antibody assays are more accurate than first- and second-generation assays. False positives with third-generation assays are estimated to be as low as 0.23%. Although PCR can also be used to diagnose hepatitis C, hepatitis C PCR reveals viremia status and is more useful for monitoring therapy.

All serology-positive patients should be evaluated with hepatic histology. Severity of hepatic disease by histology cannot be correlated with serology, PCR, or liver enzymes. Identification of severe histological damage, such as cirrhosis, is critical because these patients fare poorly after renal transplantation alone and are often not candidates for isolated kidney transplantation.

\(\alpha\) interferon is the gold standard therapy for patients with hepatitis C. Because administration of \(\alpha\) interferon after transplantation increases the occurrence of acute rejection and the risk of steroid-resistant acute rejection, it is prudent to give therapy before transplantation. However, this treatment is associated with severe morbidity. Administration of \(\alpha\) interferon with ribavirin has been tried with adequate biochemical and virologic response. Ribavirin therapy is associated with anemia, which can be counteracted with epoetin \(\alpha\).\textsuperscript{59} Therapy with \(\alpha\) interferon is expensive, and withdrawal of therapy is associated with high relapse rates. A large controlled trial is warranted to demonstrate the safety and efficacy of such treatment.

\textit{Other viral infections}. West Nile virus is increasingly recognized as an important cause of morbidity in transplant recipients.\textsuperscript{54} In immunocompromised individuals, West Nile virus infection is most commonly manifested by an acute febrile illness; however, neuroinvasive disease can occur in immunocompromised hosts, including transplant recipients.\textsuperscript{54} West Nile virus infection should be considered in transplant recipients who develop a febrile illness and neurologic symptoms. Diagnosis of West Nile virus infection can be confirmed by detection of West Nile virus-specific IgM in cerebrospinal fluid or serum.\textsuperscript{54} West Nile virus-associated encephalitis has been successfully managed with reduction of immunosuppression.\textsuperscript{54}

Influenza virus infection in organ transplant recipients is caused by person-to-person contact. Influenza virus infection is associated with organ rejection and allograft dysfunction in organ transplant recipients in addition to more frequent pulmonary and extrapulmonary complications in transplant recipients compared with the nontransplant population.\textsuperscript{57} In the presence of an influenza epidemic, a hospital outbreak, or known or suspected exposure of a transplant recipient to an infected individual, antiviral medications are administered as postexposure prophylaxis to renal transplant recipients.\textsuperscript{58} Although influenza infection can be
prevented with immunization, antibody response to inactive influenza vaccine is muted in organ transplant recipients. Furthermore, the safety and efficacy of live attenuated influenza virus vaccine in renal transplant recipients has not been systematically investigated.

Conclusions

Although progress has been realized in preventing and controlling infectious complications of renal transplantation, posttransplantation viral infections remain a significant threat to patients’ health. Preventive therapy and prompt diagnosis remain the cornerstones of effective control of viral infections in the renal transplant recipient. Measures to prevent and control posttransplantation viral infections include careful screening of recipients and donors for infectious disease, prophylactic antiviral therapy, viral surveillance for certain diseases, judicious use of immunosuppression, efficient use of laboratory and other diagnostic tests for specific diagnosis, and the combination of reduction of immunosuppression and antiviral agents targeted at causative pathogens can optimize renal transplant outcomes.

References


