

Viral Infection in the Renal Transplant Recipient

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Viruses are among the most common causes of opportunistic infection after transplantation and the most important. The risk for viral infection is a function of the specific virus encountered, the intensity of immune suppression used to prevent graft rejection, and other host factors governing susceptibility. Viral infection, both symptomatic and asymptomatic, causes the "direct effects" of invasive disease and "indirect effects," including immune suppression predisposing to other opportunistic infections and oncogenesis. Rapid and sensitive microbiologic assays for many of the common viruses after transplantation have replaced, for the most part, serologic testing and *in vitro* cultures for the diagnosis of infection. Furthermore, quantitative molecular tests allow the individualization of antiviral therapies for prevention and treatment of infection. This advance is most prominent in the management of cytomegalovirus, Epstein-Barr, hepatitis B, and hepatitis C viruses. Diagnostic advances have not been accompanied by the development of specific and nontoxic anti-viral agents or effective antiviral vaccines. Vaccines, where available, should be given to patients as early as possible and well in advance of transplantation to optimize the immune response. Studies of viral latency, reactivation, and the cellular effects of viral infection will provide clues for future strategies in prevention and treatment of viral infections.

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Immune suppression after transplantation renders the transplant recipient susceptible to a broad array of viral pathogens (Table 1). Epidemiologically, some are the result of community exposures (influenza, adenovirus), whereas some are commonly transmitted with the allograft (cytomegalovirus [CMV], Epstein-Barr virus [EBV]), and others are the result of more distant exposures reactivated in the setting of immune suppression (chicken pox and varicella zoster [VZV] as shingles). Multiple simultaneous infections, viral and non-viral, are also common, such as CMV and human herpes virus (HHV) 6 or CMV and *Pneumocystis* (1–5). This review focuses on acute and recurrent viral infections that occur after adult renal transplantation.

Impact of Viral Infection after Transplantation

The effects of viral infection are classified as "direct" and "indirect" (Figure 1). This classification serves to separate the effects of invasive viral infection (cellular and tissue injury) from effects mediated by inflammatory responses (*e.g.*, cytokines) or by alterations in host immune and inflammatory responses (6,7). Syndromes such as fever and neutropenia (*e.g.*, with CMV infection) or invasive disease resulting in pneumonia, enteritis, meningitis, or encephalitis are considered direct effects. Indirect effects of viral infections include responses to viral infections such as release of cytokines, chemokines, or growth factors. These effectors are immunomodulatory, result-

ing in further immune suppression and increasing the risk of other opportunistic infections (7–9). In addition, viral infection may alter expression of surface antigens (*e.g.*, histocompatibility antigens), provoking graft rejection and/or causing dysregulated cellular proliferation (contributing to oncogenesis). Infection with one virus may cause immune suppression or otherwise stimulate replication of other viruses (*e.g.*, CMV and hepatitis C) in a form of viral "cross-talk." Multiple observational studies implicate infection with HHV-6 and/or HHV-7 as risk factors for CMV disease (1,2,4,10–14) and CMV infection may trigger HHV-6 and HHV-7 reactivation (10). Increased viral replication and persistence may contribute to allograft injury (fibrosis) or chronic rejection (9,15).

Viral infection can also lead to the generation of cross-reactive T cells directed against shared antigens between virus and graft ("molecular mimicry") (16), or neoantigens generated by viral expression within the allograft environment. Such alloreactive T cells may bind a variety of epitopes via "alternative recognition" (17) within the T cell receptor (18–23). The degree of such "heterologous immunity" is thought to relate to previous infectious exposures by the host and may contribute to resistance to generation of graft tolerance (24–26). Heterologous immunity may also develop as a result of "bystander activation," in which virally activated T cells release growth factors, cytokines, and inflammatory mediators that activate alloreactive T cells nonspecifically (27).

Viral Latency and Reactivation

Many viral infections after renal transplantation result from reactivation of "latent" viral infection in the host or from the graft. The nature of viral latency varies with the specific virus, the tissue infected, and the nature of the host immune response.

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Table 1. Viral pathogens in transplant recipients

| |
|---|
| Herpes simplex |
| Varicella zoster |
| Epstein-Barr virus |
| Cytomegalovirus |
| HHV-6 |
| HHV-7 |
| HHV-8/KSHV |
| Parvovirus B19 |
| West Nile virus |
| Rabies |
| Hepatitis B and C |
| Papillomavirus |
| Polyomavirus BK/JC |
| Adenovirus, RSV, influenza, parainfluenza |
| Metapneumovirus |
| HIV |
| SARS (coronavirus) |

Some latent viruses are metabolically inactive, whereas others are constantly replicating at low levels determined by the effectiveness of the host's immune response. Multiple factors contribute to viral activation after transplantation, including immune suppression (especially reduction of cytotoxic immunity), graft rejection and therapy, inflammation (cytokines), and tissue injury (28–36). Cellular pathways activated after transplantation are involved in the control of viral replication, including nuclear factor κ B, I κ B, and JAK-STAT (the Janus family of protein tyrosine kinases [JAKS] and signal transducers and activators of transcription [STAT] proteins) (37,38). Treatment of rejection can also result in a significant release of proinflammatory cytokines, including TNF- α and IL-1 β , which may increase viral replication (39).

Latency and reactivation have been studied intensively in the herpesviruses, which establish life-long latent infection after initial infection. During the latent phase of infection, viral genomes, but not infectious virus, can be detected in affected cells. Studies of other viruses (*e.g.*, Friend virus in mice) suggest that the absence of protective antiviral immunity is an active process mediated by “leaky” (low-level) viral replication (40). Thus, the existence of true latency, as opposed to low-level replication, remains controversial. Herpesviruses make a limited group of “latency” proteins (*e.g.*, the “latency-associated transcripts” of herpes simplex virus [HSV]) that control the nature of viral persistence within the target cell and influence other cellular processes (such as blocking apoptosis). The latent state is characterized by low levels or the absence of detectable viral antigens, minimal transcription of productive or lytic cycle genes, and expression of the latency-associated viral transcripts (41). Viral latency may be interrupted periodically, leading to reactivation and spread of infectious virus with recurrent disease. For CMV, viral genomes can be found in CD14⁺ monocytes and CD34⁺ progenitor cells, but the primary reservoir for latent cytomegalovirus and the mechanisms by which latent CMV infection is maintained are unknown (42,43). Subclinical

activation of CMV is common. EBV establishes latency in B-lymphocytes in association with expression of a limited set of viral genes. Despite similarities, the molecular details and mechanisms of latency and reactivation are quite different among the herpesviruses. The role of antiviral immunity in maintaining latency is unclear.

CMV reactivation has been extensively studied. Allogeneic immune responses and fever (via TNF- α) have been shown *in vitro* to up-regulate both CMV promoter activity and viral replication (32,44,45). Immune suppression is not essential for the reactivation of latent CMV but serves to perpetuate such infections once activated (46–48). For other viruses (*e.g.*, BK polyomavirus), specific types of tissue damage (warm ischemia, reperfusion injury, but not cold ischemia) may precipitate viral activation (49–52). Warm ischemia and reperfusion have been linked to an inflammatory state in grafts (via activation of TNF- α , nuclear factor κ B, neutrophil infiltration, and nitric oxide synthesis), tubular-cell injury, and enhanced expression of cell-surface molecules (53–55). These changes contribute to viral activation (54,55) (Figure 1). Thus, immune injury, inflammatory cytokines, and ischemia-reperfusion injury stimulate viral replication and alterations in the expression of virus-specific cell-surface receptors. The host response is also less effective because of the mismatch in major histocompatibility antigens between the organ donor and host, which reduces the efficacy of direct pathway antiviral cellular immune responses. These factors render the allograft susceptible to invasive viral infection.

Epidemiology: Infections from Donor and Community

Because viruses are cell-associated, transplantation of viable tissues is a uniquely effective method for viral transmission. As a result, pretransplant screening (Table 2) is designed to avoid the inadvertent transmission of significant infections and to allow the design of individualized preventative strategies (*i.e.*, prophylaxis) for known infections. Thus, known CMV and EBV infections may be transmitted from a latently infected donor (the marker being seropositivity) to a recipient without pre-existing immunity (seronegative). Use of organs carrying active hepatitis B virus and hepatitis C virus (HBV and HCV) or HIV infections are generally avoided, although some institutions use HCV-positive donors with informed consent for HCV-positive recipients or for expanded access under special circumstances. In a recent study of 38,270 US Renal Data System Medicare beneficiaries awaiting kidney transplantation who presented with end-stage renal disease, Cox regression was used to compare the adjusted hazard ratios for death among recipients of kidneys from deceased donors *versus* donors with antibodies against hepatitis C (56). Transplantation from HCV-positive donors was associated with improved survival, compared with remaining wait-listed and dialysis-dependent. To expand the pool of available organs, kidneys from HBV core antibody-positive donors are commonly used; transmission of HBV in this setting is uncommon (57). These organs should be preferentially used in HBV-vaccinated or antibody-positive recipients. Rare diagnostic errors have resulted in transmission of

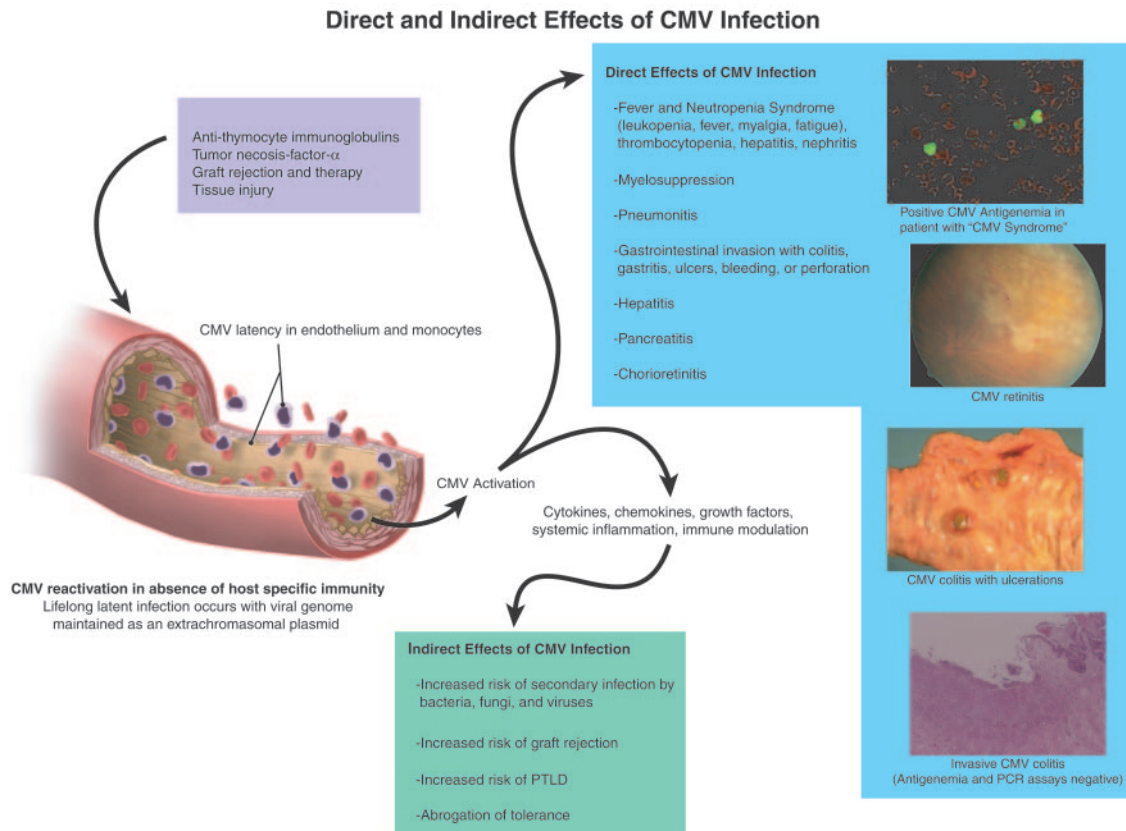


Figure 1. Viral activation and direct and indirect effects of cytomegalovirus infection in transplantation.

Table 2. Viral screening in transplant candidates

| Virus screened | Donor | Recipient |
|------------------------------|--------------------|-----------|
| Cytomegalovirus | X | X |
| Epstein-Barr virus | X | X |
| Herpes simplex virus | X | X |
| Varicella zoster virus | X | X |
| Hepatitis B surface antibody | X | X |
| Hepatitis B surface antigen | X | X |
| Hepatitis B core antibody | X | |
| Hepatitis C | X | X |
| HIV | X | X |
| HTLV-I | X | X |
| HTLV-II | X | X |
| West Nile virus | Endemic areas only | |
| Encephalitis, unknown | Excluded from Tx | |

HTLV indicates human T-lymphotropic virus.

HBV, HCV, and HIV, resulting from serologic testing before seroconversion and false-negative molecular assays (58,59).

New or uncommon pathogens may be transmitted accidentally (rabies, West Nile virus) or during a period after exposure but before seroconversion (HIV, CMV, others) by the donor. Molecular assays are needed to assess infectious risk from such donors. Viruses for which assays are either not performed or

not available may result in the accidental transmission of uncommon infections (rabies, West Nile, SARS virus) (60).

Prevention of viral infection is enhanced by limiting exposure to blood products. Leukocyte filters should be used during transfusions, notably in seronegative recipients, to reduce (although not eliminate) risk (61). Nosocomial transmission is common (e.g., respiratory syncytial virus [RSV], influenza) and

can be reduced by careful hand sanitation and vaccination of staff. Pre-exposure vaccination (for example, HBV or varicella vaccine) should occur at the earliest signs of chronic renal failure, before the response to vaccines wane; for example, patients with higher GFR levels are more likely to respond to hepatitis B vaccination (62). Patients at risk for sexual transmission of viral infections should be counseled about sexual practices.

Time Course of Viral Infections after Transplantation

The risk for infection after transplantation varies with a variety of factors, including the intensity, virulence, and mechanisms of viral exposures; the nature of the immunosuppressive regimen; and the presence or absence of pre-existing antiviral immunity. The immunosuppressive programs used in solid-organ transplantation have great variety, although the calcineurin inhibitors (cyclosporine or tacrolimus) are commonly the cornerstones of maintenance anti-rejection therapy. Such factors as the use of steroids (now often absent in HBV- and HCV-infected recipients), the use of induction T cell-depleting antibodies (monoclonal or polyclonal, which tend to activate herpesviruses and HIV), alemtuzumab, or costimulatory blockade will alter susceptibility to viral infection. Specific immunosuppressive agents have been suggested as increasing risk for specific viral infections, including tacrolimus in BK nephropathy (63–65), anti-thymocyte globulin in CMV (66), mycophenolate mofetil (MMF) in late CMV (67). The interpretation of these data is complex and a direct association in individual patients is often difficult to assess.

There is a general time pattern of posttransplant viral infections. Patients with a history of HSV infections may have early reactivation (1 or 2 mo after transplantation). Infections acquired from the donor such as HBV, HCV, or HIV may also appear in the first month after surgery. Hemophagocytic syndrome may occur soon after transplantation and combines febrile hepatosplenomegaly, pancytopenia, hypofibrinemia, and liver dysfunction; it has an estimated prevalence of 0.4% in renal transplant recipients (68). Hemophagocytic syndrome has been described in association with many viral and nonviral infections including EBV, CMV, HSV, VZV, HIV, HHV8, parvovirus B19, and measles, as well as with Gram-negative and fungal sepsis, tuberculosis, and leishmaniasis. CMV (both reactivation disease and new disease acquired in the peritransplant period) tends to appear in months 1 to 4 or after the cessation of antiviral prophylaxis (approximately day 100). Other latent viruses such as EBV and VZV (shingles) also tend to appear in months 2 to 6. CMV retinitis and CMV colitis tend to be later manifestations of disease (6 to 12 mo or later). Half of BK polyomavirus nephropathy is seen in the first 6 mo after transplantation but half is seen at a later time period. Individual risk factors must be considered in the evaluation of skin and anogenital lesions because of papillomavirus. Community-acquired infections such as influenza, RSV, and adenovirus can appear at any time.

Presentation and Diagnosis

Presentations of viral infections in renal transplant recipients are often atypical. Rashes may be either more extensive or less impressive than in the normal host—shingles may disseminate beyond dermatomes, cause varicella pneumonia, or present as cholangitis or as a macular rash without vesicles. Infection caused by BK polyomavirus may present as graft rejection (*i.e.*, nephropathy), ureteric obstruction, or sterile pyuria. Specific diagnosis is essential to the selection of appropriate antiviral therapies (if available) and to avoid toxicities of other antimicrobial agents. Notably, *the first line of therapy for viral infection in the organ transplant recipient is to reduce immune suppression*, whereas apparent rejection might suggest the need for increased intensity of suppression. To this end, microbiologic assays including molecular, ELISA, or immunostaining for viral antigens may provide a rapid diagnosis.

Therapy

The treatment of viral infections in the renal transplant recipient includes: (1) reduction of immunosuppression; (2) antiviral therapy; (3) diagnosis and treatment of co-infections such as CMV, EBV, HHV-6, or HHV-7; and (4) use of adjunctive therapies such as immunoglobulins or colony stimulating factors. *The first therapeutic decision is whether and how to reduce the intensity of immune suppression.* The risk of this therapy is graft rejection. Because protective cytotoxic immunity to viruses is generally T cell-mediated (CD8+), an initial reduction of anti-metabolites (if neutropenic) and calcineurin inhibitors merits consideration. By contrast, a reduction of the steroid dose during the acute phase of a febrile illness risks adrenal insufficiency. Reversal of immune deficits (neutropenia, hypogammaglobulinemia) may be possible using adjunctive therapies (*e.g.*, colony-stimulating factors or antibody) (69).

Specific Infections: CMV

CMV is the single most important pathogen in transplant recipients due to both direct and indirect effects (Table 3) (6,7). Infection presents most often as asymptomatic viremia or with fever and neutropenia—often a “flu-like” illness with myalgias and fatigue. Chorioretinitis and colitis are often later in the posttransplant course.

Indirect effects are often significant (Table 3). CMV infection suppresses host defenses, predisposing to secondary invasion by such pathogens as *Pneumocystis jiroveci*, *Candida*, and *Aspergillus* species, and some bacterial infections (7,9). Prophylaxis against β -herpes virus infection decreases the risk of opportunistic infection (70,71). CMV also contributes to the risk of graft rejection, EBV-mediated posttransplant lymphoproliferative disorder (PTLD), HHV-6, and HHV-7 infections. The mechanisms for these effects include altered T cell subsets and synthesis and display of major histocompatibility antigens, and elaboration of the array of proinflammatory cytokines, chemokines, and growth factors.

Patterns of Transmission

Primary CMV infection occurs when seronegative individuals receive grafts from latently infected seropositive donors

Table 3. Direct and indirect effects of CMV infection

| Direct Effects of CMV Infection | Indirect Effects of CMV Infection |
|--|--|
| Fever and neutropenia syndrome (leukopenia, fever, myalgia, fatigue, thrombocytopenia, hepatitis, nephritis) | Increases risk of secondary infection by bacteria, fungi, and viruses (70, 71) |
| Myelosuppression | Increases risk of graft rejection (70) |
| Pneumonia | Increases risk of PTLD |
| Gastrointestinal invasion with colitis, gastritis, ulcers, bleeding, or perforation | May increase risk of HHV-6 and HHV-7 infection (1–4) |
| Hepatitis | |
| Pancreatitis | |
| Chorioretinitis | |

Pathophysiology; see Figure 1. CMV indicates cytomegalovirus; PTLD, posttransplant lymphoproliferative disorder; HHV, human herpes virus.

(D+/R-) with subsequent reactivation of the virus and systemic dissemination after transplantation. Before the era of effective prophylaxis, 40 to 50% of these patients experienced direct infectious disease manifestations of CMV; the majority were viremic, often without symptoms. Primary CMV infection may also occur in seronegative individuals after transfusion or sexual contact.

Reactivation CMV infection occurs in seropositive individuals (R+) who reactivate virus after transplantation (donor seropositive or seronegative). When conventional immunosuppressive therapy is used (*e.g.*, no antilymphocyte antibody treatment), approximately 10% to 15% experience direct infectious disease syndromes; a higher rate occurs with the use of induction antilymphocyte therapy.

Diagnosis

For any discussion of CMV, "infection" must be distinguished from "invasive disease." "CMV infection" is defined as isolation of the CMV virus or detection of viral proteins or nucleic acids in any body fluid or tissue specimen. The diagnosis of "CMV disease" (pneumonia, colitis, hepatitis) is defined by the presence of signs and/or symptoms of tissue injury combined with virus isolation and/or histopathologic or immunohistochemical evidence of CMV in tissue samples. Thus, secretion of CMV into lung fluids or urine is common in immunosuppressed seropositive individuals *in the absence of invasive disease*. Although it may be useful *clinically* to initiate therapy on the identification of CMV in a bodily fluid, the diagnosis of CMV disease should await appropriate microbiologic data.

Microbiologic Assays. CMV cultures are too slow and insensitive for timely clinical utility. Positive CMV cultures (or shell vial culture) derived from respiratory secretions or urine are of little diagnostic value—many patients secrete CMV in the absence of invasive disease. Serologic tests are useful before transplantation to predict risk for disease but are of little value after transplantation in defining acute clinical disease; seroconversion may not occur until well after the resolution of symptoms. Seroconversion after renal transplantation occurs in the majority of seronegative recipients of seropositive donors

within 6 to 12 mo. This may correlate with some degree of immunological protection against CMV.

Quantitation of the intensity of CMV infection is related to the risk for infection in transplant recipients and is essential for management of acute infections (72). Two types of quantitative assays exist. The antigenemia assay is a semiquantitative fluorescence assay in which circulating neutrophils are stained for CMV early antigen (pp65 or pp67, a later antigen). The molecular assays (direct DNA PCR, hybrid capture, amplification assays) are highly specific and sensitive for the detection of viremia. Two of the more common assays are plasma-based PCR testing and the whole-blood hybrid capture assay. In a recent study using a molecular assay, regular CMV plasma viral load measurements were only of modest value in predicting CMV disease (72). Quantitative CMV assays have two prominent gaps: neurologic disease, including chorioretinitis, and gastrointestinal disease, including invasive colitis and gastritis. In these syndromes, the CMV assays are often *negative* and invasive (biopsy) diagnoses are often necessary.

The schedule for screening should be linked to the individual's risk for infection. In the patient being treated for CMV infection, the assays provide an endpoint (a negative assay) for therapy and the re-initiation of prophylaxis. In the patient at high risk after the completion of prophylaxis, weekly to bi-weekly screening should be considered to assure the absence of infection for 3 to 6 mo.

CMV Prevention

CMV prevention must be individualized by risk group and immunosuppressive regimen. Patients at risk for primary infection (D+/R-) are generally given valganciclovir prophylaxis for 3 to 6 mo after transplantation (73); 6 mo of prophylaxis is often used in patients (D+/R- or R+) receiving depleting antilymphocyte antibodies. Patients at lower risk (R+) may also be followed-up using quantitative assays at predefined intervals (weekly) to detect and treat early disease (preemptive therapy). Breakthrough disease and ganciclovir resistance have been observed using either approach. In renal transplant recipients receiving either prophylaxis (oral ganci-

clovir) or weekly PCR surveillance and treatment for either a positive assay or invasive disease, prophylaxis was more effective at preserving renal function and had the lowest risk of rejection (74).

Treatment

The standard of care for treating CMV disease is 2 to 3 wk of intravenous ganciclovir (5 mg/kg twice daily, dose adjustments for renal dysfunction) with demonstration of clinical and virologic responses to therapy (75,76). In seronegative patients and those slow to respond to therapy, the addition of CMV hyperimmune globulin (100 to 150 mg/kg per dose intravenously, given monthly) may be useful. Relapses occur primarily in those not treated to achievement of negative quantitative assays. Thus, we treat intravenously until viremia has cleared and follow-up with secondary prophylaxis with oral valganciclovir for 3 to 6 mo. This approach has resulted in rare relapses and appears to decrease emergence of antiviral resistance. Relapse is more common in those failing to seroconvert during prophylaxis. In the face of neutropenia (*e.g.*, induced by immunosuppressive agents such as azathioprine, MMF, sirolimus, antibody therapies, or other agents), the use of reduced doses of ganciclovir to avoid exacerbation of neutropenia may contribute to the risk for ganciclovir resistance.

Alternative therapies (not Food and Drug Administration–approved for use in solid organ transplant recipients) include foscarnet, cidofovir, and leflunomide; these are reserved for treatment of antiviral resistance. Foscarnet is active against most ganciclovir-resistant strains of CMV but has neurotoxicity and renal toxicity with severe magnesium wasting. Cidofovir has been used in renal transplant recipients, however often with nephrotoxicity. Both foscarnet and cidofovir may exhibit synergistic nephrotoxicity with calcineurin inhibitors. Combination therapy (ganciclovir and foscarnet) has been used for such individuals given the toxicities of each alternative agent and the antiviral synergy (77). Leflunomide has been approved for immune suppression and treatment of rheumatologic diseases; it also appears to be helpful in organ transplantation (78) and have useful activity against CMV (79–82) (and possibly BK polyomavirus (83)).

The role of oral valganciclovir in treatment of invasive disease has not been well studied. Some relapses occur after oral therapy of gastrointestinal CMV disease. Microbiologic assays using blood samples are unreliable in gastrointestinal disease and repeat endoscopy is needed to demonstrate resolution of infection. The optimal dose of valganciclovir for *prophylaxis* in renal transplant recipients merits study. Although 900 mg/d orally is approved, many, if not most, centers use 450 mg/d orally, given the anticipated reduced creatinine clearance, the cost of the medication, and the frequency of neutropenia. Given the impact of CMV infection on graft survival, formal measurement of the creatinine clearance helps assure appropriate dosing.

HSV

HSV infection is a common early infection after organ transplantation, with secretion of virus in the throats of the majority

of seropositive individuals. Disease may be more severe, invasive, and prolonged in transplant recipients (84). Transmission of HSV with an allograft has been reported (85). HSV lesions may present as mild oral or lip ulcers or vaginal lesions that should prompt HSV testing. A direct fluorescent antibody (DFA) or Tzanck smear from a vesicle or ulcer often provides rapid diagnosis. Acyclovir and related drugs (valacyclovir, famciclovir) are mainstays of HSV treatment. Ganciclovir and foscarnet also treat HSV. A small subset of immunocompromised patients (approximately 3.5%) carry ACV-resistant HSV strains (86). HSV esophagitis may present with superficial, punched-out lesions that may be superinfected with *Candida*. HSV is the most common form of encephalitis in transplant recipients. HSV PCR and cultures from cerebrospinal fluid can assist diagnosis. Diffuse interstitial pneumonitis may complicate disseminated disease. Multivisceral involvement with HSV infection is often fatal.

VZV

VZV causes a spectrum of disease in solid organ transplant recipients, ranging from localized dermatomal zoster (involving a few adjoining dermatomes) to multidermatomal or disseminated zoster with or without visceral involvement. In a cohort of 869 adult solid organ transplants (434 renal transplant recipients), 7.4% of the renal transplant recipients had herpes zoster with a median time to onset of 9 mo (87). There was a high rate of cutaneous scarring (43.8%) and postherpetic neuralgia (18.8%) in renal transplant recipients (87). In seropositive pediatric patients with disseminated zoster, 3 of 19 patients (15.8%) taking MMF had generalized vesicular lesions without dermatomal distribution within 12 mo of transplantation, an uncommon event in the pre-MMF period (88). Disseminated intravascular coagulation (DIC) and hepatitis occur in up to half of these patients, with pneumonitis in 29%; overall mortality was 34% (89). Infections of the allograft and of the central nervous system as well as pancreatitis have been described.

New onset varicella infection is less common and significantly more severe in renal transplant recipients. In our center, 8 of 83 children with renal transplants required admission for primary varicella; all eight had cutaneous disease, whereas four also had evidence of visceral disease (90). Three of the eight children had disease develop despite receiving varicella zoster immune globulin (VZIG) after exposure to varicella. Two children died of complications of varicella infection despite therapy.

In immunocompromised hosts with zoster, DFA or Tzanck smears from new vesicles will assist in the diagnosis of multidermatomal or disseminated zoster. Disseminated VZV must be treated with high-dose acyclovir and reduction in immunosuppression. Therapeutic use of VZIG is not recommended for established VZV infection, but it has been used in some patients with disseminated or pulmonary disease.

Varicella vaccination in the pretransplant period may help protect this vulnerable population (87,89,91). After transplantation, most authorities defer vaccination with live vaccines; killed vaccine appears to be beneficial (92,93). (VZIG) is recom-

mended for immunocompromised individuals with exposures to varicella or zoster; protection is incomplete (94,95).

EBV/PTLD

In immunosuppressed transplant recipients, primary EBV infection (and relapses in the absence of antiviral immunity) causes a mononucleosis-type syndrome, generally presenting as a lymphocytosis with or without lymphadenopathy or pharyngitis. Meningitis, hepatitis, and pancreatitis may be also observed. Remitting-relapsing EBV infection is common in transplant recipients and may reflect the interplay between evolving or inadequate antiviral immunity and immune suppression. *This syndrome should suggest relatively excessive immune suppression.*

EBV has a central role in the pathogenesis of PTLT (96–98), although not all PTLT is EBV-related. The most clearly defined risk factor for PTLT is primary EBV infection, which increases the risk for PTLT by 10- to 76-fold (99,100). Posttransplant non-Hodgkin's lymphoma is a common complication of organ transplantation. The spectrum of disease ranges from benign polyclonal B cell infectious mononucleosis-like disease to malignant monoclonal lymphoma. The majority is of B cell origin, although T cell, NK-cell, and null cell tumors have been described. T cell PTLT has been demonstrated in 10 to 15% of cases, especially in the late transplant period; within allografts, it can be confused with graft rejection or other viral infection. Lymphomas comprise up to 15% of tumors among adult transplant recipients (51% in children), with mortality of 40 to 60%. Many deaths are associated with allograft failure after withdrawal of immune suppression during treatment of malignancy. Compared with lymphoma in the general population, PTLT has increased extranodal involvement, poorer response to conventional therapies, and poorer outcomes.

The clinical presentations of EBV-associated PTLT include: (1) unexplained fever (fever of unknown origin); (2) a mononucleosis-type syndrome with fever, malaise, with or without pharyngitis or tonsillitis (may be diagnosed incidentally in tonsillectomy specimens); (3) lymphocytosis, usually without lymphadenopathy until late in the course; (4) gastrointestinal bleeding, obstruction, perforation; (5) back pain; (6) abdominal pain or obstruction, caused by mass lesions; (7) infiltrative disease of the allograft; (8) hepatic or pancreatic dysfunction; (9) headache or other central nervous system disease; and (10) nodules on a chest x-ray.

Serologic testing is not useful for the diagnosis of acute EBV infection or PTLT. Quantitative EBV viral load testing may be helpful for the diagnosis and management of PTLT (101–104). Serial assays of whole blood may be useful in individual patients; specific diagnostic levels of viral loads are not available. EBV assays are not standardized and cannot be easily compared between centers.

EBV-negative PTLT may occur later after transplantation and may be more severe (95). The diagnosis is sometimes difficult and depends on a high index of suspicion when presented with a variety of symptoms, including hypergammaglobulinemia.

Clinical management depends on the stage of disease. In the

polyclonal form, particularly in children, reduction of immune suppression may cause PTLT to regress. In extra-nodal disease and/or monoclonal malignant forms, reduction in immune suppression is often inadequate, with alternate therapies required. Combinations of anti-B cell therapy (anti-CD20; Rituximab), chemotherapy (CHOP), irradiation (for central nervous system disease), and/or adoptive immunotherapy with stimulated T cells have been used (105–109). Cessation of immune suppression may precipitate allograft loss. However, chemotherapy will generally suffice for immune suppression and individuals with active EBV infection rarely have graft rejection until EBV infection and PTLT have resolved.

HHV-6 and HHV-7

HHV-6 and HHV-7 are increasingly recognized as pathogens in transplant recipients (5,7,10,110–112). HHV-6 and HHV-7 are homologous to CMV (113,114). Childhood infection with these viruses is common; >90% of adults are seropositive. The role of HHV-6 and HHV-7 in solid-organ transplant recipients is incompletely defined. HHV-6 has been associated with fever, rash, encephalitis, hepatitis, myelosuppression, and interstitial pneumonitis (115–119). HHV-6 and CMV are significantly and independently associated with biopsy-proven graft rejection after liver transplantation (119,120). Multiple studies report an association between CMV activity and HHV-7 (1–5); each virus may serve as a cofactor for the other.

Diagnoses of HHV-6 and HHV-7 infections are made by qualitative and quantitative molecular assays, by tissue immunohistochemistry, and/or peripheral blood mononuclear cell culture (10). Treatment includes reducing immunosuppression and antiviral agents. *In vitro*, HHV-6 and HHV-7 are most susceptible to cidofovir, with ganciclovir or foscarnet preferred because of lower nephrotoxicity (121,122). Ganciclovir used to prevent and treat CMV appears to have little effect on HHV-7 viremia (123).

HHV-8

HHV-8 is associated with Kaposi sarcoma (KS), Castleman disease, and primary effusion lymphoma in immunocompromised individuals from endemic regions. Seroconversion is common at the time of solid-organ transplantation (124,125). Transplantation-associated KS occurs in 0.2 to 5% of renal transplant recipients, varying by ethnic group and immunosuppressive regimen (126). Of all of the tumors in solid-organ transplantation, KS occurs at the shortest interval after transplant. KS progenitor cells may be transmitted from donor to recipient at the time of transplant; five of eight renal transplantation patients had posttransplant KS with genetic or antigenic markers of their matched donors (127). In addition, HHV-8 may be associated with some cases of EBV-negative PTLT (128–131). HHV-8 has also been linked with hemophagocytic syndrome, a combination of febrile hepatosplenomegaly, pancytopenia, hypofibrinemia, and liver dysfunction. Treatment usually involves reducing the immunosuppressive regimen and treating with chemotherapy or foscarnet (132).

BK Polyomavirus

BK virus is associated with a range of clinical syndromes in immunocompromised hosts: viruria and viremia, ureteral ulceration and stenosis, and hemorrhagic cystitis (133,134). The majority of patients with BK virus infections are asymptomatic. BK virus appears to achieve latency in renal tubular epithelial cells. Active infection of renal allografts has been associated with progressive loss of graft function ("BK nephropathy") in some individuals (133,134). BK nephropathy is rarely recognized in recipients of nonrenal organs (135,136). The clinical presentation of disease is usually sterile pyuria, reflecting shedding of infected tubular and ureteral epithelial cells, which are detected by urine cytology as "decoy cells." The cause of decreased renal function must be evaluated and a *choice must made between increasing immune suppression* to treat suspected graft rejection *and reducing immune suppression* to allow emergence of antiviral immunity. Patients with BK nephropathy treated for acute rejection have a high incidence of graft loss. Reducing immune suppression may stabilize renal function while risking graft rejection.

Risk factors for nephropathy are poorly defined. Several risk factors have been implicated, although there is no consensus. Nicleleit *et al.* found treatment of cellular rejection was more common in patients with BK nephropathy than in controls (137). Other studies have implicated high-dose immunosuppression (particularly tacrolimus and MMF), high-dose steroids, severe ischemia-reperfusion injury, exposure to antilymphocyte therapy, increased number of HLA mismatches between donor and recipient, cadaveric renal transplants, and presence and degree of viremia in the pathogenesis of disease. The role of specific immunosuppressive agents has not been confirmed. BK nephropathy is most often reported at centers with the most intensive immunosuppressive regimens.

Diagnostically, the use of urine cytology to detect the presence of infected decoy cells in the urine has approximately 100% sensitivity for BK virus infection (excellent screening tool) but a low (29%) positive predictive value (50,51). The use of molecular techniques to screen blood or urine has also been advocated but is more useful in management of established cases (viral clearance with therapy) than in specific diagnosis (138–142). Hirsch *et al.* showed that patients with BK nephropathy have a plasma viral load statistically significantly higher compared with patients without invasive disease (50). Rejection may co-exist with BK nephropathy; thus, renal biopsies are essential for management. Renal biopsies will demonstrate cytopathic changes in renal epithelial cells without cellular infiltration with the gradual evolution of cellular infiltration consistent with the diagnosis of interstitial nephritis. Fibrosis and calcification may be observed. Immunostaining for cross-reacting SV40 virus large T antigen demonstrates patchy staining of viral particles within tubular cells.

There is no accepted treatment for BK nephropathy other than reduction of immune suppression. Given the toxicity of calcineurin inhibitors for tubular cells and the role of injury in the activation of BK virus, as well as the need for anti-BK T cell activity, we have generally reduced these agents first while other centers advocate primary reduction of MMF.

Low-dose cidofovir has been used to treat BK nephropathy (143–146). Renal toxicity may result, especially with calcineurin inhibitors, although it is unclear how much BK infection also contributes to the renal dysfunction. Clinical studies are needed to further evaluate the efficacy of cidofovir in the treatment of BK nephropathy. Successful retransplantation has been achieved in patients with failed allografts, usually at least 6 to 12 mo after cessation of immune suppression (144,147). Le-flunomide and derivatives and fluoroquinolone antimicrobials are under investigation for BK nephropathy.

JC Virus

Infection by JC polyomavirus (JCV) has been observed in renal allograft recipients as both nephropathy (in association with BK virus or alone) (148) and/or progressive multifocal encephalopathy (149–153). JCV establishes renal latency but receptors are present in multiple tissues including in the brain. Infection of the central nervous system generally presents with focal neurologic deficits or seizures and may progress to death after extensive demyelination. Progressive multifocal encephalopathy nephropathy may be confused with calcineurin toxicity; both may respond to a reduction in drug levels.

SV40

Recent studies have reported SV40 in renal allografts from children and in the urine, blood, and kidneys of adults with focal segmental glomerulosclerosis (154). One patient with cystic fibrosis developed nephrotic syndrome 3 yr after bilateral lung transplantation and progressed to end-stage renal failure. The nephropathy was thought to be caused by SV40 (155). However, the role of SV40 in nephropathy or oncogenesis remains uncertain (155).

HBV

Before the institution of specific infection control practices (1977) and HBV vaccination (1982), 50 to 67% of hemodialysis patients had evidence of current or past infection, and 40% had new infections during the first year on dialysis (156). The current prevalence in hemodialysis patients is <5% (157). HBV infection is associated with increased morbidity and mortality after renal transplantation (158–164).

HBV reactivation has occurred in kidney transplant recipients. The risk of reactivation of HBV under long-term immunosuppression in hepatitis B core antibody-positive, hepatitis B surface antigen (HBsAg)-negative transplant recipients was evaluated over a 3-yr period in 49 transplant recipients (27 liver, 18 kidney, 4 pancreas); 37 recipients (76%) were HBsAb-positive at transplantation (165). There was no incidence of HBV reactivation defined as recurrence of HBsAg and/or HBV DNA positivity, suggesting that the risk of reactivation of HBV in hepatitis B core antibody-positive, HBsAg-negative transplant recipients was low with immunosuppression. In the absence of HBsAg positivity, the reactivation of HBV should be assessed using HBV viral loads.

Because of the risk of rejection and lack of proven efficacy, IFN- α is not recommended for HBV in renal transplant recipients (166). Lamivudine is effective in normalizing aminotrans-

ferases and eliminating HBV DNA (167,168). Lamivudine resistance has emerged; in one study of renal transplant recipients, half of the patients had resistance 17 mo after initiating therapy (169). Adefovir dipivoxil and entecavir are effective in treating lamivudine-resistant disease, best studied in the liver transplant population (170–174). Adefovir dipivoxil can be nephrotoxic (175). Combination therapy is undergoing evaluation.

Vaccination against HBV in nonimmune renal transplant candidates is essential. Compared with the immune response after immunization before transplantation, the efficacy of standard HBV vaccination is reduced when the vaccine is administered after transplant (with response rates of 5% to 15%) (92,176,177–179). Alternative vaccination strategies have been studied. Twenty liver transplant patients given extra doses of hepatitis B vaccine with one of two new adjuvants demonstrated a serologic response rate of 80% (180). Twenty-four renal transplant recipients who did not respond to intramuscular vaccine had an overall response rate of 63% to a series of eight intradermal vaccinations followed by an intramuscular vaccination (181). In hemodialysis patients given intradermal vaccination, immunity waned more rapidly (182). For immunocompromised persons, the Centers for Disease Control recommends Recombivax-HB or Engerix-B at a higher (40 μ g) dose given at one site in a four-dose schedule at 0, 1, 2, and 6 mo (183).

HCV

The incidence and prevalence of HCV infection among patients on dialysis has declined (184). In 308 dialysis centers in seven industrialized countries, the mean HCV prevalence was 13.5%, varying among countries from 2.6% to 22.9%. Many patients are infected before renal transplantation (185). HCV infection is associated with increased morbidity and/or mortality in renal transplant recipients (159,186–191). In a retrospective study on the impact of hepatitis C virus infection on kidney transplant patients >20 yr old, HCV antibody carriers had a poor survival rate (because of liver dysfunction) in the second decade compared with the noninfected group (63.9 *versus* 87.9% for 20-yr survival; $P < 0.05$) (186).

HCV infection is diagnosed serologically, although some patients with active disease and positive HCV viral load remain antibody-negative (192,193). A smaller group remains HCV serum RNA-negative and HCV liver RNA-positive (161).

IFN treatment of HCV infection carries a risk for graft rejection in renal transplant recipients and such use needs to be very carefully evaluated (186,194). This observation has stimulated studies of lower-dose IFN- α (1×10 units subcutaneously three times/wk) plus ribavirin (600 mg/d). In eleven patients completing 48 wk of such therapy, five cleared HCV RNA at the end of treatment, with sustained biochemical and virologic responses in three; three patients terminated the therapy prematurely because of acute graft failure (one case) and urosepsis (two cases) (195). When ribavirin monotherapy was used in 13 kidney transplant recipients with HCV infection and severe hepatic fibrosis, the transaminase level decreased significantly and subjects experienced histologic improvement without sig-

nificant change of serum quantitative HCV load (196). Amantadine monotherapy was not effective in small trials in HCV-infected renal transplant recipients (197).

Respiratory Viruses: Influenza, Adenovirus, Parainfluenza, Metapneumoviruses, Respiratory Syncytial Virus

Respiratory viruses are the most common community-acquired infections in transplant recipients (156). Transplant recipients tend to have a more prolonged and complicated course, with higher rates of pneumonia and bacterial and fungal superinfection.

Diagnosis of respiratory viruses within a few hours via ELISA or immunofluorescence staining is available in many centers. Viral cultures are more time-consuming and expensive. Metapneumoviruses are diagnosed using both molecular biology and culture techniques (198).

All transplant recipients should receive inactivated influenza vaccination on an annual basis, unless contraindicated by allergy. Live attenuated influenza vaccine (Flumist) should not be given to this population. There are no data to suggest that influenza vaccine precipitates graft rejection.

Transplant recipients should avoid contact with individuals with active respiratory virus infections. Antiviral medications (rimantadine, amantadine, or oseltamivir) may help prevent or reduce the severity of illness. The use of ribavirin or RSV immune globulin in adults to prevent RSV infection is unproven. Ribavirin is commonly used for documented RSV infections of the lower respiratory tract.

Parvovirus B19

Parvovirus B19 commonly causes a benign childhood infection typically manifesting as a “slapped-cheek” rash. In transplant recipients, this infection can cause erythropoietin-resistant anemia, myocarditis, pneumonitis, or pancytopenia. Direct renal involvement has been reported in renal transplant recipients with glomerulopathy and allograft dysfunction (199–201). Infections may occur in the immediate posttransplant period (200). Clinical and virologic responses to treatment with intravenous Ig are usually excellent. Parvovirus B19 infection should be actively considered in transplant patients presenting with anemia or pancytopenia and allograft dysfunction.

Human Papilloma Virus

Human papilloma virus infections can cause significant disease in renal transplant recipients, including oral, skin, genital, and rectal lesions ranging from warts and dysplasia to malignancy. Renal transplant recipients have a significantly increased risk of ano-genital cancer (202–204) and nonmelanoma skin cancer (205). Treatment requires decreasing immunosuppression, topical, or surgical treatment. Topical immunotherapies such as imiquimod should be used with caution (205–207).

Human T-Lymphotropic Virus 1 and Human T-Lymphotropic Virus 2

Human T-lymphotropic virus 1 (HTLV-I) is endemic in the Caribbean and parts of Asia (Japan) and can progress to HTLV-I-associated myelopathy/tropical spastic paraparesis or to

adult T cell leukemia/lymphoma. HTLV-II is similar to HTLV-I serologically but is less clearly associated with disease. Use of organs from such donors is avoided (208,209), because transplant recipients can experience more aggressive disease. Optimal therapy (antiretrovirals) remains to be defined (210–212).

West Nile Virus

West Nile virus was recently transmitted from one donor (likely related to a blood transfusion) to multiple recipients (60). Transplant recipients are at higher risk than the general population for meningoencephalitis after exposure (213–217). In West Nile virus endemic regions, donors should be tested for West Nile virus. The diagnosis is based on clinical suspicion and serologic or molecular testing. Treatment involves support and reduced immunosuppression.

Rabies

Rabies transmission has been reported with transplantation of organs from deceased donors. The diagnosis was confirmed in four recipients of transplanted organs and in their common donor, who was found subsequently to have serologic evidence of rabies infection (<http://www.cdc.gov/ncidod/dvrd/rabies/>). The recipients had encephalitis of unknown cause after transplantation. Rabies is acute encephalitis caused by neurotropic virus with an incubation time generally of several weeks to months. Rabies postexposure prophylaxis is highly effective in preventing rabies when administered before onset of clinical signs.

Gastrointestinal Viruses

Many viruses cause infection in renal transplant recipients. Gastrointestinal viruses such as rotavirus or Norwalk virus can cause significant diarrhea and dehydration; the diarrhea in turn can precipitate supertherapeutic or toxic levels of tacrolimus (218–220). Enteroviral infections in the summer months in the northern hemispheres are common and can have a more complicated and prolonged course in renal transplant recipients.

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