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Human Herpes Viral Infection in Adult Kidney Transplant Recipients

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Introduction

Transplant recipients are at higher risk for viral infections. When compared with the general population, they shed virus and become infected more frequently, are more likely to develop more severe disease, and may respond more slowly to standard therapy. This discussion will focus on the more common human herpes viral infections affecting kidney transplant recipients, highlighting recent advances in the prevention and treatment of disease.

Human Herpes viruses (HHV) are human, double-stranded DNA viruses. There are eight known pathogenic HHV, of which we will review HHV-1 and -2 (herpes simplex viruses [HSV] 1 and 2), HHV-3 (Varicella Zoster Virus [VZV]), HHV-4 (Epstein-Barr virus [EBV]), and HHV-5 (cytomegalovirus [CMV]).

Common risk factors for viral infection in transplant recipients include:

- The net state of immunosuppression

  The dose, duration, and temporal sequence of immunosuppressive therapy are important to consider. The use of lymphocyte depleting agents and intensified immune suppression for rejection have both been associated with higher rates of viral infection. Quantitative immunodeficiency, including low immunoglobulin levels and leukopenia, are also common in kidney transplant recipients.

- Infectious status of the donor and recipient before transplantation

  For VZV, EBV, and CMV, serological mismatch, where the recipient is seronegative (IgG negative) and the donor is seropositive (IgG positive), has been shown to be the strongest risk factor for recipient infection.

The following case will serve to illustrate some of the main points of interest on this topic.

Case

A 61-year-old Caucasian woman with a history of deceased donor kidney transplantation for end-stage renal disease secondary to autosomal dominant polycystic kidney disease, on peritoneal dialysis for three years prior to transplant, was admitted in her sixth year after transplant with pruritic and painful vesicular skin lesions, which started from the left buttock and had spread to both lower and upper extremities, torso, and her face, associated with moderate-to-severe pain and paresthesia. Eight days prior to this admission, she was evaluated and prescribed oral prednisone at an urgent care facility. Her past medical history was notable for hypertension, past CMV infection, brain aneurysm requiring clipping, cholecystectomy, chronic obstructive pulmonary disease, non-melanomatous skin cancer, and pancreatitis. With respect to her transplant history, she received a kidney from a 65-year-old deceased 4 HLA mismatch donor, CMV status (D-R+), HSV serostatus unknown. She had no history of acute rejection. She received alemtuzumab for induction at the time of transplant, and was prescribed tacrolimus and mycophenolate mofetil for maintenance immunosuppression. On physical exam, she was alert and in mild distress due to pain. Her vitals were stable. Her skin was notable for a confluent, erythematous, vesicular rash with some crusted erosions on her thighs bilaterally *(Figure 1)*, her inguinal creases, buttocks, abdomen, upper extremities, and face.

Laboratory results showed:
WBC=8.7 x 10^3/µL, Hb=12.8 g/dL, platelets=180 x 10^3/µL, Na=116 mEq/L, K=4.2 mEq/L, Cl=88 mEq/L, tCO2=21 mEq/L, BUN=28 mg/dL, creatinine=1.6 mg/dL

Treatment was initiated immediately after hospitalization for presumed disseminated herpes zoster with acyclovir 10mg/kg IV every eight hours, and her mycophenolate mofetil was discontinued. Hyponatremia and elevated serum creatinine were attributed to acute kidney injury from volume depletion and corrected with intravenous normal saline administration.

On the second day of admission, the patient became progressively confused and was febrile to 103 F. CT of the head showed no acute lesions. Cerebrospinal fluid PCR was positive for VZV. She developed an aspiration pneumonia, requiring intubation and after a prolonged hospitalization, eventually succumbed to sepsis.

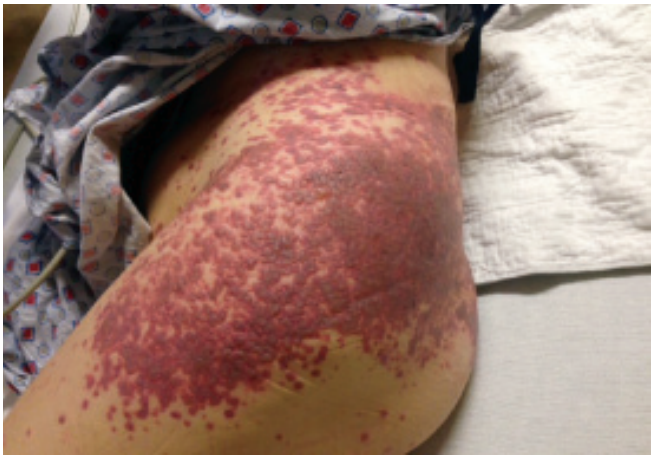

FIGURE 1

Final Diagnosis:
Disseminated HZV infection with VZV encephalitis

HHV-1 AND -2: Herpes Simplex Viruses (HSV)-1 and -2

HSV is an α-herpesvirus with a double-stranded DNA core. The prevalence of HSV-1 in the United States increases from ~40% in teenagers to ~80% by the age of 60.[1] For HSV-2, the estimated prevalence increases rapidly as individuals become sexually active, from ~2% in persons aged 14 to 19, to >25% by the fourth decade of life, with notable racial disparity and higher prevalence among minority populations.[2,3] After kidney transplantation, most cases are caused by reactivation of latent virus in the setting of immunosuppression. Primary infection transmitted by the allograft is rare but has been reported.[4] Primary infection, either from the allograft or environmental exposure, may be associated with more severe disease due to the lack of a protective immunological memory response.

Without prophylaxis, HSV infection occurs most often in the first three months. HSV is detectable in 50% to 66% of sero-positive recipients within 5 to 14 days following transplant, and symptomatic disease occurs in 35% to 68% of adult transplant recipients in the absence of prophylaxis.[5] There have been no studies to date comparing different induction or maintenance regimens with respect to risk of HSV reactivation. Historically, the anti-CD3 antibody muromonab (OKT3) and mycophenolate mofetil have been reportedly associated with increased risk of HSV reactivation, and the use of mTOR inhibitors, such as rapamycin, may be associated with a decreased risk.[6,7]

As in the general population, most patients present with painful oral or genital vesicular lesions, but complicated infections, including disseminated mucocutaneous disease, keratitis, esophagitis, hepatitis, encephalitis, or pneumonitis, do occur.[5] Fever, leukopenia, and hepatitis are the most common presenting features of disseminated disease. Organ involvement without skin or mucosal findings is rare.

Diagnosis historically was made by positive culture of vesicular fluid, mucosal swabs, cerebrospinal fluid, or urine. HSV grows well in tissue culture, and most diagnoses can be made within five days. The sensitivity of culture is best when new mucocutaneous lesions are sampled. Direct fluorescent antibody (DFA) testing can produce faster results but has a lower sensitivity (60% to 75%) when compared to culture.[8] By contrast, polymerase chain reaction (PCR) has increased sensitivity over tissue culture and is currently the diagnostic test of choice.[9] Its use with cerebrospinal fluid in the diagnosis of HSV encephalitis has a reported sensitivity of 98% and specificity approaching 100%.[10] The clinical significance of a positive HSV PCR in the blood of asymptomatic patients has not been established. The usefulness of serological testing is limited to assessing pretransplant risk of reactivation and disease. Facial involvement should prompt referral to ophthalmology for evaluation of HSV keratitis, which remains a clinical diagnosis based on slit lamp microscope findings. The Tzanck smear is not specific and no longer used as a diagnostic tool for HSV infection.

Unfortunately, there are no available vaccines to prevent primary HSV infection. A Phase I study by the NIH to evaluate a potential vaccine against HSV-2 (HSV529) is currently underway (www.ClinicalTrials.gov, NCT 01915212). Seronegative transplant recipients should be counseled about disease prevention. Because the majority of infected patients are asymptomatic, transplant recipients should consider asking new sexual partners to be tested. Barrier contraception and antiviral prophylaxis have been shown to decrease HSV-2 transmission in the nontransplant population, although these may be less effective in minority or co-infected populations.[11-15] There is no data on the efficacy of postexposure prophylaxis.

HSV prophylaxis should be considered for all kidney transplant recipients when either the donor or recipient, or both, are seropositive for HSV. Most kidney transplant recipients receive antiviral prophylaxis against EBV and CMV early after transplant with ganciclovir, acyclovir, valacyclovir, or valganciclovir. The standard doses for EBV and CMV prophylaxis are also effective for the prevention of HSV replication. In the rare patient who is not receiving either CMV or EBV prophylaxis, and who is a HSV seronegative recipient of an HSV seronegative donor organ, either prophylaxis or close clinical monitoring are reasonable clinical strategies. Prophylaxis should be considered both at the time of transplant and again during treatment for rejection episodes when immunosuppression. Because severe HSV infection occurs most often in the first month after transplant or lymphocyte depleting treatment for rejection, prophylaxis is recommended for at least one month. Patients who have symptomatic recurrence once prophylaxis is discontinued may be candidates for chronic suppressive therapy with acyclovir 200mg daily, which has been shown to be associated with development of less acyclovir-resistant disease than frequent episodic treatment.[16]

Both acyclovir and ganciclovir are effective for treatment and prophylaxis of HSV. Randomized studies performed in solid organ transplant recipients demonstrating the effectiveness of acyclovir at 200mg three or four times daily were performed in the 1980s.[17,18] Higher doses given less frequently have been shown to be effective for HSV prophylaxis in other immunocompromised patients, such as hematopoietic stem cell transplant recipients.[16,19] Valacyclovir and famciclovir are acceptable alternatives for prophylaxis.[15,20-22] Doses should be adjusted if glomerular filtration rate (GFR) is less than 50mL/min.

Mild disease can be treated with oral acyclovir, valacyclovir, or famciclovir for a minimum of five days or until lesions have crusted over. More severe mucocutaneous infection should be treated with intravenous acyclovir 5mg/kg every eight hours for 14 to 21 days.[23] The higher dose of 10mg/kg every eight hours is recommended for more severe involvement, including disseminated infection or central nervous system infection.[24] Higher doses require slower infusion to prevent crystallization in renal tubules. Doses should be adjusted for GFR. Prompt initiation of therapy is critical.[25] Reduction in immunosuppression should be considered for severe or drug-resistant infection. Rates of acyclovir resistance in immunocompromised patients have been reported at ~5% and should be considered in patients who fail to respond to appropriate therapy.[26] Mutations that decrease thymidine kinase activity are the most common cause of drug resistance. Resistance testing requires viral culture, and results may not be available for days to weeks, so empiric change to alternate therapy may need to be considered. Because acyclovir, valacyclovir, and famciclovir all rely on thymidine kinase, resistance to one implies resistance to all of the nucleoside analogues. Foscarnet is thus the recommended treatment when acyclovir resistance is suspected.[27-29] Intravenous cidofovir is another option for resistant infection, although it is associated with significant nephrotoxicity. Investigational therapies that may become available in the future include an oral lipid-ester formulation of cidofovir

(CMX-001). Pritelivir, an inhibitor of HSV-2 helicase-primase complex, has shown some efficacy in early human trials, but unexpected toxicity in non-human primates has prompted the FDA to put a hold on additional studies.[30] HSV keratitis is treated with both systemic and topical therapy. Ophthalmological consultation is recommended. Adjunctive therapy with analgesics to manage pain may be required. Occasionally, sacral nerve root involvement can be associated with urinary retention and may require temporary intermittent catheterization or placement of an indwelling catheter.

HHV-3: Varicella Zoster Virus

Varicella zoster virus is another α-herpesvirus. More than 90% of adults in the United States are exposed to VZV in childhood. Most children and young adults have been vaccinated with live virus vaccine.[31-33] The CDC estimates that more than 30% of people in the United States will suffer from an episode of herpes zoster infection in their lifetime.[34] The incidence of herpes zoster (HZ) infection in the United States has been reported between 1.5 to 5 per 1000 patient-years and increases significantly with age, presumably related to senescence of VZV-specific T-cell mediated immunity.[35,36] The incidence of VZV infection in solid organ transplant recipients is 10 to 100-fold higher than in the general population.[37] HZ is seen in approximately 10% of solid organ transplant recipients within the first four years following transplant.[38] Risk factors for HZ in kidney transplant patients have not been studied in large prospective trials. Some data suggest that the use of mycophenolate mofetil is a potential risk factor for HZ. The effect of pretransplant HZ on the development and severity of HZ posttransplant is unknown.

All patients being considered for kidney transplantation should undergo serological testing for VZV. Seronegative patients should receive two doses of the live attenuated varicella vaccine at least four weeks apart, to be given, when possible, at least four weeks prior to transplantation. Lower seroconversion rates in the setting of end-stage renal disease (~60%) have been reported in some but not all studies.[39-41] Serological testing to confirm vaccine effectiveness can be performed four weeks after the second vaccine.[42-44] If transplantation occurs within four weeks of vaccination, posttransplant prophylaxis with acyclovir or the other nucleoside analogues should prevent development of infection. A single booster vaccine dose may be considered for seropositive adults over the age of 60, although it is not universally recommended. While the risk of breakthrough infection in previously vaccinated individuals is not known, it is felt to be less severe than disease associated with natural infection with wild-type virus.[45-47] Donor transmission in solid organ transplantation is rare but has been reported.[48]

Patients with previous VZV infection or vaccination are at risk for HZ. As with primary varicella infection, the clinical course with HZ in VZV-vaccinated individuals is thought to be less severe than HZ presenting in patients previously infected with wild-type virus.[47] Transplant recipients are at high risk of developing HZ.[38] The updated December 2012 recommendations of the Advisory Committee on Immunization Practices (ACIP) recommend that all adults age 50 and older with chronic kidney disease or on dialysis, who do not have a contraindication to the HZ vaccine, be vaccinated against HZ *prior* to transplant. Vaccination with live attenuated VZV after transplantation due to potential risk of disseminated disease in immunosuppressed patients is not approved and generally not recommended, although it has been given safely in small studies to pediatric transplant recipients taking immunosuppression.[49] Current HZ vaccine contains approximately 10 times more plaque-forming units of live virus than the VZV vaccines and is contraindicated after transplant.[44] Transplant recipients should avoid contact with individuals who develop a varicella-like rash after vaccination.[50,51] The antiviral agents typically used for CMV or HSV prophylaxis early after transplant also are effective against VZV, so additional prophylaxis is not needed. Because transplant recipients remain immunosuppressed for the life of their graft, the risk of HZ persists beyond the initial posttransplant period. However, there is insufficient data to recommend long-term VZV/HZ prophylaxis.

Post-exposure prophylaxis is recommended against primary infection for seronegative patients after exposure to active VZV infection, although lack of availability may limit its use.[52] Nonspecific intravenous immunoglobulin (IVIG) may be a possible alternative to varicella-specific immunoglobulin, although it has not been studied in clinical trials. Seropositive kidney transplant recipients do not require postexposure prophylaxis. When available, varicella zoster immunoglobulin (VZIG) or VariZIG, which is a purified human varicella zoster immunoglobulin preparation, are recommended for use as soon as possible but can be used up to 10 days following exposure. If prolonged exposure, defined as household contact or significant face-to-face contact, is expected beyond three weeks, a second dose may be considered. A course of oral acyclovir, or valacyclovir which has better bioavailability, begun 3 to 7 days after exposure and continued for 21 to 28 days can be used if VZIG or VariZIG were unavailable or begun after day 10.[53] Patients should be monitored closely for the development of symptoms that should prompt admission for inpatient treatment with intravenous acyclovir. All transplant recipients admitted to the hospital with VZV or HZ infection should be placed on contact and airborne isolation until skin lesions have crusted over. Zoster lesions should be covered. Close contacts

should be evaluated for possible vaccination or prophylaxis within three days of exposure. Any patients exposed to infected individuals should also be placed on contact and airborne isolation from day 10 to 21 (day 28 if given immunoglobulin prophylaxis) following exposure.

VZV is an exclusively human infection that can result from primary infection or reactivation. It is spread through respiratory droplets or direct contact with vesicular skin lesions, with an incubation period after exposure to manifestation of disease of between 10 to 21 days. In primary infection, acute varicella, or "chickenpox," patients present with fever, constitutional symptoms, and pruritic disseminated vesicular lesions primarily over the trunk and face, with relative sparing of palms and soles, that appears over several days and presents in different stages (papules, vesicles, and crusted lesions). Symptoms usually resolve in 7 to 10 days. In transplant patients, primary infection most often occurs in the first 1 to 6 months following transplant.[54]

After primary infection, VZV establishes lifelong latency in cranial nerve and dorsal-root ganglia, and can reactivate at any time as herpes zoster (HZ) or "shingles." VZV reactivation presents with a painful vesicular rash, usually limited to one to three adjacent dermatomes that may be preceded by pain. Well-described syndromes that involve specific ganglia have been given various eponyms (e.g., Ramsay-Hunt, which involves the geniculate ganglion). Transplant recipients can have atypical presentations and are at increased risk of more severe disease following both primary and reactivation disease, especially during periods of intense immunosuppression. Up to two-thirds of reports of VZV infection in transplant recipients describe generalized cutaneous rash and/or solid organ involvement (e.g., pneumonitis, hepatitis, encephalitis, disseminated intravascular coagulation).[55] On rare occasions, visceral involvement can present before, or even in the absence of, cutaneous manifestations.[56,57] Even with the institution of prompt empiric therapy, mortality remains high with decimated disease.[58]

Typical presentations are often diagnosed clinically. Atypical and severe cases should be confirmed with definitive laboratory testing. The most sensitive test, PCR, can be used to detect virus from skin vesicles, serum, CSF, bronchoalveolar lavage, and tissue.[59,60] DFA, another quick and reliable test, can be performed from scrapings of skin at the base of vesicles.[61] Viral culture is less sensitive and requires more time to obtain results but can distinguish VZV from other herpes viruses. Serological testing is not useful in the acute setting.

Posttransplant patients who develop primary VZV infection are at risk for developing severe disseminated disease. Prompt initiation of intravenous acyclovir 10mg/kg every eight hours, ideally within 24 hours of developing rash, is recommended. Reduction in immunosuppression should be considered. Immunoglobulin therapy is not recommended for established infection. Patients with disseminated HZ, trigeminal ganglion involvement (herpes zoster ophthalmicus), or geniculate ganglion involvement (herpes zoster oticus/Ramsay-Hunt syndrome) also should be treated with intravenous acyclovir, and patients with trigeminal involvement should have prompt ophthalmological evaluation. Localized, mild disease can be treated with oral valacyclovir or famciclovir with close clinical follow-up and a low threshold to convert to intravenous therapy with any evidence of clinical deterioration. Treatment should be continued until all skin lesions are crusted over.[62,63] The use of steroids to prevent post-herpetic neuralgia may potentially increase the risk for disseminated disease and has not been proven to be of clinical benefit for decreasing long-term symptoms, and thus is not recommended.

HHV-4: Epstein-Barr Virus (EBV) and Post-Transplant Lymphoproliferative Disorder

EBV is a γ-herpesvirus with a double-stranded DNA core. Up to 90% to 95% of adults in the United States are seropositive for EBV by age 40. The disease is spread by intimate contact. Primary infection often occurs in infancy or early childhood. Infectious manifestations can vary from no symptoms to otitis, diarrheal and other GI symptoms, upper respiratory tract involvement, or classic infectious mononucleosis with cervical lymphadenopathy, pharyngitis, and severe fatigue. EBV remains latent in lymphocytes. Unlike other herpes viruses, EBV has the ability to transform and immortalize its host cells, and has been linked with a variety of malignancies, including nasopharyngeal carcinoma, Burkitt's lymphoma, and in transplant patients, posttransplant lymphoproliferative disease (PTLD). While viral reactivation in immunocompetent individuals is not common (in contrast to the other human herpes viruses), the impairment of T cell immunity following transplantation allows the replication of virus and the lymphocytes that serve as the virus' reservoir, and can lead to the development of PTLD.

PTLD is the most common malignancy, excluding non-melanomatous skin cancer, in solid organ transplant recipients, accounting for up to 20% of all malignancies. The incidence of PTLD following kidney transplant is 1% to 3%.[54,64] The type and intensity of immunosuppression may be associated with development of PTLD.[65,66] Other risk factors include active primary EBV infection at the time of transplant, co-infection with CMV and other viruses, and prior splenectomy. By far, the highest risk for PTLD is seen with seromismatching.

Seronegative recipients with a seropositive donor are at the highest risk for PTLD. Thus, PTLD is more commonly seen in pediatric and young adult transplant recipients. There is currently no universal approach to disease prevention. Some transplant centers conduct viral surveillance in high-risk patients and decrease immunosuppression with the development of viremia.[67] Effective CMV prophylaxis may decrease the risk of PTLD by limiting the effect of CMV on immune regulation.

PTLD occurs most commonly in the first year after transplant.[54] As in primary EBV infection, symptoms are often nonspecific. Some patients have no symptoms while others can develop symptoms such as fever, night sweats, anorexia and weight loss, or lymphadenopathy with local mass effect. The World Health Organization (WHO) subdivides PTLD into four types. These include:

- Infectious mononucleosis-like PTLD with plasmatic hyperplasia
- Polymorphic PTLD
- Monomorphic PTLD
- Classic Hodgkin's Lymphoma type PTLD

Younger patients are more likely to present earlier (within six months after transplant), more often with polyclonal proliferation. Older patients more often present later (six years posttransplant), with monoclonal or extranodal involvement. PTLD progresses rapidly to death unless promptly diagnosed and treated.

The diagnosis of PTLD is confirmed by biopsy. EBV viral load is commonly used to assist in diagnosis and to track response to therapy. Monitoring viral load has also been recommended by European Best Practices and by the Kidney Disease: Improving Global Outcomes (KDIGO) publications to guide preemptive therapy with reduction in immunosuppression, anti-CD20 antibody (rituximab), or donor T cells in high risk patients.[68,69] If immune-directed therapy is insufficient, traditional cancer combination chemotherapy and radiation strategies may be employed.[70,71] The optimal therapy for PTLD is tailored to the patient. Reduction in immunosuppression has been reported to lead to disease remission in 23% to 86% of patients.[54] Surgical resection may be an option for some kidney transplant recipients with disease limited to the allograft. CD20, present on many B cell clones in PTLD, activates the cell cycle, and anti-CD20 therapy with rituximab has been shown to affect complement and antibody-dependent cytotoxicity and initiate apoptosis leading to response rates over 65%.[72,73] Available antiviral drugs like acyclovir or ganciclovir are not active against the latent form of EBV, thought to be responsible for PTLD, and their use is controversial.

Outcomes with PTLD depend on the WHO type and the site of involvement, and have improved significantly in recent years. With CD20 positive disease, five-year patient survival approaches 90% and graft survival 65%. However, survival in patients with extra-allograft involvement or CD20 negative disease remains poor.[74,75] A prior history of PTLD is not a contra-indication to future transplant, and survivors of PTLD have been successfully retransplanted.[76]

HHV-5: Cytomegalovirus (CMV)

CMV is a β-herpesvirus. About 60% to 70% of the adult population in the United States is CMV seropositive, and rates are even higher, up to 90%, in the elderly and in developing countries.[77] In healthy individuals, primary CMV infection is usually asymptomatic or presents with mild nonspecific viral symptoms. Like other herpes viruses, CMV establishes latency in infected hosts and disease can occur with both primary infection and reactivation.

CMV is one of the most common infections that affect renal transplant recipients.[78] CMV infection in kidney transplant recipients can present as asymptomatic viremia, often detected during routine surveillance. When infection is associated with symptoms, it is referred to as *CMV disease.* Symptoms can range from a CMV syndrome of nonspecific flu-like symptoms with fever, malaise, and cytopenias to tissue-invasive disease that involves, most commonly, the gastrointestinal tract but can involve any organ (e.g., carditis, pneumonitis, pancreatitis, nephritis, hepatitis, myelitis, etc.). The effect of CMV infection on the immune system is also associated with a number of indirect effects in kidney transplant recipients, which include acute and chronic allograft rejection, increased susceptibility to bacterial, fungal, and other viral co-infection, and increased risk of developing PTLD. The reported magnitude of CMV's contribution to morbidity and mortality in the transplant population varies significantly, depending on the study population, differing prevention strategies, and choice of endpoints, with some studies showing no overall effect on transplant outcomes and others reporting substantial risk.[79-83]

The incidence of CMV infection varies based on the CMV serological status of recipient and donor, and the recipient's net state of immunosuppression, including treatment for episodes of acute rejection, use of lymphocyte depletion agents, and the choice and duration of preventive strategy (preemptive versus prophylactic).[84] Rates of CMV infection appear to be lower with the use of mammalian target of rapamycin (mTOR) inhibitors.[85,86] The seronegative recipient paired with the seropositive donor (D+/R-) is at highest risk for CMV infection and symptomatic disease. The rate of CMV disease

in seropositive recipients is <10% and minimal when both donor and recipient are seronegative. For high-risk patients in the absence of prophylaxis, CMV infection usually occurs within six months after transplant. The incidence of disease is lessened with prophylaxis, but it continues to occur in approximately 20% to 40% of high-risk patients, with a delayed onset of three to six months following cessation of antiviral prophylaxis. CMV reactivation or reinfection can occur in seropositive recipients (R+).

Viral culture is not clinically useful for diagnosing CMV viremia due to slow turnaround time and poor sensitivity, although it may be helpful in detecting CMV in tissue and body fluids. CMV PCR has supplanted pp65 antigen testing as the diagnostic test of choice since the WHO standardized reporting in 2010.[87,88] Definitive diagnosis of tissue-invasive disease requires histopathology, although the combination of viremia documented by either viral load or pp65 antigen testing, combined with clinical suspicion, is often sufficient grounds to make a presumptive diagnosis and begin therapy. Histopathological diagnosis of tissue-invasive disease may be necessary in seropositive recipients who often have low-to-undetectable virus levels in the blood.[89]

Serology is recommended for all kidney transplant recipients pretransplant for risk stratification. Seroconversion in previously negative recipients is thought to decrease the risk of late-onset disease, and serological testing posttransplant may be useful in guiding duration of prophylaxis.[90] Tests of CMV-specific T-cell responses, such as cytokine flow cytometry, ELISpot, and interferon-gamma release assays, are being investigated to improve CMV management after kidney transplant, although none have yet been approved in the United States for clinical use.[91]

There are two main approaches to preventing CMV disease in kidney transplant recipients. A preemptive strategy involves regular CMV PCR or antigenemia testing, usually once a week for three months after transplant, with treatment to be initiated once the virus is detected at specified thresholds. Treatment is then begun with valganciclovir 900mg po BID or IV ganciclovir 5mg/kg q12hour for at least two weeks and until two consecutive negative tests are obtained. A prophylactic strategy involves use of antiviral agents in moderate to high-risk recipients with valganciclovir 450mg to 900mg po daily for six months for D+/R-, three months for R+, and no anti-CMV prophylaxis D-/R- pairs (HSV prophylaxis with acyclovir is still recommended for D-/R- pairs.). Alternatives to valganciclovir which can be very costly (>$4000 per 1 month supply), include valacyclovir (3-8g/d), although the higher doses, especially, are associated with significant neurotoxicity. The success of a preemptive strategy depends critically on an adequate infrastructure for ensuring patient compliance with testing and sufficient staff resources to monitor and respond to weekly testing. In addition, the preemptive strategy may increase the risk to patients of the indirect effects of CMV infection.[92] In a recent Cochrane review, the prophylactic approach was found to be associated with decreased rates of CMV disease and CMV-associated mortality, and is the recommended approach of the American Society of Transplantation for all CMV D+/R- solid organ transplant recipients, as well as R+ lung transplant recipients.[93,94]

The approach to treatment of CMV infection combines antiviral therapy and, when possible, immunosuppression reduction or conversion to mTOR inhibitors. Ganciclovir 5mg/kg IV q12h is the recommended first-line treatment for severe disease and for patients with unreliable gastrointestinal absorption. For mild to moderate disease, oral valganciclovir has demonstrated similar efficacy and safety.[94] Immunoglobulin may also be added in life-threatening cases. Treatment is usually continued for at least two weeks and until two negative consecutive weekly CMV viral load or antigenemia tests. Recurrence occurs in approximately 30% of recipients, often one to three months after initial infection.[95,96] Secondary prophylaxis or continued PCR monitoring should be considered after treatment.

Ganciclovir/valganciclovir resistance occurs in up to 3% of previously treated patients.[97] Risk factors for resistance include high-risk serological mismatch, high viral load, prolonged antiviral drug use, inadequate drug dosing or drug levels, and higher degrees of immunosuppression. Drug resistance can be confirmed by genotypic assays that detect mutations in UL97 kinase (indicating ganciclovir resistance) or UL54 DNA polymerase (indicating multidrug resistance).[98] Foscarnet is the recommended treatment with UL97 kinase mutations. Cidofovir and off-label use of leflunomide, maribavir, letermovir, brincidofovir (CMX001), an oral non-nephrotoxic pro-drug of cidofovir, are being investigated as alternative therapy. Vaccine development has remained a challenge due to, among other concerns, inconsistent correlation between host immunology and protective immunity, and uncertainty regarding the appropriate viral proteins to include in a vaccine. Several CMV vaccines are in various stages of clinical development.[99-102]

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UPCOMING EVENTS

Nephrotic Syndrome Symposium: Clinical Challenges and Evidence-Based Management

A one-day event to engage glomerular kidney disease researchers, clinicians, and other health care providers. Sessions also are available for families of patients.

Course Directors: Agnieszka Swiatecka-Urban, MD, and Hoda Kaldas, MD

May 12, 2016 — 9 a.m. to 6 p.m.

Children's Hospital of Pittsburgh of UPMC

To register, visit **nephcure.org/pittsburgh-registration**.

6th Annual Acute Kidney Injury Symposium

Save The Date: Thursday, October 13, 2016

Hosted by the Pittsburgh Center for Kidney Research-O'Brien Kidney Research Core Center; Center for Critical Care Nephrology; Renal-Electrolyte Division of the Department of Medicine; Department of Critical Care Medicine; Thomas E. Starzl Transplantation Institute; and the Division of Pediatric Nephrology of the Department of Pediatrics.

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About the Renal-Electrolyte Division:

The Renal-Electrolyte Division is devoted to clinical care and academic excellence, and training the next generation of nephrologists. Our multidisciplinary approach provides the highest quality care for patients with complex kidney and electrolyte disorders.

- Inpatient services at UPMC Presbyterian tend to patients awaiting or who have received kidney transplants, and the on-site dialysis center performs nearly 10,000 dialysis treatments a year in various ICU settings.
- Outpatient services are provided at our specialized kidney and multidisciplinary clinics treating a variety of kidney and hypertensive disorders.
- The Pittsburgh Center for Kidney Research, one of seven nationwide NIDDK-supported O'Brien Kidney Research Core Centers, supports more than 140 investigators and provides funding for pilot projects.

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