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Review

Cytomegalovirus and Kidney Transplantation: An Update

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Abstract

Cytomegalovirus (CMV) infection is the most common infection affecting kidney transplant recipients [1]. CMV may be present as asymptomatic viremia or with symptoms ranging from mild to significant tissue-invasive disease [1-3]. Optimal kidney graft function and survival requires that transplant care teams carefully assess individual patient risk of CMV [2, 3]. Appropriate patient surveillance and prophylaxis are essential to ensure the best long-term kidney transplant results. Effective treatment of CMV disease requires a high degree of suspicion and appropriate diagnostic tests. The choice of antiviral medication and duration of treatment are important considerations to ensure optimal patient outcomes and kidney graft function and survival.

Keywords

Cytomegalovirus; CMV; kidney transplant; immunosuppression

1. Background

Cytomegalovirus (CMV) is a beta variant of the Herpes Simplex Virus (HSV), a highly prevalent opportunistic pathogen with over 50% of adults infected worldwide by age [1]. CMV is the most common viral infection in patients that have received a kidney transplant [2-4]. While CMV is often clinically quiescent in otherwise healthy individuals, transplant recipients are at a substantially increased risk both for reactivation of latent infection as well as primary infection due to inherent stresses and immunosuppressive therapies. The most common routes of primary CMV infection include saliva in pediatric patients or as a sexually transmitted infection in adults via saliva, semen, or vaginal secretions [4], but it may also be transmitted congenitally or during transplantation and has been shown to have widespread deleterious effects on organ function and patient mortality in high-risk populations. While CMV prophylaxis for kidney transplant recipients is widely used and has helped diminish early onset CMV disease (within 3 months of transplantation), a subsequent increase in delayed onset of clinically significant CMV disease including tissue-invasive CMV disease has been seen and is associated with allograft failure within 6 months of completing prophylactic antiviral therapy [4, 5]. In kidney transplant patients who receive CMV prophylaxis, delayed onset of CMV syndrome and CMV tissue-invasive disease are the predominant forms of CMV infectious presentation. CMV has also been linked to deadly post transplantation lymphoproliferative disease, although this is less likely to occur as a delayed onset form of CMV infection [6, 7]. Thus, CMV prophylaxis may be protective in transplant patients at particular risk of developing post transplantation lymphoproliferative disease, including patients of young age and seronegative status which are independent risk factors for this condition [8-10]. While some studies demonstrate a higher risk of graft loss associated with CMV infection [5, 8, 11, 12], others do not [13]. However, there is a consensus that CMV confers an increased risk of CMV-associated mortality in patients who have undergone kidney transplants [9, 13].

2. Risk Factors

At particular risk of CMV disease are patients with already reduced humoral immunity, such as patients undergoing solid organ transplantation, battling autoimmune diseases, or on immunosuppressive therapies for other reasons. Patients undergoing solid organ transplantation are at the highest risk for developing clinically significant CMV infection out of all patient subsets [12]. Among transplant patients, clinically significant CMV incidence varies depending on the degree of immunosuppression and time out from surgery. Those patients taking mTOR inhibitors are at a lower risk than other immunosuppressives. For kidney transplant recipients the median time for symptomatic detection from transplantation is approximately 21 months [13].

2.1 Serologic Risk Factors

Clinically significant CMV disease also varies based on serostatus and viral burden. As such, serology has a particularly useful role in determining the risk of CMV disease [10]. CMV-specific IgG antibodies are screened for in both donors and recipients, as serostatus is the most important predictor of CMV risk following transplantation [14, 15]. Solid organ transplantation, particularly from seropositive donors (D+) to seronegative patients (R-), confers the single greatest risk for both transmission and developing clinically significant CMV infection [16-19]. In seronegative recipients,

up to 58% of transplant recipients from seropositive donors (D+/R-) can develop clinically significant CMV infections if prophylactic antivirals are not taken, while this risk can be as low as 2.4% if serostatus is D-/R- [5, 20]. Higher viral burden is independently associated with increased mortality in renal transplant patients [21]. ICU stays, advanced age of donors/recipients, pregnancy, certain forms of immunosuppressive therapy, and concurrent infections such as HIV increase the risk of developing clinically significant CMV infection [3, 22, 23].

2.2 Immunosuppressive Risk Factors

CMV can invade a wide variety of cell types, contributing to the variable symptomatology seen with clinically significant CMV infection. Donor leukocytes and parenchymal cells have been implicated in the transmission process during solid organ transplantation [3]. Patients using lymphocyte-depleting antibodies for immunosuppression such as alemtuzumab and anti-thymocyte globulin (ATG) are at a higher risk for developing clinically significant CMV disease compared to patients on mTOR inhibitors such as Sirolimus or its analogs Everolimus and Temsirolimus, who have the lowest incidence of CMV disease [24]. This is thought to be due to the restoration of T-cell functionality with mTOR inhibitor therapy which helps to circumvent viral masking of CMV-specific epitopes as well as viral avoidance of T-cell recognition via intracellular sequestration of MHC Class I [25, 26]. It is important to note that mTOR inhibitors, particularly sirolimus, convey an increased risk of mortality in kidney transplant recipients compared to other forms of immunosuppression such as calcineurin inhibitors. As such they should be used judiciously based on the patient's overall health and risk of developing CMV infection compared to the risk of mortality [27-29]. In a recent study, a combination of Everolimus and calcineurin inhibitors conveyed the greatest protective effect regarding CMV infection [30]. Combined therapies including an mTOR inhibitor have consistently demonstrated the greatest protective effect in kidney transplant recipients and should be considered for those patients at highest risk (D+/R-) [31].

2.3 Socioeconomic Risk Factors

Based on US census data, mortality rates in renal transplant patients related to CMV infection vary across ethnic groups, with Native and African Americans nearly twice as likely to die from congenital CMV infection compared to Non-Hispanic Caucasians, and Non-Hispanic Caucasians in turn nearly twice as likely to die compared to Asian and Hispanic Americans [32]. Transplant patients who are Non-Hispanic Caucasians are independently at higher risk for developing potentially deadly morbidities such as post transplantation lymphoproliferative disease, the risk of which is also associated with CMV infection [7]. An increase in CMV-related death has also been noted in older populations, due to cardiovascular complications in CMV seropositive individuals over 65 compared to an age-matched seronegative cohort [33]. It is important to note that socioeconomic status plays a significant role in worsening the clinical outcomes for transplant patients with CMV infection. Patients of lower socioeconomic status from low-income households or with less than a high school education have statistically significant covariate-adjusted hazard ratios compared to age, race, gender, and urbanicity-matched seropositive patients [34]. Social determinants of health affect patient outcomes, and as such physicians should investigate to identify those patients who could be at higher risk for developing CMV-associated comorbidities.

3. Prophylaxis

There is currently no vaccine for CMV. Therefore, prophylactic measures are recommended in the form of antiviral therapy unless both donor and recipient are seronegative (D-/R-). Antiviral drugs such as ganciclovir and valganciclovir have been shown to decrease the incidence of clinically significant CMV from 25-30% to 5% in seropositive patients, although this does not correlate to a reduction in the development of delayed CMV disease in high risk (D+/R-) patients [35]. Interestingly, studies have shown that while the use of prophylaxis delays allograft rejection in kidney transplant patients, it does not stop graft loss. This is particularly true in seronegative recipients with seropositive donors (D+/R-) [36, 37].

Prophylactic recommendations vary based on serostatus in renal transplant patients. Universal prophylaxis in the form of oral valganciclovir is recommended for those patients who are seropositive, particularly if they are over 65 years old, as these patients are at highest risk of developing clinically significant CMV disease either via primary infection or latent reactivation [38, 39] Currently valganciclovir at oral doses of 900 mg daily remains the gold standard, although oral and IV ganciclovir have been used in the past [8, 39, 40]. While the efficacy of oral valganciclovir as a prophylactic therapy is not contested, the recommended duration of treatment is [41, 42]. It is important to weigh the benefits of valganciclovir with the risks when developing a treatment protocol.

For patients who are seronegative and have donors that are also seronegative (D-/R-) universal prophylaxis is not recommended. This is due to the potential adverse effects of valganciclovir including leukopenia [43]. Another reason for avoiding universal prophylaxis in these patients is the development of resistance to antivirals which is of growing concern [44]. Mutations in the UL54 gene which encodes a viral polymerase can confer resistance to valganciclovir and ganciclovir as well as Cidofovir and Foscarnet. Other mutations in the UL97 gene which encodes a protein kinase responsible for drug phosphorylation can also contribute to valganciclovir and ganciclovir resistance. Instead of universal prophylaxis in D-/R- patients, preemptive therapy of either valganciclovir or ganciclovir is preferred if CMV infection is detected during monitoring PCR or other surveillance testing in posttransplant patients [21]. Patients with an initial viral load of >2,000 copies/mL respond equivalently to preemptive treatment compared to universal prophylactic treatment procedures, and those with >3,000 copies/mL cleared their viremia with appropriate treatment [19]. Table 1 demonstrates the relationships between serostatus, risk of developing CMV disease, recommended prophylaxis protocols, and graft survival if these recommendations are followed. Of note, the highest risk serostatus (D+/R-) has the longest recommended prophylactic course as well as a lower rate of graft survival even with appropriate prophylaxis compared to all other renal transplant recipients.

Table 1 Impact of Donor/Recipient Serostatus.

Serostatus	CMV Disease Relative Risk	Prophylaxis Protocol	Recommended Treatment	Graft Survival Rate with appropriate treatment
D+/R+	Intermediate: 6.3%	Universal	3 months of daily 900 mg oral Valganciclovir	95%
D+/R-	High: 16.9%-21.4%	Universal	3-6 months of daily 900 mg oral Valganciclovir	75%
D-/R+	Intermediate: 4.9%	Universal	3 months of daily 900 mg oral Valganciclovir	94%
D-/R-	Low: 2.4%	Preemptive	As needed Oral Valganciclovir or Ganciclovir	96%

Notes: Column one differentiates between donor (D) and recipient (R) serostatus as either CMV+ or CMV-, while column two shows the risk of developing clinically significant CMV disease based on serostatus. Column three shows the current recommendations for prophylaxis based on serostatus, while column four differentiates between the recommended prophylactic treatments. Column five described the percent graft survival for each serostatus combination if the patients are treated as recommended.

4. Clinical Manifestations

The effects of Cytomegalovirus in solid organ transplant recipients and other immunocompromised populations are significant and the clinical manifestations variable. Asymptomatic viremia, seen in up to 34% of CMV-infected transplant recipients, may be present in the absence of any overt manifestations of infection [15, 45]. Symptomatic CMV infection, in addition to detectable viral replication in blood, requires the presence of clinical symptoms or illness [17, 46]. The detection of CMV in blood is further discussed below, but may include PCR or antigenemia assay. Symptomatic CMV infections (66%) are further differentiated into CMV syndrome manifesting as fever, malaise, arthralgia, leukopenia, thrombocytopenia, elevated liver enzymes, and/or myelosuppression and tissue-invasive disease such as pneumonitis, esophagitis, colitis, retinitis, encephalitis, nephritis, myocarditis, hepatitis, or pancreatitis [47, 48].

Pneumonitis is the most frequent manifestation of CMV infection in SOT patients, seen in 15% CMV-positive patients who did not receive prophylaxis [49]. Among the signs and symptoms are cough, shortness of breath, hypoxia, tachypnea, and pulmonary infiltrates on radiographic imaging in addition to the identification of CMV in bronchoalveolar lavage specimens. Unlike the pulmonary consolidation seen in bacterial infection, CMV causes diffuse interstitial infiltrates. CMV pneumonitis is associated with a greater than 60% mortality rate in solid organ transplant recipients [49]. However, mortality rates are significantly decreased with donor and recipient serostatus matching and the use of antiviral prophylaxis.

Invasion of the gastrointestinal (GI) system by CMV is the second most seen manifestation of CMV infection and is seen in 81% of cases. CMV invasion usually occurs in the lower GI tract (62%) leading to colitis or enteritis [50]; however, upper GI esophagitis is seen in 27% of cases and often appears as linear, deep, erythematous ulcerations along the wall of the esophagus [41, 49]. The diagnosis of CMV infection requires a high index of suspicion due to its variable presentation and nonspecific symptoms. Gastrointestinal infection may result in nausea, vomiting, diarrhea, weight loss and abdominal pain as well as odynophagia with esophageal involvement [51]. CMV invasion within the gastrointestinal tract is diagnosed by endoscopy with biopsy showing CMV inclusion bodies within tissue biopsy specimens stained with H&E fixed with formalin [50].

Renal involvement, seen in 14.5% of CMV-infected graft recipients, should be suspected in the presence of an unexplained elevation in creatinine with low-grade fever, diarrhea, or anemia [52].

CMV often has indirect effects in the kidney such as Renal artery stenosis, interstitial nephritis, thrombotic microangiopathy or allograft ureteral strictures or nephritis leading to kidney dysfunction [53].

Hepatitis and pancreatitis may occur as a result of invasive CMV infection and can be identified in those with CMV viremia along with elevated transaminases or lipase, respectively [54]. In addition to microbiologic and histologic features of CMV in kidney, liver, or pancreatic biopsy specimens [55].

Retinitis is another common manifestation of CMV infection in transplant recipients and usually presents with discrete foci of retinal edema and necrosis and with or without retinal hemorrhages visualized on fundoscopy [26]. The signs and symptoms of meningoencephalitis from CMV include headache, nuchal rigidity, altered mental status, or paralysis, in addition to the presence of CMV detected in cerebrospinal fluid [56]. Among the less commonly seen are cutaneous lesions which present as poorly-healing wounds unresponsive to traditional treatments and antibiotic therapies.

Because CMV tends to invade allografts, the end-organ damage most often seen is related to the graft organ. Additionally, the average time between transplantation and CMV disease differs between graft organs. The mean time to infection in kidney and liver transplant patients is 338 days and 158 days, respectively [57]. In addition to the system-specific manifestations of CMV, its immunomodulatory effects may lead to additional opportunistic infections and, regardless of the specific organ system involved, the outcome is often graft rejection or decreased graft survival [58].

In addition to CMV, several other causes of kidney dysfunction must be considered such as graft rejection, bacterial pyelonephritis, and BK virus (polyomavirus). BK virus frequently leads to graft damage in kidney transplant patients, but although BK viremia does not produce systemic symptoms, it leads to nephropathy which is as harmful to kidneys as acute rejection [59]. Pyelonephritis on the other hand, causes interstitial and tubular polymorphonuclear infiltrates rather than lymphocytes seen in CMV.

5. Diagnosis

Several methods exist for the detection and diagnosis of cytomegalovirus however, many have limited clinical utility. Among the less frequently used tests are latex agglutination, complement fixation, and enzyme-linked immunoassays (ELISA) [53]. However, CMV infection is primarily diagnosed by the detection of CMV replication in blood or tissues using nucleic acid testing (NAT), antigen testing, or viral culture.

Current primary CMV diagnostic options include the pp65 antigenemia assay and DNA polymerase chain reaction (PCR) [60]. These are aimed at the detection of viral replication which allows for early identification of disease [26]. Histology is useful in diagnosing invasive disease by identifying infected cells as well as highlighting host inflammatory responses. While the confirmation of systemic infection does not require histopathological evaluation, it is necessary to definitively diagnose end organ disease [49]. Tissue-invasive disease is diagnosed by histological examination and by the detection of CMV antigens using immunohistochemistry [61].

Cell and tissue culture, although highly specific, have very limited practical utility in the prevention, diagnosis, and treatment of CMV in SOT patients due to long turnaround time for testing. Despite the growing availability of CMV-specific cell-mediated immune assays such as interferon gamma release assay (QuantiFERON, ELISpot) for posttransplant risk stratification, their role in the prevention and treatment of CMV infection has yet to be established [12, 18, 62].

6. Treatment

Treatment of CMV viremia in the setting of renal allografts depends on both symptomatology as well as analysis of viral load assay testing. Table 2. Asymptomatic CMV viremia in the setting of a SOT patients does not have an agreed-upon threshold for viral load currently, with some studies recommending a cut-off as high as 10,000 copies/mL and others finding increased mortality, all-cause death in patients with values as low as 656 copies/mL [63, 64]. These CMV viral load values are typically determined by PCR testing [65]. Based on current literature, the accepted threshold values for asymptomatic CMV viremia appears to be determined by individual transplant institutions or may be decided upon by the primary healthcare expert managing the patient's treatment plan. Once the determined threshold of viremia is reached, the first step in clinical management is typically a reduction of immunosuppressive therapy.

Table 2 CMV Treatment.

Asymptomatic CMV Viremia	
stop antimetabolites, recheck viral load if viremia persists, initiate oral Valganciclovir 900 mg twice per day	monitor CMV viral load after 1 week following withdrawal of antimetabolite medications (via PCR viral load assay)
Symptomatic CMV Viremia	
oral Valganciclovir 900 mg BID or… intravenous Ganciclovir 5 mg/kg every 12 hours	resistance may develop via UL97, UL54 phosphorylation
intravenous Foscarnet 60 mg/kg every 8 hours (or 90 mg/kg every 12 hours)	alternative for CMV strains resistant to -ciclovir medications
intravenous Cidofovir 5 mg/kg once weekly for two week period, then once every other week thereafter	alternative for CMV strains resistant to -ciclovir medications

Alternatives, Adjuncts	
Intravenous Immunoglobulin (IVIG)	has not been fully elucidated in studies specific to CMV in renal transplant patients, but thought to have a role as an adjunct by improving host antiviral defense
Oral Maribavir	inhibits UL97 phosphotransferase - particularly useful for resistant strains, favorable side effect profile

Acceptable immunosuppressive regimens for post-renal transplantation patients include: a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate), and a glucocorticoid (prednisone) [66]. In patients with asymptomatic CMV viremia specifically ceasing administration of the antimetabolite agent, e.g. azathioprine or mycophenolate, is recommended [67]. One week after reduction of immunosuppressive therapy follow-up PCR evaluation of CMV viral load should be done to monitor if the virus has continued to replicate. If the patient subsequently demonstrates persistent CMV replication, it is recommended that oral valganciclovir therapy at a dosage of 900 mg twice daily be initiated [68]. Valganciclovir should be continued with weekly PCR viral load assays to monitor for persistent viremia until resolution [69].

Currently, there are no universally accepted management strategies on when to resume antimetabolite medications nor are there definitive titration recommendations for their resumption [65]. Some authors even recommend withholding antimetabolite medications indefinitely following CMV viremia in the setting of renal transplant patients which potentially increases the risk of renal allograft rejection. However, the presence of CMV infection and disease has been associated with the development of rejection independent of reduction of immunosuppression [70]. Clinicians should therefore determine whether to resume antimetabolite therapy on a case-by-case basis.

As with the treatment of asymptomatic CMV viremia, treatment of symptomatic CMV viremia in renal transplant patients begins with the reduction of immunosuppressive therapy. Although CMV may progress as a primary infection in these patients, the concept of diminishing immunosuppressive therapy correlates with the idea that many cases of CMV in renal transplant patients are caused by a reactivation of latent CMV [53].

For patients with mild or moderate symptoms, the treatment includes a reduction of antimetabolite immunosuppressive agents as well as initiation of oral valganciclovir 900 mg BID [71]. Mild to moderate CMV disease can encompass a wide range of symptoms, including non-specific viral signs symptoms (e.g. flu-like symptoms, malaise, fever, sinusitis, diarrhea). The distinction between CMV syndrome vs. tissue-invasive CMV disease can be made as CMV syndrome has not yet progressed to end-organ involvement [14]. The VICTOR study demonstrated comparable efficacy between oral valganciclovir and intravenous ganciclovir for treating CMV infection in these patients, [62] which has relevant treatment implications due to the ease of oral compared to IV treatment modalities while mitigating the risks of intravenous or indwelling catheter lines. Oral valganciclovir compared to IV ganciclovir may also have cost-saving implications for renal transplant patients [72, 73].

Intravenous ganciclovir at a dose of 5 mg/kg every 12 hours is the first-line treatment of tissue-Invasive CMV disease in renal allograft recipients [17]. A second-line alternative that may be used in cases resistant to ganciclovir is IV foscarnet 60 mg/kg every 8 hours (or 90 mg/kg every 12 hours). IV cidofovir 5 mg/kg once weekly for two weeks, then every other week thereafter, may also be considered in these patients [17]. Monitoring viral load helps inform duration of therapy, while monitoring cell counts and renal function helps with recognition of common side effects from these medications including leukopenia and nephrotoxicity.

Adjuncts and alternatives to current treatment regimens have emerged with the evolution of biologic medications. Intravenous immunoglobulin (IVIG) can be used as an adjunct to previously mentioned therapies, by improving host antiviral defenses [65]. However, no prospective randomized controlled trials on the use of IVIG for treatment of CMV in renal transplant patients have been completed to date. Another medication of use treating post-renal transplant CMV disease is maribavir, which is an oral medication that inhibits UL97 phosphotransferase, stopping CMV maturation/replication [74]. As previously mentioned, the main form of resistance to valganciclovir and ganciclovir involves substitutions viral UL97, UL54, or both, which is why maribavir's mechanism of action is particularly useful for treatment resistant CMV infection [75]. Maribavir is also an oral medication, and the side effect profile does not include myelosuppression and nephrotoxicity, unlike first-line treatments [76].

7. Conclusion

CMV infection, whether symptomatic or not, remains a significant challenge for kidney transplant patients and the teams treating them. The best long-term outcomes require prediction of risk and appropriate prophylaxis. Monitoring patients or asymptomatic CMV viremia should be considered for patients deemed to be at increased risk. Treatment of symptomatic CMV requires holistic consideration and balancing of immunosuppression and antiviral medications along with monitoring of viral load.

Author Contributions

Michelle F. Sener: Literature review and manuscript preparation. Thaddeus Rogozinski: Data collection, manuscript preparation. James S. George: Data collection, manuscript preparation. Deepak Mital: Manuscript editing. Douglas P. Slakey: Project design and development, manuscript preparation and editing.

Competing Interests

The authors have declared that no competing interests exist.

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