Suppression of the immune system makes solid organ transplant recipients vulnerable to opportunistic infections. Because of its serious direct and indirect effects, cytomegalovirus (CMV) is the single most important pathogen that presents a threat to transplant recipients. Most commonly CMV manifests as an asymptomatic infection or as a mononucleosis-like illness. Like all viruses, CMV is cell-associated and has the ability to spread by means of organ transplantation. As a herpesvirus, it has other characteristics that make it particularly problematic for transplant recipients. The cornerstone of viral diagnosis is the CMV viral load assay. The gold standard for treatment of CMV disease is intravenous ganciclovir, but ganciclovir-resistant infection is not an infrequent cause of late morbidity and mortality. Antiviral drugs are administered to many patients for CMV prophylaxis or preemptive therapy, but there is evidence that prevention simply delays CMV disease in predisposed patients. Strategies to reduce the incidence and impact of late-onset disease will be an important area for future research.

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recipients. Most notably, it has the ability to become latent.\(^1^3\) After the initial illness or infection, CMV can become latent in cells such as peripheral blood mononuclear and polymorphonuclear leukocytes and hematopoietic progenitor cells.\(^3\) In a person with a normally functioning immune system, CMV is kept in a subclinical state. However, as described in more detail below, in a person who is immunosuppressed, processes that release proinflammatory mediators, such as allograft rejection, sepsis, and antilymphocyte antibody (ALA) therapy, can reactivate the virus.

In up to 75% of transplant recipients, there is evidence of active CMV infection within the first posttransplant year.\(^4\) The major sources of CMV infection in these patients are the latently infected cells in the allograft from a CMV-seropositive organ donor or the endogenous latently infected cells of a seropositive recipient.\(^4^5\) (The rate of seropositivity in the general population in North America and Western Europe is 15% by age 2, 30% in young adults, and 50% to 60% in individuals older than 50 years.\(^4^6^7\)) Patients are at highest risk if they receive a CMV-positive organ from a donor and have never had experience with CMV infection themselves (CMV seronegative). One transplant center has reported a significant increase in recent years of the occurrence of donor-positive, recipient-negative transplants, from 11% in the period from 1989 to 1992 to 24% between 2000 and 2003.\(^5\) If a CMV-negative patient receives a CMV-positive organ, the risk of symptomatic CMV infection is 50% or greater.\(^2\) The risk of infection also varies with the type of organ transplanted with the highest incidence of infection observed in kidney/pancreas and lung and heart/lung transplant recipients.\(^5^9\)

**Pathogenesis of Cytomegalovirus Infection**

The initial step in the pathogenesis of CMV infection is the reactivation of the virus from latency. Several processes that are not uncommon in a transplant patient provide the appropriate environment for reactivation to occur. Processes such as allograft rejection, sepsis, and administration of ALA therapies, such as antilymphocyte globulin or muromonab-CD3, result in the release of cytokines and other proinflammatory mediators that play a role in the reactivation of virus from latency (Figure 1).\(^1^7\) The primary cytokine responsible for reactivation is tumor necrosis factor (TNF)-\(\alpha\). TNF-\(\alpha\) binds to the TNF receptor on latency infected cells and activates protein kinase C and nuclear factor \(\kappa B\) (NF-\(\kappa B\)). In turn, NF-\(\kappa B\) acts on the immediate early enhancer/promotor of the virus to activate virus replication.\(^1^0\) Stress catecholamines and proinflammatory prostaglandins also have the ability to reactivate the virus via intracellular messengers.\(^2^4^6^10\) These molecules work by increasing concentrations of cyclic adenosine monophosphate and stimulating the immediate early enhancer/promotor region of the virus.

Once CMV has reactivated and is actively replicating, the subsequent course of CMV infection is determined by the type and intensity of immunosuppression administered.\(^1^0\) ALA therapy, being a very potent form of immunosuppression that reactivates virus, increases the incidence of viremia and the incidence and severity of clinical disease.\(^1^0^2^5\) Cyclosporine A, tacrolimus, rapamycin (sirolimus), and corticosteroids do not reactivate virus but are potent in promoting viral replication and hence dissemination. ALA therapy, followed by a cyclosporine A-based or tacrolimus-based immunosuppression regimen that promotes viral replication and blocks the host’s response to the virus results in a high incidence of CMV disease. Cyclophosphamide and azathioprine are moderately potent in reactivating virus.

The major histocompatibility complex (MHC)-restricted, CMV-specific, cytotoxic T cells are crucial for controlling CMV replication.\(^1^0^6\) They limit the viral load, a key determinant of the clinical effects of CMV infection.\(^5\) The immune response that a transplant recipient is able to mount determines the clinical outcome (Figure 1). If the cellular immune response is functioning properly, viral infection will be eliminated and the host will recover. If there is a significant degree of impairment in the T-cell response, then a controlled infection may arise with persistent inflammation in the host. If the host is profoundly immunocompromised,

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**Figure 1. Some Triggers of Cytomegalovirus Reactivation**

<table>
<thead>
<tr>
<th>Stress</th>
<th>Inflammation</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>cAMP/PKA</td>
<td>TNF</td>
<td>ATG</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>PKC</td>
<td>OKT3</td>
</tr>
<tr>
<td>Stress</td>
<td>Inflammation</td>
<td>Drugs</td>
</tr>
<tr>
<td>CMV reactivation</td>
<td>Immuneological surveillance</td>
<td></td>
</tr>
<tr>
<td>Elimination</td>
<td>Controlled infection</td>
<td>Spreading</td>
</tr>
<tr>
<td>Recovery</td>
<td>Persistent inflammation</td>
<td>CMV disease</td>
</tr>
</tbody>
</table>

\(cAMP = \text{cyclic adenosine monophosphate}; \ TNF = \text{tumor necrosis factor}; \ PKC = \text{protein kinase C}; \ ATG = \text{antithymocyte globulin}; \ OKT3 = \text{muromonab-CD3}; \ NF-kB = \text{nuclear factor kB}; \ CMV = \text{cytomegalovirus.} \)

\(^*\) This figure also shows that the immune response determines the outcome of an active infection.

Adapted with permission from Reinke et al, 1999.\(^*\)
viral replication will be relentless and can cause tissue-invasive disease and possibly death.

**TWO PATTERNS OF CYTOMEGALOVIRUS INFECTION**

There are 2 patterns of CMV infection in transplant recipients: primary and recurrent infection (Table 1). In primary infection, the recipient has no prior history of CMV infection; therefore, CMV IgG is negative. More than 90% of the time, the seronegative transplant recipient is infected with virus derived from latently infected cells within the allograft. In the remainder of cases, blood products from seropositive donors that contain latent virus are the source.

Primary infection derived from blood products is a particular problem in liver transplant recipients who receive multiple blood products. In a study evaluating CMV immunoglobulin prophylaxis, about 15% of seronegative individuals who received a liver from a seronegative donor developed symptomatic disease, in the absence of CMV prophylaxis or the utilization of CMV-negative blood products. A large seroepidemiologic study involving 46 renal transplantation centers and 1245 renal transplant recipients found that about 20% of seronegative recipients of kidneys from seronegative donors who received blood transfusions seroconverted. Hence, it is common practice to transfuse transplant recipients with CMV-negative or leukoreduced blood products to prevent transmission of CMV via blood products.

With recurrent infection, replicating virus is detected in a previously infected patient in whom virus has not been detected within the past 4 weeks (Table 1). Recurrent infection can be characterized as reactivation or superinfection. With reactivation infection, the recipient has had prior CMV infection (CMV IgG is positive pretransplant) and the reactivating virus is endogenous to the transplant recipient. Superinfection occurs when the patient is reinfected with a CMV strain that is different from the patient’s original infection. Cases of superinfection have been confirmed by DNA restriction enzyme analysis. It is not known whether superinfected patients are at greater risk of clinical disease from CMV than are those with reactivation of their own endogenous virus. One study found that 40% of individuals with superinfection became symptomatic, versus none of those with endogenous reactivation. Others have failed to find such a difference. Still, the possibility of superinfection justifies the use of CMV-negative blood products even in seropositive individuals.

Several risk factors for the development of CMV disease have been identified in organ transplant recipients (Table 2). The CMV serostatus of the donor and recipient is the most important predictor of CMV disease with D+/R- recipients being at greatest risk of infection and active disease. D+/R+ and D-/R+ recipients are next in line, followed by D-/R- patients who are at least risk. Allograft rejection is a risk factor for CMV disease. As noted in the pathogenesis section, virus reactivates in the milieu of rejection. The risk also varies with the type of organ transplanted, being highest in lung or heart-lung and kidney-pancreas transplant recipients, intermediate in liver, heart, and small bowel recipients, and lowest in kidney transplant recipients. Viral kinetic studies have revealed that the risk of CMV disease increases exponentially with increases in viral load. Reactivation of other herpesviruses, HHV-6 and HHV-7, has been associated

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**Table 1. Definitions of Cytomegalovirus Infection and Disease in Solid Organ Transplant Recipients**

- CMV infection: the isolation of the CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen.
- Primary infection: the detection of CMV infection in a previously CMV-seronegative individual.
- Recurrent infection: detection of CMV in a previously seropositive individual who has not had virus detected during 4 weeks of active surveillance. Recurrent infection can result from infection with reactivated latent virus or infection with a strain that is different from the original infecting strain (superinfection).
- CMV syndrome: a viral syndrome characterized by fever, malaise, leukopenia, thrombocytopenia, atypical lymphocytosis, and elevation of hepatic transaminases plus detection of CMV in the blood.
- CMV disease: the presence of signs and symptoms of tissue injury with isolation of virus and/or histopathologic or immunohistochemical evidence of CMV infection.

CMV = cytomegalovirus.

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**Table 2. Risk Factors for Cytomegalovirus Disease in Solid Organ Transplant Recipients**

- CMV serology: D+/R- > D+/R+, D-/R+ > D-/R-
- Allograft rejection
- Type of organ transplanted: lung or heart-lung, kidney-pancreas > liver, heart, small bowel > kidney
- Greater viral load
- Concomitant herpesvirus infections: HHV-6, HHV-7
- Potent immunosuppressive drug therapy: antilymphocyte globulin, muronomab-CD3, antithymocyte globulin, alemtuzumab (anti-CD52), high-dose corticosteroids, mycophenolate mofetil

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with CMV disease. The immunomodulating properties of these viruses may enhance CMV replication. Lastly, newer, more potent immunosuppressive agents such as T-cell depleting mono- or polyclonal antibodies and newer monoclonal antibody therapies, such as alemtuzumab, increase the risk of CMV disease.

**CLINICAL EFFECTS OF CYTOMEGALOVIRUS INFECTION**

The clinical effects of CMV infection in solid organ transplant patients can be direct (clinical manifestations of the infection itself) or indirect (consequences of the infection, either immediate or downstream) (Table 3). Standardized definitions of CMV infection in transplant patients have been developed (Table 1).14,47

**DIRECT EFFECTS**

In the absence of prophylaxis, the direct clinical effects of CMV are primarily seen during the period of most intense immunosuppression, usually 1 to 4 months after transplantation. However, if the patient receives antiviral prophylaxis, CMV clinical disease is usually detected after discontinuation of prophylaxis. Because antiviral prophylaxis is commonly given for the first 90 to 100 post-transplant days, the direct clinical effects of CMV infection commonly occur 4 to 6 months after transplantation.

In patients at risk of primary CMV infection, CMV disease arises initially in the transplanted organ, resulting in problems such as pneumonitis in a lung transplant recipient or hepatitis in a liver transplant recipient. Because CMV-restricted, virus-specific CD8 cells are unable to effectively eliminate virally infected cells in the allograft in the face of MHC mismatch between the donor and recipient, the allograft becomes a privileged site for viral replication.1,10 Patients with primary infection commonly have disease manifestations outside the transplanted organ, because of the initial absence of a robust immune response that can prevent spread of the infection outside the allograft.

After the virus reactivates from latency, CMV infection initially manifests as a febrile illness. One of the most common presentations of CMV infection in organ transplant recipients is the CMV syndrome. The CMV syndrome is characterized by fever, anorexia, malaise, myalgia, and arthralgia. Organ transplant patients with the CMV syndrome resemble normal hosts with CMV mononucleosis, however, splenomegaly and lymphadenopathy typically are absent. Laboratory abnormalities may include 5% to 10% atypical lymphocytes on a blood smear, leukopenia, thrombocytopenia, and hepatic transaminase elevations. In a patient with the CMV syndrome, CMV is present in the blood and is detected by blood viral culture, antigenemia assay, or via a DNA- or RNA-based assay.

If unchecked by the immune system and by antiviral therapy, the CMV syndrome may progress to tissue-invasive disease. CMV disease occurs when CMV infects an end organ and causes tissue injury that results in manifestations of organ dysfunction (Table 1). Examples of end-organ manifestations of CMV infection include esophagitis, gastritis, colitis, pancreatitis, nephritis, myocarditis, or encephalitis. CMV retinitis is a rare manifestation of CMV infection in organ transplant recipients, occurs late after the time of transplant (>6 months after transplant), and is much more common in patients with AIDS.

Infection of the gastrointestinal tract is one of the most common manifestations of tissue-invasive disease caused by CMV infection. Gastrointestinal CMV disease presents with functional disturbances of the upper and/or lower gastrointestinal tract. The stomach appears to be a frequent site of symptomatic CMV infection associated with nausea, a sense of abdominal fullness, emesis, and, occasionally, dysphagia. Frank ulceration, hemorrhage and perforation of the colon, and, more rarely, pneumatoisis intestinalis may occur. It is noteworthy that CMV infection of the gut can occur in the absence of fever, leukopenia, or other manifestations of CMV disease and without viremia. Therefore, definite diagnosis of CMV disease of the gastrointestinal tract may require detection of CMV in biopsy tissue.

The “lethal CMV syndrome” has been described.14 The syndrome begins with fever and leukopenia and progresses rapidly to severe pulmonary and hepatic dysfunction, central nervous system abnormalities, gastrointestinal hemorrhage, and death. Death usually is the result of bowel hemorrhage. This syndrome rarely is encountered today because preventive measures are wide-
ly employed and the diagnosis of CMV is often considered in a transplant patient who presents with fever and leukopenia. Treatment is often instituted empirically if the clinical suspicion for CMV disease is high.

**CASE PRESENTATION**

A 43-year-old white man with type 1 diabetes mellitus presented with a 3-week history of low-grade fever, intermittent nausea, abdominal pain with cramping, diarrhea, and poor appetite. He had undergone a simultaneous kidney-pancreas transplant 5 years prior and had allograft dysfunction due to chronic rejection and polyomavirus nephropathy. His immunosuppressive medications were prednisone 5 mg/day, mycophenolate mofetil 2 g/day, and tacrolimus 1 mg/day (level = 4.8 ng/dL). On physical examination, the patient was ill-appearing with a temperature of 99.8°F, and he was orthostatic per blood pressure measurements. Several aphthous ulcers involving the oral mucosa were present. His abdomen was nontender with hyperactive bowel sounds and with no masses or hepatosplenomegaly. The laboratory results are provided in Table 4.

Upper and lower endoscopies were performed, and the mucosa was reported to be macroscopically normal. However, histopathologic examination revealed large, cytomegalic cells with characteristic eosinophilic, intranuclear inclusions and inflammatory cells (Figure 2). The patient’s CMV antigenemia assay was positive at 52 CMV antigen-positive nuclei detected/150,000 cells examined. He was started on intravenous (IV) ganciclovir, and his flulike symptoms and diarrhea improved promptly. The patient’s viral blood culture grew CMV 12 days after admission.

The above case presentation is an example of a typical and common presentation of CMV infection in an organ transplant recipient—a flulike illness accompanied by gastrointestinal symptoms. As mentioned previously, CMV infection usually occurs in the early post-transplant period (1 to 6 months after transplantation). However, the above patient presented 5 years after transplantation and likely did so because of chronic allograft rejection that required increased amounts of immunosuppressive therapy.

The primary care provider may encounter organ transplant patients with excellent graft function in the early post-transplant period or later in the post-transplant course when primary care issues are addressed in stable patients. Organ transplant recipients, subsequently found to have CMV infection, are not infrequently initially diagnosed with a non-CMV viral illness or a possible bacterial infection for which they are prescribed antibiotic therapy. Hence, the primary care provider should maintain a high degree of suspicion for the diagnosis of CMV infection in at-risk patients. A quantitative CMV viral load that detects viremia or an antigenemia assay should be obtained to attempt to make a diagnosis of active CMV infection (see Diagnosis of CMV section). In certain instances, such as CMV disease of the gas-

| Table 4. Clinical Effects of Cytomegalovirus Infection in Transplant Recipients |
|-----------------|-----------------|
| WBC             | 7010/mm³        |
| Platelets       | 198,000/mm³     |
| Hemoglobin      | 7.5 g/dL        |
| Hematocrit      | 23.3 %          |
| Liver function tests | Normal       |
| Albumin         | 3.3 g/dL        |
| Blood urea nitrogen | 76 mg/dL  |
| Creatinine      | 6.7 mg/dL       |
| Bicarbonate     | 14 mEq/L        |
| Glucose         | 101 mg/dL       |
| Urinalysis      | 1+ protein, 1-2 WBC, no bacteria |
| Fecal leukocytes| Negative        |
| Hemoccult       | Negative        |
| Clostridium difficile antigen assay | Negative |
| Ova & parasite test | Negative    |
| Pretransplant CMV IgG | Positive |

WBC = white blood cells; CMV = cytomegalovirus

Figure 2. Cytomegalic Cells With Eosinophilic Intranuclear Inclusions and Inflammatory Infiltrates in the Colonic Mucosa of a Kidney-Pancreas Recipient With Cytomegalovirus Infection

Arrows point to cytomegalovirus-infected cells with eosinophilic intranuclear inclusions. Thinner arrows point to inflammatory cells. Image provided courtesy of Dr Elizabeth Montgomery.
trointestinal tract or of the lungs, the viral load or antigenemia assay may be negative. If the clinical suspicion for CMV infection remains high and the patient has gastrointestinal or pulmonary symptoms, the patient should be evaluated with the appropriate diagnostic test (e.g., endoscopy with biopsy or bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy) to make a definitive diagnosis of CMV disease. If the diagnosis of active CMV infection is made, treatment recommendations provided by an infectious diseases expert should be sought.

**INDIRECT EFFECTS**

Some experts consider the indirect effects of CMV infection to be more important and more concerning than the direct effects. The main indirect clinical effects include acute and/or chronic allograft injury or rejection, immunosuppression predisposing the patient to additional opportunistic infections, and oncogenesis (Table 3; Figure 3).

**ACUTE REJECTION AND CHRONIC GRAFT DYSFUNCTION**

A significant amount of evidence linking CMV infection with acute rejection and chronic allograft injury has accumulated. The relationship between CMV infection and rejection has been demonstrated in studies of the prevention and treatment of CMV infection. For example, in a well-designed study of renal transplant recipients, high-risk patients who received high-dose valacyclovir for CMV prophylaxis showed a significant reduction in the risk of acute rejection, compared with those who received placebo. Other studies have found an association between CMV infection and/or disease and acute or chronic rejection in renal transplant recipients. In addition, CMV infection has been identified as an independent prognostic factor for patient and graft survival.

A substantial body of research, both in animals and humans, has linked CMV infection with cardiac allograft vasculopathy in heart transplant recipients. Cardiac allograft vasculopathy is the primary cause of death in heart transplant recipients who are alive at least one year after transplantation. Clinical manifestations of cardiac allograft vasculopathy include cardiac dysfunction, sudden death, and myocardial infarction. CMV infection and pneumonitis have been linked to the bronchiolitis obliterans syndrome, which is the manifestation of chronic rejection in lung transplant recipients.

CMV has an effect on other pathogens encountered in organ transplant recipients. For example, CMV infection has been linked to graft failure in hepatitis C virus (HCV)-infected recipients of liver transplants. In one study of liver transplant recipients infected with HCV, CMV reactivation, whether the infection was subclinical or evolved into clinical disease, was highly predictive of mortality and was independently associated with allograft failure. In this study, patients with CMV disease had a trend toward a higher HCV load 16 weeks after transplantation. Hepatic fibrosis has been demonstrated to be more prominent in CMV- and HCV-infected liver transplant recipients. CMV is postulated to interact with other herpesviruses such as HHV-6 and HHV-7. Several studies have detected simultaneous herpesvirus infections in transplant recipients, which have been implicated as cofactors of graft dysfunction in renal and liver transplant recipients.

**IMMUNOSUPPRESSIVE EFFECTS**

CMV infection itself is immunosuppressive, so it predisposes patients to other opportunistic infections. Multiple mechanisms of CMV-induced immunosuppression have been proposed. CMV causes myelosuppression commonly resulting in leukopenia. In vitro studies have revealed that CMV impairs the production of cytokines by monocytes and lymphocytes, impairs the body’s response to cytokines, impairs the function of natural killer cells and cytotoxic T cells, and inhibits MHC class I and II expression, altering antigen presentation. In addition, human CMV produces a viral IL-10 homolog that is an anti-inflammatory cytokine.

Opportunistic infections with organisms such as gram-negative bacilli, *Listeria*, *Pneumocystis*, *Aspergillus*,
Cryptococcus, Candida, and Nocardia occur at a higher rate in patients who have CMV infection. Trials of CMV prophylaxis have shown a lower incidence of these opportunistic infections in patients who do not develop active CMV infection. If a transplant patient decompensates soon after an episode of CMV infection, an infection caused by one of the above pathogens should be considered in the differential diagnosis.

**Oncogenesis**

It is speculated that CMV infection plays a role in oncogenesis, as do other herpesviruses. CMV infection is particularly apt to be associated with Epstein-Barr virus-associated post-transplant lymphoproliferative disease. Patients with symptomatic CMV infection have been noted to be at a 7- to 10-fold increased risk of this complication.

**Diagnosis of Cytomegalovirus Infection**

In non-immunocompromised patients presenting with symptoms consistent with CMV infection, serologic tests often are utilized to make a probable diagnosis of acute CMV infection. Detection of CMV-specific IgM antibodies suggests recent seroconversion and acute infection. Paired serum samples revealing a 4-fold rise in CMV-specific IgG titers also would be an indication of recent infection. The serologic response lags significantly behind the time when a virologic diagnosis can be made, therefore, serology is not used for real-time diagnosis of acute disease in transplant recipients. Furthermore, in immunocompromised hosts, the antibody response can be attenuated, delayed, or totally abrogated. In an organ transplant patient, serologic tests are most useful for assessing the past experience of the recipient and of the donor and predicting the risk of subsequent clinical disease.

Guidelines of both the American Society of Transplantation (AST) and the Canadian Society of Transplantation (CST) specify that the cornerstone of diagnosis of active CMV infection is a CMV viral load assay. Standard viral cultures are too slow and insensitive to be useful for acute diagnosis of CMV infection in a transplant recipient. The pp65 antigenemia assay is a semiquantitative fluorescent assay that detects infected cells in the peripheral blood. The antigenemia assay provides an estimate of the viral load and is used for rapid diagnosis of active CMV infection and for guiding pre-emptive therapy and the duration of antiviral therapy. The limitations of the antigenemia assay include lack of standardization across centers, operator dependence, and the requirement for immediate processing.

In recent years, quantitative molecular diagnostic assays that detect CMV DNA or RNA in the peripheral blood (they detect viremia) have become the main tests employed for diagnosis of active CMV infection. In many transplant centers, the quantitative CMV DNA assay is utilized to make a rapid diagnosis of CMV infection, to monitor for infection if a preemptive antiviral strategy is employed, to assess the response to therapy and risk of relapse, and to guide the duration of antiviral therapy. In order for clinicians to administer treatment in time to have an impact on the patient’s outcome, it is crucial that laboratory results be received as soon as possible, ideally within the first 24 hours after the specimens are submitted for analysis.

The currently used viral load assays have some limitations, however. They sometimes do not detect CMV disease, especially when the infection is localized to the gastrointestinal tract or lung. When clinical suspicion for active CMV infection remains high in the setting of a negative viral load, histopathologic examination of tissue from the relevant organ remains the gold standard for diagnosis. Sensitivity is increased by using immunohistochemistry or in situ hybridization to detect viral antigens or nucleic acids within the tissue.

**Treatment of Cytomegalovirus Disease**

**Intravenous Ganciclovir**

According to US and Canadian guidelines, the gold standard for treatment of CMV disease is IV ganciclovir. The usual starting dose is 5 mg/kg every 12 hours in the setting of normal renal function, but careful monitoring is necessary. Oral ganciclovir is not recommended for treatment of active CMV infection because of its low bioavailability, which limits its viral suppressive effect. Maintenance of the correct drug level is important, because the combination of subtherapeutic dose levels and high viral load is a factor that promotes drug resistance. During active CMV infection, the doses of immunosuppressive agents should be reduced, if possible, and viral load should be monitored weekly. If renal impairment occurs, the ganciclovir dose should be adjusted. If leukopenia occurs, the addition of granulocyte colony-stimulating factor should be considered instead of dose reduction. Treatment should be continued for at least 1 week after the viral load is undetectable and/or clinical signs and symptoms have resolved. The risk of relapse is lower in patients who have no detectable CMV DNA in their blood at the end of therapy.

Valganciclovir, a prodrug of oral ganciclovir that has excellent bioavailability, is approved by the US Food and Drug Administration (FDA) for prevention of CMV infection in D+/R- kidney, pancreas, and heart transplant recipients. Valganciclovir was not FDA-approved for prevention of CMV infection in liver transplant recipients because the group of liver transplant recipients receiving valganciclovir had a higher incidence of invasive CMV disease. The safety
and efficacy of valganciclovir prophylaxis in other solid organ transplant recipients, such as lung transplant recipients, has not been established. Some centers are using valganciclovir for initial treatment of CMV disease or for early step-down therapy, based on pharmacokinetic data and on the demonstration that valganciclovir is equivalent to IV ganciclovir for treatment of CMV retinitis in patients with AIDS. However, valganciclovir is not FDA-approved for the treatment of CMV infection or disease. The role of valganciclovir in the treatment of CMV disease in transplant recipients needs further investigation.

The risks versus benefits of secondary prophylaxis after initial treatment are uncertain. It is also unclear whether the addition of polyvalent IV immune globulin or CMV hyperimmune globulin to IV ganciclovir is of any benefit.

**Ganciclovir Resistance**

In recent years, ganciclovir-resistant CMV infection has emerged as an important cause of late morbidity in solid organ transplant recipients. The patients at highest risk are CMV-negative recipients of CMV-positive organs who received highly potent immunotherapy and had high viral loads and long exposure to ganciclovir. Ganciclovir-resistant CMV is a particular problem in kidney/pancreas and lung transplant recipients, possibly because they are most immunosuppressed. Ganciclovir resistance should be suspected in patients with a stable or rising viral load or persistence of clinical symptoms after 2 weeks of appropriate IV ganciclovir therapy, and in those who develop CMV disease shortly after a prolonged course of oral or low-dose IV ganciclovir. Genotypic resistance testing (for UL97 and UL54 mutations) is available to assist with the definitive diagnosis.

Treatment of ganciclovir-resistant CMV is problematic. Depending on the type of mutation, the patient may still respond to high doses of ganciclovir. Some alternative agents, foscarnet and cidofovir, have been associated with significant toxicity, primarily renal, in transplant recipients.

**Cytomegalovirus Disease Prevention**

Antiviral drugs are commonly used for CMV disease prevention. There are 2 main strategies: universal prophylaxis and preemptive therapy. Guidelines for choosing between these strategies and for choosing a regimen have been developed by the AST and the CST (Table 5)."}

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### Prophylaxis

In the prophylaxis strategy, all or “at-risk” transplant patients receive an antiviral agent after transplantation for a defined time period, usually 100 days. The drugs that have been studied for prophylaxis are ganciclovir, valacyclovir, ganciclovir, acyclovir, and immune globulin preparations. A recent meta-analysis of 19 trials concluded that prophylaxis with acyclovir, ganciclovir, or valacyclovir significantly reduced the risk of CMV disease compared with placebo or no treatment. It also found that in direct comparisons, ganciclovir was more effective than acyclovir in preventing CMV disease, and valganciclovir and IV ganciclovir were as effective as oral ganciclovir. In addition to reducing the risk of CMV disease by 60%, treatment with these antivirals lowered all-cause mortality by 40%.

A large multicenter study comparing the efficacy and safety of valganciclovir versus oral ganciclovir for the prevention of CMV disease in D+/R- heart, liver, kidney, and pancreas transplant recipients revealed that the drugs were equally effective in preventing CMV disease. A recent study comparing oral valganciclovir prophylaxis in lung transplant recipients with IV and
oral ganciclovir prophylaxis in matched historical control patients found them to be comparably effective in preventing CMV viremia and disease. In an analysis of more than 36,000 patients treated between 1985 and 2002, CMV prophylaxis was strongly associated with graft survival in D+/R- kidney and heart transplant recipients.

**Preemptive Therapy**

Preemptive therapy involves routine laboratory screening of transplant recipients for active CMV replication; antiviral drugs are initiated only if early CMV activity is detected, while the patient is still asymptomatic. A subset of preemptive therapy, targeted prophylaxis, involves administering antiviral drugs during treatment phases associated with a high risk of CMV reactivation, for example during administration of antilymphocyte antibodies (eg, thymoglobulin, OKT3) for rejection.

An effective preemptive strategy must select the appropriate population, determine the optimal laboratory test and duration of monitoring, and identify an appropriate dose and duration of treatment with the antiviral agent. Potential benefits of preemptive therapy include avoiding unnecessary drug exposure, drug side effects and costs, and possibly a decreased risk of developing resistant CMV. Some difficulties employing such a strategy were demonstrated by Humar and colleagues who found that routine plasma viral load measurements were of only modest value in identifying patients who would benefit from preemptive therapy (their routine monitoring schedule predicted CMV disease in only 38% of patients). However, the effectiveness of this approach was demonstrated in a placebo-controlled study in which preemptive therapy with oral ganciclovir prevented CMV disease in 100% of CMV-negative patients who received livers from CMV-positive donors, significantly more than in the control group.

**Choice of Prevention Strategy**

Approaches to CMV disease prevention differ among transplantation centers, because no large, multicenter, randomized trials have compared the efficacy, safety, and cost effectiveness of different drug regimens and strategies. Preemptive therapy may decrease drug costs and toxicity, but it requires excellent logistic coordination so that physicians may obtain and act on results in a timely fashion. In addition, it can be impractical for patients who live far from the transplantation center. Prophylaxis may prevent reactivation of other viruses, including human herpesvirus 6, and may be more likely to prevent indirect effects of CMV. Guidelines published to date recommend universal prophylaxis for high-risk organ transplant recipients. Preemptive therapy is generally recommended for patients at low or intermediate risk of CMV disease.

CMV resistance has been observed with both prevention strategies. Some clinical experience suggests that prevention delays rather than prevents CMV disease in predisposed patients, and a clinical syndrome termed “late-onset CMV disease” is now recognized. Up to 20% of cases may be due to ganciclovir resistance. Strategies to reduce the incidence and impact of this syndrome will be an important area for future research.

**Conclusion**

In the past, the priority for CMV management was to address the direct effects of infection. Now, there is increasing evidence that CMV has significant indirect effects in solid organ transplant recipients. Well-designed studies are needed to delineate these effects and to find mechanistic links between the two pathoses. Prevention and treatment of CMV infection and its consequences are key to improved transplantation outcomes.

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**REFERENCES**


