Cytomegalovirus (CMV) is a ubiquitous herpes virus that, together with human herpesvirus type 6 (HHV-6) and HHV-7, belongs to the β-herpesvirus family. Like other herpes viruses, CMV establishes lifelong latent infections. Infection with CMV is common in all populations, but is infrequently associated with symptomatic illness in healthy hosts. However, CMV is a major cause of morbidity and mortality in transplant recipients. CMV infection is the single most common opportunistic infection after solid-organ transplantation and directly and indirectly affects the outcome after orthotopic liver transplantation (OLT).

Clinical Spectrum of CMV Infection After OLT

In the absence of antiviral prophylaxis, the overall incidence of documented CMV infection after OLT ranges from 23% to 85%, with approximately 50% of these patients developing clinical disease. CMV infection is defined as isolation and/or detection of the virus from any tissue or body fluids or serological conversion to CMV in a patient who was seronegative before OLT. CMV infection most commonly occurs in the first 3 months after OLT, with a peak incidence in the third and fourth week. However, only a fraction of the patients with CMV infection ultimately develop CMV disease, which is defined as CMV infection accompanied by clinical manifestations. The reasons for this disparity are discussed later (see Pathogenesis). Patients who develop CMV disease may have a distinctive viral syndrome alone or may develop organ involvement. CMV viral syndrome is manifested by fever, myalgia, malaise, leukopenia, and thrombocytopenia. Organ involvement with CMV may be localized or disseminated. Localized disease is defined as histopathologic evidence of invasion of a single organ with or without a positive viral culture of the involved tissue. Disseminated disease is defined as tissue involvement of 2 or more noncontiguous organ sites. After OLT, the liver allograft is the most common site of organ involvement. CMV hepatitis is frequently associated with a cholestatic biochemical profile characterized by marked elevations in gamma-glutamyltransferase and alkaline phosphatase levels. Biopsy shows microabscesses or microgranulomata gathered around the liver lobule. Occasional infiltrates of inflammatory cells are seen in the portal triads. CMV pneumonia, symptomatic gastrointestinal disease, and chorioretinitis can be other manifestations of organ involvement, but are less frequent after OLT than after bone marrow transplantation.

Although treatment of CMV disease with currently available antiviral agents controls the acute manifestations of the illness, it does not eradicate CMV, and hence CMV disease may recur after successful treatment of the initial episode. Recurrent CMV disease occurs at a rate of 26% to 31% after OLT. Primary CMV disease, antirejection therapy, initial episodes of multiorgan CMV disease, and CMV pneumonia have been shown to be risk factors for recurrent CMV disease. Mortality is greater in patients with recurrent disease. The optimum treatment for recurrent CMV disease is yet to be defined. Patients with 1 or more risk factors for recurrence may form a subgroup in whom increased clinical and laboratory surveillance may be warranted.

In addition to producing defined clinical symptoms and syndromes post-OLT, CMV has also been ascribed to indirectly affecting the outcome of transplantation. CMV infection contributes to an additional immunosuppressive state, rendering the liver transplant recipient more susceptible to opportunistic infections. An increased incidence of fungal, bacterial, and Pneumocystis carinii infections has been reported in patients with CMV disease. The exact mechanisms by which CMV alters the host immune system in a global manner remains unknown, although multiple mechanisms have been postulated. In addition, CMV infection has been hypothesized to enhance allograft rejection, although this is controversial. Although it has been difficult to show direct cause and effect between CMV infection and liver allograft rejection, in other types of solid-organ transplantations, decreased graft survival has been observed in patients at high risk for
CMV disease (e.g., donor CMV positive, recipient CMV negative [D+/R–]). However, the decrease in immunosuppressive therapy that is often part of the treatment regimen for CMV infection may favor rejection.

Development of CMV disease is also associated with increased long-term mortality of the transplant recipient. CMV disease also results in prolonged hospitalization and considerably impacts on the cost of OLT. It has been estimated that CMV disease can add 40% to the cost of transplantation, and it has been shown recently that its prophylaxis can be cost-effective.

Pathogenesis

Two main areas determine susceptibility to CMV infection and disease after transplantation: viral and host factors. Viral factors include the amount of virus transmitted with the transplanted organ, its reactivation from latency, and its virulence and dissemination. Primary infection occurs when a CMV-naive patient, usually defined by lack of anti-CMV antibody (seronegative), receives an allograft or blood products from a CMV-seropositive donor. Virtually any tissue or organ can contain latent or persistently replicating CMV and hence transmit CMV to the host on transplantation. Because CMV-seronegative recipients lack specific CMV immunity, extensive viral replication can occur before specific anti-CMV responses are triggered, especially in the setting of immunosuppressive pharmacological treatment. Hence, CMV infection in CMV-naive patients is almost always associated with CMV disease that is usually more severe than in patients with preexisting anti-CMV-specific immunity, probably reflecting a greater level of viral replication in the former group of patients.

Reactivation of CMV will not only occur within a newly transplanted organ carrying latent CMV, but will also occur within a CMV multiple-organ seropositive recipient. What triggers CMV reactivation from latency is relatively unknown. Initial viral transcription is highly dependent on the activation of specific transcription factors present within the cell carrying latent-integrated CMV DNA. Such transcription factors (nuclear factor kappa-B [NF-kB] and activator protein-1 [AP1], among others) are activated by inflammatory cytokines (e.g., tumor necrosis factor, interleukin-1), stress injury to the cell, and bacterial products such as lipopolysaccharide. Thus, it can be postulated that situations that lead to an increase of such stimuli result in CMV and potentially other β-herpesvirus reactivation. The use of such antilymphocyte immunoglobulin preparations as antilymphocyte globulin or OKT3, known to activate a number of inflammatory cytokines, significantly increase the risk for CMV disease. Likewise, acute fulminant hepatitis, an additional independent risk factor for CMV disease after OLT, is associated with significant release of inflammatory cytokines. Lastly, such situations as stress secondary to prolonged intra-abdominal surgery or bacterial infections, which are associated with increased levels of lipopolysaccharides, could explain their epidemiological association with an increased risk for CMV disease (Table 1).

In addition to latency, we need to postulate that CMV must also be in a state of continuous viral replication or persistence, which must be tightly controlled by specific anti-CMV immunity in the immunocompetent individual. Lack or decrease of such immunity will ultimately allow the low-grade, contained replication of CMV to increase and hence result in a greater viral burden in the transplant recipient. The effects of each immunosuppressive drug routinely used in transplantation may affect CMV replication by either directly increasing its reactivation from latency and/or acting as powerful suppressors of the immune function. Whereas cyclosporine has minimal effect on reactivation of latent virus, it interferes significantly with the ability of the host to control such infection. Steroids as monotherapy have a minimal effect on reactivation of latent CMV in vivo; however, when high doses are used, a greater incidence and increased severity of CMV disease has been observed, most likely by decreasing cellular immune function. Mycophenolate mofetil has dramatically reduced the incidence of acute allograft rejection in renal transplant

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for CMV Infection and Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor-recipient serostatus</strong></td>
</tr>
<tr>
<td>D+/R– &gt; D+R &gt; D–/R &gt; D+/R–</td>
</tr>
<tr>
<td><strong>Induction therapy with antilymphocyte agent</strong></td>
</tr>
<tr>
<td><strong>Retransplantation</strong></td>
</tr>
<tr>
<td><strong>Rejection and antirejection therapy</strong></td>
</tr>
<tr>
<td><strong>Fulminant hepatic failure</strong></td>
</tr>
<tr>
<td><strong>Hepatic artery thrombosis</strong></td>
</tr>
<tr>
<td><strong>H V-6 and H V-7 infections</strong></td>
</tr>
<tr>
<td><strong>Hepatitis C infection</strong></td>
</tr>
</tbody>
</table>
recipients, and this has been associated with an increase in the frequency and severity of CMV invasive disease. Last, the conventional antilymphocyte preparations (OKT3 and antilymphocyte globulin, among others) not only increase CMV replication by suppressing the immune system, but most importantly, by directly reactivating latent CMV by means of the activation of transcription factors.

In addition to pharmacological agents, pretransplantation and posttransplantation events that contribute to further enhance immunosuppression and/or the reactivation of latent CMV infection in the transplant recipient have been identified. For example, in liver transplant recipients, CMV disease occurring later in the posttransplantation period may be noted in association with fulminant hepatic failure, recurrent hepatitis C virus infection, HHV-6 and HHV-7 infection, and retransplantation for acute rejection.

Diagnosis

A brief summary of the diagnostic tests currently available that pertain specifically to the treatment and prevention of CMV infection are presented here. However, the reader is referred to recent reviews covering this topic.

**Viral Cultures and Antigenemia Assays**

Conventional viral culture methods aiming at observing cytopathic effect are slow and relatively insensitive. The shell vial assay has replaced conventional culture methods in most laboratories as a more rapid and sensitive type of viral culture. This assay uses a monoclonal antibody against the immediate early antigen of CMV in an indirect immunofluorescence-based test. For the diagnosis of CMV disease, it is 70% sensitive and 60% specific. This implies that a percentage of patients may have organ involvement with CMV and a recombinant negative shell vial assay in blood samples, and conversely, viremia detected by shell vial may be present in the absence of CMV disease. In addition, multiple blood cultures may be necessary to detect CMV in blood using the shell vial assay.

The presence of CMV antigenemia in blood leukocytes provides an earlier marker of active CMV infection compared with the shell vial assay. This assay uses monoclonal antibodies to detect the viral pp65 antigen, a structural late protein expressed on blood leukocytes during the early phase of the viral replication cycle. This test is limited to detection of virus in white blood cells. It gives both a qualitative and a quantitative result, which closely correlates with viremia and clinical disease severity. Although the test is highly sensitive and specific for the diagnosis of CMV infection, it is less specific for CMV disease. In addition, reproducibility between different laboratories is inconsistent and requires immediate processing of the sample.

**Nucleic Acid Amplification**

Polymerase chain reaction (PCR) has been used as a rapid diagnostic tool for CMV infection because of its extreme sensitivity and specificity in detecting viral DNA. Whereas a negative PCR test result argues strongly against the presence of CMV replication, a positive PCR result in CMV-seronegative transplant recipients is significant because it indicates primary infection. In other patients, however, the ability of the test to detect very few DNA copies raises the concern that a positive signal may not distinguish between replicating and latent virus. Reverse-transcriptase PCR selectively detects viral messenger RNA (mRNA) and hence is specific for replicating virus. It is less sensitive but more specific than the shell vial assay and the routine PCR in the diagnosis of CMV disease. Estimating viral load by quantitative PCR is the optimal manner to differentiate latent from replicating virus. PCR tests are technically challenging and need strict quality control to prevent false-positive results caused by contamination.

**Hybrid Capture CMV DNA Assay**

The hybrid capture system is a solution hybridization assay that involves amplified chemiluminescent detection. Specimens containing the target DNA hybridize with a specific CMV RNA probe complementary to the CMV genome. The resultant RNA-DNA hybrids are captured onto the surface of a tube coated with antibodies specific for RNA-DNA hybrids. The immobilized hybrids are then reacted with alkaline phosphatase-conjugated antibodies specific for the hybrids and detected with a chemiluminescent substrate. The procedure is simple, rapid, not prone to contamination risks associated with such target amplification methods as PCR, and provides a quantitative result.

A second-generation assay now available has a claimed lower detection limit of approximately 700 copies/mL of whole blood. A recent multicenter study found the Digene Hybrid Capture CMV DNA assay (version 2.0; Digene Corp, Maryland) to be very sensitive and specific for the detection of CMV viremia in various patient populations. T he high sensitivity and specificity of the Hybrid Capture assay, along with
its simplicity and flexibility, make it a clinically useful assay for the detection of CMV viremia in immunocompromised patients. Further evaluation to determine its role in predicting CMV disease and for monitoring the therapeutic response to anti-CMV therapy is needed.

The prognostic value of the currently available tests for the detection of CMV in peripheral blood and the lead time, i.e., the time between the first positive test and the appearance of clinical CMV disease, is listed in Table 2.

### Histopathologic Diagnosis

Histological diagnosis of tissue-invasive CMV disease is based on the presence of characteristic intranuclear inclusions (Cowdry type A) in enlarged cells. These findings are focal in nature and hence subject to a sampling error. Sensitivity and specificity may be enhanced by complementary use of immunostaining and in situ hybridization. The risk of an invasive procedure to obtain tissue samples also needs to be considered.

### Treatment

Treatment of CMV infection can be either preemptive, i.e., treatment of asymptomatic CMV infection to prevent the future development of clinical disease, or can be initiated at the time of CMV disease diagnosis with the goal of limiting subsequent disease severity and organ involvement. All currently available anti-CMV agents are virostatic, and their mechanism of action involves inhibition of viral replication at a specific step in the virus cycle. The inhibitory effect requires viral replication and thus these drugs are not active against latent virus. The agents currently available for the treatment of CMV are briefly described next.

#### Acyclovir and Valacyclovir

Acyclovir, an acyclic deoxyguanosine analogue, is the prototype of a group of antiviral agents that are activated by viral thymidine kinases to become inhibitors of viral DNA polymerases and block viral DNA synthesis. Although active for the treatment of other herpes viruses, such as herpes simplex and varicella zoster virus (VZV), acyclovir does not have a role in the treatment of CMV infections. Valacyclovir is the L-valine ester prodrug of acyclovir, and after oral administration, it is rapidly and extensively converted to acyclovir through first-pass metabolism. Its significantly greater oral bioavailability results in plasma acyclovir levels similar to those seen with intravenous (IV) acyclovir. It has been shown to be of value in the prevention and treatment of CMV infection in renal transplant recipients. However, there are no published data to support its role in either the prophylaxis or treatment of established CMV infection or disease in liver transplant recipients.

#### Ganciclovir and Valganciclovir

Ganciclovir was first introduced into clinical use in 1984 and forms the cornerstone of therapy for CMV disease in solid-organ transplantation. Ganciclovir, like acyclovir, is a prodrug. It is phosphorylated in infected cells by a CMV enzyme coded for by the CMV UL97 gene to ganciclovir monophosphate, subsequently to the di- and triphosphate forms by host cellular kinases. Ganciclovir triphosphate inhibits viral DNA polymerase by competitively inhibiting the incorporation of the guanosine triphosphate into elongating viral DNA.

### Table 2. Prognostic Value of Methods for Detection of CMV in Blood

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Lead Time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shell vial assay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>8-63</td>
<td>86-88</td>
<td>2-16</td>
</tr>
<tr>
<td>Urine</td>
<td>18-63</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>PCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum/plasma</td>
<td>50-100</td>
<td>45-63</td>
<td>12-16</td>
</tr>
<tr>
<td>Peripheral-blood mononuclear cell</td>
<td>20-100</td>
<td>35-91</td>
<td>14-21</td>
</tr>
<tr>
<td>Reverse transcriptase-PCR</td>
<td>17-83</td>
<td>35-97</td>
<td>0</td>
</tr>
<tr>
<td>Antigenemia</td>
<td>50-83</td>
<td>71-80</td>
<td>4-8</td>
</tr>
<tr>
<td>Hybrid Capture Assay</td>
<td>95-100</td>
<td>91-95</td>
<td>1-20</td>
</tr>
</tbody>
</table>

*Time in days from first positive test to the onset of disease.
The IV formulation is administered at a dose of 5 mg/kg every 12 hours in patients with normal renal function. The usual treatment is 14 days, although the exact duration of treatment remains an unsettled issue. Recent studies suggest that quantitation of viral DNA can be used to guide the duration of therapy. Discontinuation of ganciclovir when viral DNA is still detectable is associated with an increased relapse rate. Ganciclovir is excreted renally, and dosage adjustment is needed in the presence of renal failure. Dialysis reduces serum concentrations by 50%, and readministration of the dose is required after dialysis. Adverse effects of ganciclovir include cytopenia, nausea, diarrhea, fever, rash, and hepatic and renal dysfunction. Neutropenia is usually the dose-limiting side effect. Hematologic parameters and renal function should be monitored in patients receiving ganciclovir. There have been increasing reports of ganciclovir resistance caused by the mutation of the UL97 gene in patients with HIV. Recently, this has also been reported in solid-organ transplantation.

The oral formulation of ganciclovir is effective for the prophylaxis of CMV infection in solid-organ transplant recipients, as shown in a large, randomized, double-blinded, placebo-controlled multicenter trial of liver transplant recipients without significant myelotoxicity. As in the case of acyclovir, the oral formulation of ganciclovir cannot be recommended for the up-front treatment of CMV disease. Whether it may have value in treating asymptomatic CMV infection in a preemptive manner is unknown.

Valganciclovir, the valine ester of ganciclovir, is currently being studied. Valganciclovir has a bioavailability of approximately 70% compared with that of oral ganciclovir (~15%). Preliminary studies indicate that oral valganciclovir at a dose of 900 mg provides similar serum levels of ganciclovir as those provided by IV ganciclovir.

**Foscarnet**

Foscarnet (trisodium phosphonomoformate hexahydrate) is an inorganic pyrophosphate analogue that does not need to be phosphorylated into an active form by viral or host enzymes. Similar to ganciclovir, it inhibits viral DNA polymerase and is virustatic. Because it has significant toxicity (anemia, hypercalcemia, hypomagnesemia, renal failure, and seizures), its use is limited to patients who are intolerant of ganciclovir therapy or in whom ganciclovir has failed. IV foscarnet has been shown to be as efficacious as ganciclovir for the treatment of established CMV infection based on the experience of transplant centers in Europe.

Foscarnet is administered IV at a dose of 60 mg/kg three times daily, with dose adjustments for decreased renal function. It is important to achieve adequate hydration and to monitor electrolyte levels carefully while the patient is receiving foscarnet.

**CMV Immune Globulin**

CMV hyperimmune globulin (CMVIG) is obtained from plasma donors who have high titers of antibody to CMV. CMVIG is a 5% protein solution administered IV at a dose that varies between 50 and 150 mg/kg. In comparison to unselected IV immune globulin, it can be administered at a much smaller dosage with lower volumes and provides more predictable antibody levels. The incidence of adverse effects related to its administration is usually less than 5%, and manifestations are usually mild and include headaches, nausea, vomiting, fever, chills, myalgia, and shortness of breath. Anaphylactic reactions have very rarely been reported. Although shown to be effective in the prevention of CMV disease in kidney and liver transplant recipients, its indication as a therapeutic agent for CMV disease alone or in combination with antiviral therapy remains to be proven in randomized trials.

**Cidofovir**

Cidofovir is a nucleotide analogue that acts directly on viral DNA polymerase after phosphorylation by a cellular enzyme to an active intracellular metabolite. This drug effectively inhibits CMV replication in vitro. Its oral bioavailability is very poor and hence only an IV preparation is effective. However, it has a long half-life and can be dosed very infrequently (usually once every 2 weeks). It has been shown to be effective in the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome, but there is little experience with this agent in solid-organ transplantation. As resistance to ganciclovir emerges, it is important that more information is gathered with regard to its safety and efficacy in transplant recipients.

**New Agents**

**Antisense oligonucleotides.** Synthetic oligonucleotides represent a novel addition to currently available antiviral drugs. Antisense oligonucleotides complementary to the RNA of essential viral genes bind to the mRNA in a sequence-specific manner. As a result, they are substrates for endogenous cellular ribonuclease H, which cleaves the mRNA, and subsequently the message is degraded. Inhibition of viral replication in cell culture using synthetic oligonucleotides has been re-
ported for several viruses, including CMV.60 ISIS 2922 (Fomivirsen) has recently been approved as therapy for CMV retinitis in HIV-infected patients.

UL36ANT1, another antisense oligonucleotide complementary to the intron-exon boundary of CMV, has been shown to inhibit DNA replication of ganciclovir-resistant strains.60 The specificities and low levels of toxicities of these compounds make them attractive alternatives to other antivirals.

Adoptive transfer of CMV-specific cytotoxic T lymphocytes. Because immunosuppression has a key role in the pathogenesis of CMV disease, boosting the CMV-specific immune system after transplantation should be beneficial in decreasing CMV disease. It has been shown that class-I major histocompatibility complex-restricted cytotoxic T lymphocytes are important in the control of CMV infections in both immunocompetent and immunosuppressed hosts.61,62 Successful reconstitution of CMV-specific immunity has been achieved by the infusion of clones of CMV-specific CD8+ cytotoxic T-lymphocytes derived from their donors into allogenic bone marrow transplant recipients.63,64 This may have a role after solid-organ transplantation as well.

Treatment Strategies

At the current time, IV ganciclovir remains the standard treatment of established CMV disease in solid-organ transplantation. In uncontrolled studies, ganciclovir achieves a clinical response in 67% to 72% of the patients in both first-time and recurrent episodes of CMV disease when used at a dose of 5 mg/kg every 12 hours for a mean of 16 days.63 Despite this, the relapse rate of CMV disease remains in the range of 20% to 35%, indicating that the length or dose of treatment has not been optimized. New diagnostic techniques, such as those measuring viral load, may be useful to identify those patients in whom more aggressive treatment is required. Because testing for CMV resistance to ganciclovir is not performed routinely, the clinician needs to be aware of this possibility and initiate treatment with an alternative antiviral such as foscamet if there is strong clinical suspicion of this situation. As previously discussed, there is no evidence from controlled trials of solid-organ transplantation that the addition of CMVIG to an antiviral agent increases its efficacy. However, this practice remains in place in some solid-organ transplant programs because of the theoretical benefit of this approach and the proven superiority of the combination of CMVIG and ganciclovir alone in the treatment of CMV pneumonia in the setting of bone marrow transplantation. Last, whether the combination of 2 antivirals with different mechanisms of action could result in a more rapid clearing of the virus and thus improve the clinical outcome of the CMV-infected transplant recipient remains unknown.

CMV Prophylaxis

Currently, CMV prophylactic regimens differ widely among transplant programs, even though new, albeit small numbers of randomized controlled trials are shedding some light on the optimal preventative regimen. The numerous small studies reported in the literature are difficult to evaluate and reproduce because of the large number of variables involved, i.e., definitions of infection and disease, methods, type of transplant, and various immunosuppressive regimens. The ideal CMV prophylactic agent should be available in an oral formulation or an IV formulation that can be administered at infrequent intervals. It should be safe, with minimal requirements for laboratory evaluations and also not interact adversely with other medications used in organ transplantation. Last, its antiviral activity should cover other herpes family viruses as well as CMV, and it should be cost-effective.

The principal prophylactic strategies currently used to avoid CMV infections are described next.

Avoidance of infection. Because of the scarcity of organ donors and the wide prevalence of CMV seropositivity, protective matching of seronegative liver transplant recipients with seronegative donors is not routinely feasible in the majority of transplant programs. Another way to reduce the risk for peritransplantation CMV infection is the use of seronegative blood products. All CMV-seronegative transplant recipients should ideally receive CMV-seronegative blood. This is the simplest way to reduce the risk for primary infection in seronegative patients. This may be difficult in centers in which blood donor seropositivity is high or the demand for blood products is high, as commonly occurs soon after OLT. Use of filtered blood products or leukocyte-poor blood products in these situations is an alternative.

Active/passive immunization. Administration of a CMV vaccine to seronegative transplant recipients is theoretically a simple way to reduce the risk for CMV infection after transplantation. Administration of a live attenuated vaccine prepared from the Towne and Toledo strains of CMV has been shown to reduce disease severity among high-risk (D + R−) renal transplant recipients, although the incidence of infection and disease were not significantly reduced.66 Theoretically, although complete protection against CMV may not
be achieved by vaccination, partial immunity may suffice to prevent the development of serious manifestations of CMV infection and disease.

Both unselected immune globulin and CMVIG have been studied as prophylactic agents against CMV infection. Unselected immune globulin has not been shown to reduce CMV disease after OLT, whereas in a randomized, placebo-controlled trial, CMVIG has been shown to reduce severe CMV-associated disease in kidney and liver transplant recipients, including those receiving antilymphocyte therapy. However, the protective effect of prophylactic CMVIG was minimal.

### Table 3. Clinical Trials of Prophylaxis of CMV Infection After OLT: Universal Prophylaxis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>n (D:R)</th>
<th>Prophylaxis</th>
<th>CMV Infection (%)</th>
<th>CMV Disease (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>Prospective, randomized, ACV v no prophylaxis</td>
<td>60 (0) 60 (0)</td>
<td>ACV, 500 mg/m², q8h for 10 d followed by oral ACV, 3,200 mg/d, to complete 3 mon v no prophylaxis</td>
<td>18 v 38</td>
<td>7 v 23</td>
<td>No D·R· patients</td>
</tr>
<tr>
<td>83</td>
<td>Prospective, randomized, GCV IV v ACV IV/po</td>
<td>126 (11) 124 (10)</td>
<td>GCV, 6 mg/kg, IV d 1-30, then 6 mg/kg/d M-F d 31-100 v ACV, 10 mg/kg/IV until discharge followed by 800 mg po qid to d 100</td>
<td>5 v 38</td>
<td>8 v 10 in first 120 d 9 v 41 at 640 d</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>Prospective, randomized, GCV followed by ACV v Acyclovir alone</td>
<td>68 (7) 71 (11)</td>
<td>GCV bid IV for 14 days followed by ACV, 800 mg, po qid to complete 3 mon v ACV, 800 mg, po qid × 3 mon</td>
<td>24 v 61</td>
<td>9 v 28</td>
<td>No difference in CMV disease in R· patients</td>
</tr>
<tr>
<td>85</td>
<td>Prospective, randomized, pediatric patients (1 mo to 18 y), retransplantations excluded. IV GCV alone v IV GCV followed by ACV</td>
<td>19 (3) 10 (1)</td>
<td>IV GCV × 14 d v GCV IV × 2 wks followed by ACV, 800 mg/m², qid to complete 3 mon</td>
<td>10 v 30</td>
<td>5 v 20</td>
<td>No benefit to adding ACV</td>
</tr>
<tr>
<td>86</td>
<td>Prospective, randomized, adults and children, CMVIG + ACV v CMVIG + GCV</td>
<td>52 (9) 52 (7)</td>
<td>Sandoglobulin 2 × wk IV + ACV, 5 mg/kg/d IV followed by oral ACV at 5 mg/kg/d v sandoglobulin + GCV, 5 mg/kg/d, IV followed by oral ACV, 5 mg/kg/d, to day 90</td>
<td>Not reported</td>
<td>15 v 4</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>Prospective, randomized, excluded D·R·, GCV d 14-28 v no prophylaxis</td>
<td>33 (3) 32 (7)</td>
<td>GCV, 10 mg/kg/d, oral IV prophylaxis GCV in 3rd and 4th week v no prophylaxis</td>
<td>50 v 75</td>
<td>27 v 34</td>
<td>Incidence of CMV disease not altered by GCV d 14-28</td>
</tr>
<tr>
<td>88</td>
<td>Prospective, randomized, multicenter in US and Europe. Adults, 1st OLT, D·R· excluded, oral GCV v placebo</td>
<td>150 (3) 154 (11)</td>
<td>GCV, 1,000 mg, po bid to day 98 v placebo</td>
<td>25 v 52</td>
<td>5 v 19</td>
<td>Reduced CMV disease in high-risk group, use of ALG did not attenuate effect of oral GCV; no significant myelotoxicity as with oral GCV</td>
</tr>
<tr>
<td>89</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>25 (0) 25 (4)</td>
<td>Sandoglobulin, 500 mg/kg d 1, 7, 14, 21, 28, 42, 56, 70, 84 v placebo (albumin)</td>
<td>44 v 56</td>
<td>32 v 20</td>
<td>No benefit</td>
</tr>
<tr>
<td>86</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>69 (19) 72 (19)</td>
<td>CMVIG (MAPBL), 150 mg/kg, at 72 h after transplant, then at wk 2, 4, 6, 8, 100 mg at wk 12 and 16 v placebo (1% albumin)</td>
<td>No difference</td>
<td>19 v 31</td>
<td>Reduction in severe CMV disease</td>
</tr>
</tbody>
</table>

Abbreviations: ACV, acyclovir; GCV, ganciclovir; po, orally; q, every; qid, 4 times daily; bid, twice daily; MAPHBL, Massachusetts Public Health Biological Laboratory; ALG, antilymphocyte globulin.
in the CMV D+R− group of liver transplant recipients. Despite this, it has been shown that CMVIG prophylaxis is associated with increased survival after OLT.67 A secondary benefit of immune globulin prophylaxis is that it appears to protect against other opportunistic infections, such as fungal infection.68 The cost of CMVIG remains high, and thus its cost-effectiveness needs to be considered within each transplant program.

**Prophylaxis With Antiviral Agents**

Universal prophylaxis. Universal prophylaxis implies that all transplant recipients receive antiviral prophylaxis irrespective of the risk status for CMV disease. A relative disadvantage of this approach is that a number of patients may unnecessarily receive antiviral therapy, with associated increases in costs and side effects. Universal prophylaxis has been studied with various agents in prospective, randomized trials, listed in Table 3. Ganciclovir IV is superior to oral acyclovir when started immediately after transplantation and continued for up to 3 months. It has also been shown to be effective when administered for the first 2 weeks and followed by high-dose oral acyclovir for an additional 3 to 4 months. Unselected immune globulin is not of benefit, and although CMVIG alone reduces the incidence of severe CMV disease in all subgroups of kidney transplant recipients, it is not effective in the high-risk group (D+/R−) of liver transplant recipients.

Oral ganciclovir (3 g/d) administered as soon as the patient is able to take oral medications and continued up to day 98 post-OLT is effective in reducing the incidence of CMV infection and disease without the potential myelosuppression associated with IV ganciclovir. Importantly, oral ganciclovir is also effective in preventing disease in high-risk liver transplant recipients (D+R− patients and those receiving antilymphocyte antibodies). Its use should at least be recommended to D+/R− patients in whom the incidence of disease is greatest. The quandary is whether D+/R+ or D−/R+ should receive prophylaxis with oral ganciclovir. Based on the relatively low incidence of CMV disease in these 2 groups when not receiving prophylaxis (~25% and ~12%, respectively), a cost-effective analysis should be performed by each transplant center depending on their relative incidence of CMV disease. It is currently being debated whether such lower risk solid-organ transplant recipients would be better served by applying preemptive approaches (discussed later). Once more, the relative cost of the surveillance used in the preemptive approach and the cost of CMV disease that may occur need to be compared against the cost of prophylaxis.

Based on the current data from different randomized controlled trials and because of the relatively high incidence of CMV disease (~50% to 70% in the absence of prophylaxis) in such high-risk patients as D+/R−, the current recommendation is to provide some degree of antiviral prophylaxis to this patient risk category. However, it still remains controversial whether this is cost-effective or if patients should go without prophylaxis and be allowed to develop CMV disease or infection. In a previously published study from our group, we showed that a combination of IV ganciclovir followed by high-dose oral acyclovir was more effective than high-dose oral acyclovir in preventing CMV disease in liver transplant recipients, including the high-risk patient category, D+/R−.69 Based on these

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Type of Surveillance</th>
<th>Reference Type of Study</th>
<th>CMV Infection (%)</th>
<th>CMV Disease (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>Prospective, randomized</td>
<td>Culture for CMV of buffy coat and urine every 2-4 wk</td>
<td>Type of Surveillance n/[D+/R−]</td>
<td>Preemptive Therapy</td>
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**Abbreviation:** GCV, ganciclovir.
## Table 5. Clinical Trials of Prophylaxis of CMV Infection After OLT: Targeted Prophylaxis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study/ Targeted Patients</th>
<th>n(D−R−)</th>
<th>Prophylaxis</th>
<th>CMV Infection (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>Randomized, prospective, patients receiving OKT3 for rejection, unselected immune globulin</td>
<td>50 (14) 50 (3)</td>
<td>Lamivudine, 0.5 g/kg, on d 1, 3, 5 then weekly × 3 weeks along with ACV, 400 mg, po 5 × d for 3 months</td>
<td>36 v 42 P = NS</td>
<td>No effect on CMV infection. HSV and EBV infections reduced, fungal infections reduced</td>
</tr>
<tr>
<td>91</td>
<td>Nonrandomized, uncontrolled, patients receiving OKT3 for rejection</td>
<td>51 (8)</td>
<td>GCV, 5 mg/kg/d, IV M-F starting with OKT3 continued for 4 or more weeks after OKT3</td>
<td>Not reported</td>
<td>Uncontrolled, expensive, long duration of IV access</td>
</tr>
<tr>
<td>92</td>
<td>CMV seronegative patients, open-label, nonrandomized, patients compared with seronegative patients randomized to receive placebo in</td>
<td>21 (9) 44 (19)</td>
<td>CMVIG (MAPH BL), 150 mg/kg, within 72 h of transplant and at weeks 2, 4, 6, 8, 10 mg/kg at wk 12 and 16 v placebo (1% albumin)</td>
<td>33 v 50</td>
<td>Nonrandomized, less OKT3 use in the open-label group, 3/3 of patients in open-label group received high-dose ACV in addition to CMVIG</td>
</tr>
<tr>
<td>93</td>
<td>Prospective, randomized, CMV seronegative patients</td>
<td>22 (15) 12 (7)</td>
<td>CMVIG, 250 mg/kg/d, day 0 then 125 mg/kg every 10 d × 3 months</td>
<td>D−R− 0.27 v 86 D−R− 0.27 v 86</td>
<td>Nonrandomized, less OKT3 use in the open-label group, 3/3 of patients in open-label group received high-dose ACV in addition to CMVIG</td>
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<td>94</td>
<td>R+ patients receiving OKT3, historical controls nonrandomized</td>
<td>25 (0)</td>
<td>GCV IV, 5 mg/Hg q.12h for 14 days in patients on OKT3, 5 mg/d IV for at least 7 d</td>
<td>88 v 72 52 v 12</td>
<td>Reduction in CMV disease in seropositive patients receiving OKT3</td>
</tr>
</tbody>
</table>

Abbreviations: ACV, acyclovir; po, orally; GCV, ganciclovir; MAPH BL, Massachusetts Public Health Biological Laboratory; q, every; NS, not significant; HSV, herpes simplex virus; EBV, Epstein-Barr virus.

Data, we determined whether the incidence of CMV disease resulted in higher costs. By performing multivariate analysis, it was shown that CMV disease was the main cause for high resource utilization in a cohort of 140 liver transplant recipients. Moreover, we showed that if a high-risk patient receives prophylaxis with an effective antiviral regimen, such as the one described in the published study, there was a 40% reduction in resource utilization. These results indicate that an effective antiviral therapy is cost-effective, and prevention of CMV disease is of significant importance to decrease the overall cost of the transplant.

A recent trial of kidney transplant recipients evaluating the safety and efficacy of 8 g/d of valacyclovir has been completed, showing its efficacy in reducing CMV disease in all risk groups with an additional potential benefit of reducing acute allograft rejection.

Preemptive therapy Preemptive therapy of CMV infection involves the administration of antiviral agents to a subgroup of patients at risk before the appearance of CMV disease. The introduction of rapid and sensitive molecular diagnostic tests to detect CMV viral replication allows us to identify infection before the onset of disease. Administration of antiviral therapy at this time constitutes preemptive therapy. Compared with universal prophylaxis, and assuming that the identification at an asymptomatic stage is flawless, only patients at high risk for developing disease would receive antiviral therapy, with resultant cost savings and reduced side effects and risk for emerging drug resistance.

For preemptive therapy to be effective, careful monitoring for CMV infection before clinical disease is essential. Different tests used for early diagnosis include PCR-based assays that detect CMV DNA or RNA, antigenemia tests, and rapid viral cultures. The sensitivity, specificity, and lead time of these tests is essential. Different tests used for early diagnosis include PCR-based assays that detect CMV DNA or RNA, antigenemia tests, and rapid viral cultures. The sensitivity, specificity, and lead time of these tests is important. For preemptive therapy to be effective, careful monitoring for CMV infection before clinical disease is essential. Different tests used for early diagnosis include PCR-based assays that detect CMV DNA or RNA, antigenemia tests, and rapid viral cultures. The sensitivity, specificity, and lead time of these tests is essential. Different tests used for early diagnosis include PCR-based assays that detect CMV DNA or RNA, antigenemia tests, and rapid viral cultures. The sensitivity, specificity, and lead time of these tests is important. For preemptive therapy to be effective, careful monitoring for CMV infection before clinical disease is essential. Different tests used for early diagnosis include PCR-based assays that detect CMV DNA or RNA, antigenemia tests, and rapid viral cultures. The sensitivity, specificity, and lead time of these tests is important.
sheding detected on surveillance cultures. Hence, using less sensitive assays may miss some patients who would then develop CMV disease, and thus it is important that more sensitive techniques, such as PCR, be thoroughly evaluated in this clinical setting. However, the drawback of such techniques is its poor specificity. Quantitation of virus may be of value to discern which patients with positive PCR would ultimately develop CMV disease if not treated.

Targeted prophylaxis. Because it is known that patients are at increased risk for CMV disease after receiving antilymphocyte preparations for acute rejection,22,27 targeting these patients for CMV prophylaxis is another strategy. This strategy has been reported to be successful in renal transplant recipients.23 Similar studies have also been performed in different transplant recipients (Table 5).

Studies addressing the utility of PCR to guide preemptive therapy with ganciclovir are currently underway.

**Conclusion**

CMV infections are a significant cause of morbidity and mortality after OLT. Substantial strides have been made over the last few years in early diagnosis and monitoring of patients with CMV infection. Strategies to prevent and treat CMV infection and disease after transplantation are still in the process of evolution. Currently, IV ganciclovir is the agent of choice for the treatment of established infection. Traditionally, patients have been treated for 2 weeks. In the future, quantitation of CMV viral loads may be used to guide duration of therapy. To date, there have only been scattered reports of ganciclovir resistance in organ transplant recipients. If this occurs, then testing for resistance and such alternative agents for treatment as foscarne may be necessary.

Proven prophylactic strategies in low- and intermediate-risk groups include both IV and oral ganciclovir and CMVIG. Prolonged IV or oral ganciclovir and CMVIG have been successful in reducing CMV disease in high-risk groups (D+R- patients and those receiving antilymphocyte therapy). Better diagnostic techniques may help make prophylaxis more cost-effective by enabling preemptive therapy and eliminating the need for unnecessary prophylaxis. Successful prevention and treatment of CMV infection will have a significant impact on improving outcome after transplantation.


