

Cytomegalovirus Infection in Transplant Patients

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Objectives

1. To understand the pathogenesis of cytomegalovirus (CMV) in transplant patients.
2. To know the risk factors for CMV in this population.
3. To identify the clinical syndromes caused by CMV encountered in transplant recipients.
4. To understand the options for prophylaxis of CMV disease.
5. To understand the options for treatment of CMV disease.

Key words

cytomegalovirus; ganciclovir; immunosuppression; pneumonitis; prophylaxis; transplantation

Abbreviations

CEC = circulating endothelial cell; CMV = cytomegalovirus; NK = natural killer; PCR = polymerase chain reaction

Cytomegalovirus (CMV) is a member of the herpesvirus family and shares with other herpesviruses the capacity to remain latent after recovery from an acute infection. A low degree of viral persistence, tightly controlled by immune surveillance, may be present in infected cells. Immunosuppression after transplantation will result in enhanced viral replication and eventually in the development of CMV infection or disease.

CMV infection occurs in the majority of solid organ and bone marrow transplant recipients. It continues to be responsible for a substantial fraction of the morbidity and mortality in this population. The three major consequences of CMV infection on the transplanted organ are CMV direct damage of the organ, development of infection by opportunistic pathogens, and indirect CMV-mediated injury to the organ.

In the last decade, considerable progress has been made in elucidating risk factors for CMV disease, in rapid detection of CMV in clinical specimens and other clinical samples, and in the use of antiviral chemotherapy to prevent and treat CMV disease after transplantation. With the introduction of preventive ganciclovir therapy and a better understanding of the immunology of CMV in transplant recipients, there has been a significant change in the management of

CMV disease in these patients. This lesson discusses the impact of these advances on patient outcome after transplantation and the challenges for the next decade. We will refer here specifically to organ transplant recipients, although the majority of our comments should be applicable also to bone marrow recipients.

Epidemiology of CMV Infection in Transplant Recipients

CMV infection, defined as asymptomatic CMV excretion or viremia, occurs in the majority of transplant recipients, primarily in the first 3 months after transplantation when immunosuppression is more aggressive, but some patients develop CMV infection > 1 year posttransplant, specially if ganciclovir prophylaxis has been administered. Otherwise, symptomatic CMV disease occurs among 8 to 40% of transplant recipients, depending on the type of transplanted organ.^{1,2}

CMV may be transmitted to transplant recipients via infected donor organs or blood products, the former being the primary source of CMV infection after solid organ transplantation, and the last being the more important means of transmission in bone marrow transplantation. There are three major patterns of CMV infection in transplant recipients, each with its own rate of clinical illness. Primary infection develops when a CMV-seronegative individual receives cells latently infected with the virus from a seropositive donor followed by viral reactivation. Secondary infection or reactivation infection develops when endogenous latent virus is reactivated in a CMV-seropositive individual after transplantation. Superinfection or reinfection occurs when a seropositive recipient receives latently infected cells from a seropositive donor and the virus that reactivates after transplantation is of donor origin.

Patients with primary infection are at a higher risk of developing CMV disease than patients with secondary infection or superinfection. For example, approximately 50 to 60% of liver transplant recipients at risk for primary CMV infection, as defined by the donor being seropositive and the recipient seronegative, become clinically affected by CMV.³ Traditionally, it has been stated that approximately 20% of individuals at risk for reactivation infection become clinically ill, although the accuracy of this statement is now in question.⁴ What is less clear is whether superinfected individuals have the same risk of clinical disease from CMV as those with reactivation of their own endogenous virus.

Risk Factors for the Development of CMV Disease

Despite recent advances in prevention of CMV in transplant recipients, these patients continue being at risk of acquiring CMV disease. Any factor that increases the incidence of CMV infection increases the risk of CMV disease ([Table 1](#)). Serologic status is important, as was previously mentioned, but its influence is related to the organ transplanted. In solid organ transplantation, CMV disease is more common among patients with primary infection. In bone marrow transplantation, on the other hand, patients who are seropositive for antibody before transplant have a greater incidence of virus reactivation

compared with seronegative patients who receive granulocytes from seropositive granulocyte donors treated with high-efficiency leukocyte filters to remove the viable leukocytes.

Table 1—*Risk Factors for CMV Disease in Solid Organ and Bone Marrow Transplant Recipients*

Primary infection (donor positive/recipient negative)
Use of antilymphocyte preparations (OKT3)
Inadequate cytotoxic response
Intercurrent infection with human herpesvirus 6
Type of organ transplanted (lung, heart-lung)
Graft-vs-host disease
Use of conditioning agents

The most important exogenous factor influencing the course of CMV infection posttransplant is the type and intensity of immunosuppression administered. Steroids by themselves appear to have minimal effects in terms of reactivating latent CMV. However, the use of other immunosuppressive drugs, especially antilymphocyte preparations, is one of the more important factors.⁵ In this regard, it does not seem to be important whether the antilymphocyte antibody preparation used is polyclonal (antithymocyte globulin, antilymphocyte serum, or antilymphocyte globulin) or monoclonal (OKT3). It has been proposed that immunosuppression with tacrolimus (FK 506) may be associated with a lower incidence of CMV disease compared with cyclosporine, but this remains to be proved. Large studies are under way to evaluate the impact of newer immunosuppressive agents such as mycophenolic acid or rapamycin.⁶ Other significant risk factors for CMV disease include older patient age, use of conditioning agents for patients with leukemia, and the occurrence of acute graft-vs-host disease in these patients.

It is presumed that this proclivity to CMV disease can be explained by differences in the specific immune response to CMV after transplantation. Recent attention has been focused on the cytotoxic response to CMV-infected target cells. Patients who develop cytotoxic responses to CMV-infected target cells after transplant, mediated either by natural killer (NK) cells or by cytotoxic T lymphocytes, appear to have better survival than patients without such responses.⁷ By contrast, rising antibody titers to CMV have a lesser impact on the outcome of disease.

Other events have been recently identified as risk factors for symptomatic CMV infection. These include fulminant hepatitis before liver transplantation, occurrence of bacterial infection after transplantation, and intercurrent infection with human herpesvirus 6.² Hepatitis C virus is another controversial factor that could influence the development of CMV disease.

Clinical Manifestations

General Considerations

CMV infection exhibits a wide range of clinical manifestations, from asymptomatic infection to severe, lethal CMV disease. Patients who develop CMV disease can be further subdivided into those with and those without organ involvement. Symptomatic infection (disease) without documentation of organ involvement is usually named *viral syndrome* (fever, leukopenia, thrombocytopenia, and other constitutional symptoms such as malaise and arthralgias).

Organ involvement with CMV correlates with the organ transplanted. This means that CMV hepatitis occurs more frequently in liver transplant recipients, CMV pancreatitis in pancreas transplant recipients, CMV myocarditis in heart transplant recipients, and CMV pneumonitis in lung and heart-lung transplant recipients. This could be related to the yet-to-be-proved hypothesis regarding the issue of the viral load inherent to each organ. Another explanation would be that the allograft is more prone to be investigated by means of biopsies than other organs, giving the false impression that CMV has a predisposition to cause disease in the allograft.

Other sites of CMV disease involvement include the GI tract, gallbladder, epididymis, biliary tree, retina, skin, endometrium, and CNS. Respiratory complications related to CMV and the other visceral complications in organ transplant recipients will be commented on in more detail in the following section.

Pulmonary Manifestations of CMV Infection in Transplant Recipients

Pneumonitis is one of the most important diseases related to CMV affecting organ transplant recipients.⁸ It contributes directly and indirectly to both morbidity and mortality in these patients. In addition to actual invasive disease of the lung caused by CMV, careful studies have documented the presence of subtle abnormalities in pulmonary function in the majority of patients with CMV infection.

Clinical manifestations of pneumonitis are primarily seen in the time period 1 to 4 months posttransplant. Pneumonitis results in fever, dyspnea, and cough with findings of hypoxemia and pulmonary infiltrates. As with most viral infections, CMV usually begins insidiously with constitutional symptoms of anorexia, malaise, and fever, often accompanied by myalgias and arthralgias. Initially, dyspnea and tachypnea are not noted, but over several days progressive respiratory distress can ensue; however, most patients with CMV pneumonia experience little respiratory distress at rest. Auscultation of the lungs is usually unrevealing, and the respiratory rate is the best correlate on physical examination with the degree of respiratory embarrassment, hypoxemia, and extension of pneumonia on chest radiography.

The attack rate for CMV pneumonia is far greater in lung and heart-lung recipients than in the other organ transplant populations. In the nonpulmonary organ transplant patient, CMV causes a subacute process that evolves over several days. Although CMV pneumonia progresses rapidly to respiratory failure in some kidney, heart, or liver transplant recipients, in most individuals the lung

involvement is relatively minor at onset and would go undetected if no chest radiograph were obtained. The severe form of pneumonia is far more common in lung and heart-lung transplant patients.² The bone marrow transplant recipient is at particular risk for developing severe CMV pneumonitis. Approximately one half of marrow graft recipients develop interstitial pneumonia, usually after successful engraftment; nearly one half of these cases are associated with CMV infection. The attack rate is higher for those with underlying malignancy than for those with aplastic anemia, and the mortality rate approaches 90%.⁹ The occurrence of CMV interstitial pneumonia appears closely linked with the presence of graft-vs-host disease. In addition, recipients of marrow from CMV-seropositive donors appear more likely to develop CMV pneumonia than recipients of marrow from seronegative donors. The radiographic manifestations of CMV pneumonia in the transplant patient may take a variety of forms. By far the most common form is a bilateral, symmetrical, peribronchovascular (interstitial) and alveolar process predominantly affecting the lower lobes. Less commonly, CMV may cause a focal consolidation suggestive of bacterial or fungal disease or even a solitary pulmonary nodule. Positive gallium or indium scans of the lungs have been reported in patients with CMV pneumonitis, although such information usually adds little to the diagnostic decision-making process in most patients.

Indirect Respiratory Effects of CMV in Organ Transplant Recipients

In addition to producing pulmonary infection, CMV has been implicated in causing increased immunosuppression and secondary opportunistic lung infection in the organ transplant recipient.¹⁰ In the lung, *Pneumocystis carinii*, *Aspergillus fumigatus*, and a variety of Gram-negative pathogens are the primary culprits. Alveolar macrophage dysfunction induced by CMV (in addition to the leukopenia in the case of *Aspergillus*) appears to be an important factor in the pathogenesis of superinfection with these organisms. CMV appears to facilitate the colonization of the upper respiratory tract with Gram-negative bacilli, with these serving as the reservoir from which Gram-negative pulmonary infection is then derived.

The clinical marker that appears to identify those organ transplant patients at a higher risk for pulmonary superinfection appears to be CMV-induced leukopenia. As with other clinical manifestations of CMV, pulmonary superinfection appears to be more common in patients with primary, as opposed to reactivation, disease. In addition to the abnormalities in leukocyte number and, possibly, function induced by the virus, a variety of other defects in host defenses also play a role. Cell-mediated immunity is markedly impaired. The mechanism by which CMV causes depressed cell-mediated immunity has received extensive investigation. At present, it would appear that CMV infection is associated with suppression of both monocyte and NK cell function, and that monocyte-induced suppression of T lymphocyte function is the end result. The great majority of opportunistic lung infections occur in the subset of transplant patients with these changes in circulating T cells.¹¹

Recently, in the murine model, CMV has been shown to reactivate latent *Toxoplasma gondii* infection in the lungs, producing active pneumonia.

Pathogenically, it was suggested that a CMV-induced fall in the number of CD4-positive lymphocytes played a role in the reactivation of the protozoan, while the subsequent influx of CD8-positive cells was responsible for the active pneumonia that developed.¹² There is evidence that human herpesvirus 6 activation in the transplant patient is promoted by CMV infection, particularly primary infection; this suggests that CMV-induced traffic in lymphocytes, and the elaboration of a variety of cytokines in conjunction with it, can play a role in the pathogenesis of a variety of secondary infections in the transplant recipient. One of the most compelling pieces of evidence linking CMV infection with allograft injury is found in lung and heart-lung transplantation.¹³ Some authors have clearly linked bronchiolitis obliterans in the allograft to both symptomatic and asymptomatic infection with the virus. This appears to be the result of previous lung injury, with CMV being one of the causes of such lung injury, but clearly not the only one. CMV infection of both vascular smooth muscle and endothelium is a regular occurrence during CMV lung infection, thus providing a mechanism for vascular injury thought to be the foundation of chronic allograft injury. Indeed, CMV-infected endothelial cells can be found in the circulation, presumably providing a means of viral dissemination as well as a possible means of amplifying vascular injury at the capillary level.

Other Clinical Manifestations

In addition to the lung, CMV involves other organs. After the lung, the second major organ system to be invaded by CMV, in a fashion that can be life-threatening, is the digestive tract. The more severe form of digestive tract disease is hepatitis. Serious CMV hepatitis requiring intensive therapy is not uncommon in liver transplant patients and it typically manifests as elevated concentrations of γ -glutamyltransferase and alkaline phosphatase in addition to increased levels of transaminases. However, far more important clinically is the occurrence of infection of the gut itself. CMV can affect any segment of the GI tract, including the esophagus, stomach, and small and large intestines. The stomach appears to be the most frequent site of symptomatic CMV infection. Symptoms of GI disease include dysphagia, odynophagia, nausea, vomiting, delayed gastric emptying, abdominal pain, GI hemorrhage, and diarrhea. Endoscopic findings include erythema and diffuse, shallow erosions or localized ulcerations; however, biopsy is essential because endoscopic findings are not specific. A high index of suspicion of CMV colitis should be maintained in any transplant who presents with lower GI bleeding in the first 4 months after transplantation.

Hematologic abnormalities are common during the course of CMV infection. Small numbers of atypical lymphocytes may be detected on examination of the peripheral blood smear. The most important effects, however, are on the WBC and platelet counts. Leukopenia and/or thrombocytopenia occur in 20 to 30% of patients with CMV infection. The addition of leukopenia to fever as a manifestation of CMV infection is often the first indication that serious clinical disease is developing, and prompt and aggressive therapy is mandatory. Uncommon infectious disease syndromes occurring in the organ transplant patient as a result of CMV infection include the following: endometritis,

epididymitis, encephalitis, transverse myelitis, and skin ulcerations associated with an apparent cutaneous vasculitis. CMV retinitis is infrequent in this population and it usually presents > 6 months after transplantation. Patients may be asymptomatic or may experience blurring of vision, scotomata, or decreased visual acuity. The diagnosis is made fundoscopically.

Indirect Clinical Effects in the Organ Transplant Recipient

As previously we pointed out, CMV has immunomodulatory effects, and it exerts two major indirect effects on the transplant recipient: increasing the patient's susceptibility to opportunistic infections and possibly playing a role in the pathogenesis of allograft injury. This last effect would be the more important consequence of CMV infection of the allograft. Recent studies have compellingly demonstrated that CMV infection of both vascular smooth muscle and endothelium is a regular occurrence during CMV infection, thus providing a mechanism for vascular injury and chronic allograft injury.²

CMV might also have a role in the pathogenesis of malignancy in the transplant patient. Like other herpes group viruses, CMV must be thought of as a potentially oncogenic agent. So far, only weak associations have been made between CMV and human colonic carcinoma and prostatic carcinoma.

Diagnostic Difficulties

The diagnosis of CMV disease has traditionally been based on the recognition of cytomegalic inclusion bodies in the involved tissue. Biopsies demonstrating the typical histology of CMV infection (*ie*, "cytomegalic cells" with intranuclear inclusions, associated with focal inflammation) are excellent indicators of clinically important disease meriting therapy. In addition, biopsies that demonstrate focal inflammation without the pathognomonic inclusions, but are associated with the demonstration of the presence of CMV antigen by monoclonal antibody staining or CMV DNA by *in situ* hybridization, provide strong evidence for clinically important disease. Conversely, the presence of a few "CMV cells" in the absence of evidence of tissue inflammation or organ dysfunction is of unknown significance.^{14,15} The simultaneous detection of CMV by culture or polymerase chain reaction (PCR) in blood, respiratory secretions, or even in tissue may help in the diagnosis, but it does not constitute a strict criterion for the diagnosis of CMV disease. In the presence of compatible clinical symptoms, viremia is highly suggestive of CMV disease, but not diagnostic. A breakthrough in the rapid diagnosis of systemic CMV infections has been the introduction of the antigenemia assay. The method is based upon detection of a CMV protein (pp65) in the nucleus of polymorphonuclear leukocytes, which is evidenced by the immunoperoxidase technique. The presence of pp65 antigenemia in blood leukocytes provides an early marker of active CMV infection. The usefulness of antigenemia quantitation and its correlation with CMV disease has been evaluated in solid organ and bone marrow transplant recipients as well as in AIDS patients. In general, high levels of antigenemia are detected in patients with symptomatic CMV infection, whereas low levels mostly correlate with asymptomatic infections. The assay is easy to perform, does not

depend on cell culture technology, and has a greater sensitivity than viral isolation. Its ability to quantify the viral burden is its best feature. Recently, CMV-infected circulating endothelial cells (CECs) have been found in the blood of immunocompromised patients with disseminated CMV infection. In solid organ transplant recipients, CEC counts > 10 were associated with high levels of antigenemia and viremia as well as with an overt clinical syndrome.¹⁶ CECs were found to be fully permissive to CMV replication and to be of endothelial origin, indicating extensive endothelial damage in immunocompromised patients. CECs derive from infected endothelial cells of small blood vessels that progressively enlarge until they come off the vessel wall and enter the blood stream. CECs may represent a new helpful marker for both disseminated CMV infection and organ localization, and for the study of the pathogenesis of disseminated infections and chronic rejection. More data on the applicability of this test in organ transplant recipients are needed. Several methods have been utilized for the detection and quantification of CMV DNA. Nucleic acid amplification by PCR has become a widely available diagnostic tool and is increasingly being used for monitoring of CMV infection following solid organ and bone marrow transplantation.¹⁷ PCR can be used to detect viral DNA in tissues, blood leukocytes, plasma, serum, and other body fluids including cerebrospinal fluid, BAL fluid, and urine. Although qualitative PCR for CMV DNA detection in peripheral blood is currently the most sensitive procedure, it is of little clinical value because the positive predictive value of this assay is much lower than its negative predictive value. Quantitative PCR has the potential for early identification of patients at risk of developing CMV disease and is therefore an excellent candidate for targeting and monitoring antiviral treatment in solid organ transplant recipients.

Prevention of CMV Disease in Transplantation

There are three strategies for prevention of CMV disease that merit attention ([Table 2](#)): (1) decreasing the risk of virus acquisition and reactivation; (2) induction, either actively or passively, of immunologic protection; and (3) use of antiviral drugs. These strategies are not mutually exclusive, and probably are best used in combination. The benefits of all these prophylactic approaches are lessened by the use of antilymphocyte antibody therapies.

Table 2—Options for Prevention of CMV Disease in Transplantation		
Strategy	Advantages	Disadvantages
<i>Prophylaxis</i>		
IV Ig-CMV	Few side effects	Low efficacy
High-dose acyclovir	Few side effects	High cost
Ganciclovir	Highly effective	High risk of neutropenia (especially in BMT*); late CMV disease possible

Pre-emptive therapy

Based on PCR for CMV DNA or pp65 antigenemia

Effective; **targeted treatment**

Close monitoring is required

*BMT = bone marrow transplantation.

The two major sources of exogenous CMV infection for the transplant patient are leukocyte-containing blood products and the allograft itself. The first of these, transfusion-related infection, should be totally preventable, whereas the issues regarding allograft-transmitted infection are more complex. Ideally, all transplant patients, not just seronegative ones, should receive blood only from seronegative donors, or high-efficiency leukocyte filters should be used to remove the viable leukocytes that harbor the virus. Both of these strategies are useful but not always feasible. The issue of protective matching of donor and recipient so that an organ from a seropositive donor is not placed in a seronegative recipient is less clear-cut. Although eminently reasonable, such a policy would seriously curtail the donor pool, which is already in short supply. Two possible immunologic interventions against CMV have been evaluated in transplant recipients: active immunization with a CMV vaccine and passive immunization with a variety of IV Ig preparations. The administration of live, attenuated CMV vaccine (Towne strain) to seronegative patients before renal transplantation resulted in a decrease in the severity of CMV disease, including CMV pneumonitis.¹⁸ Vaccination of seropositive patients prior to transplant had no discernible clinical benefit. This experience has not been tested in other organ transplant recipients. Preliminary clinical studies with a subunit CMV vaccine are ongoing.

The administration of IV Ig preparations prophylactically to solid organ transplant patients is moderately effective in preventing CMV pneumonitis, particularly in renal and liver transplant patients¹⁹ (Table 2). However, immunoprophylaxis has not been useful in bone marrow transplantation. Furthermore, it must be taken into account that both standard and hyperimmune Ig preparations are very different from one another in terms of their anti-CMV Ig content. Otherwise, the use preventive of Ig has a high cost, and it is difficult to define a dosage schedule for administering the preparation. High-dose oral or IV acyclovir (Table 2) administered for a long time has shown to be only moderately effective in preventing CMV pneumonitis disease in organ transplant recipients. However, ganciclovir (Table 2), a far more potent anti-CMV drug than acyclovir, was shown to be quite effective in preventing CMV pneumonitis in solid organ transplant recipients who are CMV-seropositive prior to transplant, but ineffective in preventing disease in those at risk for primary infection.²⁰ Sequential therapy of ganciclovir followed by high-dose oral acyclovir has proved to be considerably more effective than high-dose acyclovir by itself in liver transplant patients.²¹ Likewise, the combination of hyperimmune anti-CMV Ig plus an antiviral drug could be more effective than either agent alone, at least in liver transplant recipients receiving OKT3.²² Oral ganciclovir has demonstrated to be useful for the prevention of CMV disease in liver transplant recipients,²³ but its role in the prophylaxis of CMV pneumonitis

in other types of transplants is not known; recently, evidence that these patients are at risk for the development of resistance to ganciclovir has been published.²⁴ Valacyclovir, a prodrug of acyclovir, is more rapidly absorbed than its parent drug, and it has been shown effective in avoiding the development of disease in kidney transplant recipients, even in seronegative patients receiving an organ from a seropositive donor.²⁵ Valganciclovir, the valine ester of ganciclovir, is another promising drug expected to be useful in the prophylaxis and treatment of CMV disease in transplantation.

All preventive programs discussed above have been prophylactic in nature; *ie*, the anti-CMV regimen is administered to all individuals undergoing transplantation to prevent an infection that is both common enough and important enough to merit such an approach. Another way to administer prophylaxis is *pre-emptive therapy*, defined as a strategy in which antimicrobial agents are administered to a subgroup of patients prior to the appearance of clinical disease.²⁶ Initiation of pre-emptive therapy is based on the identification of a clinical epidemiologic characteristic or laboratory marker that characterizes patients at high risk of serious disease (CMV culture, pp65 antigenemia, or PCR for CMV DNA). An example of the first point is the use of ganciclovir therapy administered pre-emptively during the 10- to 14-day course of OKT3 therapy. This regimen has demonstrated to be effective in eliminating the excessive rate of disease associated with antirejection therapy with antilymphocyte antibodies.²⁷ An example of the second point is the triggering of pre-emptive therapy on the basis of the preclinical demonstration of virus replication. Studies in bone marrow transplant patients have shown that initiating ganciclovir therapy in asymptomatic patients with replicating virus demonstrable in blood or BAL specimens is quite effective in preventing CMV pneumonia. It would seem possible that pre-emptive therapy triggered by the demonstration of viremia (antigenemia assay and PCR) should be equally effective in transplant recipients at a point in time when the patient is still asymptomatic. Several approaches using ganciclovir pre-emptive therapy for prophylaxis of CMV pneumonia in bone marrow transplantation have now been described. In the first report of successful prophylaxis, BAL fluid positive for CMV at day 35 after transplant was used to randomize patients between ganciclovir and observation (control group).²⁸ Patients were then watched for the development of CMV pneumonia. It was found that 25% of patients who received ganciclovir died or had CMV pneumonia, compared with 70% of those who did not receive the drug. No patient who received the full course of ganciclovir prophylaxis developed CMV pneumonia in that study.

A double-blind controlled study of a second strategy—using the first positive CMV culture from any site (urine, blood, or throat) to randomize patients between ganciclovir and placebo—showed that the predicted probability of developing CMV disease was 53% in the placebo group compared with 3% in the ganciclovir group. There were no CMV-related deaths by day 100 in the ganciclovir group vs six deaths related to CMV pneumonia in the placebo group.²⁹ Mortality at day 100 after bone marrow transplantation was 17% in the placebo group vs 3% in the ganciclovir group.

Because 12% of patients in the previous study presented with CMV disease without prior CMV excretion, a third strategy was studied, comparing ganciclovir

given at the time of engraftment with ganciclovir initiated at the time of the first positive CMV culture.³⁰ In this study, 45% of placebo patients and 3% of those who received ganciclovir developed CMV infection, and 29% of placebo patients and no ganciclovir patients developed CMV pneumonia during the first 100 days.

Unfortunately, marrow toxicity neutropenia was a significant finding in all the above-mentioned randomized studies, occurring in approximately 30% of patients. There was also a significant risk of subsequent development of neutropenia-associated bacterial sepsis in ganciclovir patients in these studies. Safer strategies are clearly needed.

A particular problem has been the prevention of CMV pneumonitis in lung and heart-lung transplant recipients.³¹ This group of patients provides an excellent population for assessing new anti-CMV strategies, as the attack rate for viremia and/or pneumonia appears to be > 75% in those at risk for primary infection. Furthermore, a strategy that works in these patients will almost unquestionably work in the other solid organ transplant populations. In this special situation, the demonstration of CMV in respiratory secretions is highly associated with active or soon-to-be-active clinical disease, and should be aggressively treated with effective antiviral drugs, even in the absence of clinical disease (pre-emptive therapy), in a manner analogous to what has been shown in bone marrow transplant patients. In these patients, however, asymptomatic viral excretion may occur after a successful course of therapy. Then, additional information such as the level of immunosuppressive therapy being used, the presence of CMV antigenemia, sensitive measures of pulmonary function, and even biopsy should be employed to determine if only asymptomatic viral excretion is present, or true relapsing infection requiring additional therapy exists.

Advances in the Treatment of CMV Disease in Organ Transplantation

Effective, currently available antiviral agents for the treatment of CMV disease include ganciclovir and foscarnet. Because of its toxicity, particularly renal toxicity (exacerbated by cyclosporine), there is little indication for the use of foscarnet in transplant recipients. The treatment of CMV disease in solid organ transplant recipients with ganciclovir has been most successful, and this therapy is clearly lifesaving. The usual dose of IV ganciclovir is 5 mg/kg every 12 h, administered as a 1-h infusion. This dosage should be decreased in patients with renal impairment. CMV disease is typically treated with 2 weeks of IV ganciclovir, although it has been suggested that a longer duration of treatment may be required for GI CMV disease. The optimal duration of antiviral therapy in an individual patient remains unknown.

Oral ganciclovir may be useful as maintenance therapy in those patients treated with IV ganciclovir who have identified risk factors for relapse. However, there is only limited experience with the use of oral ganciclovir for treatment of transplanted patients with CMV disease. The current knowledge is limited to its use as a prophylactic agent.

One caveat is that treatment of CMV disease with ganciclovir may not reduce the late immune-mediated consequences of the disease. For example, in heart transplant patients, some studies have demonstrated that although therapy interrupted viral replication and resulted in initial clinical improvement, at the 6-month follow-up, 70% of the patients had died because of late sequelae, predominantly cardiac allograft dysfunction. Although ganciclovir therapy is quite effective for treating the direct infectious disease consequences of CMV infection, the indirect effects of the virus may not be managed quite as well. In the case of CMV pneumonitis in bone marrow transplant recipients, the attempts to treat this disease with ganciclovir have been unsatisfactory, even though a prompt clearing of CMV from the sputum and pulmonary secretions was demonstrated in some patients. Global survival of bone marrow transplant recipients with CMV pneumonia treated exclusively with ganciclovir is < 35%.³² Several uncontrolled studies have reported an increased survival rate in bone marrow transplant patients with CMV pneumonia who were treated with ganciclovir and high-dose IV CMV Ig.³³ Despite this treatment, as many as 50% of bone marrow transplant recipients still succumb to this infection. Because of the increased success in bone marrow transplant recipients of treating CMV pneumonia with a combination of ganciclovir and hyperimmune globulin, many transplant groups utilize such combined therapy in solid organ transplant recipients. However, no studies have been carried out in the organ transplant recipient to document the increased benefit of such combined therapy.

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