Summary and Conclusion

CMV is the most common and single most important viral infection in solid organ transplant recipients. CMV infection usually develops during the first few months after transplantation and is associated with clinical infectious disease (eg, fever, pneumonia, GI ulcers, hepatitis) and acute or chronic graft injury and dysfunction.

CMV is found in oropharyngeal secretions, urine, cervical and vaginal secretions, semen, breast milk, and blood. CMV is transmitted *in utero* during the first 6 months of life from exposure to the mother's genital secretions and breast milk, and by oral and respiratory secretions in the preschool age group. After congenital, perinatal, or early postnatal infection, the virus may linger for years in body fluids. Sources of CMV infection in transplant recipients include latent reactivation, donor-transmitted virus, and virus present in donor WBCs.

Primary and Secondary CMV Infection

Approximately 20% to 60% of all transplant recipients develop symptomatic CMV infection. The patient at highest risk for symptomatic disease is the CMV-seropositive donor/CMV-seronegative recipient (D+/R-) who develops a primary infection after transplantation. Such patients are at particular risk for severe manifestations of CMV infection, including tissue-invasive CMV and CMV recurrence.

Reactivation infection develops in the patient who becomes CMV-seropositive before transplantation via the traditional routes of transmission and exposure during hemodialysis and blood transfusion, and is more frequent than primary CMV infection. CMV-seropositive

recipients are also at risk for superinfection by CMV from a CMV-seropositive donor, especially in the setting of intense immunosuppression (ie, OKT3 and antithymocyte globulin)

Direct and Indirect Effects of CMV Infection in the Transplant Recipient

CMV infection is a multifaceted phenomenon with a variety of direct and indirect effects in the organ transplant recipient. The symptomatology for clinical infectious disease (ie, fever, pneumonia, GI ulcers, hepatitis) ranges from the mild, subclinical case to life-threatening multi-organ disease. Most cases of symptomatic CMV infection can be characterized by a self-limiting syndrome of episodic fever spikes for a period of 3 to 4 weeks, arthralgias, fatigue, anorexia, abdominal pain, and diarrhea. However, CMV infection can disseminate to the lungs, liver, pancreas, kidneys, stomach, intestine, brain, and parathyroid glands, and can cause death. CMV retinitis, manifested by decreased visual acuity and peripheral blindness, can occur and lead to retinal detachment and blindness.

In addition to direct infectious syndromes produced by CMV, considerable attention has been given to indirect effects. The additional immunosuppression that results from CMV infection places the patient at an increased risk for fungal and other opportunistic infections. Rubin has described a "bidirectional" interaction between CMV infection and the host's immune system. The type, duration, and intensity of exogenous immunosuppressive therapy influence and enhance CMV infection. On the other hand, CMV is an immunomodulatory virus, and its effects on the host include enhanced susceptibility to opportunistic infections and, probably, chronic allograft dysfunction. Another indirect effect is acute

and/or chronic allograft injury and dysfunction. This particular effect is described in detail in another Medscape publication.

CMV causes renal allograft injury that may be indistinguishable from injury caused by rejection or other factors, and it has been linked to acute rejection and chronic rejection in the form of bronchiolitis obliterans in lung transplant recipients, coronary atherosclerosis in heart transplant recipients, vanishing bile duct syndrome in liver transplant recipients, and a variety of additional histologic lesions in renal transplant recipients, resulting in decreased allograft survival.

Transplant vascular sclerosis (TVS) is a multifactorial, delayed complication of SOT that has emerged as a major limitation to long-term graft survival. The hallmark of TVS is diffuse neointimal hyperplasia and narrowing of the vascular lumen, leading to decreased circulation to the graft tissue. This lesion develops over a period of months to years. For additional information, the reader is referred to a discussion of TVS previously published on Medscape.

Diagnosis of CMV Infection

Techniques for rapid diagnosis of CMV infection include shell vial culture, pp65 antigenemia assay, PCR, and the hybrid-capture RNA-DNA hybridization assay for qualitative detection of CMV-PCR. Recently, attention has been focused on the role of the quantitative CMV viral load as an accurate diagnostic test for CMV. Although in general, CMV viral load correlates with viral disease, CMV disease can occur in the setting of a very low viral load. In addition, viral load is an optimal parameter to use for monitoring response to antiviral therapy.

Treatment of CMV Infection

Prevention of CMV infection is the standard of care in SOT. The recent emphasis on prophylaxis has changed the temporal characteristics of CMV, once an early disease (occurring < 3 months after transplantation), to the current pattern of late disease (occurring > 3 months after transplantation). Ganciclovir is the most commonly used agent for the prevention of CMV infection and disease in SOT recipients. Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine that inhibits the replication of herpesviruses *in vitro* and *in vivo*. Ganciclovir is administered either IV or orally, and either as general prophylaxis or as part of a preemptive strategy. There is growing concern about the problem of ganciclovir resistance. However, a prodrug of ganciclovir, valganciclovir, may obfuscate this concern. outlines prophylactic and preemptive treatment regimens using ganciclovir and valganciclovir. Low-risk recipients (D-/R-) do not require prophylaxis, but high- and intermediate-risk recipients do. High-risk recipients (D+/R-) who receive induction therapy or treatment of acute rejection with antilymphocyte agents should be administered IV ganciclovir for 3 weeks, followed by oral ganciclovir. Intermediate-risk recipients (D+/R- or D+/R+) who receive induction therapy or treatment of acute rejection with antilymphocyte agents should be administered IV ganciclovir while hospitalized, followed by oral ganciclovir.

Relapse of Ganciclovir-treated CMV Infection

Relapse of CMV infection after treatment with ganciclovir is more likely to occur if ganciclovir is discontinued while viral replication is ongoing. Therefore, it has been recommended to continue ganciclovir until viral replication is no longer evident, ie -- the PCR assay is negative.

Furthermore, beginning oral ganciclovir therapy (low-dose) while the PCR is still positive is discouraged, as this may "select out" for ganciclovir resistance, meaning that the administration of an inadequate dose allows for survival of strains that are relatively resistant to the drug while sensitive strains perish.

Ganciclovir-resistant CMV

As a result of the widespread use of antiviral prophylaxis and preemptive therapy, the incidence and severity of CMV disease and its indirect effects are significantly reduced. However, there is the increasing recognition of ganciclovir-resistant CMV infection. The overall incidence of ganciclovir-resistant CMV infection is 2.1%, but this varies widely among transplant groups, with the highest incidence among recipients of lung and combined kidney-pancreas transplants. Ganciclovir-resistant CMV infection has been observed in 0%, 0.3%, 1%, 9%, and 13% among liver, heart, kidney, lung, and combined pancreas-kidney transplant recipients, respectively.