for which blood or other specimens can be used; some centers use a CMV antigenemia test, an immunofluorescence assay that detects CMV antigens (pp65) in peripheral-blood leukocytes. Such assays may yield a positive result several days earlier than culture methods. QNAT may predict the risk for disease progression, particularly in immunocompromised hosts. CMV DNA in cerebrospinal fluid is useful in the diagnosis of CMV encephalitis or polyradiculopathy. Considerable variation exists among assays and laboratories; a recently introduced international testing standard should help reduce variation in PCR test results.

Virus excretion or viremia is readily detected by culture of appropriate specimens on human fibroblast monolayers. If CMV titers are high, as is common in congenital disseminated infection and in AIDS, characteristic cytopathic effects may be detected within a few days. However, in some situations (e.g., CMV mononucleosis), viral titers are low, and cytopathic effects may take several weeks to appear. Many laboratories expedite diagnosis with an overnight tissue-culture method (shell vial assay) involving centrifugation and an immunocytochemical detection technique employing monoclonal antibodies to an immediate-early CMV antigen. Isolation of virus from urine or saliva does not, by itself, constitute proof of acute infection, since excretion from these sites may continue for months or years after illness. Detection of viremia is a better predictor of acute infection.

A variety of serologic assays detect antibody to CMV. An increased level of IgG antibody to CMV may not be detectable for up to 4 weeks after primary infection. Detection of CMV-specific IgM is sometimes useful in the diagnosis of recent or active infection; however, circulating rheumatoid factors may result in occasional false-positive IgM tests. Serology is especially helpful when used to predict risk of CMV infection and disease in transplant recipients.

PREVENTION

Prevention of CMV in organ and hematopoietic stem cell transplant recipients is usually based on one of two methods: universal prophylaxis or preemptive therapy. With universal prophylaxis, antiviral drugs are used for a defined period, often 3 or 6 months. One clinical trial demonstrated that, in CMV-seronegative recipients with seropositive donors, prophylaxis was more effective at prevention when given for 200 days rather than 100 days. With preemptive therapy, patients are monitored weekly for CMV viremia, and antiviral treatment is initiated once viremia is detected. Because of the bone marrow–suppressive effects of universal prophylaxis, preemptive therapy is more commonly employed in hematopoietic stem cell transplant recipients. For patients with advanced HIV infection (CD4+ T cell counts of <50/μL), some experts have advocated prophylaxis with valganciclovir (see below). However, side effects, lack of proven benefit, possible induction of viral resistance, and high cost have precluded the wide acceptance of this practice. Preemptive therapy is under study in HIV-infected patients.

Several additional measures are useful for the prevention of CMV transmission to CMV-naïve, high-risk patients. The use of CMV-seronegative or leukocyte-depleted blood greatly decreases the rate of transfusion-associated transmission. In a placebo-controlled trial, a CMV glycoprotein B vaccine reduced infection rates among 464 CMV-seronegative women; this outcome raises the possibility that this experimental vaccine will reduce rates of congenital infection, but further studies must validate this approach. A CMV glycoprotein B vaccine with MF59 adjuvant appeared effective in reducing the risk and duration of viremia in both seropositive and seronegative renal transplant recipients at risk for CMV infection. CMV immune globulin has been reported to prevent congenital CMV infection in infants of women with primary infection during pregnancy. Studies in hematopoietic stem cell transplant recipients have produced conflicting results.

Prophylactic acyclovir or valacyclovir may reduce rates of CMV infection and disease in renal transplant recipients, although neither drug is effective in the treatment of active CMV disease.

Ganciclovir is a guanosine derivative that has considerably more activity against CMV than its congener acyclovir. After intracellular conversion by a viral phosphotransferase encoded by CMV gene region UL97, ganciclovir triphosphate is a selective inhibitor of CMV DNA polymerase. Several clinical studies have indicated response rates of 70–90% among patients with AIDS who are given ganciclovir for the treatment of CMV retinitis or colitis. In severe infections (e.g., CMV pneumonia in hematopoietic stem cell transplant recipients), ganciclovir is often combined with CMV immune globulin. Prophylactic or suppressive ganciclovir may be useful in high-risk hematopoietic stem cell or organ transplant recipients (e.g., those who are CMV-seropositive before transplantation). In many patients with AIDS, persistently low CD4+ T cell counts, and CMV disease, clinical and virologic relapses occur promptly if treatment with ganciclovir is discontinued. Therefore, prolonged maintenance regimens are recommended for such patients. Resistance to ganciclovir is more common among patients treated for >3 months and is usually related to mutations in the CMV UL97 gene (or, less commonly, the UL54 gene).

Valganciclovir is an orally bioavailable prodrug that is rapidly metabolized to ganciclovir in intestinal tissues and the liver. Approximately 60–70% of an oral dose of valganciclovir is absorbed. An oral valganciclovir dose of 900 mg results in ganciclovir blood levels similar to those obtained with an IV ganciclovir dose of 5 mg/kg. Valganciclovir appears to be as effective as IV ganciclovir for both CMV induction (treatment) and maintenance regimens, while providing the ease of oral dosing. Furthermore, the adverse-event profiles and rates of resistance for the two drugs are similar.

Ganciclovir or valganciclovir therapy for CMV disease consists of a 14- to 21-day induction course (5 mg/kg IV twice daily for ganciclovir or 900 mg PO twice daily for valganciclovir), sometimes followed by maintenance therapy (e.g., valganciclovir, 900 mg/d). Peripheral-blood neutropenia develops in roughly one-quarter of treated patients but may be ameliorated by granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor. Whether to use maintenance therapy should depend on the overall level of immunocompromise and the risk of recurrent disease. Discontinuation of maintenance therapy should be considered in patients with AIDS who, while receiving antiretroviral therapy, have a sustained (3- to 6-month) increase in CD4+ T cell counts to >100/μL.

For treatment of CMV retinitis, ganciclovir may also be administered via a slow-release pellet sutured into the eye. Although this intraocular device provides good local protection, contralateral eye disease and disseminated disease are not affected, and early retinal detachment is possible. A combination of intraocular and systemic therapy may be better than the intraocular implant alone.

Foscarnet (sodium phosphonoformate) inhibits CMV DNA polymerase. Because this agent does not require phosphorylation to be active, it is also effective against most ganciclovir-resistant isolates. Foscarnet is less well tolerated than ganciclovir and causes considerable toxicity, including renal dysfunction, hypomagnesemia, hypokalemia, hypocalcemia, genital ulcers, dysuria, nausea, and paresthesia. Moreover, foscarnet administration requires the use of an infusion pump and close clinical monitoring. With aggressive hydration and dose adjustments for renal dysfunction, the toxicity of foscarnet can be reduced. The use of foscarnet should be avoided when a saline load cannot be tolerated (e.g., in cardiomyopathy). The approved induction regimen is 60 mg/kg every 8 h for 2 weeks, although 90 mg/kg every 12 h is equally effective and no more toxic. Maintenance infusions should deliver 90–120 mg/kg once daily. No oral preparation is available. Foscarnet-resistant virus may emerge during extended therapy. This drug is used more frequently after hematopoietic stem cell transplantation than in other situations to avoid the myelosuppressive effects of ganciclovir; in