is compromised—for example, after organ transplantation, with lymphoid neoplasms and certain acquired immunodeficiencies (in particular, HIV infection; Chap. 226), or during critical illness in intensive care units. Most primary CMV infections in organ transplant recipients (Chap. 169) result from transmission via the graft. In CMV-seropositive transplant recipients, infection results from reactivation of latent virus or from infection by a new strain. CMV infection may also be associated with diseases as diverse as coronary artery stenosis and malignant gliomas, but these associations require further validation.

## PATHOGENESIS

Congenital CMV infection can result from either primary or reactivation infection of the mother. However, clinical disease in the fetus or newborn is related almost exclusively to primary maternal infection (Table 219-1). The factors determining the severity of congenital infection are unknown; a deficient capacity to produce precipitating antibodies and to mount T cell responses to CMV is associated with relatively severe disease.

Primary infection with CMV in late childhood or adulthood is often associated with a vigorous T lymphocyte response that may contribute to the development of a mononucleosis syndrome similar to that which follows infection with Epstein-Barr virus (Chap. 218). The hallmark of such infection is the appearance of atypical lymphocytes in the peripheral blood; these cells are predominantly activated CD8+ T lymphocytes. Polyclonal activation of B cells by CMV contributes to the development of rheumatoid factors and other autoantibodies during mononucleosis.

Once acquired, CMV persists indefinitely in host tissues. The sites of persistent infection probably include multiple cell types and various organs. Transmission via blood transfusion or organ transplantation is due primarily to latent infections in these tissues. If the host's T cell responses become compromised by disease or by iatrogenic immunosuppression, latent virus can reactivate to cause a variety of syndromes. Chronic antigenic stimulation in the presence of immunosuppression (for example, after organ transplantation) appears to be an ideal setting for CMV activation and CMV disease. Certain particularly potent suppressants of T cell immunity (e.g., antithymocyte globulin, alemtuzumab) are associated with a high rate of clinical CMV syndromes. CMV may itself contribute to further T lymphocyte hyporesponsiveness, which often precedes superinfection with other opportunistic pathogens such as bacteria, molds, and *Pneumocystis*.

## PATHOLOGY

Cytomegalic cells in vivo (presumed to be infected epithelial cells) are two to four times larger than surrounding cells and often contain an 8- to 10-μm intranuclear inclusion that is eccentrically placed and is surrounded by a clear halo, producing an "owl's eye" appearance. Smaller granular cytoplasmic inclusions are demonstrated occasionally. Cytomegalic cells are found in a wide variety of organs, including the salivary gland, lung, liver, kidney, intestine, pancreas, adrenal gland, and central nervous system.

The cellular inflammatory response to infection consists of plasma cells, lymphocytes, and monocyte-macrophages. Granulomatous reactions occasionally develop, particularly in the liver. Immunopathologic reactions may contribute to CMV disease. Immune complexes have been detected in infected infants, sometimes in association with CMV-related glomerulopathies. Immune-complex glomerulopathy has also been observed in some CMV-infected patients after renal transplantation.

## CLINICAL MANIFESTATIONS

**Congenital CMV Infection** Fetal infections range from subclinical to severe and disseminated. Cytomegalic inclusion disease develops in ~5% of infected fetuses and is seen almost exclusively in infants born to mothers who develop primary infections during pregnancy. Petechiae, hepatosplenomegaly, and jaundice are the most common presenting features (60–80% of cases). Microcephaly with or without cerebral calcifications, intrauterine growth retardation, and prematurity are reported in 30–50% of cases. Inguinal hernias and chorioretinitis are less common. Laboratory abnormalities include elevated alanine aminotransferase levels in serum, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and elevated protein levels in cerebrospinal fluid. The prognosis for severely infected infants is poor; the mortality rate is 20–30%, and few survivors escape intellectual or hearing difficulties later in childhood. The differential diagnosis of cytomegalic inclusion disease in infants includes syphilis, rubella, toxoplasmosis, infection with herpes simplex virus or enterovirus, and bacterial sepsis.

Most congenital CMV infections are clinically inapparent at birth. Of asymptomatically infected infants, 5–25% develop significant psychomotor, hearing, ocular, or dental abnormalities over the next several years.

**Perinatal CMV Infection** The newborn may acquire CMV at delivery by passage through an infected birth canal or by postnatal contact with infected breast milk or other maternal secretions. Of infants who are breast-fed for >1 month by seropositive mothers, 40–60% become infected. Iatrogenic transmission can result from blood transfusion; use of leukocyte-reduced or CMV-seronegative blood products for transfusion into low-birth-weight seronegative infants or seronegative pregnant women decreases risk.

The great majority of infants infected at or after delivery remain asymptomatic. However, protracted interstitial pneumonitis has been associated with perinatally acquired CMV infection, particularly in premature infants, and occasionally has been accompanied by infection with *Chlamydia trachomatis*, *Pneumocystis*, or *Ureaplasma urealyticum*. Poor weight gain, adenopathy, rash, hepatitis, anemia, and atypical lymphocytosis may also be found, and CMV excretion often persists for months or years.

**CMV Mononucleosis** The most common clinical manifestation of CMV infection in immunocompetent hosts beyond the neonatal period is a heterophile antibody–negative mononucleosis syndrome, which may develop spontaneously or follow transfusion of leukocyte-containing blood products. Although the syndrome occurs at all ages, it most

**TABLE 219-1 CMV DISEASE IN THE IMMUNOCOMPROMISED HOST**

| Population | Risk Factors | Principal Syndromes | Treatment | Prevention |
|---|---|---|---|---|
| Fetus | Primary maternal infection/early pregnancy | Cytomegalic inclusion disease | Ganciclovir for symptomatic neonates | Avoidance of exposure; possibly, maternal treatment with CMV immunoglobulin during pregnancy |
| Organ transplant recipient | Seropositivity of donor and/or recipient; potent immunosuppressive regimen; treatment of rejection | Febrile leukopenia; gastrointestinal disease; pneumonia | Ganciclovir or valganciclovir | Prophylaxis or preemptive therapy with ganciclovir or valganciclovir |
| Hematopoietic stem cell transplant recipient | Graft-vs.-host disease; older age of recipient; seropositive recipient; viremia | Pneumonia; gastrointestinal disease | Ganciclovir or valganciclovir or foscarnet, ± CMV immunoglobulin | Prophylaxis or preemptive therapy with ganciclovir or valganciclovir |
| Person with AIDS | <100 CD4+ T cells/μL; CMV seropositivity | Retinitis; gastrointestinal disease; neurologic disease | Ganciclovir, valganciclovir, foscarnet, or cidofovir | Oral valganciclovir |