Epidemiology: Cytomegalovirus (CMV) is the largest of the herpes viruses and commonest cause of congenital infections. CMV has a worldwide distribution in both adults and children. Incidence of congenital CMV infection ranges from 0.2 to 2.4% of all live births. The risk of congenital CMV infection is greatest with primary maternal infection (40%) and less likely with recurrent infection (<1%). Perinatal infection has an incidence of 10-60% in the first 6 months of life. Nosocomial infection is a hazard of transfusion of blood and blood products, especially leucocyte transfusion. In a population with a 50% prevalence of CMV infection, the risk estimate is of 2.7% per unit of whole blood. Immunocompromised patients and seronegative premature infants have a risk of infection as high as 10-30%.

Transmission: CMV can be transmitted through saliva, breast milk, cervical and vaginal secretions, urine, semen, stool, blood, tissue and organ transplants. Close and intimate contact is required for transmission. Perinatal transmission occurs mainly through genital tract secretions at the time of delivery and through breast milk. Approximately 6-12% of seropositive mothers transmit the infection through cervical-vaginal secretions, while 50% transmit through breast milk. Infants are usually asymptomatic, but may present occasionally with pneumonitis and sepsis-like syndrome. Neurologic sequelae and psychomotor retardation could be seen in later life.

Clinical Presentation in Acquired CMV: In most patients, the infection is subclinical. In older children, adolescents and adults, it may cause a heterophil-antibody negative mononucleosis syndrome. Myalgias, headache, splenomegaly are frequent. The characteristic laboratory abnormality is relative lymphocytosis in peripheral blood with more than 10% atypical lymphocytes. Transient immunologic abnormalities and elevated liver enzymes may also be seen. In immunocompromised patients, most common presentation is of pneumonitis, followed by hepatitis, chorioretinitis, gastrointestinal disease or fever with leucopenia.

Congenital CMV infection: Congenital CMV infection has a different mode of transmission and pathogenesis. CMV spreads from sites of infection in uterine arteries to invade cytotrophoblasts, then to placental villi floating in maternal blood. IgG antibodies with a low neutralizing titre allow viral replication to continue in the villus cytotrophoblasts. The infection then spreads to the stromal fibroblasts and the fetal vasculature. It is associated with defective interferon-gamma and proliferative responses of CD4 T lymphocytes. Studies have suggested that CMV induced CD4 deficiency may be a
factor for the slow clearance of the virus in children and its continued excretion in saliva and urine for up to 10 years.

Only 5% of congenital CMV infection present with the severe cytomegalic inclusion disease. Another 5% will have a mild involvement and the remaining will present with subclinical disease. Petechiae, hepatosplenomegaly and jaundice are the most common presenting features seen in 60-80% of cases. Microcephaly with or without cerebral calcifications, intrauterine growth restriction and prematurity are seen in about 30-50% of cases. Inguinal hernia and chorioretinitis are seen, but are less common. An important sequel of congenital CMV infection, whether symptomatic or asymptomatic is sensorineural hearing loss. CMV is a leading cause for sensorineural hearing loss, which is seen in 7% of all infants with the infection. The prognosis of severely infected infants is poor, with a mortality rate of 20-30%.

**CMV and neonatal cholestasis:** Neonatal cholestasis is caused due to various conditions includes biliary atresia and a number of intrahepatic problems such as infections, metabolic conditions, and chronic familial cholestatic diseases. Several serologic studies suggest that various viral infections are associated with intrahepatic forms of neonatal cholestasis. Neonatal cholestasis gives rise to mainly two types of manifestations i.e. mechanical obstruction causing biliary atresia and functional impairment causing neonatal hepatitis. Congenital CMV infection as a cause of neonatal cholestasis is being seen with increasing frequency in the recent past. Although Cytomegalovirus (CMV) is known to cause intrahepatic bile duct destruction and paucity, its role as a cause of biliary atresia has been a topic of much debate. It has been suggested that neonatal hepatitis and biliary atresia represent two ends of a spectrum of a single disease process, described by Landing as ‘infantile obstructive cholangiopathies’, and viruses have been proposed as a likely cause, CMV, reovirus, rotavirus, HPV and retroviruses among the probable agents. Cytomegalovirus is the most commonly implicated virus, and CMV antigen has been detected in liver biopsy specimens from these patients. Here, CMV may be a causative agent or a factor not initiating but aggravating the cholestatic process.

**Diagnosis of CMV:** Congenital CMV is commonly diagnosed using serological tests. Maternal testing for CMV is desirable. Because of the infant’s reduced ability to produce IgM, the diagnosis may be missed by use of serological methods alone. The gold standard for diagnosis is viral culture, and CMV can be cultured from a number of specimens like blood, urine, saliva, CSF, broncho-alveolar lavage fluid and tissue biopsy specimens. Newer molecular diagnostic methods include PCR techniques for detection of CMV-DNA in urine, serum or liver biopsy, which is more sensitive than culture. Other methods include CMV antigenemia studies like detection of CMV IEA (immediate early antigen) or a lower matrix protein (p65) in peripheral blood leucocytes, which are more frequently used in transplant recipients.

Fetal infection can be identified by in utero diagnosis carried out by viral isolation and PCR in amniotic fluid. This method has excellent sensitivity after 22 weeks of gestation.

**Treatment:** The use of blood from seronegative donors or blood that has been frozen, thawed, deglycerolized, and blood that has been gamma-irradiated, has been shown to decrease the rate of transfusion associated CMV infection. Also, matching of organ or bone marrow transplants by CMV serology, has been shown to reduce rates of primary infection following transplantation. Life-
threatening CMV infections in immunocompromised patients may be treated with ganciclovir with / without immune-globulin, either standardized IVIG or hyperimmune CMV IVIG. The drugs recommended for use in children are IV ganciclovir and its oral prodrug valganciclovir. Other drugs such as cidofovir and foscarnet are not used in children as their safety profile is not known.

Ganciclovir, a guanosine derivative, is a selective inhibitor of CMV DNA polymerase. A randomized controlled phase III study with ganciclovir (6mg/kg/dose) every 12 hourly iv for the 1st 6 weeks of life has shown that treatment prevents hearing deterioration and improves or maintains normal hearing function at 6 months of age, and may prevent the hearing deterioration that may occur after 1 year of age. Ganciclovir therapy has been recommended for congenital CMV infection as the first line treatment modality by a study conducted in Turkey in 2006.

Valganciclovir is being increasingly studied for use in CMV infection. It is an oral prodrug, valyl derivative of ganciclovir. It is supplied as 450 mg tablets. Due to primarily renal excretion, dosage needs to be adjusted in impaired renal function. The adverse effect profile is similar to that of ganciclovir. A controlled trial of valganciclovir as induction therapy has been shown to be convenient and effective for long-term management of CMV retinitis in AIDS patients.

Ganciclovir and its oral prodrug valganciclovir may have a useful role in Neonatal CMV cholestasis if given early in the course of the disease before severe liver cell damage occurs as has been used in few studies in Sweden and case reports. Untreated these patients can progress to chronic liver disease and portal hypertension. A study conducted by us on use of valganciclovir has found good results in neonatal hepatitis without biliary atresia with increased chances of recovery (Odds ratio: 3: 0.7). However a randomized controlled trial would be essential before recommending it for treatment of neonatal cholestasis with CMV. Caution is required in view of significant adverse effect profile of ganciclovir, most important of which is bone marrow suppression. Other adverse effects include rash, fever, vomiting and neuropsychiatric disturbances.

Newer Research: Various trials and studies are being conducted the world over for developing an effective vaccine against CMV infection. This will require an effective pre-conceptual immunity in women of child-bearing age. The ideal vaccine should elicit both humoral and cell-mediated immune response. Such immunity should directly prevent infection or reduce viral replication so as to decrease transmission. DNA vaccines are being developed to target multiple, specific CMV proteins, for example, glycoprotein B (gB), CMV tegument protein pp65 and CMV immediate early gene product IE1.

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