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REVIEW

A review of Cytomegalovirus (CMV)

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Abstract
Human cytomegalovirus (CMV) is a ubiquitous virus that has a significant impact on the health of children in Africa and globally. It can be acquired antenatally in utero (cCMV) or postnatally (pCMV) via breastmilk, genital secretions, or blood products. CMV can also be transmitted via solid organ or hematopoietic stem cell transplants. Clinical presentation of CMV varies based on the age and immune status, with children living with HIV exhibiting significant complications from co-infection. Most children with cCMV are asymptomatic but may develop deafness and neurodevelopmental delay later in childhood. pCMV in preterm or low birth weight babies may lead to pneumonitis, necrotizing enterocolitis, or a severe sepsis-like syndrome. Ganciclovir and valganciclovir, its oral prodrug, are the only anti CMV drugs available in most African countries though their use is not widespread. New drugs and vaccines are being developed to improve treatment options and prevent the transmission of CMV. Strategies to manage cCMV include the use of longer durations of ganciclovir as a treatment option to prevent deafness.

Introduction

Though Human Cytomegalovirus (CMV) infection is ubiquitous and is usually asymptomatic or presents with a mild mononucleosis like disease, congenital infection and infection in immune compromised children can cause complex and life-threatening disease. CMV infection may contribute to poor health outcomes in adults and children without immune deficiency.[1]

The aim of this article is to review the various clinical presentations of CMV in children and to highlight advances in the prevention, diagnosis and treatment of CMV as well as to describe future innovative strategies that are being explored.

Epidemiology

Human CMV, also known as human herpesvirus 5, is a member of the herpesvirus family (Herpesviridae), the beta-herpesvirus subfamily (Betaherpesvirinae), and the
Cytomegalovirus genus. The viral genome contains double-stranded DNA that ranges in size from 196 000 to 240 000 base pairs encoding at least 166 proteins and is the largest of the human herpesvirus genomes. CMV virus establishes latency by persisting in leukocytes and tissue cells after a primary infection. It can be intermittently shed leading to symptomatic infection especially if the host becomes immune suppressed.[2]

CMV can be acquired antenatally in utero (cCMV) or postnatally (pCMV) via breastmilk, genital secretions, and blood products. CMV can also be transmitted with solid organ or hematopoietic stem cell transplantation. The incubation period for horizontally transmitted CMV infections is highly variable. Infection usually presents 3 to 12 weeks after blood transfusions and between 1 and 4 months after organ transplantation. For vertical transmission through breast milk in preterm infants, the median time to onset of CMV viruria is 7 weeks (range, 3–24 weeks).[3]

CMV infection results in various clinical presentations dependent on the age and immune status of the child.[4] Older infants can acquire CMV at day care centres through direct contact with virus containing secretions and transmit the virus to their mothers or day care staff.

Pathogenesis

CMV establishes latency in its host, but reactivation can occur in response to various stimuli, and this results in infection of new cells causing end organ infection. Reactivation causes the release of cytokines such as tumour necrosis factor alpha and interferon gamma resulting in inflammation. CD8+ T-cells play a critical role in controlling CMV infection and disease. Therefore, in patients with T cell deficiency viral replication is uncontrolled and results in excessive shedding of CMV.
Major disease from CMV is often linked to inflammation, including pro-inflammatory cytokine production and is usually limited to situations where the immune system is significantly suppressed or still immature.

Diagnosis

CMV can be diagnosed by detecting virus (culture, molecular testing such as PCR or viral load) or by detecting antibodies to CMV infection. The diagnosis is complicated by the ubiquity of the virus, the high rate of asymptomatic shedding and the frequency of reactivation**.**

Most laboratories now use quantitative real-time polymerase chain reaction (PCR; viral load) tests to diagnose active CMV disease and monitor response to therapy. Testing can be done on a range of specimens including cerebrospinal fluid, amniotic fluid, human milk, aqueous and vitreous humor, urine, saliva, nasopharyngeal and tracheal aspirates as well as blood; however, detection of CMV DNA does not always indicate disease. The test is usually done on urine or saliva for the diagnosis of cCMV. Dried blood spots have been shown to have a low sensitivity for diagnosing cCMV.[5]

Viral load testing can be done using plasma or whole-blood specimens. Higher values are observed in whole-blood specimens compared with plasma. The same assay and specimen type should be used for monitoring patients over time.

COBAS AmpliPrep/COBAS TaqMan CMV test is a real-time PCR test that targets the polymerase gene and is calibrated to the World Health Organization (WHO) international standard to quantify the CMV load in plasma with a reported range from 137 to 9,100,000 international units (IU)/mL. Viral load is usually reported in IU/mL and as a logarithmic value. Viral load can be used to assess response to treatment.

CMV can be cultured using human fibroblast cells. Conventional culture may take one to six weeks to show cytopathic changes, so it has largely been replaced by shell vial culture which is faster. This technique involves low-speed centrifugation and detection of CMV early antigen prior to the development of characteristic cytopathic effects in tissue culture. The centrifugation of specimens increases the absorption of virus. Cell monolayers are then exposed to monoclonal antibodies against early antigen and antibody binding indicates "early" CMV replication within the cells.

Histologic examination of tissue is useful for the diagnosis of invasive disease. Diagnosis is based on the presence of inclusion bodies. These are usually basophilic intranuclear inclusions, although eosinophilic cytoplasmic inclusions have also been reported. The diagnosis of CMV in tissue sections can be confirmed with specific immunohistochemical stains.[6]

As CMV establishes latency and virus is shed periodically, the diagnosis of CMV related end organ disease relies on demonstrating the presence of CMV virus with clinical and or histological features that is suggestive of disease. Detection of viral DNA from the target organ can provide strong evidence that the disease is caused by CMV infection. Lung biopsies, while being invasive and usually only done post-mortem are the “gold standard” for diagnosing CMV pneumonia.[7,8]

Current and or prior infection with CMV can also be assessed through serology. However, CMV IgM may persist for several months and can be representative of past infection rather than current infection.

IgG avidity assays measure the binding strength between IgG antibodies and CMV. This can help differentiate a primary CMV infection from a past CMV infection. Following primary infection IgG antibodies have low binding strength (low avidity) but over 2 to 4 months they mature and then have high binding strength (high avidity). Avidity testing can be used in pregnancy.

Congenital CMV (cCMV)

CMV is usually transmitted antenatally from mother to child in the setting where the mother acquires CMV for the first time while pregnant or when CMV is reactivated during pregnancy. CMV IgM can be detected in pregnant women with non-primary infections, so it is often interpreted along with CMV IgG avidity. A positive IgM with a low IgG avidity implies a recent infection whereas a high IgG avidity implies a lower risk of infection to the fetus. cCMV is defined as detection of the CMV virus in urine or saliva of the neonate before 3 weeks of age. Previously, the earliest age that prenatal CMV infection could be detected in the urine by culture was 3 weeks thus providing the time to differentiate between perinatal and congenital infection. However, specimens now need to be taken as soon as possible after birth to confirm cCMV. Most neonates with cCMV are asymptomatic with around 10% being symptomatic.

Symptomatic neonates can present with jaundice, petechiae, purpura, hepatosplenomegaly, microcephaly, intracerebral (typically periventricular) calcifications and retinitis. Developmental delay and sensorineural hearing loss can occur among affected infants in later infancy and early childhood.

Both symptomatic and asymptomatic infants may go on to develop sensorineural hearing loss with around a third of symptomatic and 10% of asymptomatic neonates developing hearing loss. The

majority of these neonates will have normal hearing at birth. [9] cCMV is the most common non-genetic cause of sensorineural hearing loss in resource rich countries. [10] Symptomatic neonates treated with 6 weeks of intravenous ganciclovir have shown improved hearing outcomes.[11] While treatment with valganciclovir for 6 months moderately improved hearing and developmental long term outcomes, there was no difference between 6 weeks versus 6 months of treatment on hearing outcomes at the 6-month time point.[12]

Recently analyses of initial samples of cCMV infants have identified a 16-gene signature associated with the development of sensorineural hearing loss with 92% accuracy[13] which could potentially lead to a biomarker predicting hearing loss.

Table 1. Prevalence of cCMV in various African countries

Author and year of publication	Country	Screening method	Special population	Prevalence
Schopfer 1978	Cote d'Ivoire	Urine culture	NA	28/2032 (1.4%)
van der Sande 2007	Gambia	Urine PCR	NA	40/741 (5.4%)
Mwaanza 2014	Zambia	Urine & saliva PCR	HIV	15/395 (3.8%)
Manicklal 2013	South Africa	Saliva swab PCR	HIV	22/748 (2.9%)
Otieno 2019	Kenya	Saliva swabs and DBS PCR	NA	39/1078 (3.6%)
Olusanya 2015	Nigeria	Saliva PCR	NA	10/263 (3.8%)
Kaye	Gambia	Urine PCR	NA	11/281 (3.9%)
Morgan 2003	Egypt	Urine PCR	NA	10/175 (5.7%)
Salwa 2011	Egypt	Urine culture	NA	2/178 (1.3%)
Pathirana 2019	South Africa	Saliva swab PCR	HIV + and HIV-	67/2685 (2.5%)
Tshabala 2018	South Africa	Saliva swab PCR	HIV+ and HIV-	18/302 (6%)

The prevalence of cCMV in Africa varies between 1.3-6.3%.[14] Table 1 shows the prevalence of cCMV in various African countries. This is higher than the global prevalence that is reported at around 1%.[15] Children infected with human immunodeficiency virus (HIV) are at higher risk of cCMV than those that are HIV-exposed but uninfected.[16] In addition, CMV may increase the risk of in-utero HIV transmission.[17]

Postnatal CMV (pCMV)

pCMV is defined as detection of the virus after 21 days of life with the exclusion of cCMV.[18] Healthy term neonates are usually asymptomatic probably as a result of protection induced by maternal antibodies.

Preterm (less than 32 weeks gestational age) and very low birth weight (less than 1.5kg)(VLBW) neonates are at risk of a severe sepsis like syndrome, pneumonitis, bronchopulmonary dysplasia and necrotizing enterocolitis (NEC) after acquiring CMV postnatally via breastmilk ingestion. [19] Almost no CMV is detected in colostrum but CMV DNA is increasingly detected in breastmilk from about three weeks and reaches a maximum limit at 4 to 8 weeks.[20] In a prospective cohort study that followed infants born to CMV positive mothers who were CMV negative at birth and followed for 14 weeks, about half the VLBW preterm infants became CMV infected and a fifth developed clinically significant symptoms. None of the infants included in this study received treatment for pCMV infection with valganciclovir or ganciclovir during the study period[21] Those that became CMV infected had longer hospital stays and more episodes of prolonged neutropenia. However, NEC and bronchopulmonary dysplasia were not increased in those that became CMV-infected.

An infectious mononucleosis-like syndrome with prolonged fever and mild hepatitis may occur in about 10% of immunocompetent older children and adolescents.

CMV and HIV

As previously stated cCMV is more common in children infected with HIV and can increase the risk of in utero transmission of HIV. In addition, it may impact on HIV-exposed and uninfected (HEU) children as highlighted by a study of Zambian HEU infants in whom cytomegalovirus infection was associated with poor growth and lower cognitive development. [22] In addition, children not on antiretroviral therapy (ART) can present with pneumonia, oesphagitis, colitis, retinitis, meningoencephalitis, or transverse myelitis.[23,24] A syndrome that includes fever, thrombocytopenia, leucopenia and mild hepatitis may also by typical of CMV infection.

Human cytomegalovirus is a plausible driver of immune activation and inflammation in immunocompromised people.[25,26] Higher levels of CMV-specific IgG are associated with atherosclerosis in adults living with HIV on ART.[27] In an Italian cohort of adults living with HIV virally suppressed on ART, CMV seropositivity was associated with a 2.3 -fold higher incidence of cardiovascular events.[28] In addition, in asymptomatic adults living with HIV that were treated with valganciclovir, inflammatory biomarkers that strongly predict myocardial infarction and arterial inflammation (sCD163 and sICAM-1) were decreased. [29,30] There is limited evidence on how CMV infection affects future atherosclerosis or cardiovascular outcomes in perinatally HIV-infected children.

CMV and TB

Recently the association between CMV and tuberculosis (TB) has been highlighted in a study that showed that infants who acquired CMV before 24 months of age had an increased risk of tuberculosis disease between ages 1 and 9 years with an adjusted hazard ratio of 4.2 (95% CI 2·0–8·8; p<0·0001). Those with a high cytomegalovirus viral load seem to be at the highest risk.[31] Interestingly, CMV was not associated with higher rates of tuberculin skin test conversion but rather progression from infection to disease. Another case control study in South African infants found that the presence of IFN-γ responses specific to cytomegalovirus were associated with activated CD8+ T cells and a 22-times increase in the risk of tuberculosis disease.[32]

CMV in children with Primary Immune deficiencies

Infants with a primary immune disorder of cellular function for example severe combined immune deficiency; natural killer (NK) cell disorders may also present with severe or fatal pCMV infection.[33]

CMV infection in children with NK cell disorders can lead to
haemophagocytic lymphohistiocytosis (HLH). This is a life-threatening condition characterized by excessive immune activation and can be diagnosed clinically when patients meet five out of eight criteria: fever, splenomegaly, cytopenias affecting two or more blood lineages, hypertriglyceridemia and/or hypofibrinogenemia, haemophagocytosis, low/absent NK cell activity, hyperferritinemia and high soluble interleukin-2 receptor levels.[34] In addition, active and latent CMV infection induces sustained systemic inflammatory responses and immune dysregulation and predisposes patients to the development of autoimmune phenomena.[35] Persistent CMV can also drive progression to lymphoid malignancy. CMV retinitis, colitis and pneumonitis may also be seen in children with primary immune deficiencies.

Treatment

Antiviral therapy is not usually indicated for CMV infections in immunocompetent children. For symptomatic cCMV, treatment with ganciclovir or valganciclovir (depending on severity of illness) is recommended for 6 months and should be started within the first month of life and as soon as the diagnosis is confirmed. pCMV colitis and pneumonitis are also indications for ganciclovir treatment. Treatment is usually continued until there is clinical resolution but for at least 3 weeks and often up to 6 weeks.

Table 2 summarizes drugs that have been used to treat CMV. Only 5 drugs have been approved by the Food and Drug Administration for the treatment of CMV: Foscarnet (1991), Ganciclovir (1994), Valganciclor (2001), Cidofovir (1996) and Letermovir (2017).

Table 2. Drugs for the treatment of CMV infection

Anti-CMV Drugs	**Route of administration**	**Toxicity**
Ganciclovir	Intravenous	myelotoxicity + nephrotoxicity
Valganciclovir	oral	myelotoxicity + nephrotoxicity
Foscarnet	Intravenous	myelotoxicity + nephrotoxicity
Cidofovir	Intravenous	myelotoxicity + nephrotoxicity
Brincidofovir	oral	myelotoxicity + nephrotoxicity
Letermovir	Oral and Intravenous	none
Maribavir	oral	dyseugia, nausea, diarrhea, vomiting

Ganciclovir/valganciclovir (prodrug of Ganciclovir) phosphorylates CMV specific kinases and is incorporated into viral DNA and inhibits the viral polymerase by acting as a chain terminator. Resistance develops through mutations in UL97 that encodes for viral kinases or mutations in UL54 that encodes the viral polymerase.

Foscarnet inhibits the pyrophosphate binding site on viral polymerase while Cidofovir or Brincidofovir (its oral derivative) is also phosphorylated by cell kinases and acts as a chain terminator. Viral polymerase is the common target and certain mutations in UL54 can confer cross resistance to ganciclovir and Foscarnet. As a result of cross resistance as well as hematological and nephrotoxicity of currently available anti-CMV drugs, new drugs are being developed.

Letermovir inhibits the terminal phase of the viral lifecycle, targeting the sub-unit pUL56 of the terminase enzyme complex. It is CMV specific and does not have activity against herpes simplex virus (HSV). It can be given orally or intravenously and is currently approved for adult stem cell transplant recipients. Unfortunately, it has a low barrier for resistance and a single mutation can lead to resistance.[36]

Maribavir, a benzimidazole, is a competitive inhibitor of ATP binding to pUL97 (a protein kinase that phosphorylates itself and other proteins essential for the viral lifecycle).[37] Mutations in UL97 and UL27 confer resistance. pUL97 is needed for phosphorylation and antiviral activity of ganciclovir, thus ganciclovir and maribavir are antagonistic. It has in vitro activity against Epstein Barr virus (EBV) but not HSV 1 and 2, Varicella Zoster virus, Human Herpes virus 6 and 8. It can cause dysuegisia.[36] The primary indication for Maribavir is for latent infection and refractory CMV, however recurrence has been documented. It is available for compassionate use for children in the United Kingdom and resistance has already been described in this population.[38]

Passive human immunoglobulin (HIG) has been used to prevent mother-to-child transmission of CMV and delay progression of CMV disease in solid organ transplant patients. A monoclonal antibody that would mimic this response would be of great benefit. Trials are ongoing for TRL345 and this appears to be the most promising candidate. [39]

Sirtuins are host-targeted antivirals (HTAs) that are directed against the host cell processes upon which viruses are dependent. Compared to directly acting antivirals, HTAs have the potential to reduce or eliminate viral resistance and demonstrate broad-spectrum activity. First-generation HTAs, such as interferons, broadly activate the host's innate and adaptive immune responses (e.g. hepatitis B and C) but are limited by toxicity.

Prevention

Due to the ubiquity of CMV infection the development of a safe and efficacious vaccine is of great interest. However there are three major obstacles to achieving this goal: lack of clarity as to the best population to target for vaccination (pregnant mothers or breastfeeding infants) ; virological obstacles such as the latency of CMV, reactivation of CMV disease during periods of immune suppression and, CMV's ability to evade immune response by using cell to cell spread; and laboratory-based obstacles such as unknown correlates of protection and a lack of animal models available for experimentation. [40,41]

The earliest published efforts were in the mid-1970s which used attenuated virus but these did not provide sufficient clinical protection. [42,43]While an increasing number of vaccine candidates has been developed none have, as yet been licensed. Live-attenuated vaccines based on an attenuated AD169 strain are currently undergoing a phase 2 trial in Japan. [44] Subunit vaccines that contain only the antigenic parts of CMV have been described since the 1990s.[45] However, these vaccines often need boosting or combination of an adjuvant due to their poor immunogenicity and the most recent trial from 2016 showed a vaccine that was safe but not efficacious.[46] Other methods that have been tried include virus vectored vaccine using modified Vaccinia Ankara or lymphocytic choriomeningitis virus; chimeric peptidic vaccines which place pathogenic antigen coding genes in safe organisms and more recently messenger RNA vaccines which use similar methodology to that used in the successful Covid vaccines .[47-49]

Valganciclovir have been used to prevent cCMV in CMV positive pregnant women.[50]
Hyperimmune globulin did not consistently prevent cCMV in pregnant women who were CMV positive.[51]

Conclusion

In summary, CMV is an ubiquitous virus that may often be asymptomatic but can cause a significant burden of morbidity in children through various clinical presentations. Diagnosis can be made on multiple specimens and usually requires molecular techniques as well as clinical or histological presence of disease. There are relatively few drugs licensed to treat CMV, however new drugs are being developed and vaccines to prevent CMV infection are in the pipeline.

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References

1. Griffiths PD. Burden of disease associated with human cytomegalovirus and prospects for elimination by universal immunisation. The Lancet Infectious Diseases 2012; 12(10): 790-8.
2. Dupont L, Reeves MB. Cytomegalovirus latency and reactivation: recent insights into an age old problem. Reviews in Medical Virology 2016; 26(2): 75-89.
3. Kurath S, Halwachs-Baumann G, Müller W, Resch B. Transmission of cytomegalovirus via breast milk to the prematurely born infant: a systematic review. Clinical Microbiology and Infection 2010; 16(8): 1172-8.
4. Adler SP. Cytomegalovirus and child day care: risk factors for maternal infection. The Pediatric Infectious Disease Journal 1991; 10(8): 590-4.
5. Koontz D, Baecher K, Amin M, Nikolova S, Gallagher M, Dollard S. Evaluation of DNA extraction methods for the detection of cytomegalovirus in dried blood spots. Journal of Clinical Virology 2015; 66: 95-9.
6. Wreghitt T, Teare E, Sule O, Devi R, Rice P. Cytomegalovirus infection in immunocompetent patients. Clinical Infectious Diseases 2003; 37(12): 1603-6.
7. Goussard P, Kling S, Gie R, et al. CMV pneumonia in HIV-infected ventilated infants. Pediatric Pulmonology 2010; 45(7): 650-5.
8. Chintu C, Mudenda V, Lucas S, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. The Lancet 2002; 360(9338): 985-90.
9. Fowler KB McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. The Journal of Pediatrics 1997; 130(4): 624-30.
10. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. Journal of Clinical Virology 2006; 35(2): 226-31.
11. Kimberlin DW, Lin C-Y, Sánchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. The Journal of Pediatrics 2003; 143(1): 16-25.
12. Kimberlin DW, Jester PM, Sánchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. New England Journal of Medicine 2015; 372(10): 933-43.
13. Ouellette CP, Sánchez PJ, Xu Z, et al. Blood genome expression profiles in infants with congenital cytomegalovirus infection. Nature Communications 2020; 11(1): 1-11.
14. Zenebe MH, Mekonnen Z, Claeys G, Padalko E. Congenital cytomegalovirus infections:(no) focus on Africa: a review. Gynecology & Obstetrics (Sunneyvale Calif) 2021;11(1): No. 545.
15. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Reviews in Medical Virology 2007; 17(4): 253-76.
16. Elington SR, Clarke KE, Kourtis AP. Cytomegalovirus infection in human immunodeficiency virus (HIV)–exposed and HIV-infected infants: a systematic review. The Journal of Infectious Ciseases 2016; 213(6): 891-900.
17. Pathirana J, Groome M, Dorfman J, et al. Prevalence of congenital cytomegalovirus infection and associated risk of in utero human immunodeficiency virus (HIV) acquisition in a high-HIV prevalence setting, South Africa. Clinical Infectious Diseases 2019; 69(10): 1789-96.
18. Kadambari S, Whittaker E, Lyall H. Postnatally acquired cytomegalovirus infection in extremely premature infants: how best to manage? Archives of Disease in Childhood-Fetal and Neonatal Edition 2020; 105(3): 334-9.
19. Martins-Celini FP, Yamamoto AY, Passos DM, et al. Incidence, risk factors, and morbidity of acquired postnatal cytomegalovirus infection among preterm infants fed maternal milk in a highly seropositive population. Clinical Infectious Diseases 2016; 63(7): 929-36.
20. Prendergast AJ, Goga AE, Waitt C, et al. Transmission of CMV, HTLV-1, and HIV through breastmilk. The Lancet Child & Adolescent Health 2019; 3(4): 264-73.
21. Bimboese P, Kadambari S, Tabrizi SN, et al. Postnatal Cytomegalovirus Infection of Preterm and Very-low-birth-weight Infants Through Maternal Breast Milk: Does It Matter? Pediatr Infect Dis J 2022 Apr 1;41(4):343-351. doi: 10.1097/INF.0000000000003400.
22. Bates M, Brantsaeter AB. Human cytomegalovirus (CMV) in Africa: a neglected but important pathogen. Elsevier; 2016. p. 136-42.

23. Goussard P, Gie R. The role of bronchoscopy in the diagnosis and management of pediatric pulmonary tuberculosis. Expert Review of Respiratory Medicine 2014; 8(1): 101-9.
24. Zampoli M, Morrow B, Hsiao N-Y, Whitelaw A, Zar HJ. Prevalence and outcome of cytomegalovirus-associated pneumonia in relation to human immunodeficiency virus infection. The Pediatric Infectious Disease Journal 2011; 30(5): 413-7.
25. Schnittman SR, Hunt PW. Clinical consequences of asymptomatic cytomegalovirus in treated human immunodeficency virus infection. Curr Opin HIV AIDS. 2021;16(3):168-176. doi: 10.1097/COH.0000000000000678.
26. Patel EU, Gianella S, Newell K, et al. Elevated cytomegalovirus IgG antibody levels are associated with HIV-1 disease progression and immune activation. AIDS 2017; 31(6): 807-13.
27. Hsue PY, Hunt PW, Sinclair E, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. AIDS 2006; 20(18): 2275-83.
28. Lichtner M, Cicconi P, Vita S, et al. Cytomegalovirus coinfection is associated with an increased risk of severe non–AIDS-defining events in a large cohort of HIV-infected patients. The Journal of Infectious Diseases 2015; 211(2): 178-86.
29. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA 2012; 308(4): 379-8.
30. Tenorio AR, Zheng Y, Bosch RJ, et al. Soluble markers of inflammation and coagulation but not T-cell activation predict non–AIDS-defining morbid events during suppressive antiretroviral treatment. The Journal of Infectious Diseases 2014; 210(8): 1248-59.
31. Martinez L, Nicol MP, Wedderburn CJ, et al. Cytomegalovirus acquisition in infancy and the risk of tuberculosis disease in childhood: a longitudinal birth cohort study in Cape Town, South Africa. The Lancet Global Health 2021; 9(12): e1740-e9.
32. Müller J, Tanner R, Matsumiya M, et al. Cytomegalovirus infection is a risk factor for tuberculosis disease in infants. JCI Insight. 2019;4(23):e130090. doi: 10.1172/jci.insight.130090.
33. Miguel CPV, Mejias A, Ramilo O, Ardura MI, Sánchez PJ. Cytomegalovirus meningitis in an infant with severe combined immunodeficiency. The Journal of pediatrics 2016; 173: 235-7.
34. Bateman CM, Kesson A, Powys M, Wong M, Blyth E. Cytomegalovirus Infections in Children with Primary and Secondary Immune Deficiencies. Viruses 2021; 13(10): 2001.
35. Gugliesi F, Pasquero S, Griffante G, et al. Human Cytomegalovirus and Autoimmune Diseases: Where Are We? Viruses 2021;13(2):260. doi: 10.3390/v13020260.
36. Imlay HN, Kaul DR. Letermovir and maribavir for the treatment and prevention of cytomegalovirus infection in solid organ and stem cell transplant recipients. Clinical Infectious Diseases 2021; 73(1): 156-60.
37. Prichard MN. Function of human cytomegalovirus UL97 kinase in viral infection and its inhibition by maribavir. Reviews in Medical Virology 2009; 19(4): 215-29.
38. Houldcroft CJ, Bryant JM, Depledge DP, et al. Detection of low frequency multi-drug resistance and novel putative maribavir resistance in immunocompromised pediatric patients with cytomegalovirus. Frontiers in Microbiology 2016; 7: 1317.
39. Acosta E, Bowlin T, Brooks J, et al. Advances in the development of therapeutics for cytomegalovirus infections. The Journal of Infectious Diseases 2020; 221(Supplement_1): S32-S44.
40. La Rosa C, Diamond DJ. The immune response to human CMV. Future Virology 2012; 7(3): 279-93.
41. Griffiths P, Baraniak I, Reeves M. The pathogenesis of human cytomegalovirus. The Journal of Pathology 2015; 235(2): 288-97.
42. Plotkin S, Furukawa T, Zygraich N, Huygelen C. Candidate cytomegalovirus strain for human vaccination. Infection and immunity 1975; 12(3): 521-7.
43. Elek S, Stern H. Development of a vaccine against mental retardation caused by cytomegalovirus infection in utero. The Lancet 1974; 303(7845): 1-5.
44. Merck SD, C. Double-Blind, Randomized, Placebo-Controlled Phase 2b, Multi-Center Study to Evaluate the Safety,, Tolerability EaIoa-DaaDRoVCCV, in Healthy Seronegative Women tYoACTRNAo, https://clinicaltrials.gov/ct2/show/NCT03486834. Double-Blind,

Randomized, Placebo-Controlled Phase 2b, Multi-Center Study to Evaluate the Safety,Tolerability, Efficacy and Immunogenicity of a 2-Dose and a 3—Dose Regimen of V160 (Cytomegalovirus [CMV] Vaccine)in Healthy Seronegative Women, 16 to 35 Years of Age. 2021.
45. Gonczol E, Ianacone J, Ho W, Starr S, Meignier B, Plotkin S. Isolated gA/gB glycoprotein complex of human cytomegalovirus envelope induces humoral and cellular immune-responses in human volunteers. Vaccine 1990; 8(2): 130-6.
46. Bernstein DI, Munoz FM, Callahan ST, et al. Safety and efficacy of a cytomegalovirus glycoprotein B (gB) vaccine in adolescent girls: A randomized clinical trial. Vaccine 2016; 34(3): 313-9.
47. La Rosa C, Longmate J, Martinez J, et al. MVA vaccine encoding CMV antigens safely induces durable expansion of CMV-specific T cells in healthy adults. Blood, The Journal of the American Society of Hematology 2017; 129(1): 114-25.
48. HookipaBiotech GmbH. A Randomized P-C, Phase 2 Study of HB-101, a Bivalent Cytomegalovirus (CMV), Vaccine iC-SRR-PAKTfLC-SD, https://clinicaltrials.gov/ct2/show/NCT03629080 DCTRNAo, 2022) aoA.
49. ModernaTX IAP, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1647 Cytomegalovirus (CMV) Vaccine in Healthy Participants 16 to 40 Years of AgeClinicalTrials.gov Identifier: NCT05085366 Available online: https://clinicaltrials.gov/ct2/show/NCT05085366 (accessed on 22 April 2022).
50. Shahar-Nissan K, Pardo J, Peled O, et al. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. The Lancet 2020; 396(10253): 779-85.
51. Hughes BL, Clifton RG, Rouse DJ, et al. A trial of hyperimmune globulin to prevent congenital cytomegalovirus infection. New England Journal of Medicine 2021; 385(5): 436-44.

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