



eNeonatal Review VOLUME 8, ISSUE 5

Congenital Cytomegalovirus Infection: Diagnosis and Treatment



In this Issue...

Congenital cytomegalovirus (CMV) infection is one of the most commonly encountered infections by neonatologists. Recent knowledge gains in the epidemiology of the infection (i.e., day care acquisition and transmission to susceptible mothers) suggest mechanisms for decreasing CMV infections. Improved understanding of the efficacy vs. toxicity of ganciclovir therapy offers the first therapeutic intervention. Clearly, vaccine strategies need to be developed to prevent this infection and its potentially devastating complications.

In this issue, we review the natural history and pathogenesis of congenital CMV, as well as diagnosis, treatment, and new advances in prevention.

Program Information

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Length of Activity

- 1 hour Physicians
- 1 contact hour Nurses

Release Date

September 2, 2010

Expiration Date

September 1, 2012

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss the natural history and pathogenesis of congenital cytomegalovirus (CMV) infection
- Identify and diagnose congenital CMV infection
- Describe the treatments and prevention options of congenital CMV infection, and their limitations of each

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- Step 1.** Review the CE Information and study the educational content.
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- **Christoph U. Lehmann, MD**, has indicated a financial relationship of honoraria from Mead Johnson and PediatrIX. Dr. Lehmann is also the Editor-In-Chief of *Applied Clinical Informatics Journal*. He serves on the Board of Directors for the American Medical Informatics Association.
- **Anthony Bilenki, MA, RRT, Edward E. Lawson, MD, Lawrence M. Noguee, MD and Mary Terhaar, DNsc, RN** indicated they have no relevant financial relationships with any commercial supporters.

Guest Author's Disclosures

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Guest Faculty Disclosure

Richard J Whitley, MD has disclosed he served as a consultant for Gilead Sciences and Chimerix.

Unlabeled/Unapproved Uses

The author presentation today will include discussion of the off-label or unapproved uses of ganciclovir and valganciclovir.

[Program Directors' Disclosures](#)

COMMENTARY

Cytomegalovirus (CMV) is one of the more recently discovered human pathogens, having been first isolated in cell culture only about 40 years ago. It is a ubiquitous virus that infects only humans and rarely causes disease, with a few exceptions: the newborn (congenital infection), the immunocompromised host, and a mononucleosis syndrome in otherwise healthy individuals. Other syndromes have been attributed to CMV infection as well, in particular, coronary artery graft stenosis following heart transplantation. An intense effort is under way to study this pathogen and develop potential methods of prevention. In the late 1990s, the Institute of Medicine of the National Academy of Sciences named CMV the number one target for vaccine development.¹

Because of the cytopathic effect of the pathogen, in which enlarged cells with intranuclear and cytoplasmic inclusions are produced in vitro, CMV-infected cells have a classic “owl’s eye” appearance. Although these cytomegalic cells were first discovered in the kidneys² of stillborn infants and, subsequently, in the parotid glands,³ they can be found in virtually every infected cell type in humans.⁴⁻⁹ In vitro, CMV most readily infects human fibroblasts, with less affinity for other cell types. In contrast, human infection results in viral replication in a wide variety of cells.¹⁰

The early observations of cytomegalic inclusion cells in the urine, and the subsequent isolation of CMV in cell culture, initiated diagnostic screening programs to define the true incidence of disease, as well as the development of serologic tests to evaluate the seroepidemiology of infection. The evolution of diagnostic tests has been critical for current management strategies, particularly in the immunocompromised host.

When applying serology methods to define the prevalence of infection globally, several lessons became apparent immediately. First, in countries with low socioeconomic status, humans acquired the infection much earlier in life. By the teenage years, virtually all individuals in such countries have acquired CMV. In countries with higher socioeconomic status, infection was acquired much later in life and often occurred from exposure to toddlers in day care, as described below. Third, although not directly relevant to this review, seronegative individuals who receive an organ transplant from a seropositive

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donor are at high risk for a primary infection and, because of their immunocompromised status, significant consequences. Lastly, from data acquired in Scandinavian countries, breast-fed children acquire CMV infection very early in life.¹¹ The above observations have paved the way for detailed natural history evaluations.

Congenital CMV infection poses unique diagnostic problems, in that it can be both symptomatic (10% of infected newborns) or totally asymptomatic (90% of infected newborns) at birth.¹² Neonatal infection is the most frequently known viral cause of mental retardation,^{2,13} and is the leading nongenetic cause of sensorineural hearing loss in many countries, including the United States.³⁻⁶ Each year in the United States, ~40,000 infants are born prenatally infected with CMV (i.e., ~1% of all live births annually).¹² The majority of the initially asymptomatic patients subsequently experience significant neurologic sequelae, including sensorineural hearing loss, mental retardation, microcephaly, seizures, or paresis/paralysis.⁸⁻¹⁷ The overall societal cost of providing specialized services for surviving infants and children with congenital CMV infections is in the billions of dollars annually.^{18, 19}

The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group completed a phase III randomized, controlled investigation of intravenous (IV) ganciclovir for the treatment of symptomatic congenital CMV disease involving the central nervous system (CNS).²⁰ Results from this study indicate that 6 weeks of IV ganciclovir therapy decrease the likelihood that hearing loss will worsen over the first 2 years of life. The impact of antiviral therapy on neurodevelopmental outcomes was also evaluated to define additional markers of improved outcome. This study has set the stage for a subsequent clinical trial with orally administered valganciclovir.

Prevention of congenital CMV would be the ideal strategy. Two approaches have been taken in the past and both will be considered. First, in a nonrandomized clinical trial, high-titered antibody to CMV was administered to women who seroconverted to CMV, with improved outcomes reported in the fetuses.²¹ In a randomized, placebo-controlled vaccine trial, a subunit vaccine decreased the probability of seronegative women acquiring a wild-type infection.²² The results of the latter study, while promising, will require larger numbers of patients to determine the impact on at-risk fetuses, as well as the duration of protection. Live, attenuated CMV vaccines are in a variety of phases of development.

This series of reviews will focus on the key areas of our understanding of congenital CMV infection—in particular, pathogenesis, diagnosis, treatment, and prevention.

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EPIDEMIOLOGY OF CONGENITAL CMV INFECTION

Stagno S, Pass RF, Cloud G et al. Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus and clinical outcome. *JAMA*. 1986; 256(14):1904-1908.



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Human CMV has been detected in every human population tested.¹⁻³ Overall, the seroprevalence of CMV antibodies varies between 65% and 90% among middle-age adults in the United States, with primary CMV infection reported during pregnancy in 2% of women of childbearing age in middle-income or high-income socioeconomic groups vs. 6% of those in lower-income groups.^{4,5} Crowded living conditions, poor sanitation, the number of sexual partners, and increased exposure to infants and children contribute to increased rates of infection and a higher seroprevalence. Cytomegalovirus can be isolated from urine, saliva, cervical and vaginal secretions, semen, breast milk, tears, blood products, and transplanted organs.⁶⁻¹⁰

Newborn infection occurs as the result of 1 of 3 types of transmission: (1) intrauterine; (2) intrapartum; or (3) postnatal (breast milk acquisition). Intrauterine infection is usually the result of a susceptible woman acquiring the virus from a child in the family or from a day care environment early in the course of gestation.¹¹ Infection of women both immediately prior to and during pregnancy is associated with a risk for congenital CMV infection.^{12,13} In utero transmission occurs secondary to primary maternal infection and recurrent infections, including reinfection with a different strain of the virus¹⁴ or reactivation of the latent virus.¹⁵

Infants and children are important sources for the spread of CMV. Multiple studies in Sweden and the United States have shown that the rate of CMV infection is much higher in children who attend day care than those who do not.¹⁶⁻²¹ Many children who are initially seronegative become infected with CMV from their day care peers. CMV infection, then, is transmitted horizontally from child to child, most likely through the spread of saliva on hands and toys.^{22,23} These children then excrete large amounts of CMV for extended periods of time, exposing parents and other caregivers, who may become pregnant.

The amount of maternal shedding of virus correlates directly with the risk for perinatal infection. Ingestion of infected breast milk and exposure to CMV in the genital tract lead



to high rates of peripartum and postnatal CMV transmission.⁹ Infants who breastfed from CMV-seropositive women have an estimated rate of infection of between 39% and 59%.^{6,24} The risk appears greater from ongoing studies when the maternal viral load is higher than over one billion genome equivalents/mL. Excretion of the virus in breast milk is greatest between 2 weeks and 2 months postpartum. Infected infants usually begin to excrete CMV between 3 weeks and 3 months following birth.⁸ Many of these infants excrete CMV chronically (for years), providing an opportunity to infect caretakers and others who have contact with these children.

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CLINICAL PRESENTATION OF CONGENITAL CMV INFECTION

Ross SA, Boppana SB. **Congenital cytomegalovirus infection: outcome and diagnosis.** *Semin Pediatr Infect Dis.* 2005;16(1):44-9.



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Only 10% of all infants born in the United States with congenital CMV infection have symptomatic disease at birth.¹ Thus, approximately 90% of all infected children have no evidence of clinical disease. While these children generally have a better prognosis than symptomatic children, they are at risk for hearing loss; thus, the impact of infection on their health and development is considerable. Hearing loss is the most significant developmental abnormality in children with asymptomatic infection. Those children with asymptomatic infection have about a 7% probability of developing hearing loss.²⁻⁶ In 50% of children studied the hearing loss was bilateral, and in 50% it was progressive. The median age at first progression of hearing loss was 18 months. Eighteen percent of children had delayed onset of sensorineural hearing loss, with a median age of detection of 27 months.⁷

Cumulative data suggest that CMV infection causes at least one-third of all cases of sensorineural hearing loss in young children.⁸⁻¹⁰ Universal neonatal screening for hearing loss (usually performed in the hospital after birth) will thus miss a significant proportion of CMV-associated hearing loss that develops over time. Therefore, newborn hearing screening cannot completely detect all sensorineural hearing loss in children. In contrast to asymptotically infected babies, CMV-infected neonates, who are born with signs of infection (“symptomatic congenital CMV disease”), often have dramatic presentations. Babies with symptomatic congenital CMV disease can have sensorineural hearing loss, microcephaly, motor defects, mental retardation, chorioretinitis, and dental defects. The signs and symptoms of congenital CMV infection, along with their frequency, have been reviewed.¹¹

Roughly half of the infants with symptoms of infection at birth have generalized CMV that involves many organ systems.^{12,13} The most strikingly affected are the CNS and the reticuloendothelial system. Patients with generalized congenital CMV infection most commonly present with hepatomegaly, splenomegaly, microcephaly, jaundice, and petechiae.¹³ Of those with severe disease, 30% die of multiorgan dysfunction.¹⁴ Hepatomegaly and splenomegaly are the most common findings on physical examination in neonates with symptomatic congenital CMV.¹⁵ Splenomegaly, may be the only sign of infection, but is common among all congenital infections.^{12,15} Hepatomegaly may be striking at birth, but is also relatively nonspecific and usually resolves after 1 year of age. Cutaneous manifestations of congenital CMV infection include jaundice and a generalized petechial rash. Jaundice associated with CMV infection can sometimes be distinguished from physiologic jaundice because it can begin on the first day of life and usually lasts longer than physiologic jaundice.^{12,15} Fortunately, only about half of the total bilirubin is the direct bilirubin component, so although total bilirubin levels may be high, it is unusual for the indirect component to be high enough to require exchange transfusion.

The generalized petechial rash associated with CMV is caused by thrombocytopenia.^{15,16} Platelet counts vary widely, but usually range from 20,000 to 60,000/mm³, although even patients with normal platelet counts can have petechiae. The petechial rash develops within a few hours of birth and persists for 48 hours to a few weeks after birth. The rash may also be caused, in part, by the prolongation of normal fetal extramedullary haematopoiesis.

Microcephaly affected about one-half of all surviving patients with congenital CMV in one study, as defined as head circumference of less than the 5th percentile for age or gestational age.¹² Microcephaly has been found to be the most specific predictor of mental retardation. Mental retardation can also be predicted by the presence of intracranial calcifications, which indicate at least moderate and probably severe mental retardation.

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Congenital CMV infection can also involve the eye, with chorioretinitis, strabismus, and optic atrophy the most common ocular abnormalities.^{12,15,16} About 14% of patients with symptomatic congenital CMV have some degree of chorioretinitis.^{12,17} The central retinal lesions of CMV cannot be distinguished clinically from those of toxoplasmosis.^{17,18} Eye disease can often appear as strabismus, prompting closer examination of the eye. Unlike congenital toxoplasma infection, however, the retinitis caused by CMV does not progress.¹⁷

Very few children with symptomatic congenital CMV survive with normal intellect and hearing. One or more handicaps occur in almost 90% of the patients with symptomatic congenital CMV infection who do survive.¹² Overall, 70% of children with symptomatic infection have psychomotor retardation, usually accompanied by neurologic complications and microcephaly.¹ Of the 50% children who develop hearing loss, it is bilateral in 67% and, overall, progressive hearing loss occurs in 54%. Low IQ is associated with microcephaly at birth, development of neurologic problems within the first year of life, ocular lesions, and microcephaly that becomes apparent after birth.¹ Abnormal computed tomography (CT) scans within the first month of life seem to be the best predictor of adverse neurodevelopmental outcomes.^{1,19} Findings from CT scans are abnormal in 70% of symptomatic children, with the most common abnormality being intracerebral calcifications. One study interpreted CT scans from 56 children with symptomatic CMV infection and found that only 29% of children with a normal scan developed at least 1 neurologic sequela. In contrast, almost 90% of children with abnormal CT scans had at least 1 neurologic abnormality. In all, 59% of children with abnormal CT scans had an IQ of 70, compared with only 1 child with a normal CT scan.¹⁸

If acquired congenitally, CMV infection causes distinct CNS disease.¹ CNS disease is often an ongoing process, causing progressive changes for years after birth.^{2,12,18,20,21} Infection can cause structural changes within the CNS, such as periventricular calcifications, ventriculomegaly, and loss of gray-white matter differentiation.^{19,22,23} Loss of normal brain architecture often occurs with loss of normal radial neuronal migration.²⁴ Cerebrospinal fluid findings in infected infants generally reveal increased protein levels and white cell counts. Autopsy results reveal inflammatory infiltrates within the brain parenchyma.²³ These changes vary widely with age of gestation at the time of infection or reactivation of the virus. They also vary greatly in terms of the degree of disability they cause in patients.

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DIAGNOSIS OF CONGENITAL CYTOMEGALOVIRUS INFECTIONS

Boppana SB, Ross SA, Novak Z, et al., **National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection.** *JAMA.* 2010;303(14):1375-1382.



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The clinical presentation of congenital CMV infection mimics that of congenital rubella, toxoplasmosis, and herpes simplex virus infection (when acquired in utero). Thus, laboratory studies must be performed to confirm infection of the newborn.

Serologic studies for diagnostic purposes are of little value in decision-making regarding the management and treatment of CMV infection in newborns. Specifically, immunoglobulin M (IgM) studies lack both sensitivity and specificity.¹ Although historically virus isolation in cell culture was the accepted diagnostic test of choice; it was not a rapid test. Thus, the shell vial assay (72 hours) and polymerase chain reaction (PCR) detection of viral DNA in urine have become the standard tests used by most laboratories.¹

As newer and safer antiviral agents are developed, it will be important to identify those asymptomatic children who are infected and at risk for hearing impairment. Dried blood spots provide a source of DNA, from which CMV DNA has been detected.²⁻⁶ Boppana and colleagues have applied DNA extraction of cord blood by dot blots to determine the feasibility of universal screening for congenital CMV infection, regardless of clinical symptoms. Guthrie card spots of blood are used for metabolic screens of the newborn. When seeking evidence of asymptomatic infection, Boppana demonstrated that although the use of Guthrie cards will not be an acceptable method for widespread screening, it will be accepted for use in a limited number of cases.

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TREATMENT OF CONGENITAL CMV INFECTION

Kimberlin DW, Lin C, Sanchez PJ, et al, for the NIAID Collaborative Antiviral Study Group. **Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: A randomized controlled trial.** *J Pediatr.* 2003;143(1):16-25.



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To date, ganciclovir and valganciclovir are the only two agents that have been used for the treatment of congenital CMV infection. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (NIAID CASG) conducted a pharmacokinetic/pharmacodynamic study that established a safe dose of IV ganciclovir for administration to infected infants.¹

This was followed by a phase III randomized, controlled study to determine the effects of ganciclovir therapy on hearing in the treatment of symptomatic congenital CMV disease involving the CNS. In this study, 100 neonates, less than 1 month of age, with symptomatic congenital CMV involving the CNS, as defined by microcephaly, intracranial calcifications, abnormal cerebrospinal fluid for age, chorioretinitis, and/or hearing deficits, with confirmed isolation of CMV from a urine specimen, were enrolled after parental consent was obtained.

Infected newborns were randomized to receive either ganciclovir or no therapy. The patients in the ganciclovir treatment arm received 6 mg/kg per dose IV every 12 hours for 6 weeks. The primary endpoint of the study was brainstem-evoked response (BSER) audiometry improvement between baseline and 6-month follow-up or, for those with normal hearing at baseline, preservation of normal hearing at 6 months. Secondary endpoints included laboratory and clinical improvement, rate of growth, and death.

Although the loss-to-follow-up rate was high and, therefore, denominators for each parameter vary, rigorous evaluation of dropouts indicated lack of bias in analyses. Of 25 ganciclovir-treated infants, 21 (84%) who completed the study had hearing improvement or maintained normal hearing at 6 months, compared with 10 of 17 patients (59%) in the group who received no treatment ($P = .06$). At 6-month follow-up, none (0%) of the 25 ganciclovir recipients experienced hearing deterioration, whereas 7 of the 17 control subjects (41%) did ($P = .01$). A total of 43 patients had a BSER audiometry test at ≥ 1 year of age. Of these, 5 of 24 infants (21%) who had received ganciclovir experienced hearing deterioration in the best ear, compared with 13 of 19 control patients (68%; $P = .01$).

Secondary outcomes demonstrated significant short-term improvements in weight gain and head circumference in treated patients vs. controls (both $P < 0.01$). The treated group also experienced more rapid resolution of their liver function abnormalities. Similar rates of resolution of hepatosplenomegaly and CMV retinitis were reported among treated and untreated patients.

In addition, a retrospective but blinded analysis of neurodevelopmental outcomes demonstrated that treated babies were more likely to meet milestones compared with their counterparts in the observational cohort.²



As shown in the previous study, the primary toxicity associated with ganciclovir administration was neutropenia.¹ Of 46 ganciclovir recipients, 29 (63%) developed moderate to severe neutropenia, compared with 21% of those in the control group (P = .01). Of these 29 infants, 14 (48%) required dosage adjustments and 4 (14%) had the drug permanently discontinued.

This study demonstrated that 6 weeks of IV ganciclovir therapy prevents best-ear hearing deterioration during early childhood in patients with symptomatic congenital CMV affecting the CNS. However, the use of ganciclovir should be limited to those children with symptomatic disease, since the agent is mutagenic, teratogenic, and carcinogenic.³ Currently, the agent is recommended by the Committee on Infectious Diseases of the American Academy of Pediatrics.⁴

Although ganciclovir shows promise for the prevention of poor outcomes associated with congenital CMV infection, the agent is difficult to administer because it must be infused intravenously. Thus, the administration of valganciclovir, the oral prodrug of ganciclovir, for the treatment of neonates with congenital CMV disease is being explored. In one study, a total of 24 neonates received 6 weeks of therapy with either IV ganciclovir or oral valganciclovir.^{5,6} The aim of this study was to assess the population pharmacokinetics of a pharmaceutical-grade oral valganciclovir solution in order to identify a dose that provided ganciclovir exposure comparable to that reported with the administration of IV ganciclovir in neonates with symptomatic congenital CMV disease. The study found that a 6-mg/kg IV ganciclovir dose and a 16-mg/kg oral valganciclovir dose provide similar systemic exposures as demonstrated by both peak and trough plasma levels and area under the curve drug concentrations.^{5,6} In addition, the pharmacodynamic analyses showed a median decrease in viral load of 0.7 log viral DNA copies/mL in patients overall.^{5,6} Those with the highest viral loads (0.6 log viral DNA copies/mL) experienced a greater decline in viral load than did those with lower baseline viral loads.^{5,6} The toxicity of valganciclovir is similar to that of ganciclovir, with 38% of subjects developing moderate or severe neutropenia.^{5,6} Although results of using pharmaceutical-grade valganciclovir cannot be extrapolated to pharmacy-generated formulations, these findings suggest that the oral valganciclovir solution may be a viable option for the treatment of symptomatic congenital CMV infection. Currently, the NIAID CASG is conducting a controlled clinical trial of 6 weeks vs. 6 months of valganciclovir therapy to determine whether a longer duration of treatment is associated with improved hearing and developmental benefits.

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PREVENTION OF CONGENITAL CYTOMEGALOVIRUS INFECTION

Pass RF, Zhang C, Evans A, et al. **Vaccine prevention of maternal cytomegalovirus infection.** *N Engl J Med.* 2009;360(12):1191-1199.



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Progress in the prevention of either maternal primary CMV infection or congenital CMV infection has been modest at best. Initial efforts to develop a CMV vaccine began more than 25 years ago with use of the attenuated Towne strain of virus in renal transplant recipients.¹ However, use of this vaccine has been more limited among at-risk women.²

As knowledge of CMV infections in pregnant women has increased, so has an interest in the development of a safe and efficacious vaccine. The significance of preexisting immune responses was emphasized by Fowler and colleagues,^{3,4} who reported a 69% reduction in symptomatic congenital CMV infection in the presence of maternal antibody to CMV. Capitalizing on the observation that congenital infection was less severe among seropositive women, Nigro and coworkers⁵ evaluated the impact of CMV hyperimmune globulin administered to women with primary infection on “fetal disease” (intrauterine growth retardation). The authors concluded that hyperimmune globulin significantly reduced disease burden in the newborn from 50% to 13%. Even though the study suggested a benefit, it was criticized for not being randomized or placebo-controlled.

The recent report by Pass and associates is more encouraging with respect to reducing the rates of newborn CMV disease. Using a subunit vaccine that contained glycoprotein B and MF59 adjuvant in a 3-dose series, the investigators conducted a double-blind, placebo-controlled vaccine trial to determine vaccine impact on preventing primary CMV infection in seronegative women. In more than 450 randomized women, the vaccine proved to be 50% efficacious ($P = .02$). Importantly, this is the first indication of vaccine efficacy in an at-risk population. Because of the limited number of women evaluated, however, it was not possible to assess vaccine effects on the prevention of fetal disease.

Although this provides evidence that a phase III vaccine study should be conducted, it is premature to conclude that congenital CMV infection can be prevented.

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