Review Article

Congenital Cytomegalovirus Infection: Evaluation and Management

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Received: November 27, 2018 Accepted: April 15, 2019
doi: https://doi.org/10.3329/jemc.v9i2.41414

Abstract

Congenital cytomegalovirus (CMV) infection is the most common congenital infection worldwide and most individuals are eventually exposed to this agent. In developing countries the seroprevalence in women of reproductive age approximates 100%. Cytomegalovirus (CMV) infection has great importance to obstetrician-gynecologists and pediatricians. Despite the heavy disease burden, CMV infection is severely under-diagnosed because the majority (approximately 80%) of affected mothers are asymptomatic. The clinical manifestations of congenital CMV infection vary widely, from asymptomatic infection to potentially life-threatening disseminated disease. Prenatal diagnosis of fetal CMV infection can be made by testing amniotic fluid for cytomegalovirus by amniocentesis. Diagnosis of congenital cytomegalovirus infection in neonates should include real-time PCR of saliva, urine, or both, as soon as possible after birth. Antiviral therapy is not routinely recommended for congenital cytomegalovirus infection. Neonates with life-threatening infection and moderately to severely symptomatic congenital cytomegalovirus disease, CNS involvement is considered for immediate treatment that should be initiated within first month of life.

Key words: *Congenital cytomegalovirus (CMV) infection; Seroprevalence; Neonate; Real-time PCR*

J Enam Med Col 2019; 9(2): 116–126

Introduction

Cytomegalovirus (CMV) is an important viral pathogen for humans and most individuals are eventually exposed to this agent.[1,2] CMV is a double-stranded DNA virus, member of the human herpes virus family, ~235 kb in size. Humans are its only known host and that replicates within the nucleus of an infected cell and may remain latent in host cells after the primary infection.[3] CMV infection is endemic and does not show seasonal variations.[4]

The genome of CMV is divided into two regions – unique long (UL) region and a unique short region. UL region contains UL54 gene and UL97 gene which are important in antiviral therapies. UL54 gene produces DNA polymerase and is the target of several antiviral agents. UL97 gene produces phosphotransferase required for phosphorylation of ganciclovir. CMV has two special envelop proteins: glycoprotein B and glycoprotein H, against these humoral immune response occurs. CMV infect CD8 cells, endothelial cells, epithelial cells, fibroblasts, macrophages, and myocytes.[2]

In developed countries, CMV seroprevalence in women of reproductive age ranges from 50 to 85%, and in developing countries the seroprevalence approximates 100%.[5-7] Incidence of congenital CMV infection in developed countries is 0.6% to 0.7% of all live births.[5,6,8,9] Cytomegalovirus (CMV) infection has great importance to obstetrician-gynecologists and pediatricians. Congenital CMV infection is the most common congenital infection worldwide.[10,11] Despite

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the heavy disease burden, CMV infection is under-diagnosed because the majority (approximately 80%) of affected mothers are asymptomatic.[12,13]

1.1 Transmission

CMV is transmitted horizontally to mother as a result of contact with infected saliva and urine, sexual contact and also from organ donation and blood transfusion. CMV infection in newborns may be acquired congenitally through transplacental transmission (antepartum) and may also be perinatally (intrapartum and postpartum). Perinatal CMV infection is acquired by contact with contaminated blood and genital secretions during delivery and via breast milk after delivery. The incubation period ranges from 7 to 12 weeks, with an average of 8 weeks.[14-16]

1.2 Risk factors

- Exposure to/caring young children
- Lower socioeconomic levels
- Nonwhite races
- Sexual activity, multiple sexual partners
- History of abnormal cervical cytology
- First pregnancy at younger than 15 years
- Multiparous women
- Co-infection with other sexually transmitted diseases (STDs) such as trichomoniasis.[5-7,17]

1.3 Maternal CMV infection

Maternal CMV infection may be primary infection and non-primary infection (reactivation of latent infection or re-infection with new strain in seropositive women). Primary infection means mothers without preexisting immunity who first acquire CMV infection in pregnancy. Non-primary infection means women with preexisting antibodies (seropositive) to CMV either by reactivation of a previous maternal latent infection or by acquisition of a different viral strain.[18]

1.4 Congenital CMV infection

Congenital infection is highest following primary maternal infection. About 1–4% of CMV seronegative mothers become infected during pregnancy and women with primary CMV in pregnancy have a risk of congenital infection of 30–50%, rate is as high as 70% with third-trimester exposure.[18,19] Among women with a primary infection, 18% of their infants will be symptomatic at the time of birth.[20]

Among the symptomatic group, 30% may die. Up to 25% are not symptomatic at birth and experience long-term neuro-developmental sequelae during the first 2 years of life. Among infants followed up to 5 years of age, development of sequela occurs as late as 72 months. Severe illness appears to be more likely

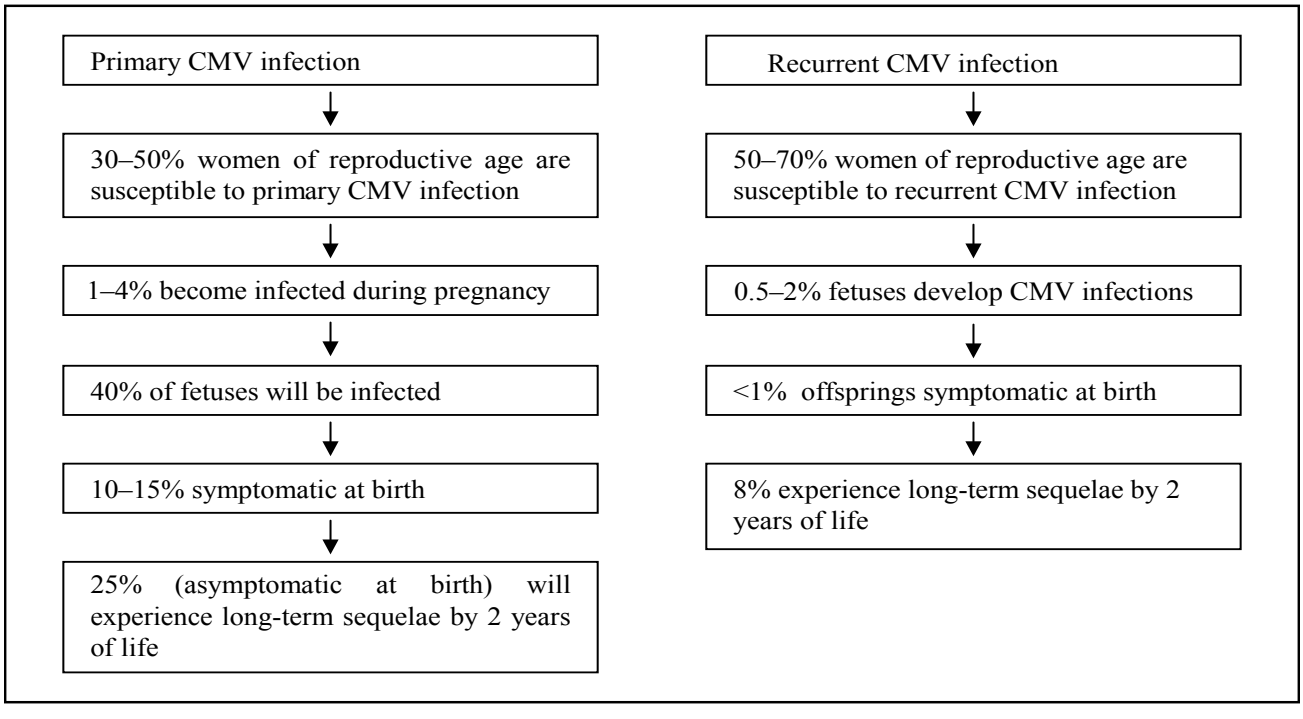


Fig 1. Maternal and neonatal risks of CMV infection[24]

among fetuses whose mothers experience primary infection during the first half of pregnancy.[21,22] About 50–70% women of reproductive age are susceptible to recurrent CMV infection and 0.5–2% fetus will develop CMV infections, <1% of offsprings are symptomatic at birth.[22,23] However, 8% of offsprings will develop neurodevelopmental sequelae by age 2 years and 14% by age 5 years.[22] Maternal and neonatal risks of CMV infection[24] are shown in Fig 1.

1. Clinical manifestations

The clinical manifestations of congenital CMV infection varies widely, from the asymptomatic infection to potentially life-threatening disseminated disease.[8,10] Clinical features include petechiae, microcephaly, lethargy/hopotonia, poor suck, seizures, jaundice, hepatosplenomegaly, small for gestational age, prematurity etc. Laboratory manifestations include elevated serum transaminases, conjugated hyperbilirubinemia, thrombocytopenia, elevated cerebrospinal fluid protein etc.[25]

According to severity of infection different types of CMV infection are summarized in Table I. Definitions of symptoms and signs are shown in Table II.

Long-term sequelae occur following both symptomatic and asymptomatic congenital infections, with the more frequent and severe sequelae occurring in symptomatic infants. It has been estimated that 40–58% of infants who are symptomatic at birth develop sequelae, and these may include sensorineural hearing loss, vision loss, mental retardation, seizure disorder, cerebral palsy, visual deficits, hypotonia, poor feeding, ventriculomegaly, polymicrogyria, periventricular pseudocysts and developmental delay.[8,25,28,29] Hearing loss is most common when CMV infection occurs in the first or second trimester.[22] Sensorineural hearing loss following symptomatic or asymptomatic congenital infection is often progressive, can be unilateral or bilateral, and may be absent at birth, only to become clinically manifest later in childhood. Among infants with symptomatic congenital CMV infection, SNHL will affect 30% at birth. Among the 90% of asymptomatic infants at birth, 7–15% will develop progressive SNHL later in childhood.[8,20,30,31] Ophthalmologic manifestations of congenital CMV include chorioretinitis, strabismus, microphthalmia, optic nerve atrophy, and cortical visual impairment.[2]

Table I: Case definitions of congenital CMV infection[26,27]

Definitions of congenital cytomegalovirus infection and disease
• Symptomatic CCMV infection: positive CMV in any secretions within the first 3 weeks of life with clinical manifestations of intra-uterine infection involving central nervous system (CNS) or lymphoreticular system. • Neonate with life-threatening infection: pneumonitis, esophagitis, colitis and severe thrombocytopenia requiring repeated platelet transfusions. • Moderately to severely symptomatic congenital cytomegalovirus disease ▪ Disseminated CCMV infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin) ▪ Central nervous system involvement: microcephaly, radiographic abnormalities consistent with cytomegalovirus central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or the detection of cytomegalovirus DNA in cerebrospinal fluid
• Mildly symptomatic congenital cytomegalovirus disease: one or two isolated manifestations that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations.
• Asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss: no apparent abnormalities to suggest congenital cytomegalovirus disease, but sensorineural hearing loss (≥21 decibels). • Asymptomatic congenital cytomegalovirus infection: positive CMV in any secretions within the first 3 weeks of life but no apparent abnormalities in clinical and laboratory findings and normal hearing.

Table II : Definitions of symptoms and signs[27]

▪ Microcephaly: head circumference (OFC) <2 SD below the mean for age or <2nd centile. ▪ Symmetric IUGR: birth weight and head circumference (OFC) <2 SD below mean for age. ▪ Thrombocytopenia: <100000/cu mm ▪ Conjugated hyperbilirubinaemia: >66 micromol /L (>3 mg/dL)

2. Investigations

Diagnosis of the cytomegalovirus-infected neonate

A newborn should be evaluated if there are features suggestive of congenital CMV infection or mother having previous history of CMV infection, have to screen for CMV infection. Diagnosis of congenital cytomegalovirus infection in neonates should include real-time PCR of saliva, urine, or both as soon as possible after birth but within the first 3 weeks of life, with saliva as the preferred sample. Both urine and saliva are reliable specimens for neonatal cytomegalovirus screening using PCR. Real-time PCR of saliva showed high sensitivity (>97%) and specificity (99%).[26,32,33]

CMV IgG and IgM antibody levels are not recommended for the specific diagnosis of congenital CMV infection because only 20–70% of infected babies will have a positive CMV IgM antibody titer and many newborns will have a positive CMV IgG antibody titer from blood passed to them from their mother[34] (Table III).

Table III: Interpretation of neonate's CMV antibody

Antibody	Antibody	Interpretation
IgG +	IgM +	Congenital infection
IgG +	IgM -	Maternal antibody
IgG -	IgM +	Acquired/recent infection

Other methods for diagnosing CMV have also been described, e.g., CMV-specific IgM, CMV DNAemia in peripheral blood leucocytes, and CMV pp65-antigenemia test, urine DEAFF test.[35,36]

Once the diagnosis is confirmed, further laboratory tests, imaging and eye and hearing assessments are indicated. CBC and LFTs may reveal pancytopenia/ thrombocytopenia and raised ALT, prolonged prothrombin time and coagulation studies may be abnormal in the setting of hepatitis. Renal function is checked prior to beginning of treatment with ganciclovir. Neuroimaging assessment such as cranial ultrasound is a good screening tool with subsequent MRI/CT is recommended for definitive evaluation (Fig 2,3).[37,38]

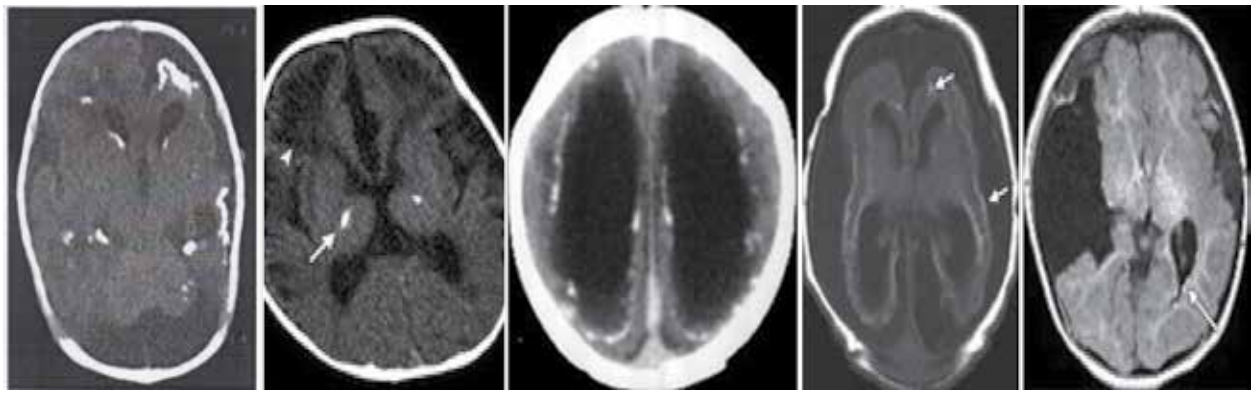
USG findings also help in prenatal diagnosis of congenital CMV infection. A cranial ultrasound should be performed as soon as possible after birth. Cranial CT and/or MRI should also be considered in the neonatal period if there is a high index of suspicion of neurological involvement with CCMV infection despite normal cranial ultrasound scan.[23]

Ultrasound abnormalities from cases of confirmed congenital cytomegalovirus infection[39,40] are cerebral calcifications, microcephaly, echogenic bowel, fetal growth restriction, subependymal

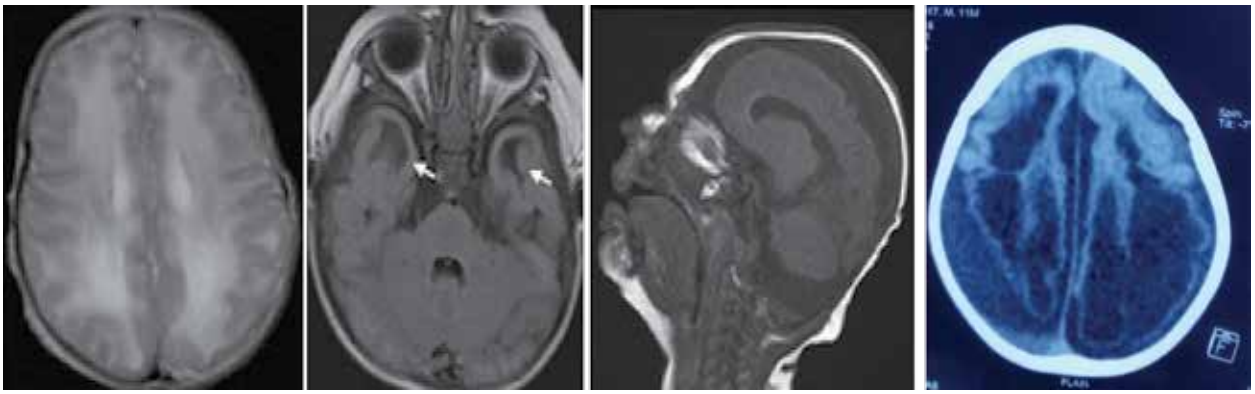
Cortical calcifications (arrow) and mild passive ventriculomegaly on USG brain

6-month-old girl with microcephaly and agyria-pachygyria and ventriculomegaly

Fig 2. Radiological findings in congenital CMV infection



a. Periventricular and parenchymal calcifications | b. Thalamic calcification | c.Ventriculomegaly and calcifications | d. Lissencephaly | e. Schizencephaly



f. Delayed myelination (diffuse hyperintensity of white matter) | g. Ventricular temporal horn dilatation | h. Generalized cerebral and cerebellar volume loss | i. Encephalomalacia

Fig 3. CT/MRI findings in congenital CMV infection

cysts, cerebral ventriculomegaly, ascites, pericardial effusion, hyperechogenic kidneys, hepatomegaly, placentomegaly or placental calcifications, hepatic calcifications and hydrops.

Ophthalmologic assessment should be performed on all infants with congenital CMV infection. Audiological assessment should be performed in all infants with congenital CMV infection: as noted, SNHL may be absent at birth, and progressive in nature, and frequent evaluations are required throughout childhood to find out the possibility of hearing deterioration.[30]

3.2 Prenatal diagnosis of fetal cytomegalovirus infection

Prenatal diagnosis of fetal CMV infection can be made by testing amniotic fluid for cytomegalovirus by amniocentesis. It is done in two situations: when there is maternal primary CMV infection during pregnancy, or when there are abnormalities on ultrasound that

Table IV: Diagnosis of CMV infection in pregnancy[14]

Type of infection	Serum PCR	Urine PCR	IgM	IgG
Primary/acute	Positive	Positive	Positive	Absent on low avidity antibody
Recurrent or reactivated	Usually negative	may be positive	Usually negative, but secondary response can occur	Positive for high avidity antibody

are compatible with fetal cytomegalovirus infection. Amniocentesis for CMV has the best sensitivity after 21 weeks gestation when fetal urination is well-established, and at least 6 weeks from the time of maternal CMV infection.[41]

The presence of cytomegalovirus can be detected using real-time PCR (most sensitive) or virus culture. If cytomegalovirus is detected in the amniotic fluid, fetal infection is confirmed.[42–44] Diagnosis of CMV infection in pregnancy is shown in Table IV.

3. Treatment

Treatment of congenital CMV infection should be given cautiously and toxicities of antivirals must balance with potential benefits. Neonates with asymptomatic congenital cytomegalovirus infection should not be given antiviral therapy. Neonates with mildly symptomatic congenital cytomegalovirus infection should not routinely be given antiviral therapy. Antiviral therapy is not routinely recommended for congenital cytomegalovirus infection with isolated sensorineural hearing loss and otherwise asymptomatic. Neonates with life-threatening infection and moderately to severely symptomatic congenital cytomegalovirus disease are considered for immediate treatment which should be initiated within first month of life. Neonates with CNS involvement should be treated. Chorioretinitis can cause sight-threatening infection and hence warrants prompt treatment.[26,27] Evidence that oral valganciclovir improves or preserves hearing in infants with symptomatic congenital cytomegalovirus infection.[45–47]

Valganciclovir treatment for 6 months is only recommended for congenitally infected neonates with moderately to severely symptomatic disease.[26] Kimberlin DW et al[48] showed that neonates receiving 6 months of valganciclovir had a 2·6 times increased likelihood of improved total hearing at 24 months than those who received only 6 weeks of valganciclovir treatment. Algorithm of congenital CMV infection management[49] is shown in Fig 4.

Acute side-effects are neutropenia (in up to 63% with ganciclovir and up to 38% with valganciclovir) and neutropenia-related sepsis (rare). Other rare side-effects are bone marrow suppression, raised liver enzymes, hypokalemia and renal impairment. All these side-effects are reversible after stopping the drug for at least 3–7 days. Other possible risks are gonadal dysgenesis, carcinogenicity etc.[2] Current therapies for petdiatric CMV infection is shown in Table V and monitoring of ganciclovir and valganciclovir is shown Table VI.

Table V: Current therapies for pediatric CMV infection[2]

Drugs	Route of administration	Suggested dosing regimens	Adverse effects
Ganciclovir	Intravenous	Congenital infection: 6 mg/kg/dose every 12 hour for 6 weeks	Myelosuppression (particularly neutropenia)
Valganciclovir	Enteral	Congenital infection in neonates >7-day-old and infants 1–3 months of age: 16 mg/kg/dose every 12 hourly	Myelosuppression
Foscarnet	Intravenous	HIV-infected infants and children with disseminated CCMV infection or retinitis: Induction: 180 mg/kg/day, every 8 hour for 14–21 days, then maintenance: 90–120 mg/kg/dose once daily. CCMV infection with central nervous system involvement: 180 mg/kg/day, every 8 hour until symptoms improve followed by chronic suppression	Nephrotoxicity
Cidofovir	Intravenous	CCMV Infection in children: Induction: 5 mg/kg/dose once weekly for 32 consecutive weeks Maintenance: 3–5 mg/kg/dose once weekly every 2 week for 2–4 doses	Nephrotoxicity neutropenia, metabolic acidosis

Table VI: Monitoring of ganciclovir and valganciclovir[27]

Drugs	Ganciclovir	Valganciclovir
Dose	6 mg/kg twice a day	16 mg/kg twice a day
Time of levels	Just before and 1 hour after second dose	Just before and 2 hours after third dose
Peak level	6–8 mg/L	6–8 mg/L
Trough level	<0.5 mg/L	<0.5 mg/L
Monitoring	3 times weekly full blood count (CBC), liver function tests(LFT), creatinine, urea and electrolytes drug levels once weekly	3 times weekly full blood count (CBC), liver function tests (LFT), creatinine, urea and electrolytes drug levels once weekly
Indication for suspension of treatment	Absolute neutrophil count (ANC) <500/cu mm Platelet count <25000/cu mm	Absolute neutrophil count (ANC) <500/cu mm Platelet count <25000/cu mm

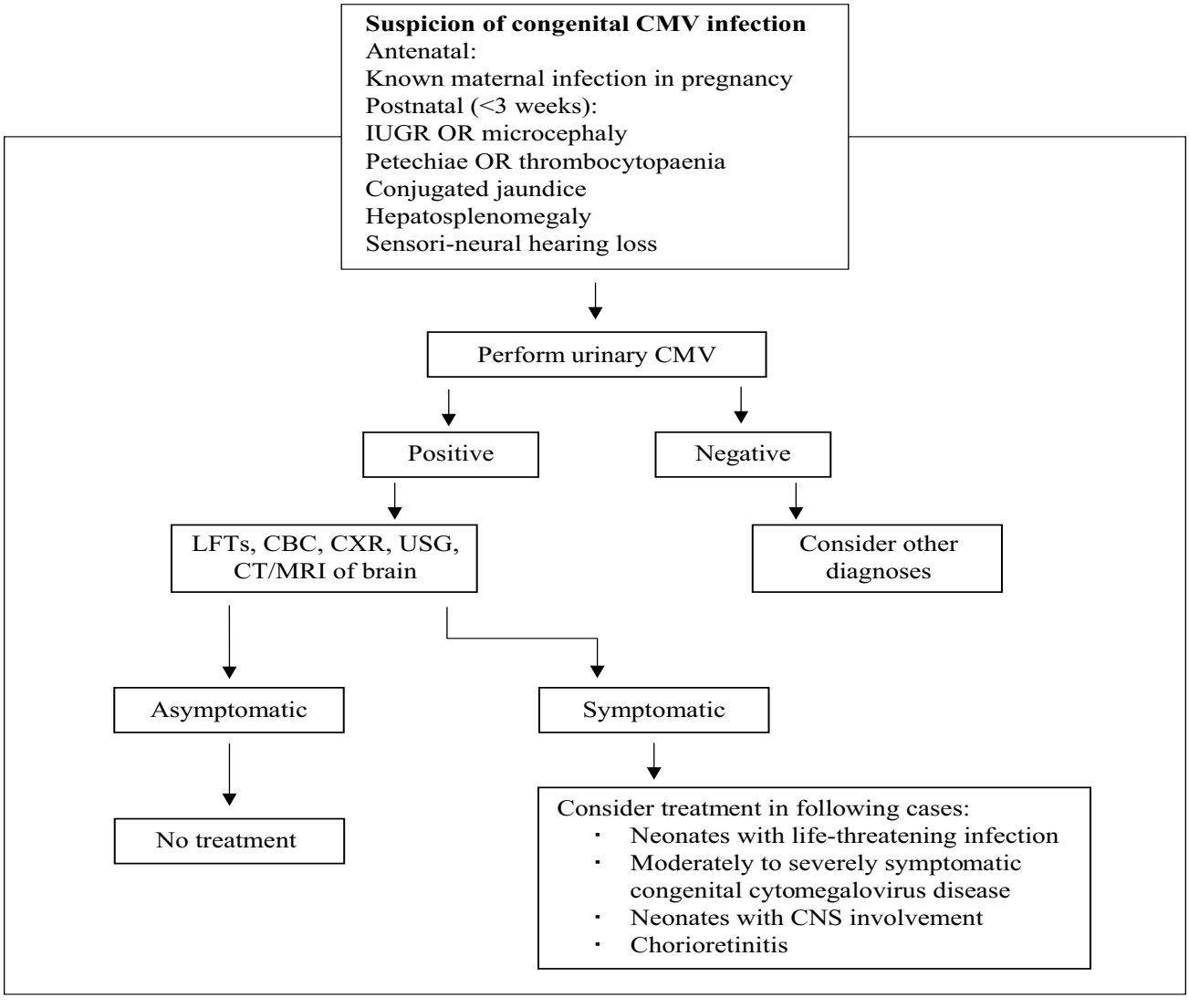


Fig 4. Algorithm of congenital CMV infection management[49]

4. Prevention of congenital CMV infection

Strategies to reduce the burden of congenital CMV disease include prevention of maternal infection, prevention of mother to child transmission (MTCT), early detection and intervention by neonatal screening, and neonatal antiviral therapy.

5.1 Active immunization

Development of a CMV vaccine is the most promising strategy for addressing the problem of congenital CMV. Ongoing and future clinical trials will hopefully lead to the licensure of a CMV vaccine in the not-to-distant future.

5.2 Passive immunization

In addition to active immunization strategies, passive immunization based on administration of anti-CMV immune globulin to women at risk of transmitting CMV to the fetus is currently an intensely active area of clinical research. La Torre et al[50] and Nigro et al[51] showed that administration of HIG to women in the primary infection has significant reductions in placental pathology, and regression of cerebral structural abnormalities in some infants.

Buxmann et al[52] showed that HIG administration reduced intrauterine transmission of CMV. The use of HIG during pregnancy has also been reported to be associated with improved neurodevelopmental outcomes in infants in the first year of life.[53]

Randomized controlled trials of HIG are warranted in high-risk pregnancies, to validate the protective effect of passive immunization. The HIG regimen was 100 U/kg monthly until delivery.[54] Society for Maternal-Fetal Medicine do not recommend antenatal treatment with ganciclovir or valacyclovir and we recommend that any antenatal therapy, either with antivirals or CMV HIG, should only be offered as part of a research protocol.[23]

5.3 Behavioral interventions for pregnant women

- Avoid sharing of food, drinks or spoon used by young children.
- Do not put anything like child's dummy, soother, pacifier, toothbrush etc. used by young children in your mouth.
- Avoid contact with saliva during kissing a child.
- Immediate hand wash with soap and water after changing any material such as nappies, diapers, toys etc. that comes in contact with child's urine and saliva and also after feeding a young child or wiping a young child's nose or saliva.
- Regular cleaning of toys, countertops, and other surfaces that come into contact with children's urine or saliva.[26,55–58]

6. Follow-up

All infants both treated and untreated should have regular auditory, ophthalmological and neurological evaluation for detection of cognitive and neurodevelopmental impairment as well as late-onset or progressive SNHL. Recommendation for follow-up is shown in Table VII.

Table VII: Recommendation for follow-up[27]

Evaluation	Age recommendation
Follow-up for neonates with CCMV infection with audiometry	At diagnosis, 3, 6, 9, 12, 18, 24, 30 and 36 months and then annually to school age
Indirect ophthalmoscopy and visual function	At diagnosis, 12 months, 3 years and preschool age
Neurological examination and developmental assessment	At each visit

Conclusion

Congenital CMV infection has significant impact and burden on the individual and the society. High index of suspicion based on high risk populations and clinical features of newborn can prevent mortality and morbidity. Effective preventive strategies for reproductive women are warranted for both developed and developing countries.

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