Congenital Cytomegalovirus: Update and Clinical Practice Proposals

Opinion Article

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Article received on February 10, 2026.
Accepted for publication on February 19, 2026.

Abstract

Cytomegalovirus (CMV) is the most common congenital infection worldwide. Its clinical presentation is highly variable, ranging from asymptomatic infection to severe neurological sequelae, which may be present at birth or manifest later during childhood. Despite its high prevalence and significant long-term impact—resulting in sequelae in 10–20% of affected cases—congenital CMV remains substantially underdiagnosed. Health literacy on this topic is generally low, limiting opportunities for prevention of maternal infection and for timely prenatal and postnatal diagnosis. This, in turn, leads to missed opportunities for early treatment and specialized follow-up that could potentially mitigate the negative consequences of the infection.

This document aims to simplify the main recommendations of the current European consensus, "Consensus recommendation for prenatal, neonatal and postnatal management of congenital cytomegalovirus infection from the European Congenital Infection Initiative (ECCI)," while also complementing areas in which the original document is less detailed (e.g., hearing assessments). The goal is to support a more informed and straightforward daily clinical practice for healthcare professionals who may be less familiar with congenital CMV.

Preamble

This study aims to integrate the most up-to-date scientific evidence and consolidate practical recommendations for healthcare professionals involved in the management of congenital cytomegalovirus (CMV) infection at the national level. The working group was initially established by otolaryngologists with a scientific interest in congenital CMV, who came together voluntarily to promote greater awareness of this infection, recognized as the leading non-genetic cause of sensorineural hearing loss in children. Over time, the initiative evolved into a multidisciplinary team comprising specialists in obstetrics,

neonatology, pediatric infectious diseases, clinical pathology, otolaryngology, audiology, psychology, and public health.

The group's primary objective is to emphasize the importance of prevention and early diagnosis of congenital CMV infection, both prenatally and postnatally; to support timely treatment decisions when indicated, and to ensure appropriate longitudinal follow-up for affected children, who may experience neonatal complications or develop late-onset manifestations throughout childhood.

The current scientific evidence indicates that primary and secondary prevention measures can decrease the risk of transmission and that early diagnosis allows for timely intervention, potentially improving the prognosis. A portion of cases could be avoided through preventive strategies and greater awareness among healthcare professionals and the general public. In this context, it is essential to promote informed, up-to-date clinical practice based on the best available evidence, guaranteeing a rigorous approach for affected children and their families. This document, **"Congenital Cytomegalovirus: Update and Proposals for Clinical Practice,"** is shaped as a frequently asked questions (FAQ) guide to provide concise, scientifically sound answers to the most common questions encountered in clinical practice.

Introduction

Congenital CMV (cCMV) is the leading cause of non-genetic hearing loss and a major cause of neurodevelopmental disorders. Despite being the most common congenital infection, affecting 0.2% to 2% of all pregnancies, cCMV remains widely unrecognized and underdiagnosed.[1] Congenital infections can result from either a primary or non-primary maternal infection, both of which can be severe. The current evidence demonstrates that the risk of sequelae in infected newborns is 10% to 20%. The clinical presentation varies significantly; however, when maternal infection occurs in the first trimester, there is a higher risk of severe complications such as hearing loss, neurodevelopmental disorders, and decreased visual acuity, among others.[2]

Thus, cCMV can have a negative individual impact, particularly regarding cognitive performance, language development, and academic achievement as well as broader family and social repercussions linked to significant direct and indirect costs .

Since there is currently no vaccine to prevent maternal infection, efforts to reduce fetal and neonatal morbidity and mortality must be multimodal. This approach includes behavioral measures to prevent maternal infection, prevention of mother-to-child transmission, treatment of the infected fetus and newborn (when indicated), and follow-up of infected children. Health literacy regarding this condition remains limited among both healthcare professionals[3, 4, 5] and the general public, thereby hindering the efforts to prevent infection, conduct pre- and postnatal diagnoses, and, consequently, seize the opportunity for timely treatment and specialized follow-up care. This document, "Congenital Cytomegalovirus: Update and Proposals for Clinical Practice," is structured as a Frequently Asked Questions (FAQ) guide addressing the key questions clinicians may encounter in their routine practice and providing concise, evidence-based answers. The questions are organized according to the relevant period: PRECONCEPTION, PRENATAL, NEONATAL, and POSTNATAL.

PRECONCEPTION

1. Is it possible to prevent maternal CMV infection? ▸ YES

1.1. How? Preventing maternal CMV infection relies primarily on behavioral risk-reduction strategies, such as proper hygiene practices.[1] The effectiveness of these measures has been well documented in women without prior infection; however, they should be followed by all women.

1.2. When is it most important? During the periconceptional period and first trimester of pregnancy[1]

1.3. Who is at the highest risk? Women with no previous exposure to the virus (non-immune). Healthcare professionals, mothers of preschool-aged children attending daycare, and early childhood educators are at a particularly high risk, as infected children shed the virus in their urine and saliva for extended periods[1].

1.4. What measures should be considered?

• Proper hand hygiene: after coming into contact with the urine or saliva of young children, such as when changing diapers, cleaning the child's nose, feeding the child, or playing with potentially contaminated toys[1];
• Preventing direct contact with the saliva or secretions of young children, particularly by not sharing food[1];
• Not sharing personal items with children such as utensils, cups, or toothbrushes[1];
• Cleaning and disinfecting surfaces[1];
• Avoiding contact with the saliva and/or urine of symptomatic children or adults[6].

1.5. What should be included in the preconception consultation regarding CMV? At this stage, it is critical to educate women planning to conceive about the nature of the disease and to assess their CMV immune status. Generally, the awareness of cCMV infection is low among the general public, and particularly among pregnant women[6]. During the preconception consultation, it is essential to provide clear information on what CMV infection is, how it is transmitted, how to prevent congenital infection, potential risks to the fetus, and the available treatment options. Screening (using CMV IgM and IgG serology) should ideally be performed during the preconception period or as early as possible in the first trimester (see question 2). A woman who tests positive for IgG does not need to undergo further serological testing.

PRENATAL

2. Should pregnant women undergo serological screening for CMV infection? ▸ YES

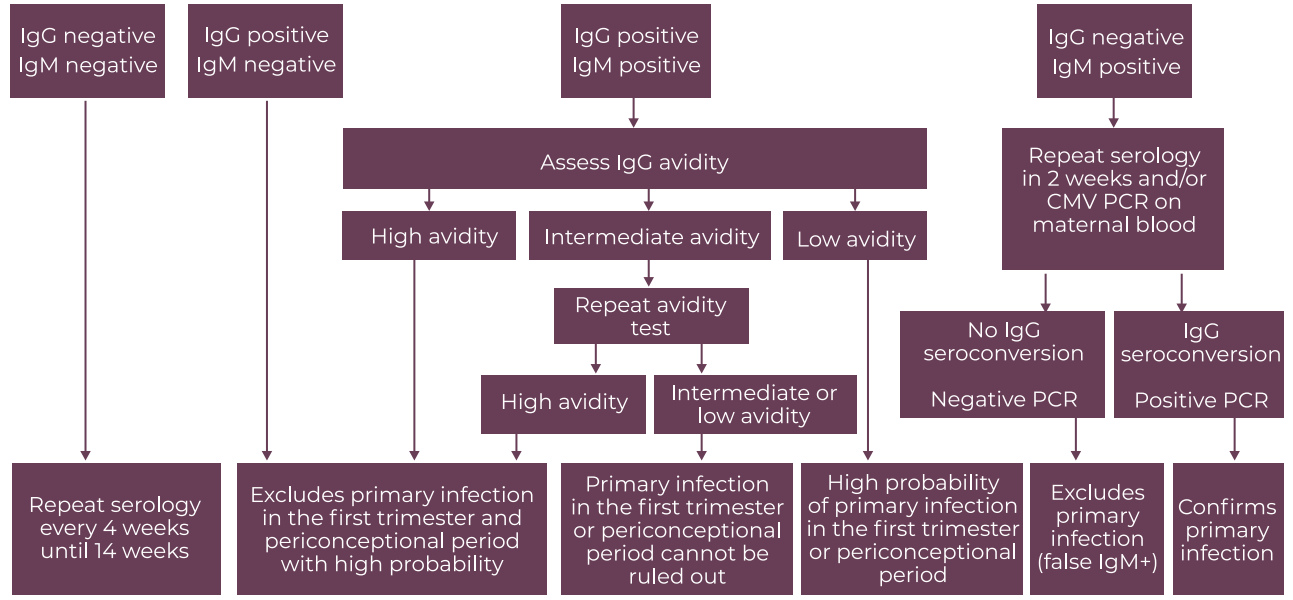
2.1. When? As early as possible at the beginning of pregnancy, if the pregnant woman was IgG-negative prior to conception or if her prior immune status is unknown[1].

2.2. How? By testing for IgG and IgM, and if the latter is positive, evaluating IgG avidity.[1]

• If IgG− and IgM−: Reinforce information on primary prevention measures and repeat serological testing every 4 weeks until the end of the first trimester (14 weeks) – susceptible pregnant woman;
• If IgG+ and IgM−: Do not repeat serological tests. Prior CMV exposure is assumed, and while a non-primary infection may occur, it cannot be diagnosed through serology;
• If IgG− and IgM+: Always repeat the serological tests 2 weeks later to confirm seroconversion (IgG should turn positive) or to assume a false-positive IgM (if IgG remains negative), which is common due to non-specific cross-reactions. Consider the pregnant woman susceptible. Maternal viremia can also be assessed via polymerase chain reaction (PCR) to establish a diagnosis during the early stages of a primary maternal infection before IgG has had time to turn positive;
• If IgG+ and IgM+: Measure the IgG avidity. If the avidity is low or intermediate (based on the specific laboratory's reference ranges), it indicates that the primary infection may have occurred during the critical window for fetal injury (periconception or first trimester).

The group advocates for prenatal screening in the first trimester, as it allows for the early detection of primary maternal infection. Identifying these cases is critical because it allows for pharmacological prophylaxis against mother-to-child transmission, thereby reducing the number of infected newborns (secondary prevention – see questions 6.1 and 6.2).

Figure 1
Algorithm for interpreting CMV serology in the first trimester of pregnancy. Source: adapted from Leruez-Ville M, 2024.[1]



3. What measures are recommended for a pregnant woman who is IgG-positive for CMV? General, non-specific hygiene measures (non-primary infections do not seem to be linked to the same risk factors as primary infections)[1] [See question 1]. A pregnant woman who is seropositive for CMV (i.e., with prior exposure or positive IgG) should not undergo further CMV serological testing as non-primary infections cannot be diagnosed via serology (see question 4).

4. How is a primary maternal infection and non-primary infection diagnosed? Maternal infections are generally asymptomatic but can sometimes present as a non-specific flu-like syndrome or with abnormal liver function tests.

4.1. Primary infection: Diagnosed through seroconversion when comparing two serological tests where the first test is IgG-negative and the second test is IgG-positive. When no prior serological testing is available, it is diagnosed by the presence of IgG+, IgM+, and low or intermediate IgG avidity in the first trimester (check laboratory reference ranges and attempt to determine the timing of the infection).

4.2. Non-primary infection: Cannot be routinely diagnosed using maternal serology. It is a retrospective diagnosis made when, following the confirmation of fetal CMV infection, it is determined that the pregnant woman had prior CMV exposure because she was already IgG-positive (for example, during a previous pregnancy).

5. A pregnant woman has been diagnosed with a primary CMV infection. What should be done? Immediately refer the pregnant woman to a referral center, which will evaluate the appropriate timing and indication to initiate prophylactic therapy for vertical transmission as early as possible (secondary prevention).

6. Should maternal CMV infection be treated? In healthy, immunocompetent pregnant women, a CMV infection is self-limiting; the primary risk is mother-to-child transmission.

6.1. Is it possible to prevent fetal transmission?
▸ **YES**, the rate of vertical transmission can be reduced by the administration of oral valacyclovir to the mother as soon as the diagnosis is made. This acts as a prophylactic

"treatment" against fetal infection – secondary prevention.

6.2. How should treatment be administered, and until what point in the pregnancy? The treatment should begin as early as possible, ideally before 15 weeks of gestation, with oral valacyclovir 2 g every 6 hours. This should be accompanied by an increased fluid intake and ensuring good renal function, which must be evaluated every 4 weeks.[1] Treatment should be maintained until the results of the amniocentesis are available, which can be performed starting at 17 weeks (ideally as early as possible, allowing at least 6–8 weeks after the presumed date of primary infection). If the CMV PCR test of the amniotic fluid is negative, prophylaxis is discontinued. Routine ultrasound surveillance should continue, and CMV PCR testing of the newborn's urine is recommended. If CMV is detected in the amniotic fluid via PCR, valacyclovir should be continued until the end of the pregnancy, with ongoing follow-up at a referral center. If the mother declines amniocentesis, it is recommended to discontinue valacyclovir prophylaxis between 17 and 18 weeks and offer monitoring through serial fetal ultrasounds.

7. When should fetal CMV infection be suspected? How is fetal infection confirmed? What are the available treatment options? Fetal infection can be suspected when central nervous system (CNS) and/or extracerebral abnormalities are detected during routine ultrasounds (Table 1).

If any of these ultrasound signs are present, an amniocentesis with **CMV PCR testing of the amniotic fluid** is proposed to determine the etiology. If the CMV PCR is positive, it is concluded that the fetus is infected. Prognostic factors are then assessed, and in cases of severe fetal disease, termination of the pregnancy may be considered. In other cases, fetal therapy is proposed, which includes maternal administration of oral valacyclovir at a dose of 2 g every 6 hours until the end of the pregnancy, following the same regimen and precautions used for vertical transmission prophylaxis.

NEONATAL

8. When should the diagnosis of cCMV infection be made? The diagnosis should be made as early as possible after birth, ideally within the first 3 weeks of life, to distinguish congenital infections from postnatal infections.

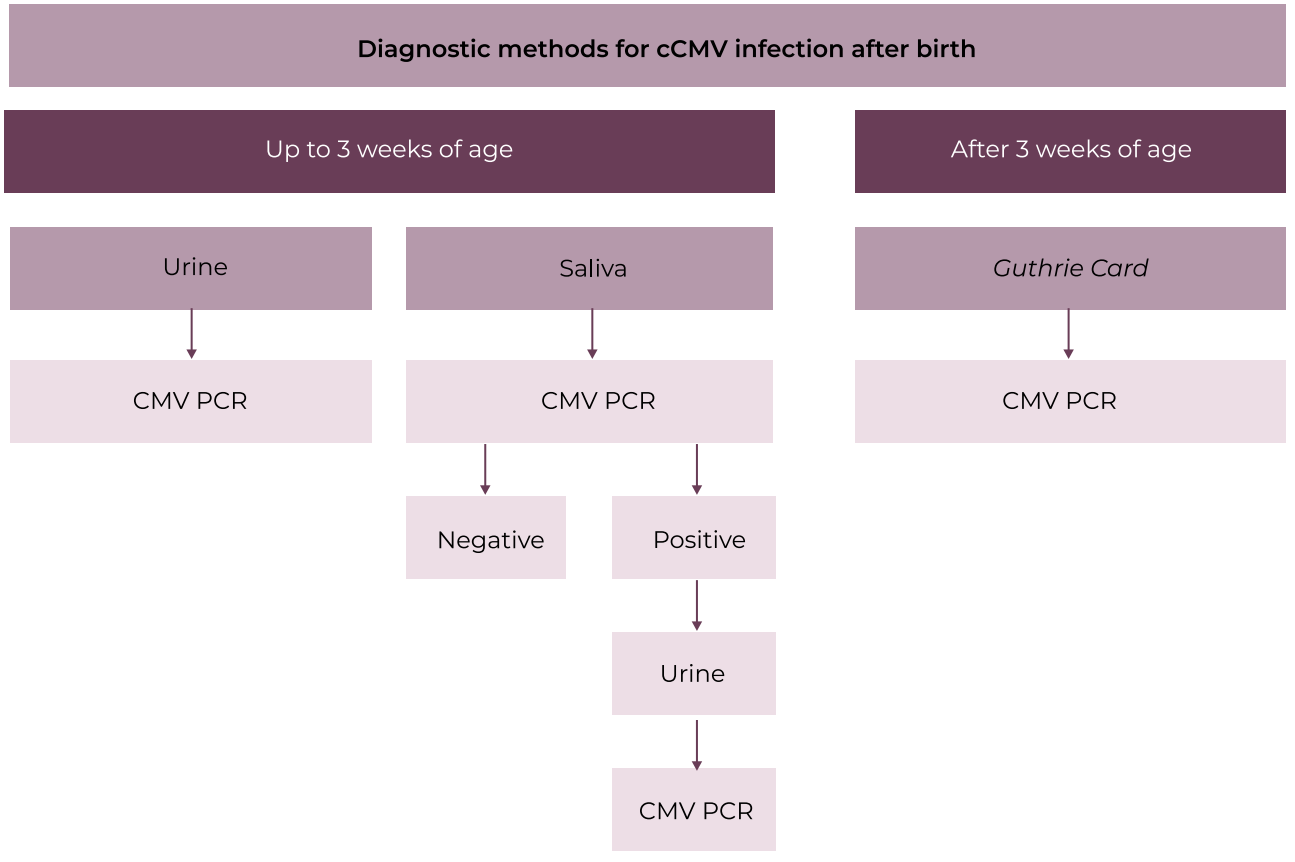
Table 1
Brain and extracerebral abnormalities identifiable by fetal ultrasound in congenital CMV infection.
Source: M. Leruez-Ville, 2017[7]

Severe Brain Abnormalities	Mild Brain Abnormalities	Extracerebral Abnormalities
- Ventriculomegaly ≥ 15 mm - Periventricular echogenicity - Hydrocephalus - Microcephaly (head circumference < −2 SD) - Cisterna magna ≥ 8 mm - Cerebellar vermis hypoplasia - Porencephaly - Lissencephaly - Periventricular white matter cystic lesions - Agenesis of the corpus callosum	- Mild ventriculomegaly (10–15 mm) - Intraventricular adhesions - Intracerebral calcifications - Subependymal cysts - Choroid plexus cysts - Calcifications of lenticulostriate vessels in the basal ganglia	- Hyperechogenic bowel - Hepatomegaly (right lobe ≥ 40 mm) - Splenomegaly (longitudinal diameter ≥ 40 mm in the 2nd trimester) - Fetal growth restriction (< 5th percentile) - Oligohydramnios (maximum vertical pocket < 2.5 cm) - Polyhydramnios (maximum vertical pocket > 10 cm) - Ascites - Pleural effusion - Hydrops fetalis, subcutaneous edema - Placentomegaly ≥ 40 mm - Intrahepatic calcifications

9. Which tests are indicated? Which biological specimen is best for detection? Both urine and saliva can be used, though there are differences between the two. CMV PCR on urine is considered the *gold-standard* diagnostic method. However, saliva collection is highly acceptable to parents and easier to perform than urine collection. Comparing the CMV PCR across both specimen types shows high sensitivity for both, but lower specificity for saliva. This lower specificity is due to "false positives" resulting from the presence of the virus in saliva—not from true salivary excretion in the context of a congenital infection, but rather from contamination during passage through the birth canal or due to recent breastfeeding and viral shedding in breast milk.[8] When the result is due to contamination, the viral load tends to be low; however, the distinction between contamination and congenital infection cannot be based solely on the viral load. Therefore, any positive CMV PCR result from a saliva sample must be confirmed with a CMV PCR on a urine sample.[9] If the initial sample collected was urine, the result is considered definitive.

Dried blood spot (DBS) samples (also known as Guthrie cards, newborn screening cards, or the "heel prick test") are routinely collected in the first week after birth for all children born in Portugal. They are sent to and stored (for at least 5 years) at the Neonatal Screening, Metabolism, and Genetics Unit of the Human Genetics Department at the National Institute of Health Doutor Ricardo Jorge in Porto. These samples can be tested retrospectively for neonatal CMV DNA via PCR to establish a diagnosis in children older than 3 weeks who are suspected of having a cCMV infection.[10] Due to the lower viral load in these samples, the test's sensitivity is significantly lower than that of saliva or urine tests, and the virus may even be undetectable. Furthermore, the different methodologies used for CMV PCR testing

Figure 2
Algorithm for the diagnosis of neonatal cCMV infection versus retrospective diagnosis. Kindly provided by Prof. Paulo Paixão



across various laboratories can have a much greater impact on DBS samples compared to urine and saliva testing. As a result, the reported sensitivity ranges from 73.2% and 93%, whereas the specificity approaches 100%.[11,12,13]

In summary, CMV PCR conducted on dried blood spot samples represents the most appropriate method for the retrospective diagnosis of congenital infection: a positive result confirms the diagnosis, whereas a negative result does not exclude it.

10. Should we screen for cCMV infection? What are the differences between targeted and universal screening? What are the advantages and disadvantages?

Targeted screening refers to testing a subgroup of newborns-specifically, those who "refer" (fail) the Universal Newborn Hearing Screening (UNHS). In **universal screening**, all newborns are tested regardless of their hearing screening results.

The main advantages of targeted screening are:

• Well-defined target population: children identified as refer/refer or pass/refer on the UNHS.

• Simpler logistics and reduced costs: with a smaller group to test that is clearly identified through hearing screening, setting up a screening system for this subpopulation streamlines the testing logistics and lowers costs (compared to universal screening).[14]

The main drawbacks of targeted screening are:

• Missing asymptomatic cases or those with mild hearing loss: we know that 90% of cCMV cases are asymptomatic at birth; however, they may develop delayed-onset hearing loss.[15]

• The UNHS detects only approximately half of all CMV-related hearing loss cases. This remains the primary restriction of targeted screening, as only universal newborn screening can detect all congenitally infected children so they can receive audiological monitoring up to school age.[16] It is worth remembering that a "pass/pass" result on the UNHS does not guarantee normal hearing; a newborn with mild hearing loss may also pass. Therefore, with targeted screening, some cases of mild hearing loss will "pass" the UNHS and will not be referred for CMV testing. For both asymptomatic infants and those infants with mild hearing loss, there is the added missed opportunity to monitor hearing progression. In cases of mild hearing loss, there is the added missed opportunity for timely and appropriate treatment. We know that treatment for isolated hearing loss is recommended, and this screening model misses the chance to treat these children. [1, 16]

• Reliance on timely and adequate UNHS: since targeted screening relies on UNHS results, it is entirely dependent on the proper functioning of the hearing screening program. On the ground, the teams conducting the UNHS (at least in most Portuguese hospitals) are not equipped to complete all phases of the UNHS—namely, the definitive audiological diagnosis—before the infant reaches 3 weeks of age. Consequently, the critical window for timely cCMV testing is lost, as is the opportunity to initiate appropriate early treatment for maximum benefit (within the first month of life).

• Lack of benefit for newborns without neonatal hearing deficits: because this screening is based solely on hearing performance, the opportunity to flag and follow newborns who may later develop neurodevelopmental issues that will only be identified "too late" is missed (by waiting until specific developmental milestones, like sitting or walking, are delayed).[17]

Universal screening overcomes all these targeted screening limitations. The main criticisms of universal screening are:

• More complex logistics,

• Higher costs,

• Inducing anxiety in parents of children who are asymptomatic at birth.[18]

The scientific evidence supports the group's position advocating for universal newborn screening of cCMV infection.

Regarding the "condition to be tested" and "screening test" itself, the requirements for screening are largely met, although logistics and test costs are often cited as limitations. New testing methodologies have proven easy to implement and are cost-effective when conducted by experienced teams. While urine is typically the first choice for individual diagnosis of cCMV infection, large-scale (universal) screening may favor saliva testing to encourage compliance among both parents and healthcare professionals. If a saliva sample is positive by PCR, it must be confirmed with a urine sample (up to 3 weeks of age). If it is negative (≥ 99% of screening samples will be negative, given the expected prevalence), no further action is required. One disadvantage of universal screening is the high cost of analysis, as it involves performing a PCR test on every single sample. Thus, alternative laboratory approaches that lower costs while maintaining the sensitivity and specificity of individual PCR tests should be considered when designing a screening program for this infection. One such approach, investigated by a multidisciplinary Portuguese team, employs sample pooling. It yields results comparable to individual analysis but with highly significant reductions in both costs and workload.[19]

The potential implementation of a screening program with these characteristics requires guaranteeing structured capacity for timely confirmatory diagnosis (up to 21 days of life) as well as appropriate treatment and follow-up for identified cases. Furthermore, it must be based on an objective health economics assessment (including cost-effectiveness and cost-benefit analyses), bridging of epidemiological gaps (such as establishing CMV seroprevalence among women of childbearing age nationwide), and determination of the most suitable operational model. Operationalizing a universal newborn screening program for cCMV infection must be a structured process involving policymakers, health authorities, the National Newborn Screening Program, scientific societies, and the frontline teams who will execute the screening program on the ground.

11. What is the clinical presentation of a newborn with cCMV?

The answer to this question is presented in Table 2.

12. After confirming cCMV infection in a child, what additional tests should I order?

12.1. All children with cCMV infection must be referred to and followed up in specialized hospital clinics. The initial clinical and laboratory evaluation should include:[1,21]

Table 2
Clinical signs and laboratory abnormalities suggestive of congenital CMV infection. Source: adapted from Swanson EC, 2013[20]

Clinical Signs Suggestive of cCMV	Laboratory Abnormalities Suggestive of cCMV
- Microcephaly - Small for gestational age - Symmetrical fetal growth restriction - Petechiae or purpura - Blueberry muffin rash - Jaundice - Hepatomegaly - Splenomegaly - Hypotonia - Lethargy - Seizures - Poor suck reflex - Chorioretinitis	- Anemia - Leukopenia - Isolated neutropenia - Thrombocytopenia - Elevated transaminases - Hyperbilirubinemia

• Physical examination;
• Complete blood count;
• Renal function: creatinine and blood urea nitrogen;
• Liver function: AST, ALT, and bilirubin (total and direct);
• Viral load: CMV DNA (quantitative blood PCR to guide monitoring).

12.2. Regarding imaging studies:[1,21]
• Transfontanellar cranial ultrasound: first-line;
• Brain magnetic resonance imaging (MRI): indicated when there are clinical manifestations at birth, sensorineural hearing loss, chorioretinitis, or abnormalities detected on a transfontanellar cranial ultrasound. It should be conducted in cases of primary maternal infection in the first trimester or when the timing of maternal infection is unknown. It can also be useful when doubts persist regarding the decision to treat after the initial evaluation.

12.3. Ophthalmology and otorhinolaryngology (ENT) assessments:
• Ophthalmology: ophthalmologic evaluation and follow-up in children with retinitis at birth. Newborns with a normal retinal exam do not require ongoing ophthalmologic follow-up.
• ENT: (see question 17).

13. When should a child with cCMV infection be treated?
Treatment is recommended for newborns **with symptomatic cCMV** who have **significant organ involvement:**[1,21,22]
• **CNS involvement** (Transfontanellar cranial ultrasound / **Brain MRI**):
  - Multiple periventricular calcifications;
  - Paraventricular germinolytic cysts;
  - Septations of the occipital horns of the lateral ventricles;
  - Moderate to severe ventriculomegaly;
  - Diffuse white matter abnormalities;
  - Temporal lobe involvement;
  - Extensive calcifications;
  - Cerebral atrophy;
  - Cortical malformations;
  - Cerebellar hypoplasia;
  - Dysgenesis of the corpus callosum;
  - Abnormal cortical sulcation.
• **Chorioretinitis;**
• **Isolated sensorineural hearing loss (unilateral or bilateral);**
• **Isolated but persistent single-organ disease (e.g., hepatitis, clinically significant thrombocytopenia);**
• **Multisystem disease** in the neonatal period.

Note: Treatment of asymptomatic children is not recommended.

14. When should treatment be initiated? Ideally, as early as possible, preferably within the first 4 weeks of life. Initiating treatment up to 3 months of age may be considered. Beyond 3 months of age, treatment should be discussed on a case-by-case basis with a pediatric infectious disease specialist.[1,21,22,23]

15. What medications are available for treating cCMV? What are the risks and adverse effects?

15.1. Medications:
• Valganciclovir 16 mg/kg/dose orally twice daily (first-line).[1,21,22,23]
• Ganciclovir 6 mg/kg/dose intravenously (IV) via central venous catheter twice daily. Switch to oral valganciclovir once the infant tolerates 50% of enteral feedings.[1,21,22,23]

15.2. Indications: Newborns > 32 weeks of gestation and/or > 1800 g birth weight, following informed consent from the family (risk-benefit assessment).[1,21,22,23]

15.3. Risks and adverse effects:[1,21,22,23]
• Neutropenia: This is the most significant and frequent side effect and may require dose reduction or treatment interruption. It is more common with IV treatment. It is generally reversible with a dose reduction or a brief pause in medication and is most common during the first 6 weeks. It can also occur spontaneously in cCMV (without treatment);

• Hepatotoxicity: This is more common after the fourth month but is generally mild and reversible upon treatment discontinuation;
• Thrombocytopenia;
• Anemia;
• Long-term: Potential gonadotoxic and carcinogenic effects, though these have only been observed in animal studies.

16. I have diagnosed a child with sensorineural hearing loss. How do I know if it was caused by CMV?

It depends on the child's age. In a child up to 3 weeks of age, cCMV can be detected in urine or saliva using PCR.

If we need to establish a diagnosis but the child is already older than 3 weeks, we must use a biological sample collected before 21 days of age-this is the only way to differentiate a congenital infection from a postnatally acquired one. The dried blood spot on the newborn screening card (*Guthrie card*) provides us with a sample collected in the correct timeframe, allowing a retrospective diagnosis via PCR.[10] (See question 9).

17. How should the ENT follow-up of a child with cCMV infection be managed? Does the follow-up change if they have hearing loss?

Hearing loss in children with cCMV infection is highly variable. It is more prevalent in children who are symptomatic at birth, reaching up to 74%.[24] Regarding the onset, hearing loss can be congenital (12.7%) or delayed-onset (4.5%). This justifies the need for audiological follow-up until at least 5 years of age, at which point the risk drops to approach that of uninfected children.[25,26] Approximately 50%–74% of symptomatic children with cCMV infection develop hearing loss during childhood. The hearing loss is progressive in over 50% of cases, and children with unilateral hearing loss at birth are at risk of developing hearing loss in the contralateral ear.[25]

Despite the significant impact of hearing loss in cCMV infection, there are no unanimously accepted recommendations for following these children.

In the absence of universal guidelines, this group refers to the recommendations of the *American Academy of Audiology*:[27]

Hearing assessment:
• Up to 12 months of age: every 3–6 months;
• From 12 months to 3 years of age: every 6 months;
• From 3 to 6 years of age: annually.

How should this assessment be performed?

Depending on the child's maturity and service availability, the following is suggested:[27]
• Auditory Brainstem Response (ABR) up to 3 years of age;
• ABR or behavioral audiometry up to 6 years of age.

If it is proven that maternal infection occurred in the third trimester and the child has normal hearing at birth as confirmed by ABR, audiological follow-up is not recommended.[28]

18. How are vestibular abnormalities diagnosed in cCMV infection? What tests should be ordered? How should follow-up be managed?

There are no universal guidelines for the vestibular diagnosis and follow-up of these patients. However, vestibular screening is recommended for all children with cCMV, regardless of their hearing status, due to the high incidence and potential for late-onset or progressive vestibular dysfunction.[29,30,31]

Children with a vestibular deficit face a significant risk of delayed motor development.[32] Therefore, the child's motor development milestones should be monitored, and they should be referred to an ENT specialist if these milestones are not met within normal timeframes.

The initial evaluation should take place at 6 months of age, and further evaluations are not required if there are no delays in motor milestones or additional risk factors.

Children with risk factors—such as maternal infection in the first trimester, sensorineural hearing loss, or periventricular cysts detected on neuroimaging—require annual testing up to 5 years of age.[33]

For screening purposes in children with cCMV, evaluating the otolithic function and vestibulo-ocular reflex is advocated. Depending on the age, the following tests are recommended:[34,35]

• Between 6 months and 2 years of age: Cervical vestibular evoked myogenic potentials (cVEMP) + video head impulse test (vHIT) of the lateral semicircular canal with a remote camera. If the latter is unavailable, rotary chair testing can be used;

• From 3 years of age: If the child cooperates, cVEMP and ocular vestibular evoked myogenic potentials (oVEMP) can be conducted, along with the vHIT of all 3 canals using adapted goggles.

Additional testing is only justified if the child is uncooperative during the primary tests. If the child cannot cooperate due to age or disability, a clinical HIT can be performed during an ENT visit. If abnormalities are detected, appropriate vestibular rehabilitation should be considered, either at home or in an accredited facility.

19. How should the infected child's neurodevelopment be followed? To which specialists should the child be referred?

• Children with an asymptomatic infection proven not to have been acquired in the first trimester of pregnancy should undergo routine pediatric well-child care. If neurodevelopmental abnormalities or hearing loss emerge, they should be referred for neurodevelopmental and ENT follow-up (if not already being seen);[21,36]

• Children with a documented congenital infection in the first trimester of pregnancy, or if the timing is unknown, or if neuroimaging abnormalities are present, should be evaluated at 6 and 12 months (neonatology / pediatrics / pediatric infectious diseases) and then annually until 8 years of age at a neurodevelopmental clinic;[37]

• All children with CMV-related hearing loss should be referred to a neurodevelopmental clinic;[21,36,37]

• Children with symptomatic infection at birth should be monitored annually up to 8 years of age in a neurodevelopmental clinic. Depending on their clinical profile, a pediatric neurology follow-up may also be required.[21,36]

• The neurodevelopmental follow-up protocol should include multidisciplinary evaluations involving psychology, speech-language pathology, and, if necessary, occupational therapy, following the guidelines similar to those for very low birth weight infants.[38]

• The neurodevelopmental follow-up protocol is grounded in established recommendations for high-risk newborns, such as very low birth weight infants.[38] It should include a formal comprehensive evaluation of global psychomotor development and cognitive functioning as well as assessment of language and other clinically relevant domains tailored to each child's individual profile. Structured, longitudinal follow-up by psychology, speech-language pathology professionals-and, when indicated, occupational therapy- is essential.

Conflicts of interest

The authors declare that they have no conflict of interest regarding this article.

Financial support

This work did not receive any grant contribution, funding or scholarship.

Scientific data availability

There are no publicly available datasets related to this work.

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Article Summary

PRECONCEPTION PERIOD

Objective: Prevention - inform/educate and determine the woman's immune status
Target population: Women of childbearing age / Preconception visit

1. CMV Education & Health Literacy	2. Assess Risk Factors	3. Primary Prevention Measures (for all)	4. CMV Serology (IgG and IgM ± avidity)
- Transmission - Fetal risks - Prevention - Available diagnosis and treatment	- Contact with children < 5 years old: - Healthcare professionals / childcare workers - Mothers of children in daycare	- Strict hand hygiene - Avoid contact with children's saliva/urine - Do not share utensils - Surface sanitization	- Ideally in the preconception period
			Results **IgG− / IgM−** → Susceptible woman → Strengthen prevention **IgG+** → Prior immunity → General hygiene measures **IgM+** → Evaluate in clinical context (follow prenatal algorithm)

PRENATAL PERIOD

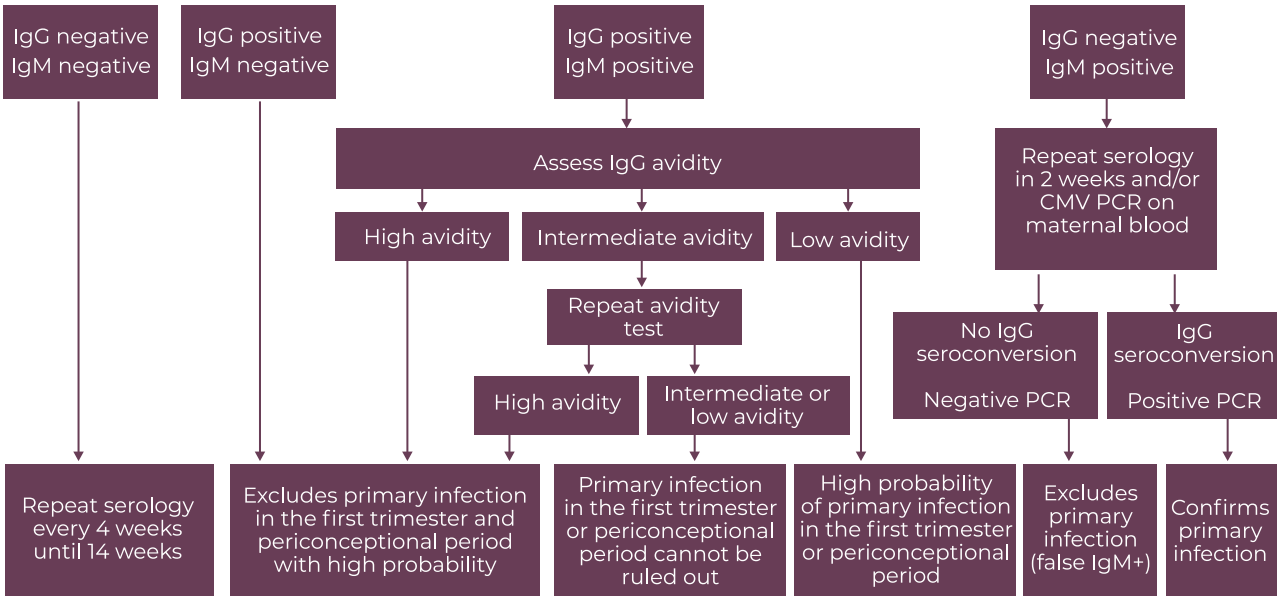
Objective: Diagnosis of primary maternal infection, prevention of vertical transmission, and fetal management

A. Early pregnancy serology (as early as possible)

First-trimester pregnant women who are susceptible or unaware of their immune status
CMV serology (IgG, IgM ± avidity)

Interpretation

- **IgG− / IgM−**
  - → Susceptible pregnant woman
  - → Reinforce prevention
  - → Repeat serological testing every 4 weeks until 14 weeks
- **IgG+ / IgM−**
  - → Prior immunity
  - → Do not repeat serological tests
- **IgG− / IgM+**
  - → Repeat serological testing in 2 weeks
  - → Maternal CMV PCR
- **IgG+ / IgM+**
  - → Assess IgG avidity
    - o Low/intermediate avidity → Recent primary infection



B. Confirmed primary maternal infection

1. Immediate Referral to a Referral Center	2. Initiate Secondary Prevention	3. Amniocentesis (≥ 17 weeks)
	- Valacyclovir 2 g PO q6h - Ideally < 15 weeks - Assess renal function every 4 weeks - Increased fluid intake	≥ 6–8 weeks after maternal infection
		Amniotic Fluid CMV PCR Result • **Negative** → Discontinue valacyclovir → Obstetric surveillance → Test newborn after birth – viruria • **Positive (infected fetus)** → Continue valacyclovir until term → Assess fetal prognosis → Consider termination of pregnancy if signs of poor prognosis → Specialized follow-up

C. Fetal ultrasound suspicion

Suggestive CNS and/or extracerebral findings

Severe Brain Abnormalities	Mild Brain Abnormalities	Extracerebral Abnormalities
- Ventriculomegaly ≥ 15 mm - Periventricular echogenicity - Hydrocephalus - Microcephaly (head circumference < −2 SD) - Cisterna magna ≥ 8 mm - Cerebellar vermis hypoplasia - Porencephaly - Lissencephaly - Periventricular white matter cystic lesions - Agenesis of the corpus callosum	- Mild ventriculomegaly (10–15 mm) - Intraventricular adhesions - Intracerebral calcifications - Subependymal cysts - Choroid plexus cysts - Calcifications of lenticulostriate vessels in the basal ganglia	- Hyperechogenic bowel - Hepatomegaly (right lobe ≥ 40 mm) - Splenomegaly (longitudinal diameter ≥ 40 mm in the 2nd trimester) - Fetal growth restriction (< 5th percentile) - Oligohydramnios (maximum vertical pocket < 2.5 cm) - Polyhydramnios (maximum vertical pocket > 10 cm) - Ascites - Pleural effusion - Hydrops fetalis, subcutaneous edema - Placentomegaly ≥ 40 mm - Intrahepatic calcifications

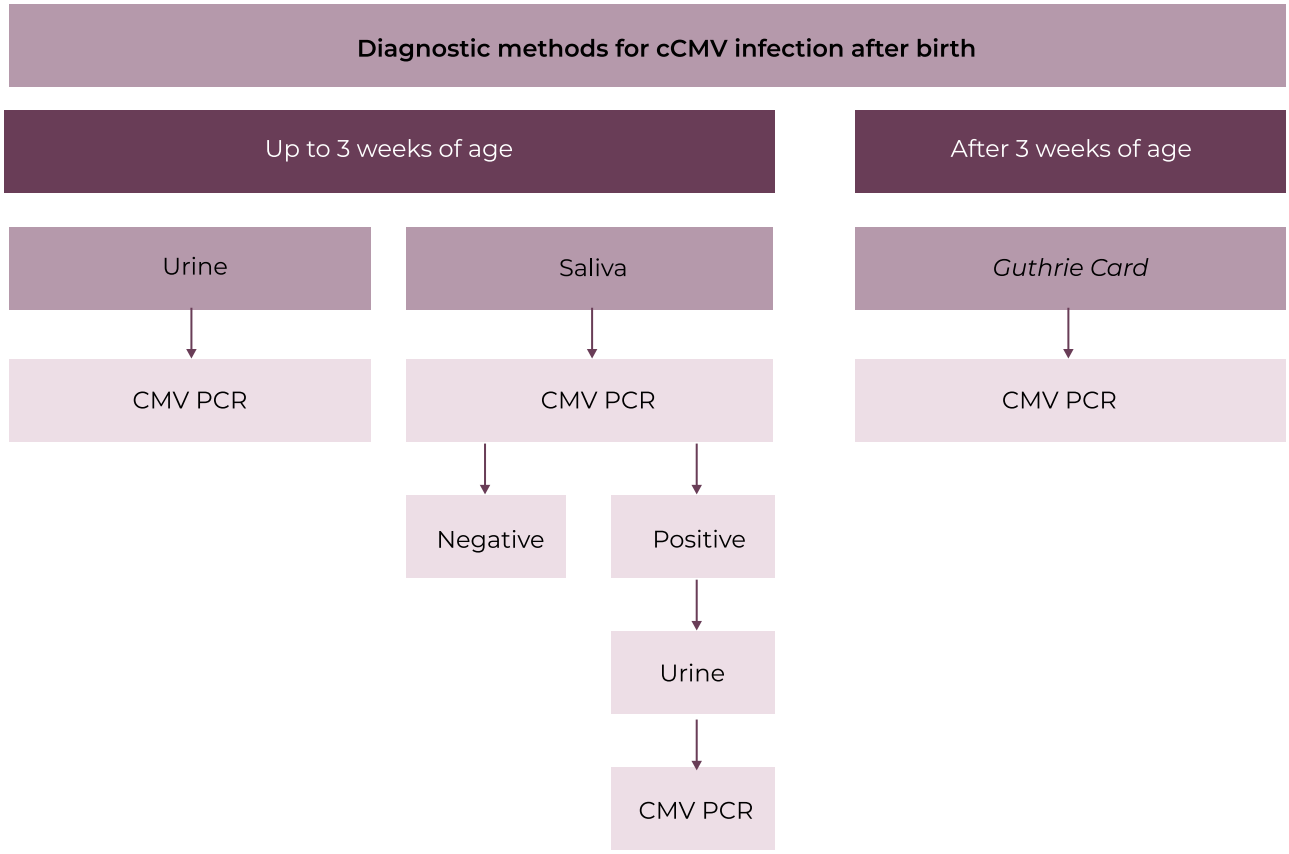
Amniocentesis with CMV PCR – if PCR positive

- Infected fetus
- Assess severity
- Fetal treatment with Valacyclovir

Neonatal planning and follow-up

NEONATAL PERIOD

A. Diagnosis



Saliva positive → Confirm with urine
Urine positive → Definitive cCMV diagnosis → Assess indication for treatment

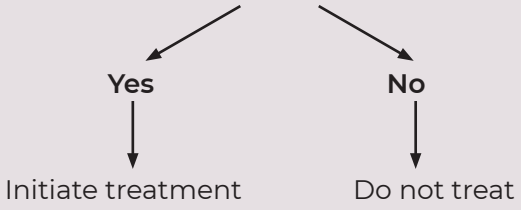
B. Initial evaluation after diagnosis

Clinical and Laboratory Evaluation	Imaging	Specialized Evaluations
- Complete physical exam - Complete blood count - Renal and liver function - Quantitative blood CMV PCR	- Transfontanellar ultrasound (1st line) - Brain MRI if indicated	- ENT / Audiology - Ophthalmology (if retinitis)

C. Treatment decision

Positive CMV PCR (urine) + Symptomatic infant?

- CNS involvement
- Chorioretinitis
- Sensorineural hearing loss
- Multisystem disease
- Persistent organ disease



- Valganciclovir PO (1st line)
- Ideally initiate at ≤ 4 weeks of age.
- Treatment initiation between 1–3 months of age may be considered
- Monitor for adverse effects

POSTNATAL FOLLOW-UP

Audiological, Vestibular, and Neurodevelopmental Follow-up

Audiological Follow-up (all children with cCMV)	Vestibular Follow-up	Neurodevelopmental Follow-up
Serial audiological evaluation **0–12 months: every 3–6 months** **1–3 years: every 6 months** **3–6 years: annually**	**Vestibular screening > 6 months of age** • No motor delay → Discharge • With risk factors → Annual evaluation up to 5 years of age **Abnormalities** • Refer to ENT • Vestibular rehabilitation	**Risk stratification** *1st-trimester infection or unknown timing / symptomatic infant / abnormal neuroimaging *Associated sensorineural hearing loss - Visits at 6 and 12 months - Annually up to 8 years of age - Multidisciplinary evaluation
- ABR (≤ 3 years) **- ABR or behavioral audiometry (≤ 6 years)**	**6 months - 2 years of age:** - cVEMP - vHIT of the lateral SCC with remote camera (alternative - rotary chair testing) **> 3 years:** - cVEMP - oVEMP - vHIT of all 3 canals with adapted goggles	Multidisciplinary evaluation with psychology, speech-language pathology, and, if necessary, occupational therapy