NCMVF Position Statement
on
The Diagnosis of Congenital Cytomegalovirus in Infants and Children

Adopted *July 1, 2024*

National CMV Foundation

It is the position of the National CMV Foundation that timely diagnosis of congenital CMV can lead to improved access to treatment, intervention and anticipatory guidance to improve outcomes of both infants and children. The diagnosis of congenital CMV can only be confirmed by testing specimens collected in the first 21 days of life. When specimens from that time period are not available, a presumptive diagnosis could be considered but not a definitive diagnosis. Furthermore, different screening and testing approaches should be used depending on the age of the child.

This statement is the position of the Scientific Advisory Committee for the National CMV Foundation, info@nationalcmv.org.

Authors and Acknowledgments

Produced by: *National CMV Foundation Scientific Advisory Committee*

Lead Authors

Megan Honor Pesch, MD, MS. Assistant Professor of Developmental and Behavioral Pediatrics, University of Michigan, Michigan

Cedric Von Pritchett, MD, Associate Professor of Pediatric Otolaryngology, Nemours Children's Hospital, Florida

Contributing Authors

Scientific Advisory Committee of the National CMV Foundation

.

Introduction

Background

Cytomegalovirus is a ubiquitous but often silent virus, that is often shed in bodily fluids of those infected[2]. While most often harmless to healthy individuals, the virus can have serious impacts on a developing fetus if transmitted via the placenta in utero.[10] This is known as congenital cytomegalovirus or cCMV. Children born with cCMV are at high risk of long term neurodevelopmental disabilities from the effects of the virus on the fetus,[11-13] whereas most infants who are infected after birth do not. Differentiating post-natal CMV infection from congenital CMV infection is important to guide treatment, anticipatory guidance and monitoring.[15] When possible timely and specific testing is critical for making a cCMV diagnosis, or ruling it out altogether.[15]

Considerations

The following factors were considered when creating recommendations for position statement.

Timing of testing. Congenital CMV can only be diagnosed using a specimen collected in the first three weeks of life (<21 days).[1] Infants who are born with a prenatal suspicion of cCMV (due to prenatal ultrasound findings or known maternal exposure) or those who have apparent clinical manifestations at birth may be tested during these first three weeks of life, as would infants who meet criteria for a newborn screening protocol, if in place at their birth hospital.[6] However, the vast majority of infants with cCMV do not show manifestations at birth, or have a subtle presentation that is easily overlooked by any clinician.[14] As such, testing for cCMV will often occur outside the 21-day window.[4,13] We recommend different approaches for confirming a diagnosis before 21 days, from 21 days to 5 months of age, and from 6 months onward.

Specimen selection. After an infection, either post-natal or congenital, CMV is shed in the bodily fluids of the host for weeks to months.[16] Of note, CMV tends to be less concentrated in the serum, therefore a positive serum CMV PCR indicates the presence of the virus in the host, a negative serum PCR cannot rule out the possibility of an infection.[16] For these reasons serum PCR is not recommended for infant testing for cCMV if urine or saliva is available.

Dried blood spot (DBS) can be a valuable specimen to test for the presence of CMV, as

specimen which was collected in the first 1-2 days of life, and may be retained by the State Newborn Screening program.[3] The time that DBS cards are retained by the state varies greatly from state to state. Due to the lower concentration of the virus in the serum in general, as well as the DBS specimen type and assays available, the sensitivity of DBS PCR is lower than saliva and urine PCR/LAAMP in the newborn period, at 65-85% sensitivity.[3-5]

Other specimen types can be used in cases when the dried bloods spot is not available, although the sensitivity of a PCR assay on these other specimen types may not be well studied. These other specimen types may include dried umbilical cord stump, placenta pathology block.[7-9]

Test selection. Virtually all infants born with congenital CMV will have virus shed in their urine and saliva at birth. Nucleic Acid Amplification Testing (NAAT), which includes Polymerase Chain Reaction (PCR) and LAMP, are highly sensitive platforms for detecting viral DNA in both saliva and urine.

Viral shell culture has been found to be less sensitive than saliva and urine NAAT, therefore is not recommended when other options are available.

Serologies, namely CMV IgG and CMV IgM, are also not recommended for cCMV testing in infants under 6 months of age. Maternal antibodies are passed to the fetus in utero and to the infant via breastmilk after birth.[10] The presence of CMV IgG in an infant indicates that either the infant or mother had been exposed to the virus at some time, in other words a positive CMV IgG indicates that either the mother, or the infant were congenitally or postnatally exposed to CMV, which may not be clinically helpful. The absence of CMV IgG also cannot provide certainty that an infant does not have cCMV, as IgG may not be produced for up to 100 days after a primary infection. Similarly, while maternal IgM indicates a more recent infection with CMV, it does not provide information about the timeline of the infection in the mother, or whether that infection was transmitted to the fetus. Persistent CMV IgM is also possible. CMV IgM can also take 2-4 weeks to rise to a detectable level in a primary infection, and in some cases does not reach a detectable level in non-primary infections. CMV IgM is not transmitted through the placenta, therefore any IgM detected in an infant's serum was produced by that infant. However, IgM is not a reliable indicator of recent infection. Therefore, a negative IgM does not rule out congenital CMV, and a positive IgM is only suggestive of congenital CMV.

Beyond 6 months of age, serologies, namely CMV IgG, can be a useful tool for congenital CMV *screenin*g. The absence of CMV IgG definitively rules out prior exposure to the virus, including congenital CMV. The presence of CMV IgG after 6 months of age suggests that the individual child has been exposed to CMV in the past, either postnatally or

Purpose of the Position Statement

The purpose of this position statement is to provide clinical guidance on the diagnostic testing for congenital cytomegalovirus in infants and children.

This document does not cover congenital CMV *screening* practice recommendations, but rather focuses on recommendations for diagnostic testing once a clinical suspicion of cCMV has been raised. Screening recommendations will be covered in a subsequent position statement.

Statement of the Position

The Diagnosis of Congenital Cytomegalovirus in Infants and Children

It is our position that making a diagnosis of congenital CMV can lead to improved access to treatment, intervention and anticipatory guidance in infants and children.

It is the position of the National CMV Foundation that the diagnosis of congenital CMV can only be confirmed by testing specimens collected in the first 21 days of life. When specimens from that time period are not available, a presumptive diagnosis could be considered but not a definitive diagnosis. Furthermore, neonates aged <21 days, infants < 6 months of chronological age and children, those 6 months to <18 years of age should be screened and tested for congenital CMV by three differing approaches. (Figures 1) The presence of CMV DNA identified in the urine of an infant <21 days, or on a dried blood spot card collected in the first days of life is consistent with a diagnosis of congenital CMV. A positive screening test (either saliva or IgG or IgM, depending on the child's age) must be verified by a secondary specimen to confirm a definitive diagnosis.

The recommended screening and testing algorithm is shown in Figure 1.

Testing in the Neonatal Period (<21 days of age)

Screening can be performed with a saliva PCR or LAMP test, or testing can be done with a urine PCR. Note that saliva samples for screening must be collected at least 1 hour after the infant has been at the breast of consumed breastmilk/colostrum. If the results are negative, this rules out congenital CMV. If the results are positive, this is concerning for congenital CMV. Due to the possibility of false positive saliva PCR/LAMP from breastmilk contamination, testing with urine PCR is necessary to confirm the diagnosis.

Testing in Early Infancy (21 days to <6 months of age)

Initial screening with a saliva or urine CMV PCR/LAMP should be performed. Note that saliva samples for screening must be collected at least 1 hour after the infant has consumed breastmilk. If the results are negative, this rules out congenital CMV. If results are positive, this indicates a prior cCMV exposure, either postnatal or congenital, and warrants further testing.

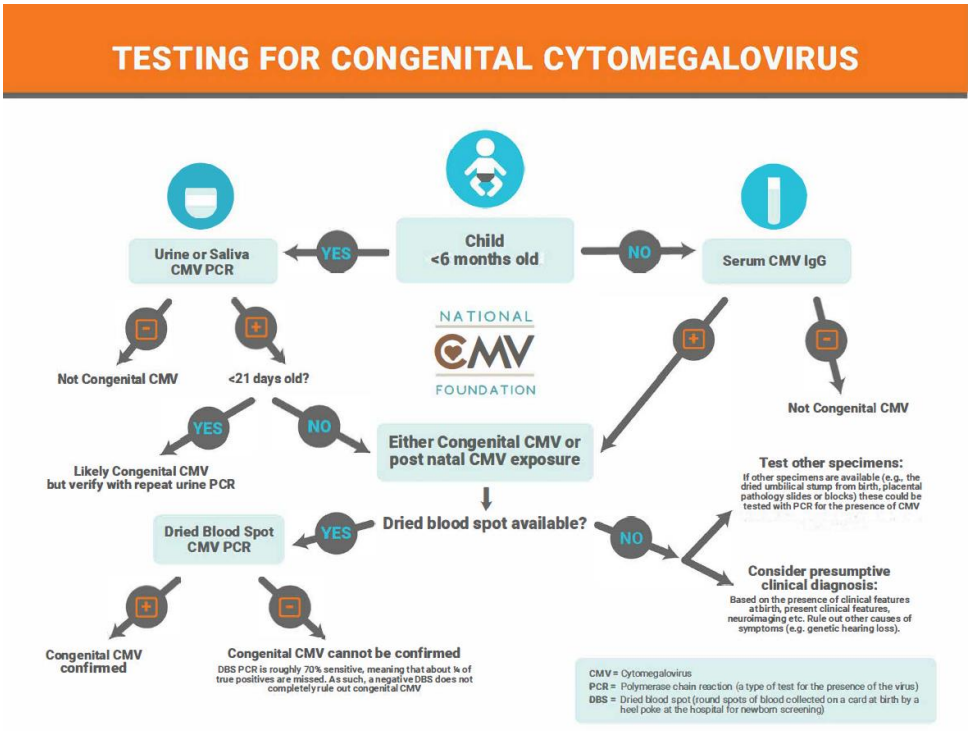
If the infants dried blood spot is available, this should be requested from the birth state and sent for CMV PCR. Note that the sensitivity of these assays range from 60-80% depending on the labs around the country. As such, detection of the presence of CMV on the DBS confirms a congenital infection, however a negative DBS CMV PCR cannot definitively rule out cCMV.

If the DBS is not available, one can inquire about other specimens that may be available such as placental pathology slides or blocks, dried umbilical stump from birth) these samples may be sent for testing. Again, the sensitivity of CMV PCR on these alternative specimens is not established, therefore the absence of the virus cannot definitely rule out congenital CMV. In this case, the provider may have to use their clinical judgement to consider a presumptive clinical diagnosis of congenital CMV. This may be made at the discretion of the provider after considering the evidence of a cCMV infection such as neuroimaging findings, birth presentation, presence of SNHL, and other clinical findings. The clinician should also consider other conditions that may have an overlap in presentation and definitively rule out those conditions prior to making a presumptive clinical diagnosis of congenital CMV. For instance, other TORCH infections, genetic conditions and genetic etiologies of hearing loss.

Testing in late Infancy and Childhood (6 months to <18 years of age)

The recommended methods for testing for congenital CMV in children 6 months old and older is nearly the same as the procedures for testing a 21 day—<6 month old, with the exception of the initial screening test. Viral shedding in bodily fluids may wane in children with cCMV by the latter half of the first year of life. As such, we recommend first screening with CMV IgG. If the child does not have CMV IgG detected, then congenital CMV is ruled out. If CMV IgG is detected, it represents either a congenital or postnatal infection, or persistent maternal antibodies, and further testing is warranted, namely dried blood spot testing. See the recommendation in the prior section for an explanation of the testing algorithm including dried blood spot testing and subsequent considerations.

Figure 1



References

1. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: Consensus recommendations for prevention, diagnosis, and therapy. *The Lancet Infectious diseases.* 2017;17(6):e177-e188.
2. Pesch MH, Schleiss MR. Emerging concepts in congenital cytomegalovirus. *Pediatrics.* 2022;150(2).
3. Dollard SC, Dreon M, Hernandez-Alvarado N, et al. Sensitivity of dried blood spot testing for detection of congenital cytomegalovirus infection. *JAMA Pediatr.* 2021;175(3):e205441-e205441.
4. Del Valle Penella A, Miller J, Rochat R, Demmler-Harrison G. Utility of Dried Blood Spots for the Diagnosis of Congenital Cytomegaloviruses within the First 21 Days of Life in a Single Center. *International Journal of Neonatal Screening.* 2023;9(3):44.
5. Gantt S, Goldfarb DM, Park A, et al. Performance of the Alethia CMV assay for detection of cytomegalovirus by use of neonatal saliva swabs. *J Clin Microbiol.* 2020;58(4):10.1128/jcm. 01951-01919.
6. Rohren L, Shanley R, Smith M, et al. Congenital Cytomegalovirus-Associated Sensorineural Hearing Loss in Children: Identification Following Universal Newborn Hearing Screening, Effect of Antiviral Treatment, and Long-Term Hearing Outcomes. *Ear Hear.* 2024;45(1):198-206.
7. Uenaka M, Morizane M, Tanimura K, et al. Histopathological analysis of placentas with congenital cytomegalovirus infection. *Placenta.* 2019;75:62-67.
8. Lindholm K, O'Keefe M. Placental cytomegalovirus infection. *Arch Pathol Lab Med.* 2019;143(5):639-642.
9. Sakamoto A, Moriuchi H, Matsuzaki J, Motoyama K, Moriuchi M. Retrospective diagnosis of congenital cytomegalovirus infection in children with autism spectrum disorder but no other major neurologic deficit. *Brain Dev.* 2015;37(2):200-205.
10. Leruez-Ville M, Foulon I, Pass R, Ville Y. Cytomegalovirus infection during pregnancy: State of the science. *Am J Obstet Gynecol.* 2020;223(3):330-349.
11. Pesch MH, Lauer CS, Weinberg JB. Neurodevelopmental outcomes of children with congenital cytomegalovirus: a systematic scoping review. *Pediatr Res.* 2023:1-18.
12. Sorichetti B, Goshen O, Pauwels J, et al. Symptomatic congenital cytomegalovirus infection is underdiagnosed in British Columbia. *J Pediatr.*

2016;169:316-317.
13. Park HW, Cho MH, Bae SH, Lee R, Kim KS. Incidence of postnatal CMV infection among breastfed preterm infants: a systematic review and meta-analysis. *Journal of Korean medical science.* 2021;36(12).
14. Wilson KL, Shah K, Pesch MH. Inconsistent provider testing practices for congenital cytomegalovirus: Missed diagnoses and missed opportunities. *Int J Neonatal Screen.* 2022;8(4):60.
15. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis.* 2017;17(6):e177-e188.
16. Cannon MJ, Hyde TB, Schmid DS. Review of cytomegalovirus shedding in bodily fluids and relevance to congenital cytomegalovirus infection. *Rev Med Virol.* 2011;21(4):240-255.