Targeted Congenital Cytomegalovirus (cCMV) Screening

New Jersey Birthing Facility Best Practices Recommendations

Background

Cytomegalovirus (CMV) is a common virus that can cause serious problems in pregnant people, newborns, and people with weakened immune systems. Since CMV generally causes common cold-like symptoms in healthy persons, infection during pregnancy is often unrecognized. Congenital CMV (cCMV) infection is estimated to occur in 1 of every 200 live births. It is the most common infectious cause of developmental disabilities and non-genetic sensorineural hearing loss (SNHL) in U.S. children.[1]

Awareness of CMV is low among the public, expectant parents, and health care providers, and the burden of cCMV disease is not fully understood. Diagnosis of cCMV is challenging since most infants (90%) with this diagnosis are asymptomatic at birth. However, 1 in 5 infected infants will experience permanent disabilities[2] which can include hearing loss, vision impairment, and intellectual disabilities.[3] The Centers for Disease Control and Prevention (CDC) has identified cCMV as a priority exposure of interest for efforts at reducing adverse outcomes for pregnant people and their infants.

Treatment with anti-viral medication may improve hearing and developmental outcomes, making screening newborns for CMV beneficial in promoting child health. New Jersey passed legislation in 2021 (PL 2021, c. 413) requiring the Department of Health to implement universal CMV screening in newborns. However, the law specifies prerequisite conditions for implementation that have not yet been met, such as the inclusion of CMV on the national Recommended Universal Screening Panel (RUSP) maintained by the U.S. Department of Health and Human Services.

In 2022 an ad hoc subcommittee of the New Jersey Newborn Screening Advisory Review Committee (NSARC) sent a recommendation to the New Jersey Department of Health Commissioner suggesting the bloodspot screening program not wait for the inclusion of cCMV screening in the RUSP. However, other prerequisite conditions, such as the acquisition of equipment and the establishment of testing protocols are also not yet met. Until universal cCMV screening is implemented in New Jersey, targeted screening has been identified as a best practice for birthing facilities to consider adopting.

The most common use of targeted CMV screening is due to failed newborn hearing screening. Since many infants with cCMV infection will develop late-onset or progressive hearing loss that is not detected on the initial hearing screening, other criteria for targeted cCMV screening candidacy should be considered. Screening criteria may also include clinical signs that may be present in newborns with

cCMV infection: hepatomegaly, splenomegaly, petechiae, microcephaly, direct hyperbilirubinemia, thrombocytopenia, and growth retardation.[4] The prevalence of cCMV is higher in infants with perinatal exposure to HIV than in the general population, so CMV screening of these infants is recommended.[5]

A key component of a cCMV screening protocol is the timeliness of testing. To determine that a CMV infection was acquired congenitally and not after delivery, testing needs to be completed by 21 days of life.

Birthing Facility Congenital CMV Screening Policy Design

Indications

A facility's screening policy should consider screening for these indications[4,5]:

- CMV infection/re-infection documented or suspected during pregnancy (low CMV IgG avidity, positive CMV IgM). Note that a positive CMV IgG during pregnancy is insufficient to indicate that an infection occurred during the pregnancy.
- Microcephaly (head circumference at or below the 3rd percentile)
- Intrauterine Growth Retardation (IUGR)
- Symmetrically small for gestational age (SGA)
- Unexplained preterm birth
- Petechiae on the body (i.e. NOT limited to the face/above the collarbone) or purpura ("blueberry muffin rash")
- Hepatomegaly
- Splenomegaly
- Thrombocytopenia
- Elevated direct bilirubin
- Perinatal exposure to HIV infection
- Seizure disorder
- Not passing a newborn hearing screening in one or both ears ("Refer" result)

Testing Methodology

CCMV testing should detect CMV DNA by polymerase chain reaction (PCR or other nucleic acid amplification testing [NAAT]), ideally using a urine or saliva specimen.

It is important to note that positive CMV IgG testing of a newborn can detect antibodies passively acquired from the pregnant person and does not indicate a congenital CMV infection.

Each testing method has advantages and disadvantages and varies concerning sensitivity and specificity.[6,7,8,9,10,11,12]

Specimen	Sensitivity	Specificity	Disadvantages	Advantages
Urine	93%	100%	- Requires waiting for the infant to urinate - Sample collection can be challenging (spillage if not a good seal)	- Non-invasive - Contains higher viral load than saliva - Highest combined sensitivity/specificity
Saliva	86-98%	92-100%	- May receive a false positive result in infants receiving breast milk	- Non-invasive - Quick and easy to collect
Whole blood	94%	100%	- Invasive - Lowest sensitivity	- If blood is being drawn for other testing (i.e. NICU infants), no additional sample collection efforts are needed
Dried blood spot	86-96%	97-100%	- Requires specialized filter paper and lab that can process specimens from the filter paper, so not feasible without state newborn screening laboratory implementation	- Easy to implement as part of routine dried bloodspot screening once the state laboratory has the capability

Birthing facilities should consider whether their facility's laboratory can handle each specimen type or whether samples should be sent to an outside laboratory. The turnaround time for obtaining results and the implications for notifying families and primary care providers of a positive result should also be considered.

Timing of Testing

For cases with clinical criteria or infection in the pregnant person:

- Test as soon as practical. If saliva testing is used and the infant receives breast milk, wait one hour after feeding.

For cases with a referred hearing screening:

- In the hospital setting, if an infant does not pass (e.g., "refers") their initial hearing screening, the screening typically is repeated one additional time several hours later and as close to nursery discharge as possible. Most infants who do not pass an initial hearing screening will pass a follow-up screening. The facility should weigh the advantages and disadvantages of waiting for a repeat hearing screening and the timing of conducting CMV screening. Sending a test after a first failed screening may lead to unnecessary costs since many infants pass the repeat screening. Those costs include the lab cost for the test, the collection materials, and staff time spent on sample collection efforts. However, waiting for a second failed screening before obtaining a cCMV test specimen can create other time and resource burdens (i.e. families waiting for the newborn to urinate before being able to be discharged home). Facilities may consider obtaining a CMV specimen (urine or saliva), holding the specimen until a repeat hearing screening is performed, and sending specimens to the laboratory only after a second failed screening. This reduces total costs, but not collection costs. It is also important to ensure that the specimen is handled appropriately. Urine specimens may need to be refrigerated or frozen if not sent immediately.
- Facilities should assess their typical hearing screening refer rates on initial screening and repeat inpatient screening before determining the time frame when they will collect a CMV specimen. Facilities with high refer rates on the first inpatient screening may consider waiting until a second inpatient refer rate for cost and effort considerations.

Procedural Considerations

Urine sample:

1. Obtain a physician's order for the test.
2. Inform the parent of the reason for testing and explain the procedure (see Attachment A for sample written information).
3. Securely affix the urine collection bag to the infant.
4. Transfer urine to a sterile container for submission to the laboratory. Follow laboratory guidelines for minimum volume needed and any need for specimen refrigeration.
5. Submit the specimen to the laboratory.

Saliva sample:

1. Obtain a physician's order for the test.
2. Inform the parent of the reason for testing and explain the procedure (see Attachment A for sample written information).
3. If receiving breast milk, wait one hour after the last feeding.
4. Insert a sterile cotton or polyester swab into the baby's mouth between the gum and cheek and swirl for several seconds.
5. Remove the swab band and place it into a buffer formulated for PCR diagnostic testing.
6. Submit the specimen to the laboratory.

Blood sample:

1. Obtain a physician's order for the test.
2. Inform the parent of the reason for testing and explain the procedure (see Attachment A for sample written information).
3. Obtain a blood specimen following usual hospital procedures for collecting blood from infants.
4. Submit the specimen to the laboratory.

General procedural considerations:

- Consider if a cCMV test order for cases meeting testing criteria should be part of a standard newborn order form.
- Facilities should consider if their policy will incorporate multiple approaches, such as adopting urine screening as the primary screening method with an option of using a saliva test if the infant is expected to be discharged home within a few hours of the hearing screening.
- Establish a communication strategy for ensuring that infants who do not pass their newborn hearing screening are reported to the appropriate staff to ensure that CMV testing is ordered, and specimens are collected.
- Establish the strategy to communicate results to the primary care provider and the parent. The results will likely be received for healthy newborns after the child is discharged home.

Procedural Considerations After Test Results

If CMV results are negative:

- Notify the ordering or primary care provider of test results. Negative results can be considered non-urgent and routed via electronic health records portals, mail, or other mechanisms.
- Notify parent(s)/guardian(s) of test results. Negative results can be considered non-urgent and routed via electronic health records portals, mail, or other mechanisms.
- If the reason for CMV testing was a failed hearing screening, remind the parent(s)/guardian(s) that they still need to schedule and attend a hearing rescreening or diagnostic audiology appointment.

If CMV results are positive:

- Notify the ordering or primary care provider of test results. The facility's policy should document the steps needed to ensure results have been communicated as a result needing action (i.e. faxing or calling information in addition to results being placed in the electronic medical record).
- The responsible physician/provider should order additional recommended testing for infants with positive cCMV testing if not previously obtained[13]:
    - Complete blood cell and platelet counts
    - Serum alanine aminotransferase (ALT) concentration
    - Serum total and direct bilirubin concentration
    - Serum creatinine concentration (if antiviral therapy is initiated)
    - Blood quantitative CMV viral load
    - Cranial ultrasound
    - Ophthalmology evaluation for retinitis and cortical visual impairment
    - Audiology evaluation (including on children who passed initial hearing screening)
- Antiviral treatment should be considered in consultation with an Infectious Disease specialist.
- Notify the parent(s)/guardian(s) of test results and expected next steps via phone call or in-person discussion as soon as feasible. Educate the parent(s)/guardian(s) about the need to attend follow-up Audiology, Ophthalmology, Infectious Disease, laboratory testing, and imaging appointments. Parents should be advised to consult with their primary care provider to make follow-up appointments with:
    a. Infectious disease – as soon as possible
    b. Audiology appointment - within 3 months of the cCMV diagnosis[11]
    c. Ophthalmology – within 3 months of the cCMV diagnosis
- Complete a New Jersey Birth Defects registration. Congenital CMV infection is a registerable diagnosis per NJAC 8:20-1.2(a)i(28).

Citations:

[1] McVicar SB, et. al. (2023) *Standardized Surveillance Case Definition for Congenital Cytomegalovirus (cCMV) Infection and Disease.* 23-ID-02. https://www.cste.org/page/PositionStatements

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Resources

CDC “About Cytomegalovirus” Page

https://www.cdc.gov/cytomegalovirus/about/index.html

National CMV Foundation Website – resources for healthcare providers and families

https://www.nationalcmv.org/resources