CLINICAL GUIDELINE

Congenital CMV: Initial work up by primary care provider

Children's MINNESOTA

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

Infant with positive dried blood spot (DBS) for congenital CMV (cCMV) (note 1)

Communication of results:
- MDH genetic counselor will contact primary provider with positive test
- Primary provider should discuss results with family, arrange additional testing

Collect confirmatory urine CMV PCR **as soon as possible but prior to 21 days of life**
- Bag specimen adequate, can be sent to commercial lab
- Fax all results to MDH at (651) 251-6285

Initial work up: see note 3 regarding timing of work up
- ❑ CBC with diff, LFTs (AST, ALT, total and direct bili)
  - Assess for thrombocytopenia (plts <100k), hemolytic anemia, direct hyperbili (D bili >2mg/dL), ALT and/or AST >80 IU/mL
- ❑ Head US, ideally interpreted by pediatric radiologist (note 4)
- ❑ **Pediatric audiology** evaluation ideally **by 1 month of life** for diagnostic ABR for all infants, even those who passed newborn hearing screen (see page 8)
  - Place referral to Children's Audiology Clinic for "**congenital CMV"**
  - Send Cerner message to "ENT Audiologist" indicating infant has tested positive for cCMV to expedite appointment
  - Scheduling phone # (612) 874-1292; provider Audiology Assistance phone # (612) 813-7610
- ❑ **Ophthalmology** evaluation **by 3 months of life.**
  - Place referral for "**congenital CMV- evaluate for retinitis and cortical visual impairment**"
  - Preference for evaluation by pediatric ophthalmologist, although comprehensive community ophthalmologists can evaluate infants.

Are there any abnormalities on work up (including isolated hearing loss)?

Physical exam (note 2)
- ❑ Growth parameters: assessment for small for gestational age (birth weight <10%ile), microcephaly (head circumference <3%ile)
- ❑ Exam with attention to hepatomegaly, splenomegaly, jaundice, petechiae/purpura, neurologic abnormalities

Urine CMV positive

Urine CMV negative

Abnormal exam

Normal exam

Discuss with ID and manage off guideline. Call through Physician Access (866-755-2121)

False positive DBS result, no further work up

Yes

No

Routine follow up with pediatrician. Audiology, ophthalmology follow up as recommended (see page 5, 6, 7).

Discuss with **Pediatric Infectious Disease** (see page 5, 6).
- Ideally to be seen in infectious disease clinic within the **first month of life**
- Referral through Physician Access (866-755-2121) or consult/referral orders
  - At a minimum for infectious disease referral to be processed, need results of urine CMV PCR, CBCd, LFTs, head US prior to triage. Can discuss with on call ID provider for any questions regarding work up, results, timing, or need for referral.

Disclaimer: This guideline is designed for general use with most patients; each clinician should use their own independent judgment to meet the needs of each individual patient. This guideline is not a substitute for professional medical advice, diagnosis or treatment.

Congenital CMV: Notes

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

Note 1: Sensitivity of DBS testing for cCMV is about 75%. If there is clinical concern for cCMV despite negative DBS result, urine CMV PCR should be collected prior to 21 days of age.

Note 2: 90% of infants with cCMV will be asymptomatic at birth. In regards to microcephaly, there is a greater concern if there is a disproportionately small head circumference compared to other growth parameters.

Note 3: Timing of work up

- **Urine CMV PCR should be collected prior to 21 days of life** to differentiate congenital CMV from perinatally acquired CMV.
  - CMV excretion in the urine begins 3-12 weeks after exposure to CMV. With congenital infection, excretion of virus should be detected at birth. With perinatally acquired infection- such as exposure at the time of delivery or from maternal breastmilk- excretion of virus will begin at 3 weeks of life at the earliest.
  - For immunocompetent infants born full term with perinatally/postnatally acquired CMV (ie DBS negative for CMV before 21 days of life, then positive CMV PCR testing after 21 days of life), no further work up is indicated.
- Ideally, evaluation (CBC with diff, LFTs, head US, audiology evaluation) should **be completed by 1 month of life** so that decision regarding antiviral therapy can be made promptly (see page 5)
  - Infants with moderate to severely symptomatic cCMV with or without CNS involvement should be started on **treatment with antiviral therapy before 13 weeks of life, although ideally by 1 month of life.**
  - Infants with cCMV with isolated sensorineural hearing loss (SNHL) should be started on **treatment with antiviral therapy before 13 weeks of life.**
- Timing of initial **ophthalmologic evaluation** is uncertain, with lack of evidence based recommendation. However, per expert opinion, recommend initial evaluation within the **first 3 months of life**. Consider earlier evaluation for symptomatic infants, such as those with SNHL or head imaging abnormalities.

Note 4: Head imaging findings in cCMV

- Head imaging findings more clearly associated with cCMV include: Intracranial calcification (often periventricular), intracranial ventriculomegaly without other explanation, white matter changes, periventricular echogenicity, cortical or cerebellar malformations, migrational abnormalities
- There is uncertainty if some nonspecific head imaging findings constitute clinically significant cCMV. These findings include: subependymal cysts, germinal matrix cysts, grade I germinal matrix hemorrhage, choroid plexus cysts, lenticulostriate vasculopathy. Recommend discussion with pediatric neuroradiology and/or pediatric infectious disease to review these findings.
- If additional imaging is indicated, brain MRI without contrast is recommended noting indication for cCMV (limited brain MRI is not sufficient). MRI may detect abnormalities not seen on head US, such as migrational disorders, leukodystrophy, and myelination disorders. There is no clear consensus on when or in whom brain MRI is needed. However, brain MRI should be considered if there are any abnormal neurologic findings, including abnormal neurologic exam, micro/macrocephaly, or abnormalities on head US.
  - At Children's Minnesota, brain MRI without contrast for cCMV can be ordered without sedation (ie with natural sleep). This can be attempted in infant <3 months of age and is most successful in those <1 month of age. This MRI is performed with the infant fed and then swaddled and requires infant to tolerate laying supine for about 30 minutes. It is most successful in a sleep deprived infant. This study may not be appropriate for an infant with reflux. If sufficient images are not obtained with this natural sleep protocol, infant may need to return on a different day for a sedated MRI (requires the infant to be NPO and may require overnight observation stay post sedation dependent on post-conception age). At Children's Minnesota, to order brain MRI without contrast and without sedation in the order select "no" sedation and in special instructions specify "use feed and swaddle protocol".
- Infants with cCMV with sensorineural hearing loss may get additional head imaging per ENT. Imaging modality and timing is individualized.

Congenital CMV: initial work up by primary care provider

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

Special circumstances:

Infant with failed newborn hearing screen and negative CMV DBS result:

- For infants with negative CMV DBS result who fail the newborn hearing screen, follow up with audiology is recommended as soon as possible (see page 8 regarding types of hearing testing).
- If sensorineural hearing loss is diagnosed in an infant with negative CMV DBS, then urine CMV PCR should be collected by **21 days of life.** The DBS for CMV will miss some cases of cCMV, but a urine CMV PCR prior to 21 days of life can be diagnostic for CMV. A negative urine CMV PCR after 21 days of life may indicate hearing loss is not due to cCMV.
    - Infants seen at Children's Minnesota Audiology Clinic who have negative CMV DBS result but are found to have sensorineural hearing loss are recommended to have urine CMV PCR testing sent from audiology clinic. Primary care providers can also order urine CMV PCR testing if there is concern for hearing loss and diagnostic audiologic testing may take place after 21 days of life. Some newborn nurseries may order urine CMV testing on newborns who refer the newborn hearing screen but before the CMV DBS result is available.
- Treatment is currently recommended for infants with isolated sensorineural hearing loss due to cCMV (see page 5).

Twin gestation:

- There can be concordant or discordant infection of twins with cCMV (ie one twin may be infected and the other may or may not be infected). There may be a higher incidence of congenital infection of both twins in monochorionic compared to dichorionic pregnancies.
- If one twin tests positive for cCMV (positive DBS and positive urine CMV PCR prior to 21 days of life), recommend screening the other twin with urine CMV PCR prior to 21 days of life even if that twin had a negative DBS for CMV.

Infants born to birthing parent with known or suspected CMV infection during pregnancy:

- In birthing parent with suspected primary CMV during pregnancy and/or had abnormal fetal imaging consistent with cCMV, infant should be tested with urine CMV PCR prior to 21 days of life, regardless of CMV DBS results.

CLINICAL GUIDELINE

Congenital CMV: NICU and inpatient care

Children's MINNESOTA

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

Special circumstances: NICU and inpatient care

Premature infants:

- Infants weighing <2 kgs with extended NICU stays will get routine newborn screening (including cCMV screen) completed at 24-48hrs of life and then at 14 and 30 days of age to find disorders obscured by prematurity and treatment artifacts.
- DBS CMV testing is a PCR based screen so there is no expected decreased sensitivity of DBS CMV testing in premature infants or those with low birth weight.
- In infants with **negative** CMV DBS at 24-48 hrs and 14 days, then **positive** at 30 days, this likely represents postnatally acquired CMV disease (see note 3 above). In preterm infants, postnatally acquired CMV has been associated with hepatitis, interstitial pneumonia, hematologic abnormalities including thrombocytopenia and leukopenia, and a viral sepsis syndrome. These syndromes should be evaluated as clinically indicated.
- In premature infants with cCMV (positive DBS for CMV and/or positive urine CMV PCR prior to 21 days of age), **audiology consultation**/referral should be placed at time of diagnosis. Timing of initial audiologic evaluation will be individualized but likely performed closer to 36 weeks gestational age. Timing of initial **ophthalmology** exam is uncertain, but should ideally be within the first 3 months of life; however, should consider earlier evaluation in symptomatic infants, such as those with SNHL or head imaging abnormalities.

Perinatally/postnatally acquired CMV:

- Infants can acquire CMV perinatally/postnatally from passage through infected birthing parent genital tract or via ingestion of CMV positive human milk.
- Among infants who acquire infection from birthing parent cervical secretions or human milk, preterm infants born before 32 weeks' gestation and with a birth weight less than 1500 g are at greater risk of developing CMV disease than are full-term infants. Most infants who acquire CMV from ingestion of human milk from CMV-seropositive birthing parent do not develop clinical illness or sequelae, likely because of the presence of passively transferred maternal antibody (AAP Red Book).
- CMV infection is very common. According to the CDC, one in three children in the US are infected with CMV by the age of 5 years. More than half of adults are estimated to be infected with CMV by age 40. Given the high prevalence of CMV, it is not routinely recommended to check birthing parents for CMV seropositivity or test maternal breastmilk for CMV.
- Human donor breastmilk is pasteurized, which should inactivate CMV. Freezing human breastmilk to decrease CMV is not advised- it may reduce the viral load of CMV, but it does not change the risk of CMV sepsis-like syndrome.

Care of children with CMV:

- Hand hygiene is recommended to decrease transmission of CMV. Standard precautions should be sufficient to interrupt transmission of CMV.
- Asymptomatic excretion of CMV is common in children of all ages.

CLINICAL GUIDELINE

Congenital CMV: treatment recommendations

Children's MINNESOTA

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

For infants with congenital CMV (**positive CMV DBS** and/or **positive urine CMV PCR** prior to 21 days of life) disease severity should be defined to determine treatment.

Disease severity is determined by initial work up in the first 13 weeks of life (see page 1 & 2). Additional details in AAP Red Book 2024.

Asymptomatic (Note A): normal/negative initial work up.

Mildly symptomatic: abnormal work up with 2 or fewer transient findings (eg <2 weeks) or clinically insignificant findings (eg, petechiae, mild hepatomegaly, thrombocytopenia, raised ALT).

Discuss with infectious disease

No treatment typically recommended

Asymptomatic with isolated sensorineural hearing loss (SNHL): SNHL and otherwise normal/negative initial work up.

Discuss with infectious disease

Valganciclovir PO for **6 weeks**, started by 13 weeks of life (Note B)

Moderate to severely symptomatic (with or without CNS involvement) (Note A)**:** abnormal work up including one or more of the following:

- Single severe or multiorgan disease or life-threatening organ dysfunction
- Multiple persistent (eg, ≥2 weeks) manifestations attributable to congenital CMV infection
- CNS involvement such as microcephaly, radiographic abnormalities, abnormal cerebrospinal fluid indices for age, chorioretinitis, or the detection of CMV DNA in cerebrospinal fluid
- Greater than 2 mild disease manifestations

Discuss with infectious disease

Valganciclovir PO for **6 months**, started by 13 weeks of life, although ideally by 4 weeks of life (Note B)

Treatment completed

Recommended long term follow up:

- ❑ Routine developmental assessments and pediatrician follow up
- ❑ Referral to Help Me Grow and Follow Along Program
- ❑ Audiology/ENT follow up as recommended (see page 7)
- ❑ Ophthalmology follow up as recommended (Note C)

Congenital CMV: Notes on treatment and follow up

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

Note A: Hearing and neurodevelopmental outcomes are best described in children who are moderate-severely symptomatic with cCMV and those asymptomatic at birth. The outcomes are less well described for mildly symptomatic infants and those with isolated head US findings not conclusively associated with cCMV.

- **Asymptomatic infants:** 90% of infants with cCMV will be asymptomatic at birth. Of those who are asymptomatic, 10-15% will develop SNHL. Neurodevelopmental sequelae uncommonly develop.
- **Moderate to severely symptomatic infants:** 10% of infants with cCMV will be symptomatic at birth. Of those, 30-40% will develop SNHL and there is a risk of neurodevelopmental sequelae.

Note B: Valganciclovir dose adjustment and medication monitoring: Infectious disease and general primary care provider may collaborate for medication dose adjustment and lab monitoring during treatment.

- Dose of Valganciclovir oral is 16mg/kg/dose every 12 hrs. For infants treated for >6 weeks, dose should be adjusted monthly for weight gain.
- With Valganciclovir there is a risk of neutropenia and hepatitis. Recommend lab monitoring, at minimum:
    - Upon starting Valganciclovir, absolute neutrophil counts (obtained from CBC with diff) should be performed weekly for 6 weeks, then at 8 weeks, then monthly for the duration of antiviral treatment
    - Serum ALT should be measured monthly during treatment
    - Consider monitoring creatinine in infants receiving other nephrotoxic medications or if underlying renal disease.
- Valganciclovir has a warning that it may cause impairment of fertility, is a potential human carcinogen, and is potentially teratogenic/mutagenic. This is based on *animal studies* of *ganciclovir*.
    - Given concerns for potential teratogenicity and carcinogenicity, the package insert recommends caution in handling the powder and re-constituted oral solution to reduce unnecessary exposure to others.

Note C: Timing of ophthalmology follow up is uncertain, with lack of evidence based recommendations. Follow up as recommended by ophthalmology.

CLINICAL GUIDELINE

Congenital CMV: Audiology follow up

Children's MINNESOTA

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

First Hearing Test

Diagnostic auditory brainstem response (ABR) by 1 month of age, or no later than one month after congenital CMV is confirmed (see page 8). Having a clear baseline of where the infant hears makes it easier to track changes over time.

Referral will be made to early childhood intervention (Help Me Grow)

Normal

Second Hearing Test*

Auditory brainstem response (ABR) by 4 to 5 months of age.

Normal

Behavioral Hearing Tests up to age 2 years*

Every 3 months, vestibular screen completed, to include ear specific measurements. ABR may be needed depending on developmental age.

Normal

Behavioral Hearing Tests ages 2 to 6 years*

Every 6 months, vestibular screen completed, to include ear specific measurements. Sedated ABR may be needed depending on developmental age.

Normal

Hearing Tests ages 6 to 10 years*

Every 12 months, vestibular screen completed, to include ear specific measurements. Sedated ABR may be needed depending on developmental age. If no hearing abnormalities are noted, routine screening ends at age 10.

Abnormal

*If at any time hearing loss is diagnosed or suspected, increased monitoring/testing will be completed.

Abnormal hearing screen:

- Children diagnosed with hearing loss, transient or permanent, will be referred to ENT.
- Children diagnosed with hearing loss that is sensorineural or permanent in nature will complete a workup for amplification (hearing aid, assistive listening device, cochlear implant) as appropriate.
- Continued audiology and ENT follow up as directed

CLINICAL GUIDELINE

Congenital CMV: Audiology follow up

Children's MINNESOTA

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

Diagnostic Audiology Assessment: Auditory Brainstem Response (ABR) Evaluation

What is a diagnostic auditory brainstem response (ABR) evaluation and how is it different than the newborn hearing screening?

Newborn hearing screening
Completed via automated auditory brainstem response (AABR) or screening otoacoustic emissions (OAE).
Both are screening tests and suggest normal hearing sensitivity, but cannot rule out minimal or mild hearing losses
Takes between 3-30 minutes to complete

Diagnostic ABR evaluation
Includes finding of thresholds using ABR, tympanometry evaluation, and diagnostic otoacoustic emissions.
Information obtained includes hearing thresholds, if middle ear dysfunction is present, health of cochlear hair cells
Takes approximately 2 hours to complete

Audiology Resources:

- StarNet: CMV Hearing Test Schedule (childrensmn.org)
- MDH Audiology Guideline: Section 4: Audiology Guidelines For Infants With Congenital Cytomegalovirus (state.mn.us)
- Developmental Milestones: CDC's Developmental Milestones | CDC
- Balance/Vestibular Screening Resources:
  - One leg standing screen (36 months=2 sec, 42 months=4 seconds, 48 months=6 seconds, 54 months=8 seconds, 60 months=10 seconds, 72 months=12 seconds)
  - Vanderbilt Pediatric Dizziness Handicap Inventory

Congenital CMV: References

Aim: standardize and expedite the identification, evaluation, and treatment of infants with congenital CMV

Additional cCMV Resources:

- Minnesota Department of Health Cytomegalovirus (CMV) and Congenital CMV: Cytomegalovirus (CMV) and Congenital CMV - MN Dept. of Health (state.mn.us)
- Minnesota Department of Health Congenital CMV Information for Families and Caregivers **(family resource)**: Congenital Cytomegalovirus - Information for Families and Caregivers (state.mn.us)
- Centers for Disease Control and Prevention Cytomegalovirus (CMV) and Congenital CMV Infection: Cytomegalovirus (CMV) and Congenital CMV Infection | CDC
- National CMV Foundation **(with family resources)**: National CMV Foundation – Cytomegalovirus (CMV) | National CMV Foundation

References

- Chung PK, Schornagel FA, Soede W, van Zwet EW, Kroes AC, Oudesluys-Murphy AM, Vossen AC. Valganciclovir in Infants with Hearing Loss and Clinically Inapparent Congenital Cytomegalovirus Infection: A Nonrandomized Controlled Trial. The Journal of Pediatrics. 2024 Feb 8:113945.
- Dollard SC, Dreon M, Hernandez-Alvarado N, Amin MM, Wong P, Lanzieri TM, Osterholm EA, Sidebottom A, Rosendahl S, McCann MT, Schleiss MR. Sensitivity of dried blood spot testing for detection of congenital cytomegalovirus infection. JAMA pediatrics. 2021 Mar 1;175(3):e205441-.
- Egaña-Ugrinovic G, Goncé A, García L, Marcos MA, López M, Nadal A, Figueras F. Congenital cytomegalovirus infection among twin pairs. The Journal of Maternal-Fetal & Neonatal Medicine. 2016 Nov 1;29(21):3439-44.
- Kimberlin DW, Aban I, Peri K, Nishikawa JK, Bernatoniene J, Emonts M, Klein N, Bamford A, DeBiasi RL, Faust SN, Jones CE. Oral Valganciclovir initiated beyond 1 month of age as treatment of sensorineural hearing loss caused by congenital cytomegalovirus infection: a randomized clinical trial. The Journal of Pediatrics. 2024 May 1;268:113934.
- Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR. Valganciclovir for symptomatic congenital cytomegalovirus disease. New England Journal of Medicine. 2015 Mar 5;372(10):933-43.
- Luck SE, Wieringa JW, Blázquez-Gamero D, Henneke P, Schuster K, Butler K, Capretti MG, Cilleruelo MJ, Curtis N, Garofoli F, Heath P. Congenital cytomegalovirus: a European expert consensus statement on diagnosis and management. The Pediatric infectious disease journal. 2017 Dec 1;36(12):1205-13.
- Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, Daly K, Doutré S, Gibson L, Giles ML, Greenlee J. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. The Lancet Infectious Diseases. 2017 Jun 1;17(6):e177-88.
- Ronchi A, Zeray F, Lee LE, Owen KE, Shoup AG, Garcia F, Vazquez LN, Cantey JB, Varghese S, Pugni L, Mosca F. Evaluation of clinically asymptomatic high risk infants with congenital cytomegalovirus infection. Journal of Perinatology. 2020 Jan;40(1):89-96.
- 2024. "Cytomegalovirus Infection", Red Book: 2024–2027 Report of the Committee on Infectious Diseases, Committee on Infectious Diseases, American Academy of Pediatrics, David W. Kimberlin, MD, FAAP, Ritu Banerjee, MD, PhD, FAAP, Elizabeth D. Barnett, MD, FAAP, Ruth Lynfield, MD, FAAP, Mark H. Sawyer, MD, FAAP

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