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

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

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

Normal exam

False positive DBS result, no further work up

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 **by 1 month of life** for diagnostic ABR for all infants, even those who passed newborn hearing screen (see slide 7)
  - 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**"
  - Comprehensive community ophthalmologists can evaluate infants

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

Yes

No

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

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.

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

- 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.
  - **Urine CMV PCR should be collected prior to 21 days of life** to differentiate congenital CMV from perinatally acquired CMV.
  - For immunocompetent infants born full term with perinatally/postnatally acquired CMV (ie DBS negative for CMV then positive CMV PCR testing after 21 days of life), no further work up is indicated.
- Infants who are identified with symptomatic cCMV should ideally start **treatment with antiviral therapy before 4 weeks of life.** Ideally, CBCd, LFTs, head US, and audiology evaluation should **be completed prior to 4 weeks of life** so that decision regarding antiviral therapy can be made prior to 4 weeks of life.
  - Work up of positive DBS for CMV may require multiple health care visits. To expedite work up, especially in infants 3 week of age or older, can consider arranging lab draw, head US, and audiology evaluation on a single day at a single health care facility. Can discuss with **Pediatric Infectious Disease** nursing staff (651-220-7148) to help arrange, if needed.
- 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 sensorineural hearing loss (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, 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.

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:

- There are higher rates of cCMV in infants who fail their newborn hearing screen. However, treatment is not currently recommended for infants with isolated sensorineural hearing loss due to cCMV.
- Recommend no additional urine CMV PCR testing unless there are other clinical concern for cCMV.
- Should be seen by audiology for follow up hearing screen, ideally within the first 4 weeks of life.

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.

Congenital CMV: NICU and inpatient care

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: follow up in primary care

Children's MINNESOTA

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

Asymptomatic with cCMV (note A)**:** Defined as child with CMV DBS positive, CMV urine PCR positive, normal/negative initial work up. *May have isolated sensorineural hearing loss (SNHL).*

- Child with isolated SNHL should be discussed with infectious disease but may not need treatment if no other abnormalities are identified.

Symptomatic with cCMV (note B): Defined as child with CMV DBS positive, CMV urine PCR positive, abnormal findings on initial work up (other than isolated SNHL, see Note A).

- Child discussed with infectious disease

Was treatment recommended by infectious disease?

No

Yes

Recommended long term follow up

- ❑ Routine developmental assessments and pediatrician follow up
- ❑ Referral to Help Me Grow
- ❑ Audiology/ENT follow up as recommended (see page 6)
- ❑ Ophthalmology follow up as recommended (note D)

Treatment completed, typically 6 months

In collaboration with infectious disease, general pediatrician may assist with Valganciclovir dose adjustment and medication monitoring (note C)

Note A:
- 90% of infants with cCMV will be asymptomatic at birth
- 10-15% will develop SNHL
- Uncommonly develop neurodevelopmental sequelae

Note B:
- 10% of infants with cCMV will be symptomatic at birth
- 30-40% will develop SNHL
- Risk of neurodevelopmental sequelae

Note C: Valganciclovir dose adjustment and medication monitoring
- Dose of Valganciclovir should be adjusted monthly for weight gain. Dose of oral Valganciclovir is 16mg/kg/dose every 12 hrs
- With Valganciclovir there is a risk of neutropenia and hepatitis. Recommend lab monitoring, at minimum with:
  - 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

Note D: 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 slide 7). 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

Congenital CMV: Audiology follow up

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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

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References

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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

Workgroup: Harrison, ID Provider group, Zamora, Chawla, Meyer, Novak, Strul