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Asymptomatic Congenital Cytomegalovirus infection Clinical Pathway

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Rationale

I. Increase awareness of the prevalence and ensure timely diagnosis of asymptomatic congenital Cytomegalovirus (cCMV) infection
II. Adhere to the 2024 Florida State Legislature for early detection of cCMV infection

Background / Published Data and Levels of Evidence

I. **Epidemiology and Transmission**
   a. CMV, or human herpesvirus 5, is a double stranded DNA and member of the herpesvirus family[1]. Maternal CMV infections can occur during pregnancy as 1) a primary CMV infection; 2) a non-primary infection through acquisition of a new viral CMV strain; or 3) reactivation of an existing infection. In utero fetal infection with CMV, termed as congenital CMV (cCMV), occurs through transplacental CMV transmission to the fetus[1]. It is estimated that the prevalence of congenital CMV (cCMV) in the United States is about 0.7%[2]. Preterm infants born at less than 32 weeks gestation and a birth weight of less than 1500 grams are at higher risk of developing cCMV disease than term infants, likely because of the lack of passively transferred maternal antibodies to CMV. CMV transmission can also occur antenatally by exposure to an infected genital tract during delivery, or postnatally by ingestion of CMV-positive human milk after birth.

II. **Clinical Manifestations**
   a. Only about 10% of infants with cCMV will have symptomatic clinical manifestations of disease including jaundice (due to direct hyperbilirubinemia), petechiae (due to thrombocytopenia), purpura, hepatosplenomegaly, microcephaly, intracerebral periventricular calcifications and retinitis. These symptomatic patients are at increased risk for sensorineural hearing loss (SNHL), developmental delays, and have a 3%-10% risk for death attributable to the disease. The remaining 90% majority of infants with cCMV are asymptomatic of the disease during the newborn period[3]. Despite the lack of symptomatology, it is estimated that 6%-23% of these infants will develop SNHL[4].
   b. cCMV is the leading non-genetic cause of SNHL in children in the US—accounting for 20% of hearing loss detected in newborns, and 25% of all hearing loss by the age of four. SNHL occurs in up to 50% of patients with symptomatic cCMV and in up to 15% of patients with asymptomatic cCMV. Alarmingly, about 40% of infected children who ultimately develop SNHL will not have hearing loss detectable within the first month of life. Furthermore, about 50% of patients with CMV-associated SNHL continue to have further progression of their hearing loss over time[1]. When not detected at birth, SNHL, as a sequela of cCMV, can silently

progress over the first few years of life with a median age of detection of 44 months corrected gestational age (CGA) with a range of detection of 24 to 182 months[4]. Given the difficulty in predicting which patients with asymptomatic cCMV are at risk of developing progressive hearing loss, early detection of cCMV disease and continued monitoring over the first few years of life are paramount.

III. **Florida Legislation on cCMV**

a. In March of 2024, the state of Florida finalized and published the CS/SB 168 (Ch.2024-164) legislation relating to congenital cytomegalovirus infection. It went into effect on July 1, 2024.
b. The bill amends newborn health screening requirements in s. 383.145, F.S., to require that all newborns who are born in a hospital that provides neonatal intensive care services, and who are born before 35 weeks gestation, require cardiac care, or require medical or postsurgical treatment for at least three weeks, be tested for the cytomegalovirus (CMV)[5].
c. Additionally, the bill requires that if the newborn is transferred to another hospital for higher-level care, the receiving hospital must administer the CMV test if the test was not already performed at the transferring hospital or birth facility. The bill clarifies that a CMV test is required if the newborn will be transferred or admitted for intensive and prolonged care, regardless of whether the newborn failed his or her hearing screening[5].
d. The bill creates a new requirement that CMV screening, and medically necessary follow-up reevaluations leading to diagnosis, are covered benefits for Medicaid patients and that private health insurance policies and health maintenance organizations that provide comprehensive coverage must compensate providers for the covered benefit at the contracted rate. The bill provides that a child who is diagnosed with CMV must be referred to a primary care physician and the Children's Medical Services Early Intervention Program[5].

PDF copy of the Congenital Cytomegalovirus Screening Bill can be found here

IV. **Hearing Screening Among Neonates**

a. A 2019 publication by the Joint Committee on Infant Hearing (JCIH) has built on previous guidelines (published in 2007 and 2013) through literature reviews and expert consensus opinion, and supports early hearing detection and intervention among infants. The goal is to identify hearing loss as early as possible and to provide intervention no later than 3 to 6 months of age.
b. Among premature infants, it is commonly recommended to obtain an ABR hearing screening at or after 34 weeks post menstrual age [6]. A small prospective cohort study among 90 preterm infants with a median gestational age of 29.5 weeks found that an AABR pass rates of greater than 80% could be obtained from 30 weeks postmenstrual age (PMA). Accordingly, testing could be performed in certain symptomatic high risk premature infants as early as 30 weeks and repeated at 34 weeks, and as needed thereafter [7].

V. **Diagnosis**

a. Quantitative nucleic acid amplification tests (NAATs) are currently the preferred method to detect CMV deoxyribonucleic acid (DNA) and can be performed on tissues and fluids such as cerebrospinal fluid (CSF), peripheral blood, urine and saliva[1]. NAATs of saliva swab specimens from neonates have been shown to be >95% sensitive for the identification of cCMV infection[1].

b. cCMV diagnosis requires detection of CMV or CMV DNA in urine, saliva, blood, or CSF obtained within three weeks of birth; detection beyond this initial period of life could reflect postnatal acquisition of virus[1].

c. Qualitative testing of saliva may be used as an initial screening test but confirmatory qualitative testing of the urine is recommended if positive because of potential CMV contamination of saliva in human milk.

d. Urine CMV qualitative NAAT has a sensitivity of >98% and a specificity of >99%[8].

VI. **Treatment** [(1,9)]

a. **Asymptomatic Infants**: defined as an infant with no apparent signs to suggest cCMV disease

i. Asymptomatic infants with no evidence of hearing loss do not require treatment and therapy is not recommended outside of a research study

ii. Asymptomatic infants with isolated SNHL have shown improved audiologic outcomes when treated with an antiviral agent. These infants **may** be offered oral valganciclovir therapy for 6 weeks. **This therapy, when indicated, should be started no later than 12 weeks and 6 days of life.**

b. **Mildly symptomatic Infants***

i. A mildly symptomatic infant is defined as having two or fewer transient (< 2 weeks) or clinically insignificant findings such as petechiae, mild hepatomegaly, thrombocytopenia, elevated levels of alanine aminotransferase

ii. As there are insufficient data to recommend routine treatment, an Infectious Disease consult is warranted and treatment will be considered on a case-by-case basis

c. **Moderately to severely symptomatic infants***

i. Such infant is defined as having one or more of the following:

1. Single severe or multiorgan disease or life-threatening organ dysfunction
2. Multiple, persistent (> 2 weeks) manifestations attributable to cCMV infection (thrombocytopenia, petechiae, hepatomegaly, splenomegaly, hepatitis)
3. Central nervous system involvement (microcephaly, ventriculomegaly, intracerebral calcifications, cortical or cerebellar malformations, migration abnormalities), abnormal cerebrospinal fluid indices for age, chorioretinitis or the detection of CMV DNA in the CSF

ii. These infants require an ID consult and oral valganciclovir for 6 months

**The approach to the symptomatic infant is outside the scope of this clinical practice pathway. As a quick reference, the symptomatic infant definition and general recommended approach to treatment is provided.*

Clinical Management

I. CMV Testing

a. **All infants** admitted to the NICU, CCDH, or CVICU will have saliva obtained for CMV DNA testing, irrespective of any prior testing.
b. If a prior testing has been performed before JHACH NICU, CCDH, or CVICU admission, results should be documented in the H&P.
c. Testing will be preferably obtained within the first 24 hours of admission
d. If infant is orally fed, perform testing at least two hours after an oral feeding
e. If the qualitative test for CMV in saliva is positive, a urine sample should be sent for qualitative CMV DNA PCR for confirmation given the risk of contamination of saliva by CMV containing milk.
f. *If CMV testing is confirmed positive, notify the State of Florida Newborn Hearing Screening (NBHS) of result through e-Reports within 7 days after receipt of results.*

II. Evaluation

a. All infants who test positive for cCMV should undergo detailed evaluation to rule out signs and symptoms characteristic of symptomatic CMV disease. This will include:
    i. Cranial ultrasound (if abnormal, obtain brain MRI without contrast)
    ii. CBC to assess for thrombocytopenia
    iii. CMP to evaluate for signs of hepatitis (AST, ALT, direct bilirubin) - obtained by venipuncture, not heel stick
    iv. Pediatric Ophthalmology consult to rule out retinitis
    v. Hearing screen as soon as appropriate
    vi. Infectious Disease consult
    vii. Obtaining CSF will be determined on a case-by-case basis after discussion with the Infectious Disease team

III. Hearing Screening

a. Infants with positive cCMV testing
    i. These infants will have a hearing screen *as soon as clinically stable*. This is defined as:
        1. ≥ 34 weeks CGA
        2. ≥ 1500 grams weight
        3. Off all ototoxic and aminoglycoside medication
        4. Able to maintain body temperature without servo heat source
        5. Requires minimal non-invasive respiratory support (heated high flow nasal cannula, 2 LPM or less) or no respiratory support
        6. Good tolerance to routine care without decompensation
    ii. Hearing examination needs to be done **no later than 12 weeks, 6 days of age** as to allow for timely antiviral treatment if such treatment is recommended by the Infectious Disease team
    iii. **If by 12 weeks, 6 days of age, infant is clinically unstable and/or if hearing screen cannot be performed**, it is recommended to consult the Infectious Disease team to discuss whether infant would qualify for empiric antiviral treatment

iv. In certain circumstances, the hearing screen could be considered between 30 and 34 weeks gestation if the clinical condition allows. It will need to be repeated at 34 weeks if negative.
v. Hearing examination could be repeated prior to discharge at the discretion of the treating team and based on the patient specific circumstances.

b. Infants with negative CMV testing
i. These infants will have a hearing screen performed preferably 48-72 hours prior to hospital discharge when clinically stable (defined above)
ii. Infants who are born at < 28 weeks gestation and/or < 1000 grams at birth who remain clinically ill, should be evaluated for the feasibility of performing a hearing screen at 40 weeks PMA even if the above criteria are not met.
iii. Infants with an initial negative saliva CMV testing who subsequently fail the hearing screen should be re-tested with a qualitative urine CMV PCR if < 21 days of life.
iv. If infant subsequently fails hearing and > 21 days of life, CMV testing is not indicated.

IV. **Treatment Recommendations**

a. Asymptomatic infected infants **with** isolated SNHL
i. Consult Infectious Disease, as infant may benefit from oral valganciclovir for 6 weeks. Treatment should be initiated no later than 12 weeks and 6 days of age.
ii. Outpatient follow-up in the Infectious Disease Clinic *one month after discharge*
iii. Consult Ear Nose and Throat (ENT) specialty inpatient, and arrange for outpatient follow-up per their recommendations
iv. Ensure outpatient follow-up with Audiology per their recommendations
1. Every 3 months for the first year of life
2. Every 6 months until the age of 3, thereafter
v. Referral to Children's Medical Services- Early Steps (CMS-ES)
vi. Add hearing loss ICD-10 code to Problem List

b. Asymptomatic infected infants **with NO** associated SNHL
i. Outpatient monitoring by Audiology for monitoring for late manifestations of hearing loss
1. Every 3 months for the first year of life
2. Consider every 6 months until the age of 3, thereafter
ii. May repeat hearing examination prior to discharge at the discretion of the treating team
iii. Referral to CMS-ES at discharge

c. Mildly symptomatic infant
i. Infectious Disease consult. Treatment will be decided on a case-by-case basis
ii. Referral to CMS-ES
iii. Detailed management is outside the scope of this clinical pathway

d. Moderately to severely symptomatic infant
i. Infectious Disease consult

ii. Treatment with Valganciclovir for 6 months is recommended
iii. Referral to CMS-ES
iv. Detailed management is outside the scope of this clinical pathway

The above guidelines apply to any newborn admitted directly to JHACH NICU, CCDH, or CVICU unit.

Summary

CMV Reporting	Required to notify the State of Florida Hearing Screening (NBHS) of result through e-Reports within 7 days after receipt of results.

Evaluation for cCMV
• CBC • CMP • Head ultrasound (If abnormal, obtain MRI) • Ophthalmology consult • CSF (case-by-case) • ID consult • Hearing screen

Medical Management of cCMV	
Asymptomatic with **NO** SNHL	Therapy is not recommended
Asymptomatic **WITH** SNHL	May benefit from oral valganciclovir therapy for 6 weeks initiated prior to 13 weeks of life. Obtain ID consult
Mildly Symptomatic*	Treatment considered on case-by-case basis. Obtain ID consult
Moderate to Severely Symptomatic*	Treatment with oral valganciclovir for 6 months. Obtain ID consult

Detailed management recommendations are outside the scope of this Clinical Pathway

Clinical Pathway Algorithm:
To view the AgileMD algorithm for asymptomatic congenital cytomegalovirus infection, click the link below or scan the QR code.

https://agile.md/a/3ETNkC8E516RHsvzch8HBnH1c2d1m6boiKkXGJ8UJkWS2eNCWW

Glossary
ABR: Auditory Brainstem Response hearing test
CGA: Corrected gestational age
cCMV: Congenital cytomegalovirus
CMS-ES: Children's Medical Services- Early Steps
ID: Infectious Disease
LPM: Liters per minute
NAAT: Nucleic Acid Amplification test
PCR: Polymerase Chain Reaction
PMA: Postmenstrual age
SNHL: Sensorineural hearing loss

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Outcome Measures
1. Number of hearing screens performed on day of discharge and whether the delay is justified.
2. Number of negative urine CMV done to confirm a positive saliva CMV testing
3. Whether oral ganciclovir was initiated by ID for asymptomatic CMV with isolated SNHL

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