Guideline for Management of Infants with Congenital CMV

This guideline was developed by the following multidisciplinary group:
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These recommendations surround the management of infants with congenital cytomegalovirus (CMV) infection (i.e., positive CMV PCR testing at ≤21 days of life). There is a lack of consensus regarding management of infants diagnosed with CMV after 21 days of life.

A. Background:

1. Approximately 0.7% of infants have congenital CMV.[1,2]
2. Congenital CMV infection is implicated in ~25% of children with sensorineural hearing loss (SNHL).[3] Infants with asymptomatic congenital CMV have approximately a 10% risk of SNHL whereas those with symptomatic congenital CMV have approximately a 35-40% risk of SNHL.[4]
3. Treatment with 6 months of valganciclovir has been associated with a decreased risk of SNHL and potentially improved developmental outcomes in infants with symptomatic congenital CMV.[5] However, hearing loss may worsen over time and may require interventions (e.g., hearing aid, cochlear implantation).
4. Consensus guidelines provide guidance on the evaluation and management of infants with suspected or confirmed congenital CMV.[6,7]

B. Evaluation of Infants with Suspected Congenital CMV

1. Urine (or salivary) CMV DNA PCR
    a. If initial salivary CMV DNA PCR testing is positive, send a confirmatory urine CMV DNA PCR
        i. There have been reports of false positive salivary CMV PCR results, likely related to "contamination" from CMV-positive breast milk
        ii. Confirmatory urine CMV PCR testing should ideally be collected prior to hospital discharge

2. If the confirmatory urine CMV DNA PCR is positive:
    a. CBC with differential
    b. CMP
    c. Baseline blood CMV DNA PCR (at the discretion of the provider based on the clinical scenario)
    d. Head ultrasound (or MRI)
    e. Audiology evaluation
    f. Otolaryngology (ENT) consultation for patients with hearing loss/abnormal audiology evaluation
    g. Ophthalmology evaluation

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C. Treatment Indications (see Appendix)

1. Valganciclovir therapy is **not routinely recommended** in the following clinical scenarios:
   a. Asymptomatic infants
   b. Infants with 1-2 mild, clinically insignificant, or transient symptoms/lab abnormalities (including petechiae, thrombocytopenia, hepatomegaly, jaundice, elevated AST/ALT)
   c. Infants with isolated SGA and preserved head growth (i.e., no microcephaly)

2. Valganciclovir 16 mg per/kg/dose BID for 6 months (50 mg/ml solution) **should be considered** in the following clinical scenarios:
   a. Infants with CNS disease (including microcephaly, CNS calcification, white matter changes, ventriculomegaly, other radiographic abnormalities consistent with CMV disease, chorioretinitis, abnormal CSF indices, detection of CMV in CSF)
      i. SGA infants with disproportionate microcephaly or any infant with severe microcephaly (head circumference >2 standard deviations below the mean) would be included in this group
      ii. Contact Audra Stewart (audrastewart@wustl.edu) and Chris Smyser (smyserc@wustl.edu) for infants with congenital CMV who have abnormal head ultrasounds results
   b. Infants with SNHL
      i. Some experts consider isolated SNHL as an indication for treatment with valganciclovir for 6 weeks, however there is insufficient data in this population[7]
      ii. Recommend discussing initiation and duration of valganciclovir with ENT
   c. Infants with severe single-organ (e.g., liver synthetic failure) or multi-organ disease
      i. Consider IV ganciclovir for 2 weeks (or until clinical improvement) prior to transitioning to oral valganciclovir
      ii. The optimal treatment duration (i.e., 6 weeks vs. 6 months) has not been determined in this setting[7]
   d. Infants with multiple (more than 2) "mild" manifestations
   e. Infants with persistent hematologic/biochemical lab abnormalities (e.g., greater than 2 weeks)

D. Timing of Treatment

1. In general, valganciclovir (when indicated) should be initiated by 4 weeks of age[5,8] and must be initiated within the first 13 weeks following birth.[11]

2. There is limited evidence from observational studies demonstrating improved hearing outcomes in infants treated with valganciclovir after 4 weeks of age.[8-10] Based on the clinical scenario, initiation of valganciclovir therapy may by considered in infants within the first 13 weeks of life.[11]

E. Lab Monitoring and Follow Up

1. CBC with differential at baseline, weekly for 6 weeks, at 8 weeks, and then monthly while on valganciclovir.
2. CMP at baseline and then monthly.
3. Audiology assessment at baseline, 4, 6, 9, 12, 15, 18, 24, and 30 months of age, and again at 4, 5, 6, 8, and 10 years of age.
4. Developmental assessment through newborn medicine, neurology, Missouri First Steps, or Illinois Early Intervention Services.
5. Monthly visits to ID clinic while on suppressive therapy with dosing adjustments based on weight gain.

References:

1. Dollard SC, et al. *Rev Med Virol* 2007; 17(5):355-63.

2. Manicklal S et al. *Clin Microbiol Rev* 2013; 26(1):86-102.

3. Morton C, et al. *N Engl J Med* 2006; 354:2151-64.

4. Bartlett AW, et al. *Rev Med Virol* 2017; doi: 10.1002/rmv.1938.

5. Kimberlin DW, et al. *N Engl J Med* 2015; 372(10):933-43.

6. Rawlinson WD, et al. *Lancet Infect Dis* 2017; 17: e177–88

7. Luck, SE, et al. *Pediatr Infect Dis J* 2017; 36(12):1205-1213.

8. Kimberlin DW, et al. *J Pediatr* 2024; 268:113934.

9. Chung PK, et al. *J Pediatr* 2024; 268:113945.

10. Dorfman L, et al. *Eur J Pediatr* 2020 May;179(5):807-812.

11. Kimberlin DW, et al. AAP Red Book 2024-2027.

Appendix – Red Book Treatment Recommendations[11]

Table 3.4. Classification of Congenital Cytomegalovirus Disease Severity and Treatment Recommendations

CMV Disease Severity	Signs and Symptoms	Treatment
Moderately to severely symptomatic	One or more of the following: • Single severe or multiorgan disease (eg, significant liver enzyme abnormalities and marked hepatosplenomegaly) or life-threatening organ dysfunction • Multiple persistent (eg, ≥2 weeks) manifestations attributable to congenital CMV infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, hepatitis (increased aminotransferases or direct bilirubin) • Central nervous system involvement such as microcephaly, radiographic abnormalities (ventriculomegaly, intracerebral calcifications, white matter changes, periventricular echogenicity, cortical or cerebellar malformations, migration abnormalities), abnormal cerebrospinal fluid indices for age, chorioretinitis, or the detection of CMV DNA in cerebrospinal fluid • Greater than 2 mild disease manifestations (see below)	Valganciclovir[a] (see Non-HIV Antiviral Drugs, p 1044) given orally for 6 **months;** treatment should be started within the first 13 weeks following birth[b]
Asymptomatic with isolated sensorineural hearing loss	No clinically apparent signs to suggest congenital CMV disease, but sensorineural hearing loss	Valganciclovir (see Non-HIV Antiviral Drugs, p 1044) may be offered and given orally for 6 **weeks;** treatment should be started within the first 13 weeks following birth[b]
Mildly symptomatic	Two or fewer transient (eg, <2 weeks) or clinically insignificant findings (eg, petechiae, mild hepatomegaly, thrombocytopenia, raised levels of alanine aminotransferase)	There are insufficient data to recommend routine treatment, but it may be considered on a case by case basis in consultation with a pediatric infectious diseases expert
Asymptomatic	No apparent signs to suggest congenital CMV disease, and normal hearing	Therapy not recommended outside of a research study