

Clinical Sequelae in Patients Receiving Valganciclovir and/or Ganciclovir Therapy for Congenital Cytomegalovirus

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Background

- Congenital CMV is the major infectious cause of congenital abnormalities and hearing loss in infants.
- The majority of maternal infection and transmission is clinically silent.

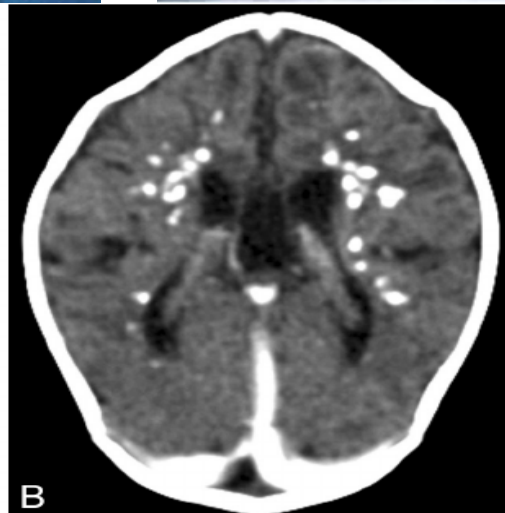
Congenital cytomegalovirus

- Overall incidence of congenital CMV (from primary and non-primary maternal infection) is approximately 0.4-0.8% in developed countries.
- About 10-15% of infants with congenital CMV present with symptoms at birth.
- Symptomatic CMV has no standard definition, but generally with signs/symptoms in utero or the immediate postnatal period.

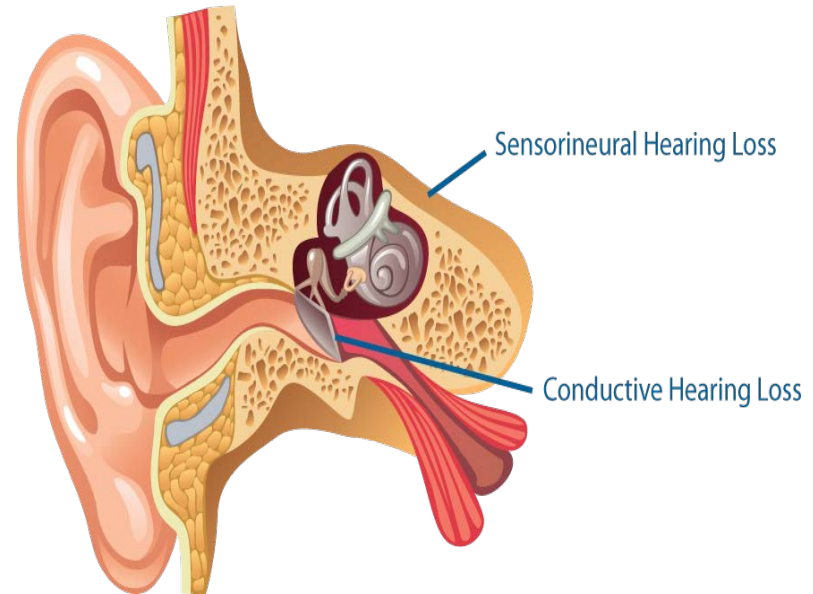
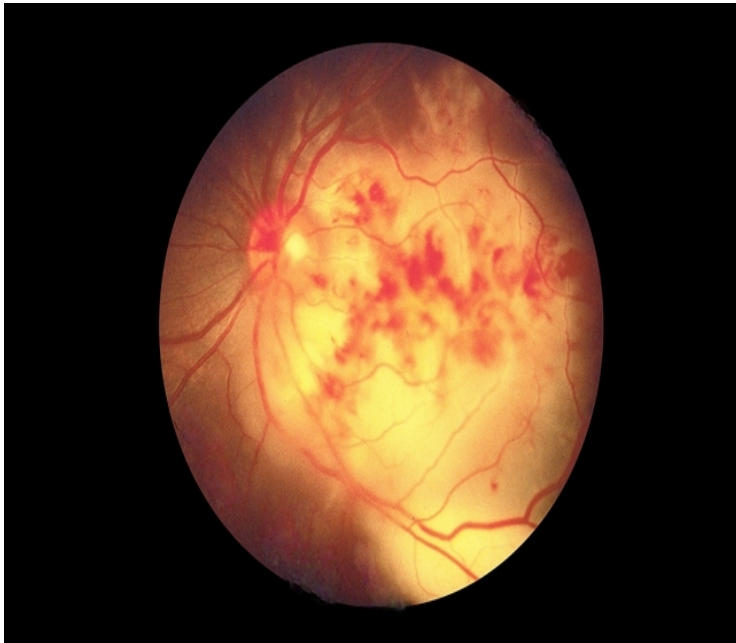
Signs/Symptoms

- Intrauterine growth restriction (IUGR)
- Thrombocytopenia/petechiae
- Splenomegaly
- Hepatomegaly
- Hepatitis
- CNS involvement-microcephaly, intracranial calcifications
- Chorioretinitis
- Sensorineural hearing loss
- Detection of CMV in CNS

Symptomatic Congenital Infection



Symptomatic Congenital Infection



Case Study

- Infant born at 36 weeks gestation due to IUGR.
- Echogenic bowel seen on 20 week ultrasound.
- At birth, noted to be 1.9kg, OFC at <3rd%ile, hepatosplenomegaly.
- Mild thrombocytopenia (74,000) on initial lab evaluation.
- Passed initial hearing screen
- Urine CMV PCR sent due to IUGR and microcephaly and returned with 6 million copies.

Case Study

- Head Ultrasound to evaluate for calcifications.



- Eye exam to evaluate for chorioretinitis was normal.

Congenital CMV

- Up to 2/3rds of infants with symptoms at birth will develop **long term neurologic sequelae** including hearing loss, visual impairment, and motor or cognitive deficits.

Congenital CMV Treatment

- Infants with symptomatic congenital CMV (<21 days of age, positive CMV PCR, and evidence of end organ disease, in particular CNS disease including SNHL).
- Generally, asymptomatic with no CNS disease, treatment is usually NOT recommended.
- Antiviral therapy is NOT ROUTINELY recommended for asymptomatic congenital CMV with isolated sensorineural hearing loss.

Why treat?

- Initial studies showed that treatment in symptomatic infection with IV ganciclovir for 6 weeks prevents hearing deterioration at 12 months.
 - Treated infants had improvements in developmental delay at both 6 and 12 months of age compared to untreated.

Congenital CMV Treatment

- More recent randomized controlled trial comparing 6 weeks versus 6 months of oral valganciclovir in symptomatic infection.
 - No change in hearing at 6 months.
 - Improved hearing at 12 and 24 months.
 - Improved neurodevelopmental scores at 24 months on the Bayley Scales of Infant Development especially language composite and receptive communication scale.

Potential risks to therapy

- Short-term toxicities include:
 - Neutropenia
 - Thrombocytopenia
 - Hepatotoxicity
- Long-term toxicity unclear, but concerns about potential fertility and carcinogenicity
- Side effect monitoring is required throughout therapy with regular checks of CBC, liver, and renal function required.

CMV Treatment

- Start in first month of life with IV ganciclovir or its oral prodrug valganciclovir.
 - Oral with less short term side effects, therefore IV only recommended if infant can not be enterally fed.
- These antiviral agents inhibit CMV replication by disrupting viral DNA synthesis.
- Doses:
 - IV ganciclovir 6 mg/kg/dose twice daily
 - Oral valganciclovir 16mg/kg/dose twice daily.

Evaluation during and after treatment

- International cCMV Recommendations Group-check ANC weekly for 6 weeks, then monthly for the duration of therapy. Liver transaminases monthly.
- F/U eye exams per ophthalmologist
- Audiology testing q 6 months for first 3 years, then annually through adolescence
- Developmental assessments on a case-by-case basis

Background

- Although longer treatment courses of valganciclovir and ganciclovir for congenital CMV improve long-term hearing and developmental outcomes, little is known about the sequelae of longer courses of these medications.
- It is important to better understand the potential side effects and courses of infants taking these drugs.

Objective

- This study aimed to identify and quantify the common side effects seen with the use of valganciclovir and/or ganciclovir in infants for the treatment of congenital CMV in a NICU population.

Methods

- The electronic medical record at the University of Minnesota Masonic Children's Hospital was queried to identify pediatric patients admitted to the neonatal intensive care unit with positive urine or serum CMV results.
- Patients identified between 2006-2016.
- Retrospective chart review of all positive patients was performed.

Results

- A cohort of 17 patients were identified as congenital infection (positive at <21 days with symptomatic infection).
- Patients characteristics

Sex	Male: 10	Female: 6
Gestational Age	Term: 11	Preterm: 6

Average Gestational Age	33 weeks (range 22w1d-39w 1d)
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Results

- Neutropenia was defined as an absolute neutrophil count <1500 .
- Severe neutropenia treated with G-CSF was a neutrophil count <500 . (Treatment was at the discretion of attending clinician).

Results

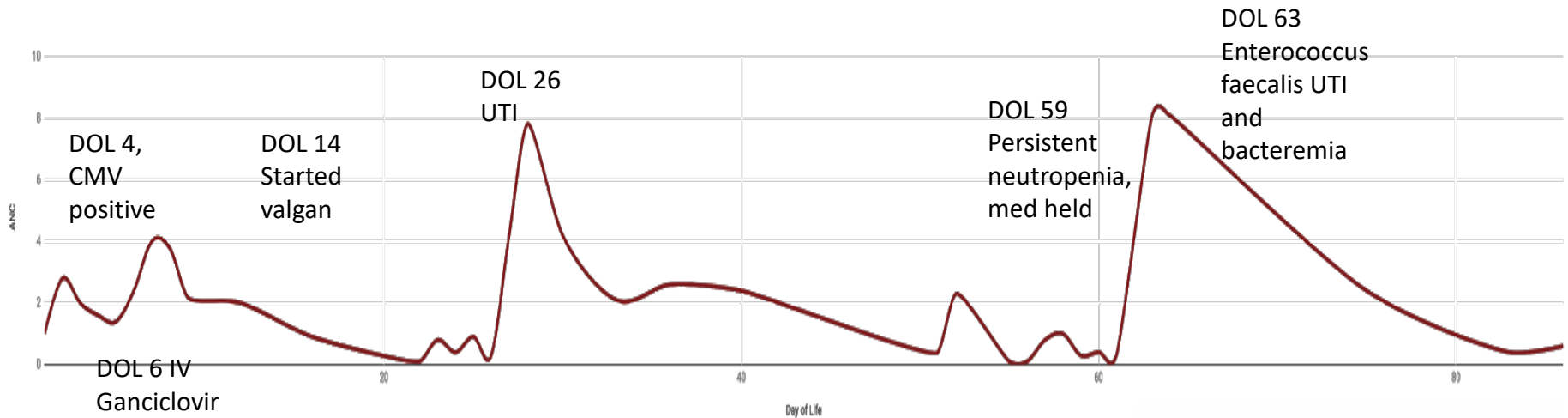
- In **term infants**:
 - **82%** experienced neutropenia at some point during the duration of therapy.
 - **71%** required G-CSF therapy.
 - **24%** had a pause in therapy secondary to neutropenia.

Results

- In **preterm infants**:
 - **92%** experience neutropenia in this cohort.
 - **82%** required G-CSF therapy.
 - **33%** had a pause in therapy due to neutropenia.
- **Preterm infants** required an average of 3.9 doses of G-CSF for neutropenia during therapy.

Results

- There were 2 serious bacterial infections during the treatment course.
- Both were in preterm infants while neutropenic.



Results

- Mild thrombocytopenia (plt 50-100) was noted in 4/6 preterm infants, 5/11 term infants.
- No bleeding complications were noted.
- 2 infants had elevations in liver enzymes at time of CMV diagnosis, but no significant worsening on therapy.

Conclusions

- The majority of infants in this NICU cohort population who received ganciclovir or valganciclovir developed neutropenia.
- Serious bacteria infections were not common, but were found in 2 preterm infants.
- Neutropenia may be of particular significance in preterm infants with immature immune systems and high risk for life threatening secondary infections.

Conclusions

- We need to better understand the complex pharmacokinetics of these drugs in order to develop better guidelines in the complex infant population.

Postnatal acquired CMV in preterm infants

- CMV infection may occur in the postnatal period primarily through transmission from maternal breast milk.
- Mothers who are CMV positive will shed into breastmilk in the majority of cases at some point in lactation.
- Most infections are asymptomatic in healthy infants, but preterm ELBW infants are susceptible to sequelae similar to other immunosuppressed populations.

Postnatal acquired CMV in preterm infants

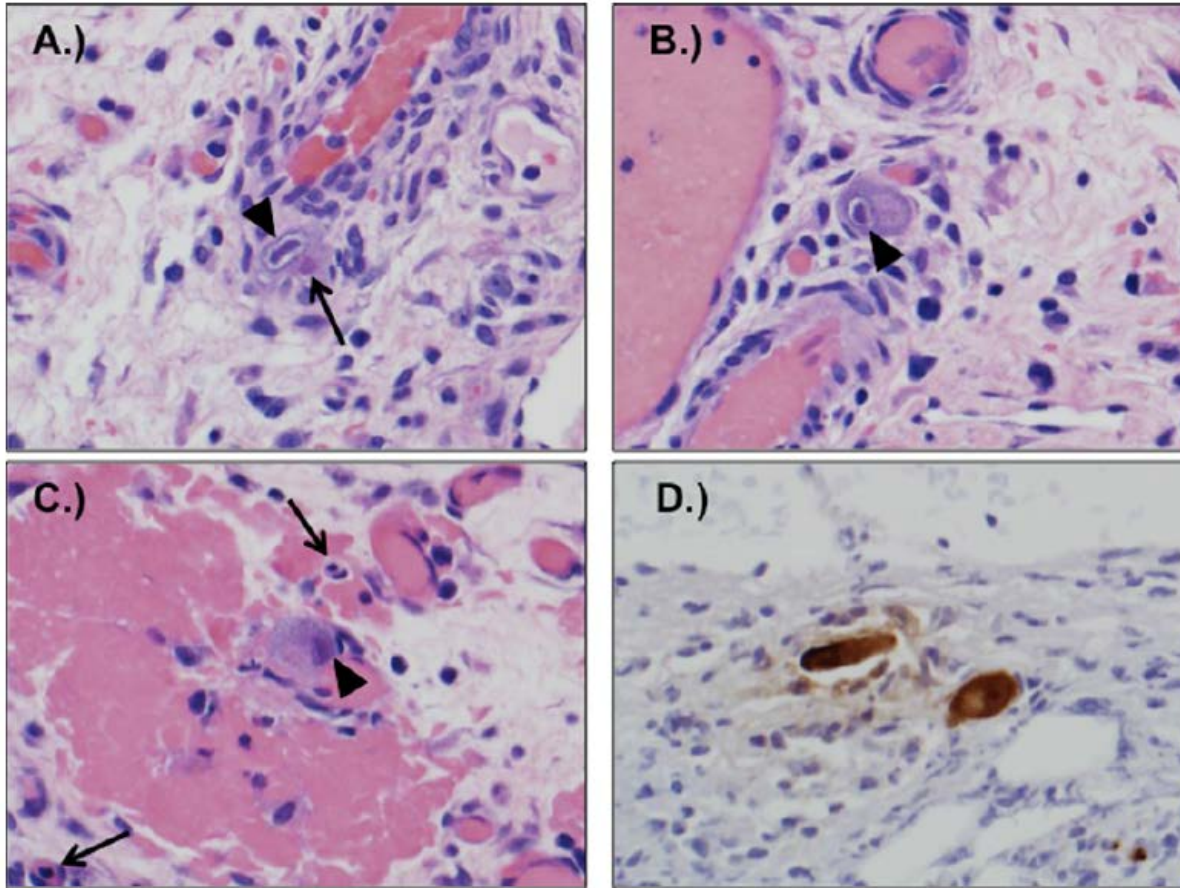
- In preterm infants, there can still be asymptomatic infection, but there is growing evidence of a severe sepsis-like syndrome in some infants (especially the very preterm 22-26week GA).
- Also, associations with increased chronic lung disease and secondary infections in very preterm infants with acquired CMV.

Clinical Case

- 24 5/7 week GA male born at 800 grams admitted to the NICU.
- Congenital CMV was ruled out with a negative PCR on DOL 12 (infant SGA).
- Started breastmilk feeds DOL 14.
- On DOL 26, developed severe abdominal distension and concern for necrotizing enterocolitis, started on antibiotics.

Clinical Case

- Blood and urine cultures were negative.
- On DOL 33, clinical worsening, thrombocytopenia to 24,000, hemodynamic instability.
- Underwent exploratory laparotomy that revealed perforations in the jejunum.
- Histology demonstrated variable ischemic necrosis and CMV inclusions.



Surgical specimens showing viral cytopathic changes, inclusions, and in D. positive stain for anti-CMV antibody in affected cells.

FIGURE 1

Clinical Case

- Systemic CMV infection was confirmed by urine and blood PCR.
- Started on ganciclovir on DOL 35 given the severity of the sepsis syndrome and the end organ disease involvement.
- Infant eventually underwent ostomy takedown and bowel re-anastomosis, however had severe sequelae of chronic lung disease and neurodevelopmental delay.

Acquired CMV in preterm infants

- Given the multitude of benefits of maternal breast milk in preterm infants, the risks of withholding MBM to avoid aCMV are high.
- Long term neurodevelopmental outcomes of preterm infants with acquired CMV are not completely clear, but concern for adverse impact on intellectual development have been raised.
- Little data on exist on the pharmacokinetics and pharmacodynamics of ganciclovir in preterm infants.

Unanswered clinical treatment questions??

- Management of infants recognized after 30 days of life?
 - Treatment?
- Treat infants with mild or asymptomatic congenital infection?
- Management of treatment in preterm infants-when how long, long-term outcomes?
- Long-term effects of ganciclovir?