Congenital CMV Infection: What You Need to Know!

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Dr. Pablo Sánchez has disclosed the following financial relationships. Unlabeled use of ganciclovir/valganciclovir will be discussed.

<table>
<thead>
<tr>
<th>Affiliation / Financial Interest</th>
<th>Organization</th>
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<tbody>
<tr>
<td>Merck</td>
<td>Grant Support</td>
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Objectives

- Describe the epidemiology of congenital/perinatal CMV infection
- Recognize the clinical manifestations and sequelae of congenital/perinatal CMV infections
- Update the management strategies as they relate to screening, diagnosis, and treatment
Congenital/Perinatal CMV Infections

- The PROBLEM
- Transmission (vertical; human milk)
- Hearing sequelae:
  - Reason to SCREEN and treat
- Treatment options
- Prevention
Baby Girl S.W.

- 2694 g FT infant
- 15 yo G1P0 mother
- Microcephaly, FOC 27 cm
- Hepatosplenomegaly
- Petechiae
- Thrombocytopenia
- Pneumonitis (IMV)
- Bilateral hearing loss (severe-to-profound)
U.S. Children Born with or Developing Long-Term Medical Conditions Each Year

- Cytomegalovirus (CMV): 5,500
- Fetal Alcohol Syndrome (FAS): 5,000
- Down Syndrome: 4,000
- Spina Bifida/Anencephaly: 3,000
- Pediatric HIV/AIDS: 200
- Invasive Haemophilus Influenzae Type B: 60
- Congenital Rubella Syndrome (CRS): 10

Annual Number
HUMAN CYTOMEGALOVIRUS

- DNA virus; herpesvirus family; 1881 (Ribbert)
- Infected cells are large (cytomegalic) and contain intranuclear and cytoplastic inclusions
- Ubiquitous distribution: serologic evidence of infection found in every human population
  - Childbearing women (USA): ~ 50%
CMV: TRANSMISSION

- Requires close or intimate contact with infected fluids or secretions
- CMV: urine, oropharyngeal secretions, semen, cervical / vaginal secretions, breast milk, tears, blood products, transplanted organs, fomites (plastic surfaces, toys)
- Viral excretion persists for years after congenital and perinatal infections, following primary infection in older children and adults; recurrent infection results in intermittent excretion
- Source of maternal infection: infected sexual partner, young children in day care (US, Israel)
CMV TRANSMISSION: DAY CARE

- ~50% of susceptible children (1-3 yrs of age) in group day care acquire CMV

- Route of transmission: transfer of virus through saliva on hands and toys

- 33% of their seronegative mothers become infected within 3-7 mo (Adler SP. *J Pediatr* 1988)

- Transmission of CMV from a child in day care to his mother and fetus has been confirmed (Pass et al., *NEJM*, 1987)
CONGENITAL CMV INFECTION

Public health impact worldwide:
- Most common congenital viral infection
- ~0.4% - 1% of all live births in USA
- ~40,000 infants born infected each year in USA
- >8000 with sequelae or fatal outcome
CMV: PERINATAL TRANSMISSION

- **In utero**: congenital infection
- **Intrapartum**: 30-50% (maternal reactivation)
- **Postpartum**:
  - Breastfeeding (30%-70%); preterm infant*
  - Blood transfusion (10-30%, BW <1250 g; currently <1%*)
- **Horizontal (nursery-acquired)**: rare

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HUMAN MILK: CMV TRANSMISSION

- CMV present in breast milk of 14% of women in the immediate postpartum period, and it is shed intermittently thereafter.
- Transmission rate to breast-feeding infant: 30 - 70%.
- Disease is uncommon because of passively transferred maternal antibody in the infant.
- Preterm infant?
CMV, BREAST MILK, AND THE PRETERM, VLBW INFANT

  - Among 299 infants fed untreated breast milk, 19% (11%-32%) acquired CMV infection and 4% (2%-7%) developed CMV-related sepsis-like syndrome.
  - Among 212 infants fed frozen breast milk, 13% (7%-24%) acquired CMV infection and 5% (2%-12%) developed CMV-related sepsis-like syndrome.

- BPD*? NEC#? ROP+?
  
  Vochem et al, PIDJ, 1998
  *Kelly MS et al. JAMA Pediatrics 2015
  #Tenqsupakul S et al. Pediatrics 2013
  #Omarsdottir S et al. J Clinical Virology 2017
  +Martins-Celini et al. CID 2016
POSTNATAL CMV INFECTION, PRETERM INFANT, AND ADOLESCENCE

Brecht et al, J Pediatr, 2015:

- Prospective, observational study: Germany
- ≤32 wks GA; <1500 g BW (1995-2000)
- Adolescents (11-17 yo): 19 CMV-infected (43%) preterm via BM vs. 23 CMV-negative (47%) preterm infants vs. 24 term
- Preterm adolescents: lower IQ and visuoperceptual abilities scores (Wechsler)
- Preterm CMV-infected adolescents: lower cognitive scores
HUMAN MILK: CMV TRANSMISSION

- Freezing at -20°C significantly decreases viral titers but does not completely eliminate infectivity

- Holder pasteurization (62.5°C for 30 minutes) inactivates CMV: donor human milk

- Short-term heat inactivation/pasteurization (5 sec at 62°C)*

- Microwave radiation (high-power; 30 sec)#

*Bapistella et al. Clin Infect Dis 2018
*Maschmann et al. Arch Dis Child Fetal Neonatal Ed. 2019
**Donor Human Milk**

- Human Milk Banking Association of N. America
- Holder Pasteurization: 62.5°C (144.5°F) for 30 min
- Eliminates immune cells in human milk but does not completely obliterate biological activity, with preservation of some bioactive components such as cytokines and growth factors (10-90%)
- IgM, lymphocytes, lipases abolished; lactoferrin (10-50%)
- DoMINO Trial+: donor milk compared with formula did not improve neurodevelopmental outcomes

*O’Connor et al. Curr Opin Clin Nutr Metab Care 2015
O’Connor et al. JAMA 2016
Breast Remains Best!
CONGENITAL CMV INFECTION

- *In utero* (transplacental): vertical transmission
  - Primary maternal infection: 40%
  - Recurrent (reactivation): 0.2-1%
  - Re-infection: ?% (Boppana et al. *NEJM* 2001)

  *São Paulo*: Yamamoto et al. *Am J Ob Gyn* 2010:

  - 18% (7/40) mothers of congenital CMV-infected infants acquired antibodies reactive with new cytomegalovirus strains during pregnancy
CONGENITAL CMV INFECTION

- 90% “asymptomatic”
- 10% “symptomatic”
CONGENITAL CMV: CLINICAL MANIFESTATIONS

• Jaundice 67%
• Hepatosplenomegaly 60%
• Petechiae 76%
• SGA 50%
• Microcephaly 53%
• Cerebral calcifications 50%
• Seizures 7%
• Pneumonitis <1%
CONGENITAL CMV: SEQUELAE

- Neurodevelopmental outcome:
  - Neuroimaging: head sono, CT scan, MRI

CONGENITAL CMV AND SENSORINEURAL HEARING LOSS

u “Symptomatic” infants:
  – 48%: hearing loss
  – 30% delayed-onset hearing loss

u “Asymptomatic” infants:
  – 7%: SNHL at initial exam (3-8 wks)
  – 18%: delayed-onset SNHL detected from 25 to 62 months (median, 27 mo)

Fowler et al. *J Pediatr* 1997;130:624
CONGENITAL CMV: DIAGNOSIS

- Isolation of virus from urine or saliva
- CMV PCR: urine preferred for diagnosis but saliva excellent for screening
- Congenital infection requires detection of virus in first 2-3 weeks of age. After 3 weeks, impossible to differentiate congenital vs. intrapartum vs. postnatal infection (e.g. breast milk) infection
- Dried blood spot from newborn screening?


20,448 newborns: 91 (0.4%) ⊕CMV saliva culture

DBS PCR:

- 1-primer (n=11422) vs. 2-primer PCR (n=9026)
  - Sensitivity: 28%; 34%
  - Specificity: 99.9%; 99.9%
  - Positive predictive value: 81%; 92%
Universal CMV screening: saliva screening?

- Saliva PCR: sensitivity; specificity
  - Liquid-saliva (n=17,662 infants)
    - 100%; 100%
  - Dried-saliva (n=17,327 infants):
    - 97%; 99.9%

Boppana et al. NEJM 2011;364:2111
CMV SCREENING: TARGETED APPROACH

- Any clinical sign, laboratory, radiographic sign associated with congenital CMV infection: e.g. SGA/IUGR, microcephaly, thrombocytopenia, lenticulostriate vasculopathy
- Infants born to HIV-positive mothers
- Infants who do not pass hearing screen
HEARING SCREENING AND CONGENITAL CMV: 1999-2004


79,047 infants (99% of live births): newborn hearing screen (aABR)

572 (0.7%): did not pass aABR and 483 (84%) had a urine CMV culture

16 of 256 (6%) infants: hearing impairment and congenital CMV infection

12 of 16 (75%) infants: diagnosed with CMV because of failed aABR
Targeted Newborn CMV Screening for Abnormal Newborn Hearing Screen

- Mandated CMV testing: Utah, Connecticut, Iowa, NY

- Utah (2013)*:
  - 509 infants “failed” NBHS
  - 62% tested for CMV; 14 (6%) of 234 infants tested within 21 days were CMV-positive; 6 (43%) had hearing loss; 70% of infants completed a diagnostic hearing evaluation within 90 days of birth

- Connecticut (2016)+:
  - 10,964 newborns: 171 “failed” NBHS; 3 (2%) infants had positive saliva CMV PCR, 2 confirmed

*Diener et al. Pediatrics 2017
+Vancor et al. J Pediatr Infect Dis Soc 2018
CMV SCREENING: TARGETED APPROACH

- Any sign, laboratory, radiographic sign associated with congenital CMV infection: e.g. thrombocytopenia, lenticulostriate vasculopathy
- Infants born to HIV-positive mothers
- Infants who do not pass hearing screen
- All <34 weeks’ gestational age infants
- All NICU admissions
Targeted screening for CMV-related hearing loss at NCH NICU (2016-2018)

- 36% (546/1498) of infants: hearing screen at >21 d of age
  - 82% (n=446) <34 wks GA
  - 8% (n=41) 34-36 weeks GA
  - 11% (n=59) ≥37 weeks

Missed opportunity for diagnosis and institution of antiviral therapy if indicated.

*Medoro et al. IDWEEK 2017, International CMV Mtg, 2019*
UNIVERSAL CMV SCREENING IN NICU: WHY?

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*Medoro et al. IDWEEK 2017, International CMV Mtg, 2019*
Congenital CMV Infection: What should the evaluation be?
THE "ASYMPTOMATIC" INFANT WITH CONGENITAL CMV INFECTION

34 infants (Dallas, Buenos Aires): normal physical exam (mean GA, 37 wk; BW, 2900 g)

- 56% (19/34): ≥1 abnormality on evaluation
  - Anemia: 12%; thrombocytopenia: 16%
  - ↑ALT, 39%; 3%, chorioretinitis
- Neuroimaging: 46% (11/24) abnormal
  - Lenticulostriate vasculopathy, 5; IVH, 6; calcifications, 4
- Hearing loss: 21% (7/34)
- 18 (53%) received antiviral therapy

EVALUATION: “ASYMPTOMATIC”
Infant with Congenital CMV Infection

- CBC, platelets
- LFTs: ALT, bilirubin T&D
- Head ultrasound; ?MRI
- Eye examination: diagnosis, follow-up at 6-12 months, every 1-2 years
- Hearing evaluation: q6 months for 1st 4 years of age, then yearly
Unsupervised Cluster Analyses in Symptomatic and “Asymptomatic” Congenital CMV Infection

Ouellette, Sanchez, Xu, et al. 2109, submitted for publication
CONGENITAL CMV: GANCICLOVIR
Kimberlin et al. J Pediatr 2003;143:16

- Ganciclovir (6 mg/kg q12 hr IV x 6 wks) vs. no rx
- 100 infants: ≤ 1 mo, ≥ 32 wks GA, BW ≥ 1200 g
- CNS involvement: microcephaly, abnormal CT / HUS / CSF, chorioretinitis, hearing loss
- 47 evaluable infants
- Primary outcome: hearing
- Neutropenia: 63%
- No change in mortality (6% vs 12%)
PHASE III GANCICLOVIR TRIAL: HEARING OUTCOME

6 months (ganciclovir vs no therapy):

- Improved hearing (or remained normal): 85% vs 56% (p=0.03)
- Worse hearing: 0 vs. 44% (p<0.001)

≥1 year:

- Improved hearing (or normal): 52% vs 25% (p=0.06)
- Worse hearing: 20% vs 70% (p=0.001)
PHASE III GANCICLOVIR TRIAL: DENVER DEVELOPMENTAL TESTS


- Performed at 6 wks, 6 months, and 12 months

- In a blinded fashion, normal developmental milestones that > 90% of children would pass were determined at each age group
  - If a milestone was not met, it was termed a ‘delay’ by the Denver
## Average Total Delays Per Subject

<table>
<thead>
<tr>
<th>Follow-up Interval</th>
<th>Ganciclovir (mean ± SE)</th>
<th>No Treatment (mean ± SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks (n=74)</td>
<td>1.5 ± 0.3</td>
<td>2.1 ± 0.3</td>
<td>0.15</td>
</tr>
<tr>
<td>6 months (n=74)</td>
<td>4.5 ± 0.7</td>
<td>7.5 ± 1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>12 months (n=72)</td>
<td>10.1 ± 1.7</td>
<td>17.1 ± 1.9</td>
<td>0.007</td>
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PHASE I/II PHARMACOKINETIC EVALUATION OF VALGANCICLOVIR

- 24 neonates (age < 30 d; UTSW, 9 subjects)
- Birth weight ≥ 1200 g
- Gestational age ≥ 32 wk

Population PK:
- Valganciclovir syrup vs. ganciclovir IV
  (6 mg/kg/dose q 12 hr) x 6 wks
- 16 mg/kg/dose q12 hr PO
VALGANCICLOVIR: 6 wks vs. 6 months?
Kimberlin et al. (CASG) NEJM 2015; 372:933

- Phase III trial, 6 wks of oral valganciclovir, then valgan or placebo for total of 6 months
- 109 infants (age $\leq 30$ d; $\geq 32$ wks GA, 1800 g):
  - “symptomatic” - with (63%) or without CNS disease
- Primary outcome: hearing at 6 months
- Bayley-III performed at 24 months
6 Weeks vs. 6 Months Oral Valganciclovir
Change in Hearing From Birth to 6 Months

Kimberlin et al. NEJM 2015;372:933

6 Weeks of Treatment

P = 0.19

6 Months of Treatment

aOR (95% CI): 1.70 (0.77, 3.79)

n=84 ears

n=82 ears

45%

63%

37%

55%

Worse or Remained Abnormal

Improved or Remained Normal
6 Weeks vs. 6 Months Oral Valganciclovir
Change in Hearing From Birth to 12 Months
Kimberlin et al. NEJM 2015;372:933

6 Weeks of Treatment

- 57% Worse or Remained Abnormal
- 43% Improved or Remained Normal

n=77 ears

6 Months of Treatment

- 27% Worse or Remained Abnormal
- 73% Improved or Remained Normal

n=79 ears

aOR (95% CI): 3.34 (1.31, 8.53)
6 Weeks vs. 6 Months Oral Valganciclovir
Change in Hearing From Birth to 24 Months

Kimberlin et al. NEJM 2015;372:933

<table>
<thead>
<tr>
<th>Duration</th>
<th>Change in Hearing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Weeks</td>
<td>64%</td>
</tr>
<tr>
<td>6 Months</td>
<td>77%</td>
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</tbody>
</table>

P = 0.04

aOR (95% CI): 2.66 (1.02, 6.91)
# 6 Weeks vs. 6 Months Valganciclovir: BSID-III Results at 24 Months

<table>
<thead>
<tr>
<th></th>
<th>6 Week Therapy</th>
<th>6 Month Therapy</th>
<th>Adjusted P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Composite</td>
<td>76.0 ± 2.6</td>
<td>84.4 ± 2.6</td>
<td>0.024</td>
</tr>
<tr>
<td>Language Composite</td>
<td>72.5 ± 2.9</td>
<td>84.6 ± 2.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Receptive Communication Scale</td>
<td>5.2 ± 0.5</td>
<td>7.3 ± 0.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Expressive Communication Scale</td>
<td>5.5 ± 0.5</td>
<td>7.3 ± 0.5</td>
<td>0.016</td>
</tr>
<tr>
<td>Motor Composite</td>
<td>74.1 ± 3.2</td>
<td>85.5 ± 3.3</td>
<td>0.013</td>
</tr>
<tr>
<td>Fine Motor Scale</td>
<td>6.4 ± 0.6</td>
<td>8.0 ± 0.6</td>
<td>0.057</td>
</tr>
<tr>
<td>Gross Motor Scale</td>
<td>5.3 ± 0.5</td>
<td>7.0 ± 0.5</td>
<td>0.020</td>
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*P-values < 0.007 (= 0.05/7) significant (Bonferroni adjustment for multiple testing)

Kimberlin et al. NEJM 2015;372:933
CONGENITAL CMV INFECTION: CONCLUSIONS

Is it time to screen?

- Universal screening:
  - no ... maybe ... yes ...
- Selective screening: YES

CONGENITAL CMV: CONCLUSIONS

Is it time to treat?

- CNS disease: YES
- Clinically apparent disease ("symptomatic") but no documented CNS disease: YES
- How long? 6 months
- Clinically inapparent infection ("asymptomatic"): NO
CONGENITAL CMV: PREVENTION

- Routine serologic screening of pregnant women is NOT recommended in USA
- No exclusion of infected children from day care or institutions
- Standard precautions
- CMV vaccine: recombinant CMV envelope glycoprotein B (Pass et al. NEJM 2009;360:1191)
CMV-IGIV IN PREGNANCY
Revello et al. NEJM, 2014

- Phase 2, randomized, placebo-controlled, double-blind study (Italy)
- 124 women with primary CMV infection diagnosed at 5 to 26 weeks of gestation:
  - CMV-IGIV vs. placebo every 4 weeks until 36 weeks’ gestation or detection of CMV in amniotic fluid
- Congenital CMV infection:
  - CMV-IGIV: 30%
  - Placebo: 44% (95% CI, -3 to 31; p=0.13)
Phase 3, randomized, placebo-controlled, double-blind study

Pregnant with primary CMV infection diagnosed at <24 wks, or <28 wks if positive CMV IgM, negative IgG screened before 23 wks but then have IgG seroconversion:

- CMV-IGIV vs. placebo (n=800)

Primary outcomes: fetal loss, confirmed fetal CMV infection from amniocentesis, neonatal death before assessment of CMV can be made, or neonatal CMV infection (positive culture)
Valacyclovir and Congenital CMV

- Phase 2, multicenter, open-label (France)
- Valacyclovir 8 gram daily: pregnant women carrying a moderately symptomatic CMV-infected fetus
- Treated from 25.9 weeks (median) until delivery
- 41 women; 43 fetuses
- 34 (82%) asymptomatic neonates and remained so through 12 months
- Historically, 43% would have been asymptomatic
Prevention of Congenital CMV Infection: CDC Recommendations for Pregnant Women

Ways a pregnant woman may help reduce her exposure to CMV:

- Washing hands frequently with soap and water, especially after changing diapers, feeding a child, wiping a child’s nose or drool, or handling children’s toys.
- Not sharing cups, plates, utensils, food, or toothbrushes.
- Not sharing towels or washcloths.
- Not putting a child’s pacifier in her mouth.
- Cleaning toys, countertops, and anything else that comes in contact with children’s urine or saliva.
IT’S TIME TO ACT!
Nationwide Children’s Hospital
Center for Perinatal Research

RESEARCH SAVES BABIES!