Infecciones por Citomegalovirus. Más allá del período neonatal, interpretación de estudios y tratamiento

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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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<td>AstraZeneca MedImmune, Inc</td>
<td>Grant Support</td>
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Objectives

◆ Review the incidence of neonatal CMV infection
◆ Discuss the concept of screening for CMV infection
◆ Review the treatment of CMV infection
◆ Discuss precautions for preventing occupational exposure in pregnant women
Congenital/Perinatal/Postnatal CMV Infections

◆ The PROBLEM
◆ Transmission (vertical; human milk)
◆ Hearing sequelae:
  – Reason to SCREEN and treat
◆ Treatment options
◆ Prevention
• 2694 g FT infant
• 15 yo G1P0 mother
• Microcephaly, FOC 27 cm
• Hepatosplenomegaly
• Petechiae
• Thrombocytopenia
• Pneumonitis (IMV)
• Bilateral hearing loss (severe-to-profound)
HUMAN CYTOMEGALOVIRUS

◆ DNA virus; herpesvirus family; 1881 (Ribbert)

◆ Infected cells are large (cytomegalic) and contain intranuclear and cytoplasmic 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

CMV: PERINATAL TRANSMISSION

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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.

*Kelly MS et al. JAMA Pediatrics 2015
#Tengsupakul S et al. Pediatrics 2013
#Omarsdottir S et al. J Clinical Virology 2017
#Pannesso S et al. J Pediatrics, 2019
+Martins-Celini et al. CID 2016

◆BPD*? NEC#? ROP+?
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

◆ Treatment?
  – Ganciclovir? valganciclovir?
  – Who, when, how long?

◆ Prevention?
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
#Ben-Shoshan et al. Breastfeed Med 2016
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

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

◆ “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, laboratory, radiographic sign associated with congenital CMV infection: e.g. SGA/IUGR, microcephaly, thrombocytopenia, lenticulostriate vasculopathy: urine PCR

◆ Infants born to HIV-positive mothers (3-9% CMV-infected): urine PCR

◆ Infants who do not pass newborn hearing screen (6-8% CMV-infected): urine PCR
Targeted Newborn CMV Screening for Abnormal Newborn Hearing Screen

- Dallas, TX (1999-2004)*: 6% (16/256) who referred on newborn hearing screen (NBHS) were CMV-positive

- Mandated CMV testing (law): Utah, Connecticut, Iowa, NY
  - Utah (2013)**: 6% (14/234) who “failed” NBHS were CMV-positive
  - Connecticut (2016)+: 2% (3/171) newborns who “failed” NBHS had positive saliva CMV PCR

*Stehel et al. Pediatrics 2008
**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
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
UNIVERSAL CMV SCREENING IN NICU: WHY?

♦ 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*
Targeted screening for CMV-related hearing loss at NCH NICU (2016-2018)

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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): $\geq 1$ abnormality on evaluation
    - Anemia: 12%; thrombocytopenia: 16%
    - $\uparrow$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

Ronchi et al. J Perinatology, 2019, in press
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
Congenital CMV Infection: Evaluation

- Physical examination
- CBC, platelets; (CMV blood viral load - repeat at 6 mo)
- LFTs: ALT, bilirubin T&D; creatinine (rx)
- 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
- Neurodevelopmental assessments: 3-4, 9-12, 24, and 36 months
Unsupervised Cluster Analyses in Symptomatic and “Asymptomatic” Congenital CMV Infection

Ouellette, Sanchez, Xu, et al. 2109, submitted for publication
Unsupervised Cluster Analyses in Symptomatic and “Asymptomatic” Congenital CMV Infection

Ouellette, Sanchez, Xu, et al. 2019, submitted for publication
“Asymptomatic” Congenital CMV Infection and Sensorineural Hearing Loss: Random Forest Analyses

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
<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>
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<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. (CASH) 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 Between Birth and follow-up

6 months

6 weeks of Tx

12 months

6 months of Tx

24 months

6 weeks of Tx

Worse or Remained Abnormal

Improved or Remained Normal

p = 0.19

p = 0.01

p = 0.04

6 weeks of Tx

6 months

63%

37%

55%

45%

57%

43%

64%

36%

n=82 ears

n=79 ears

n=70 ears

n=84 ears

n=77 ears

n=58 ears
6 Weeks vs. 6 Months Oral Valganciclovir
Change in Hearing From Birth to 6 Months

Kimberlin et al. NEJM 2015;372:933

<table>
<thead>
<tr>
<th></th>
<th>6 Weeks of Treatment</th>
<th>6 Months of Treatment</th>
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</thead>
<tbody>
<tr>
<td>Improved or Remained Normal</td>
<td>55%</td>
<td>63%</td>
</tr>
<tr>
<td>Worse or Remained Abnormal</td>
<td>45%</td>
<td>37%</td>
</tr>
</tbody>
</table>

n=84 ears
n=82 ears

P = 0.19

aOR (95% CI): 1.70 (0.77, 3.79)
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% Improved or Remained Normal
- 43% Worse or Remained Abnormal

6 Months of Treatment
- 73% Improved or Remained Normal
- 27% Worse or Remained Abnormal

P = 0.01

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

6 Weeks of Treatment 6 Months of Treatment

<table>
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<th>6 Weeks of Treatment</th>
<th>6 Months of Treatment</th>
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<td>36%</td>
<td>23%</td>
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<tr>
<td>Improved or Remained Normal</td>
<td>64%</td>
<td>77%</td>
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P = 0.04

aOR (95% CI): 2.66 (1.02, 6.91)

n=58 ears n=70 ears
# 6 Weeks vs. 6 Months Valganciclovir: BSID-III Results at 24 Months

<table>
<thead>
<tr>
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<th>6 Week Therapy</th>
<th>6 Month Therapy</th>
<th>Adjusted P-value*</th>
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</thead>
<tbody>
<tr>
<td>Cognitive Composite</td>
<td>76.0 ± 2.6</td>
<td>84.4 ± 2.6</td>
<td>0.024</td>
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<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>
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<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>
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<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)
CMV-IGIV IN PREGNANCY
Maternal-Fetal Medicine Network, NICHD

- 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 outcome: fetal loss, confirmed fetal CMV infection from amniocentesis, neonatal death before assessment of CMV can be made, or neonatal CMV infection (positive culture)
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!