CONGENITAL CMV INFECTION

Pablo J. Sánchez, MD

20th International Symposium on Neonatology
São Paolo, Brazil
9/10-12/15
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
- Brazil: >90% maternal seroprevalence; 0.3% congenital CMV birth prevalence

**CONGENITAL CMV INFECTION**

- Public health impact worldwide:
  - ~40,000 infants born infected each year (USA)
  - >8000 with sequelae or fatal outcome
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
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)
- Source of maternal infection: infected sexual partner, young children in day care (US, Israel)
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

CONGENITAL CMV INFECTION

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

- São Paolo: 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: INTRAUTERINE TRANSMISSION

- Transplacental route: maternal viremia
- Same transmission rate throughout pregnancy, but fetal infection more severe in first half of pregnancy
- CMV infection more common among HIV-infected neonates (21% vs. 4%) and infants born to HIV-infected mothers (2-7% vs. 1%)
  (Duryea et al. PIDJ 2010;29:915)
CONGENITAL CMV INFECTION

◆ Most common congenital viral infection
◆ ~ 1% of all live births in the United States:
  • 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
<table>
<thead>
<tr>
<th>Sequelea</th>
<th>Symptomatic % (n=104)</th>
<th>Asymptomatic % (n=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss:*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorineural</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>Bilateral</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Mod-profound</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Overall:+§</td>
<td>22-65%</td>
<td>8-15%</td>
</tr>
</tbody>
</table>

*Stagno, 1994; +Fowler, Boppana, 2006; §Yamamoto, 2011
PREDICTORS OF HEARING LOSS: SYMPTOMATIC CONGENITAL CMV

◆ 48% (87/180): hearing loss
  – 70% hearing loss at birth
  – 30% delayed-onset hearing loss
  – 63% had progressive hearing loss
◆ **Predictors**: petechiae, intrauterine growth restriction, thrombocytopenia, hepatitis, hepatosplenomegaly
◆ **Not predictive**: CNS signs (microcephaly, seizures); prematurity
CONGENITAL CMV AND SENSORINEURAL HEARING LOSS

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

- 307 children: **ASX** congenital CMV infection
- 7%: SNHL at initial exam (3-8 wks)
- 50%: further deterioration in hearing from age 2 to 70 months (median, 18 mo)
- 18%: delayed-onset SNHL detected from 25 to 62 months (median, 27 mo)
- Fluctuating SNHL: 23%
CONGENITAL CMV: DIAGNOSIS

◆ Isolation of virus from urine or saliva

◆ PCR: urine, saliva (Yamamoto et al. J Clin Virol 2006), blood, CSF

◆ 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—usefulness of dried blood spot from newborn screening?
DRIED BLOOD SPOT (DBS) CMV PCR: CHIMES STUDY (NIDCD)
Boppana et al. JAMA 2010;303:1375

- 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%
CMV SCREENING: CHIMES STUDY

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 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 newborn hearing screen
- All ≤34 weeks’ gestational age infants
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
CONGENITAL CMV INFECTION AND NEWBORN HEARING SCREEN

- 99,775 newborns screened for both hearing impairment and CMV (CHIMES: 2007-2012)
- 7% of CMV-infected infants did not pass hearing screen vs. 0.9% of CMV-negative infants (p<0.001); 64% of cCMV infants had confirmed SNHL
- Overall, 8% of cCMV infants had SNHL
- BUT, newborn hearing screen identified only 60% of CMV-related hearing loss

*Fowler, PAS 2014
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)
Phases 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>
</tr>
</tbody>
</table>

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
- Current study: 6 weeks vs. 6 months of valganciclovir for “symptomatic” congenital CMV infection
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 ≤30 d; ≥32 wks GA, 1800 g):
  - “symptomatic” - with or without CNS disease
◆ Primary outcome: hearing at 6 months
◆ Bayley-III performed at 24 months
CASG 112: 6 Wk v. 6 Mo PO Valganciclovir
Inclusion Criteria

- CMV: urine/throat swab by culture, shell vial, or PCR tests
- **Symptomatic** congenital CMV disease: one or more
  - Thrombocytopenia and/or Petechiae
  - Hepatomegaly and/or Splenomegaly
  - Intrauterine growth restriction
  - Hepatitis (elevated transaminases and/or bilirubin)
  - Central nervous system: microcephaly, neuroimaging abnormalities, abnormal CSF indices for age, chorioretinitis, hearing deficits as detected by brainstem evoked response, and/or positive CMV PCR from CSF
- ≤ 30 days of age at study enrollment
- Gestational age ≥ 32 weeks; Weight ≥ 1800 grams (enrollment)
6 Weeks vs. 6 Months Oral Valganciclovir
Change in Hearing Between Birth and 6 Mo

6 Weeks of Treatment

- 55% Worse or Remained Abnormal
- 45% Improved or Remained Normal

n=84 ears

P = 0.19

6 Months of Treatment

- 63% Improved or Remained Normal
- 37% Worse or Remained Abnormal

n=82 ears

aOR (95% CI): 1.70 (0.77, 3.79)
6 Weeks vs. 6 Months Oral Valganciclovir
Change in Hearing Between Birth and 12 Mo

6 Weeks of Treatment

P = 0.01

6 Months of Treatment

Worse or
Remained
Abnormal

Improved or
Remained
Normal

6 Weeks of Treatment

43%

57%
n=77 ears

6 Months of Treatment

27%

73%
n=79 ears

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

6 Weeks of Treatment

- 36% Worse or Remained Abnormal
- 64% Improved or Remained Normal

n=58 ears

P = 0.04

6 Months of Treatment

- 23% Worse or Remained Abnormal
- 77% Improved or Remained Normal

n=70 ears

aOR (95% CI): 2.66 (1.02, 6.91)
## 6 Weeks vs. 6 Months Oral Valganciclovir Bayley III Developmental 24 Mo Outcomes

<table>
<thead>
<tr>
<th>Scale</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>0.0236</td>
</tr>
<tr>
<td>Language Composite</td>
<td>72.5 ± 2.9</td>
<td>84.6 ± 2.9</td>
<td>0.0037</td>
</tr>
<tr>
<td>Receptive Communication Scale</td>
<td>5.2 ± 0.5</td>
<td>7.3 ± 0.5</td>
<td>0.0027</td>
</tr>
<tr>
<td>Expressive Communication Scale</td>
<td>5.5 ± 0.5</td>
<td>7.3 ± 0.5</td>
<td>0.0158</td>
</tr>
<tr>
<td>Motor Composite</td>
<td>74.1 ± 3.2</td>
<td>85.5 ± 3.3</td>
<td>0.0130</td>
</tr>
<tr>
<td>Fine Motor Scale</td>
<td>6.4 ± 0.6</td>
<td>8.0 ± 0.6</td>
<td>0.0566</td>
</tr>
<tr>
<td>Gross Motor Scale</td>
<td>5.3 ± 0.5</td>
<td>7.0 ± 0.5</td>
<td>0.0198</td>
</tr>
</tbody>
</table>

P-values < 0.007 (= 0.05/7) statistically significant (Bonferroni adjustment for multiple testing)
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
EVALUATION OF “ASYMPTOMATIC” INFANT DIAGNOSED WITH CONGENITAL CMV INFECTION

- CBC, platelets
- LFTs: ALT, bilirubin T&D
- Head ultrasound
- Eye examination: diagnosis, follow-up at 3-6 months
- Hearing evaluation: q6 months for 1st 3 years of age, then yearly
THE “ASYMPTOMATIC” INFANT WITH CONGENITAL CMV INFECTION

- 63 infants: normal physical exam (GA, 39 ± 2 wks; BW, 3265 ± 453 g)
  - 35% (22/63): ≥1 abnormality on evaluation
    - Anemia: 11%; thrombocytopenia: 3%
    - ↑ALT, 11% (6/54); ↑direct bili, 2% (1/47)
  - Hearing loss: 6% (4/63)
  - Head sono: 26% (14/53) abnormal
    - Lenticulostriate vasculopathy, 9; Grade I IVH, 8; periventricular calcification, 1
  - 4 (6%) received antiviral therapy for CNS

"Symptomatic" infants tend to have greater degree of CMV viremia (PCR) than "asymptomatic" infants.

Higher degree of viremia has been associated with sensorineural hearing loss in both symptomatic and asymptomatic infants.

BUT, viremia is poor positive predictor.

Absence of viremia may be a marker for lack of hearing loss.
CMV-IGIV IN PREGNANCY
Nigro et al. NEJM, 2005

181 Italian women with primary CMV infection (1995-2003):

- 55 women seroconverted >6 wks and amniotic fluid CMV-positive (“Therapy”):
  - 3% (1/31) infants whose mothers received CMV-IGIV (200 U/kg) had CMV disease vs. 50% (7/14) whose mothers did not receive CMV-IGIV (n=14)
181 Italian women with primary CMV infection (cont):

- 102 women infected at < 20 wks or within 6 wks, and declined amnio (“Prevention”):
  - 16% (6/37) of infants whose mothers received CMV-IGIV (100 U/kg monthly) had CMV disease vs. 40% (19/47) whose mothers did not receive CMV-IGIV (p=0.02)

CMV-IGIV: significantly lower risk of congenital CMV infection (OR 0.32, 95% CI 0.1-0.9, p=0.04)
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)
Women's Awareness of Conditions Affecting Children

- Cytomegalovirus (CMV): 22%
- Parvovirus B19: 32%
- Congenital Toxoplasmosis: 37%
- Congenital Rubella Syndrome (CRS): 53%
- Group B Strep (GBS): 59%
- Spina Bifida: 76%
- Fetal Alcohol Syndrome (FAS): 83%
- Sudden Infant Death Syndrome (SIDS): 94%
- Down Syndrome: 97%
- HIV/AIDS: 98%

Percentage of women who had heard of these diseases
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)
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.