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

Pablo J. Sánchez, MD

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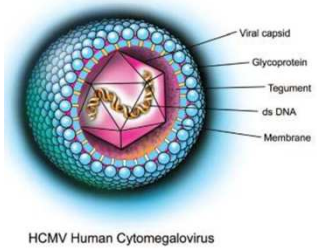


HCMV Human Cytomegalovirus

39° Congreso Argentino de Pediatría
Rosario, Argentina; 9/25/19

DISCLOSURE STATEMENT

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

Affiliation / Financial Interest	Organization
Merck	Grant Support
AstraZeneca MedImmune, Inc	Grant Support

Objectives

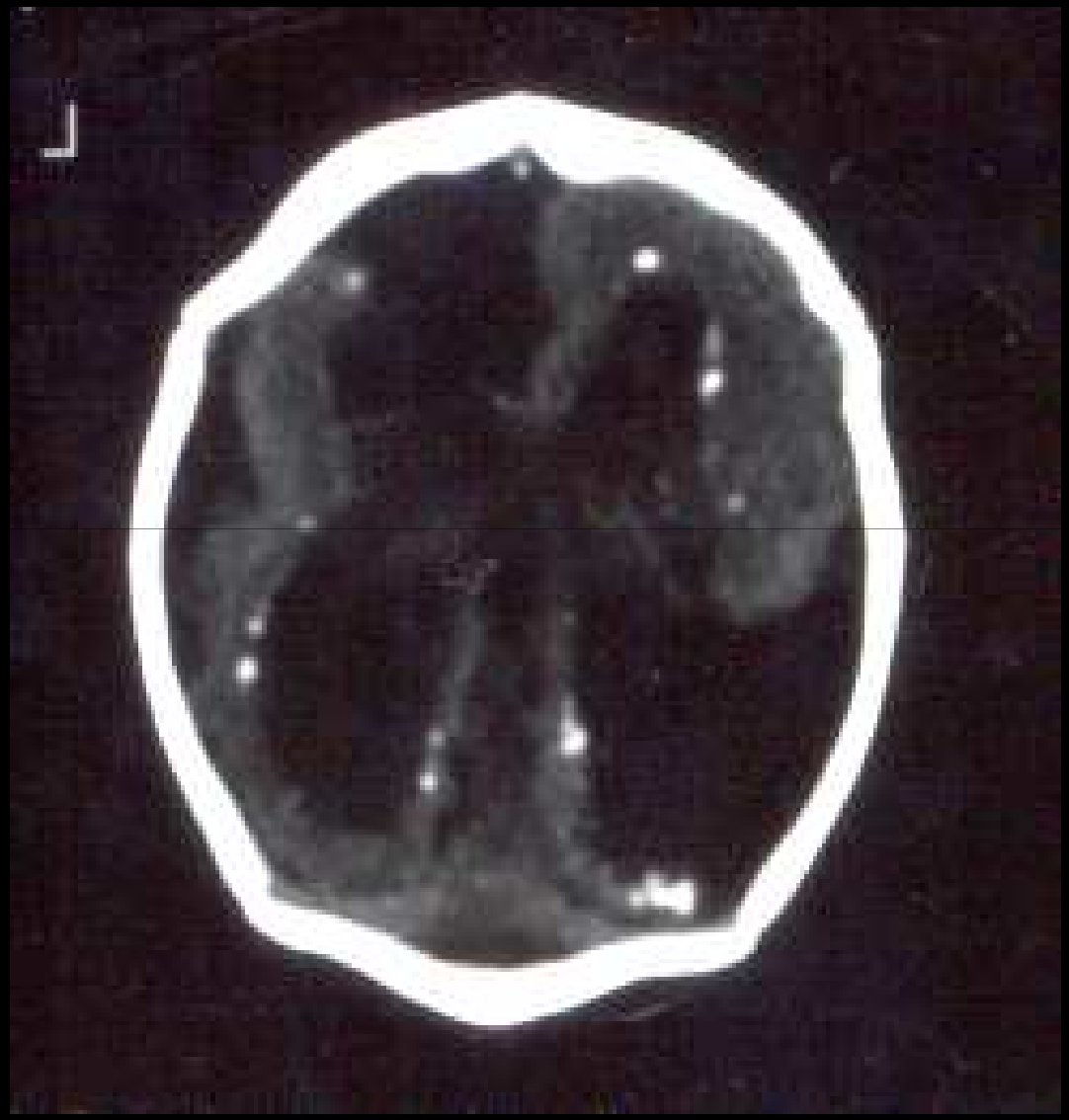
- Review the incidence of neonatal CMV infection
- Discuss the concept of screening for CMV infection
- Review the treatment of CMV infection
- Discuss precautions for preventing occupational exposure in pregnant women

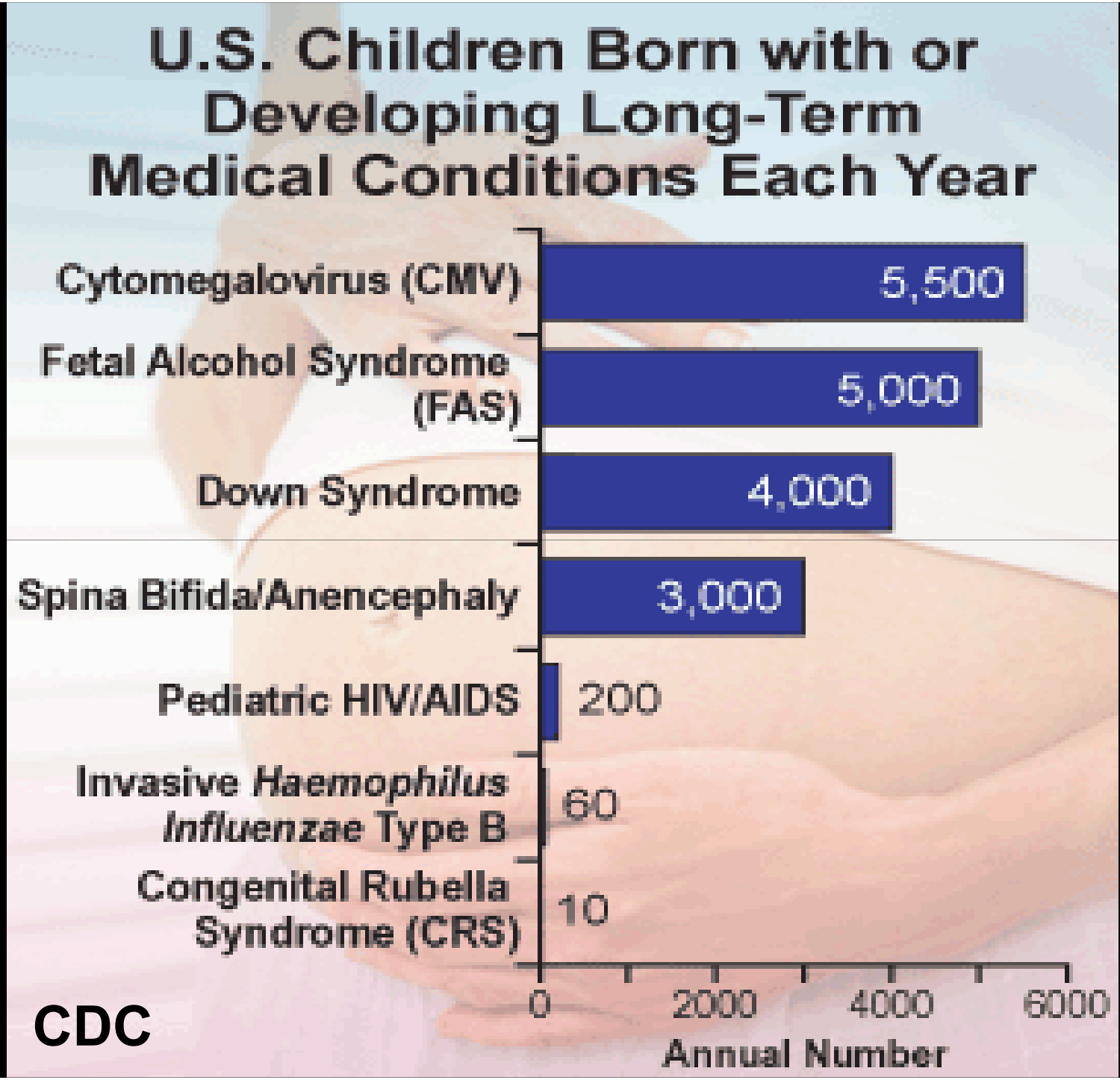
Congenital/Perinatal/Postnatal CMV Infections

- The PROBLEM
- Transmission (vertical; human milk)
- Hearing sequelae:
  - Reason to *SCREEN* and treat
- Treatment options
- Prevention

Baby Girl S.W.

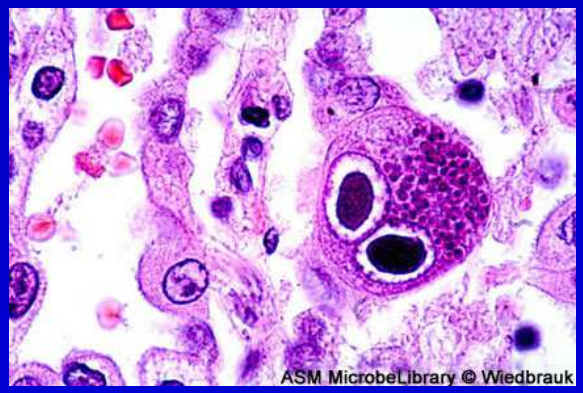
- 2694 g FT infant
- 15 yo G1P0 mother
- Microcephaly, FOC 27 cm
- Hepatosplenomegaly
- Petechiae
- Thrombocytopenia
- Pneumonitis (IMV)
- Bilateral hearing loss (severe-to-profound)

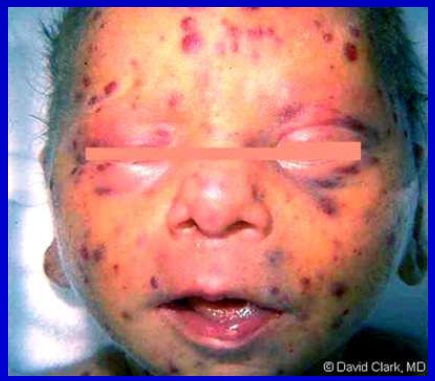



U.S. Children Born with or Developing Long-Term Medical Conditions Each Year
Cytomegalovirus (CMV)
5,500
Fetal Alcohol Syndrome (FAS)
5,000
Down Syndrome
4,000
Spina Bifida/Anencephaly
3,000
Pediatric HIV/AIDS
200
Invasive Haemophilus Influenzae Type B
60
Congenital Rubella Syndrome (CRS)
10
0
2000
4000
6000
Annual Number
CDC

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

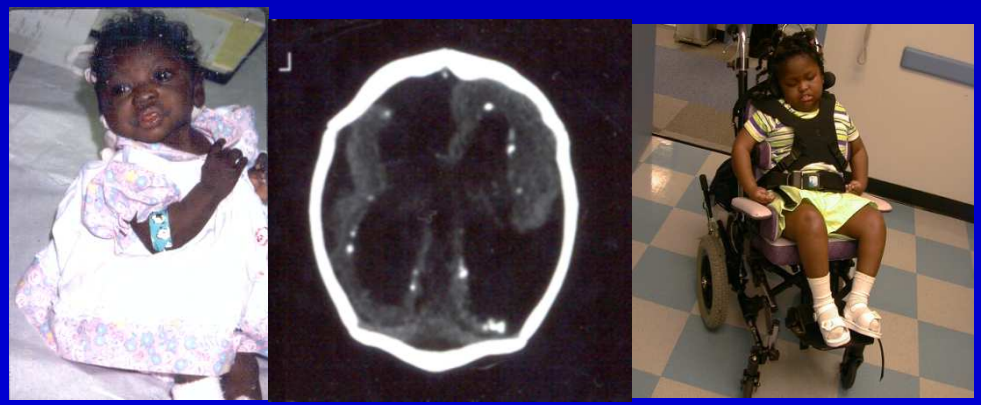
- Requires close or intimate contact with infected fluids or secretions
- CMV: urine, oropharyngeal secretions, semen, cervical / vaginal secretions, breast milk, tears, blood products, transplanted organs, fomites (plastic surfaces, toys)
- Viral excretion persists for years after congenital and perinatal 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

* Turner KM, Pediatrics 2014;
Josephson CD, JAMA Pediatrics 2014

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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

- Lanzieri et al, *Pediatrics*, 2013: meta-analysis
  - 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
#Panesso S et al. J Pediatrics, 2019
+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 visuoperceptive abilities scores (Wechsler)
  - Preterm CMV-infected adolescents: lower cognitive scores

HUMAN MILK: CMV TRANSMISSION

- Treatment?
  - Ganciclovir? valganciclovir?
  - Who, when, how long?
- Prevention?

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 62ºC)*
- Microwave radiation (high-power; 30 sec)#

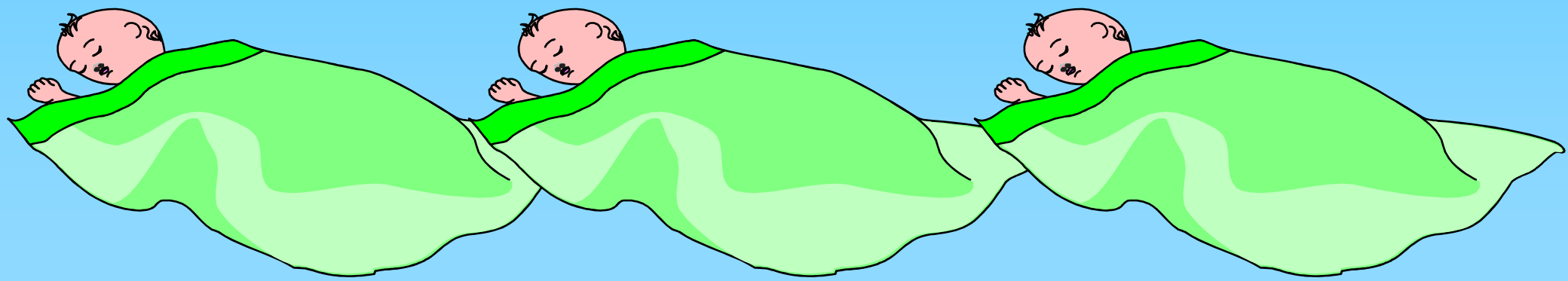
*Hamprecht et al. Pediatr Res 2004
*Bapistella et al. Clin Infect Dis 2018
*Maschmann et al. Arch Dis Child Fetal Neonatal Ed. 2019
#Ben-Shoshan et al. Breastfeed Med 2016
Hamprecht, Goelz. Clin Perinatol 2017

Donor Human Milk

- Human Milk Banking Association of N. America
- Holder Pasteurization: 62.5ºC (144.5ºF) 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!



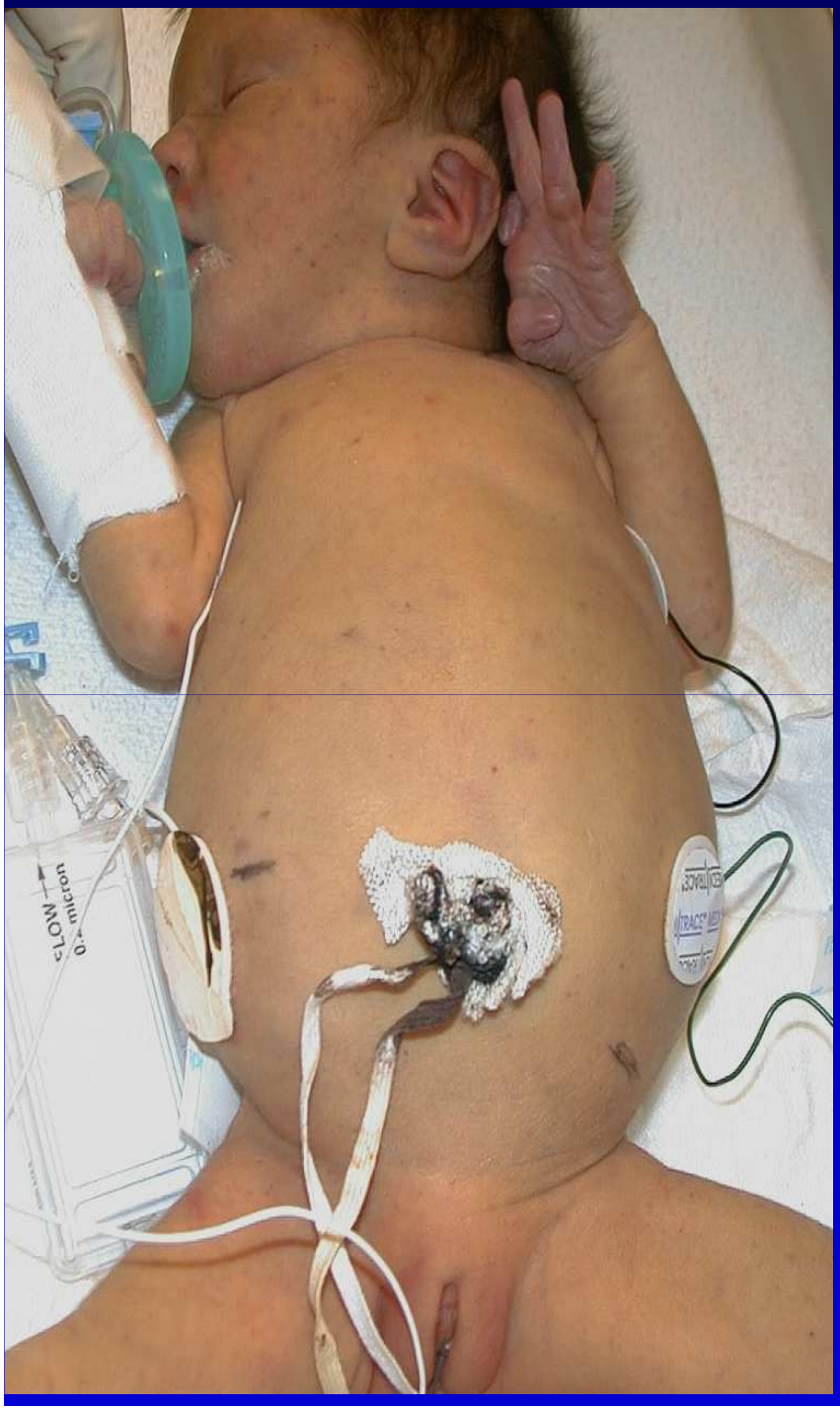
CONGENITAL CMV INFECTION

- *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”

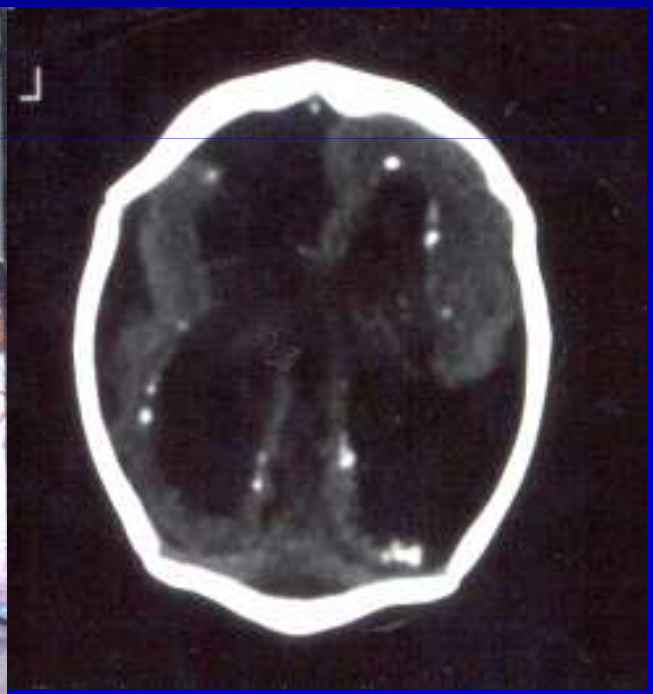


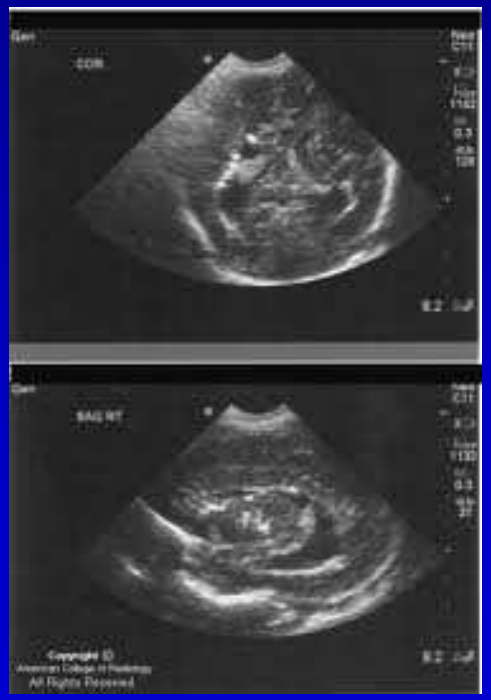
CONGENITAL CMV: CLINICAL MANIFESTATIONS

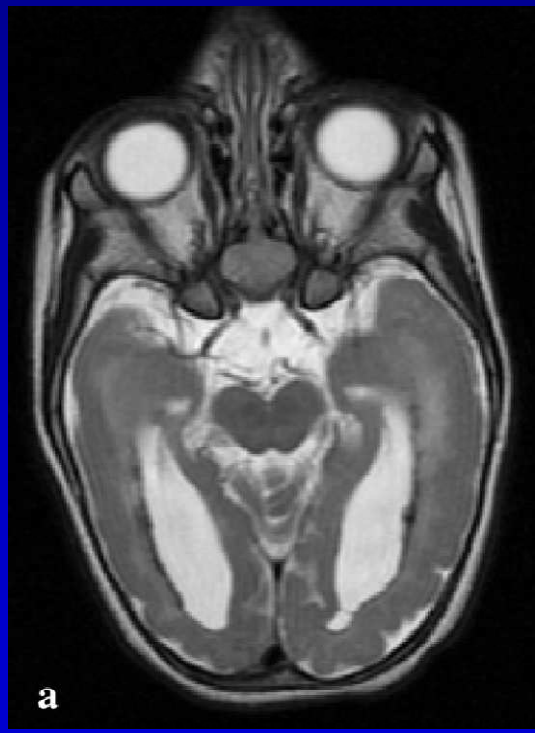
• Jaundice	67%
• Hepatosplenomegaly	60%
• Petechiae	76%
• SGA	50%
• Microcephaly	53%
• Cerebral calcifications	50%
• Seizures	7%
• Pneumonitis	<1%

CONGENITAL CMV: SEQUELAE

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







Capretti et al. Brain Dev. 2014; De Vries et al. Neuropediatrics 2004

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
Rivera LB et al. *Pediatrics* 2002;110:762

CONGENITAL CMV: DIAGNOSIS

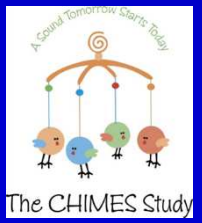
- Isolation of virus from urine or saliva
- CMV PCR: urine preferred for diagnosis but saliva excellent for screening
- Congenital infection requires detection of virus in first 2-3 weeks of age. After 3 weeks, impossible to differentiate congenital vs. intrapartum vs. postnatal infection (e.g. breast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

Pinnitti et alPIDJ 2015; Ross et al. JID 2014; Yamamoto et al. J Clin Virol 2006; Balcarek et al. JID 1993; Halwachs-Baumann et al. Scand J Infect Dis 2000; Stagno et al. J Clin Microbiol 1985

DRIED BLOOD SPOT (DBS) CMV PCR: CHIMES STUDY (NIDCD)

Boppana et al. JAMA 2010;303:1375

- Newborns at 7 medical centers screened for congenital CMV infection using saliva shell vial culture assay and DBS PCR: 3/2007 – 5/2008
- 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 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

Stehel E et al. *Pediatrics*, 2008

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

UNIVERSAL CMV SCREENING IN NICU: WHY?

- Targeted screening for CMV-related hearing loss at NCH NICU (2
- 36% (546/149 creen at >21 d of age
  - 82% (n=4
  - 8% (n=41
  - 11% (n=5
- Missed opportunity for diagnosis and institution of antiviral therapy if indicated.

*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

Ronchi et al. J Perinatology, 2019, in press

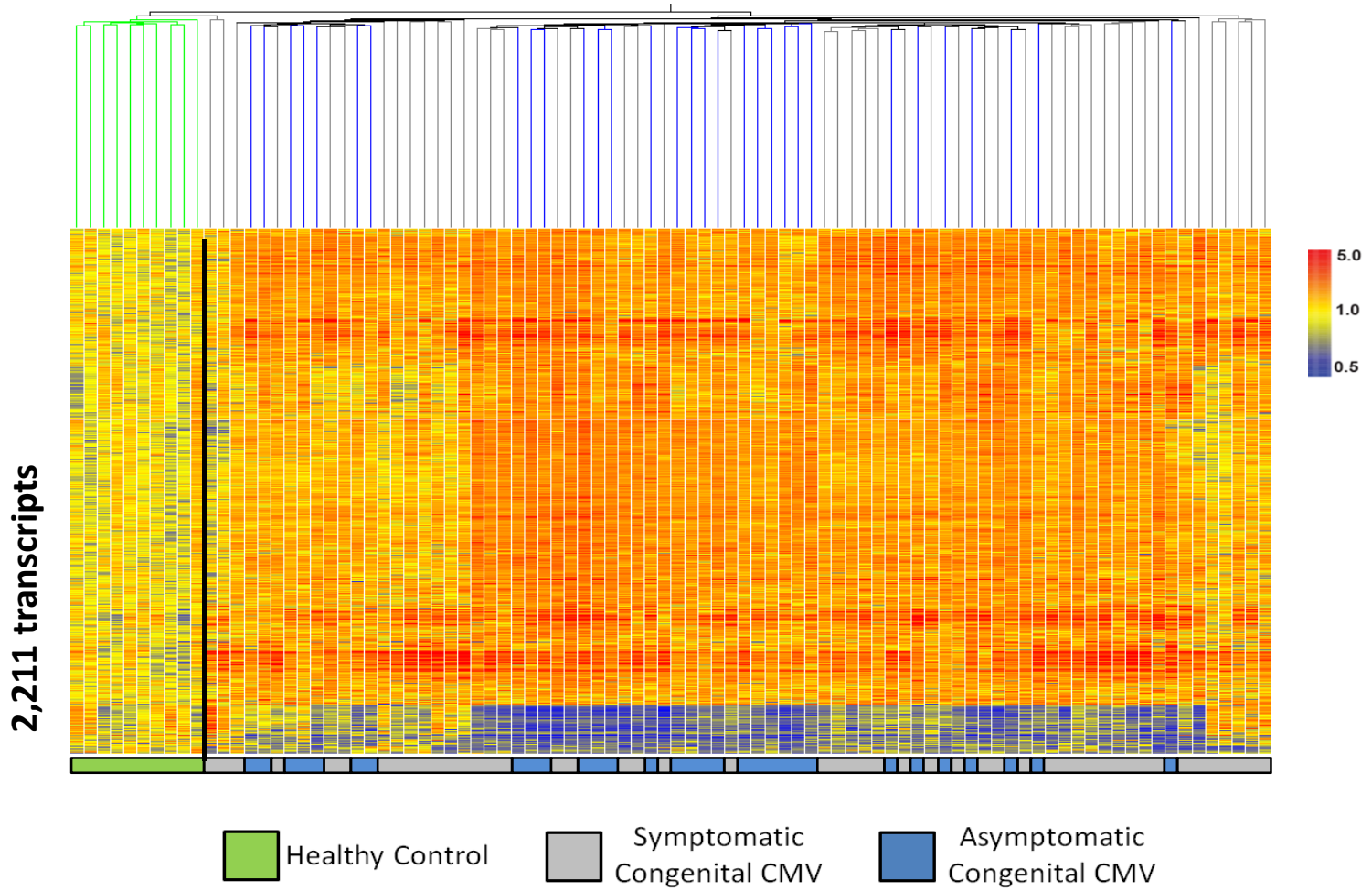
EVALUATION: "ASYMPTOMATIC" Infant with Congenital CMV Infection

- 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

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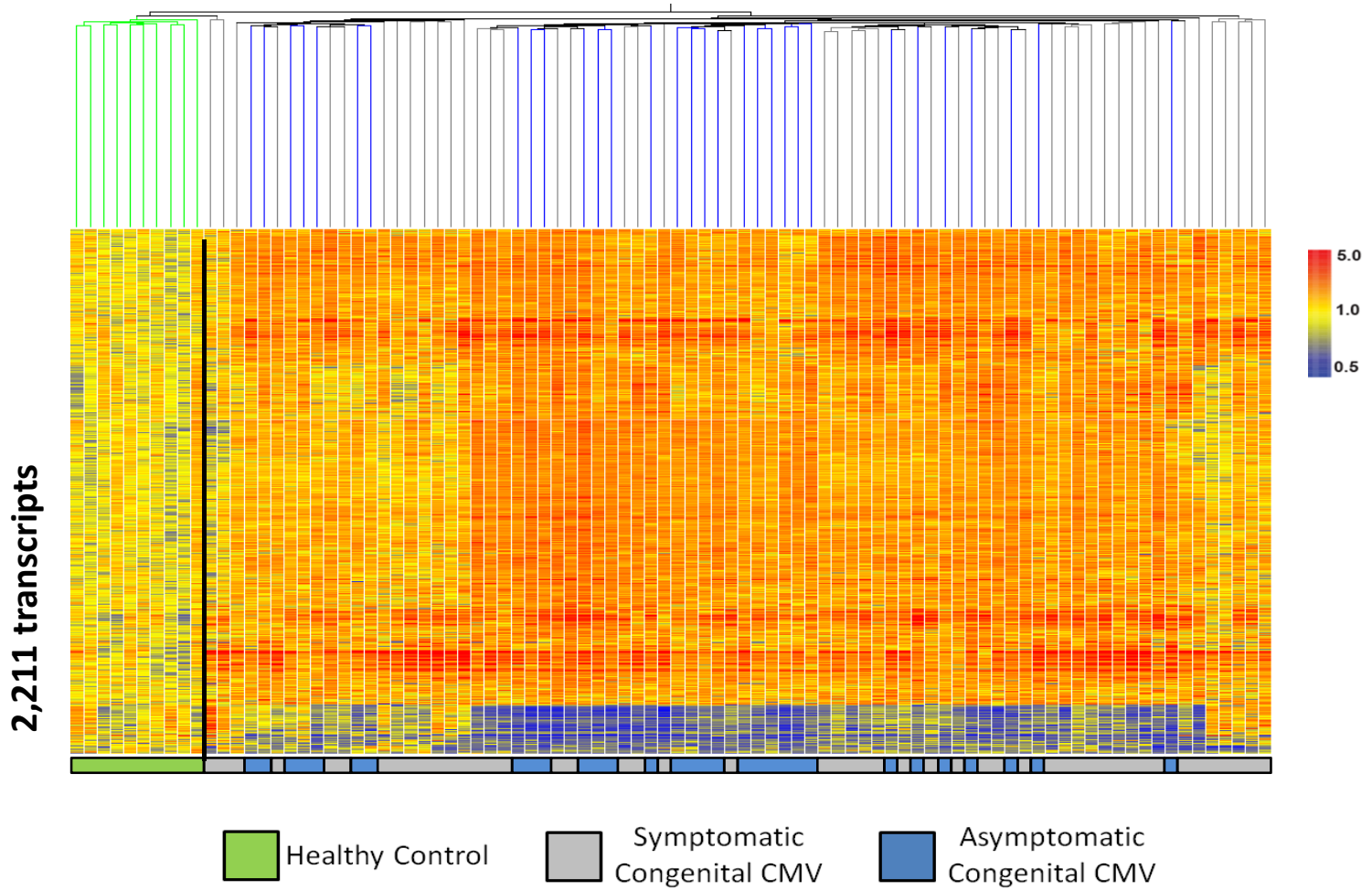

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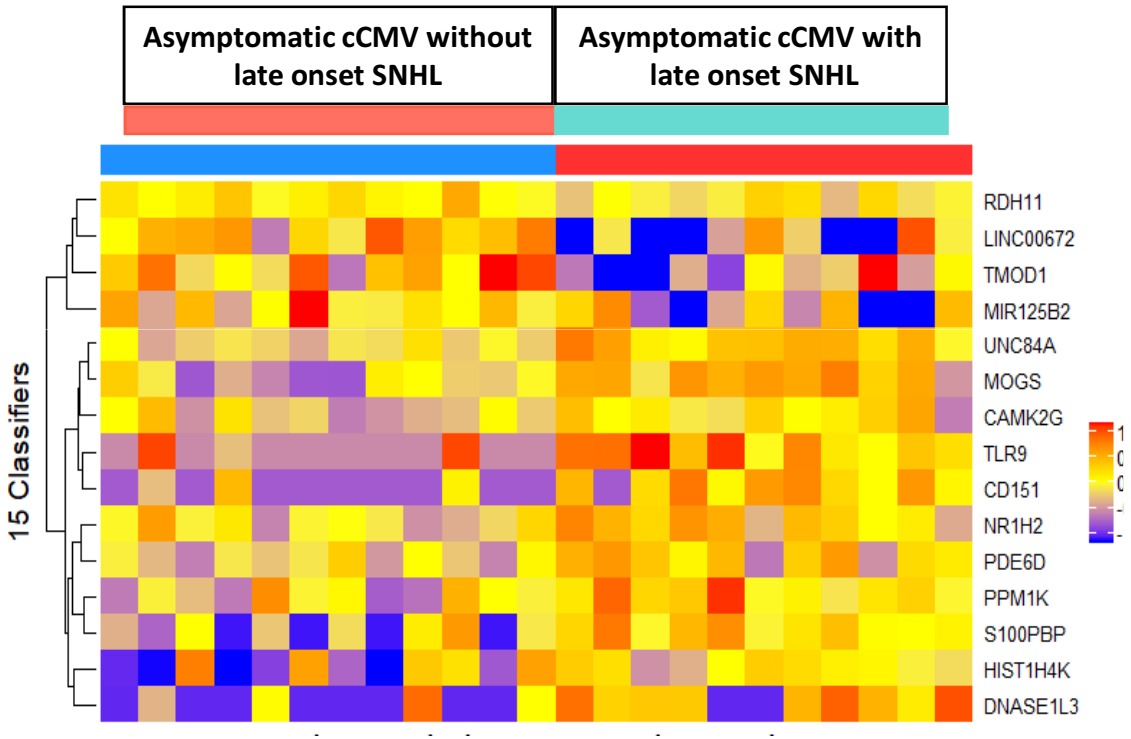
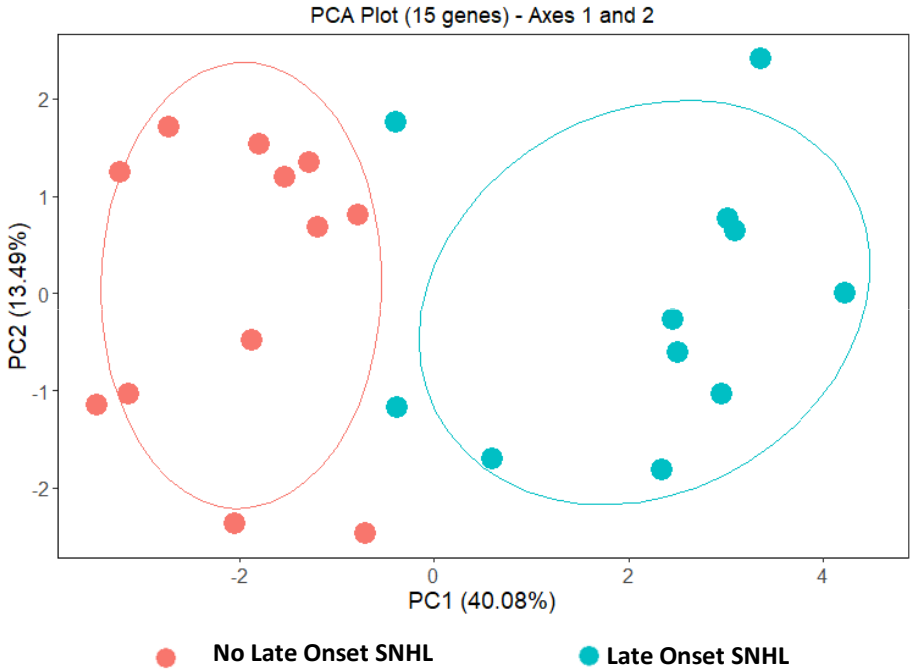
“Asymptomatic” Congenital CMV Infection and Sensorineural Hearing Loss: Random Forest Analyses





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CONGENITAL CMV: GANCICLOVIR

Kimberlin et al. *J Pediatr* 2003;143:16

- Multicenter, randomized: 1991-1999
- 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

Oliver SE, et al. J Clin Virol, 2009

- 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

Follow-up Interval	Ganciclovir (mean ± SE)	No Treatment (mean ± SE)	P-value
6 weeks (n=74)	1.5 ± 0.3	2.1 ± 0.3	0.15
6 months (n=74)	4.5 ± 0.7	7.5 ± 1.0	0.02
12 months (n=72)	10.1 ± 1.7	17.1 ± 1.9	0.007

*Oliver SE, et al. J Clin Virol, 2009

PHASE I/II PHARMACOKINETIC EVALUATION OF VALGANCICLOVIR

Acosta et al. Clin Pharmacol Ther, 2007

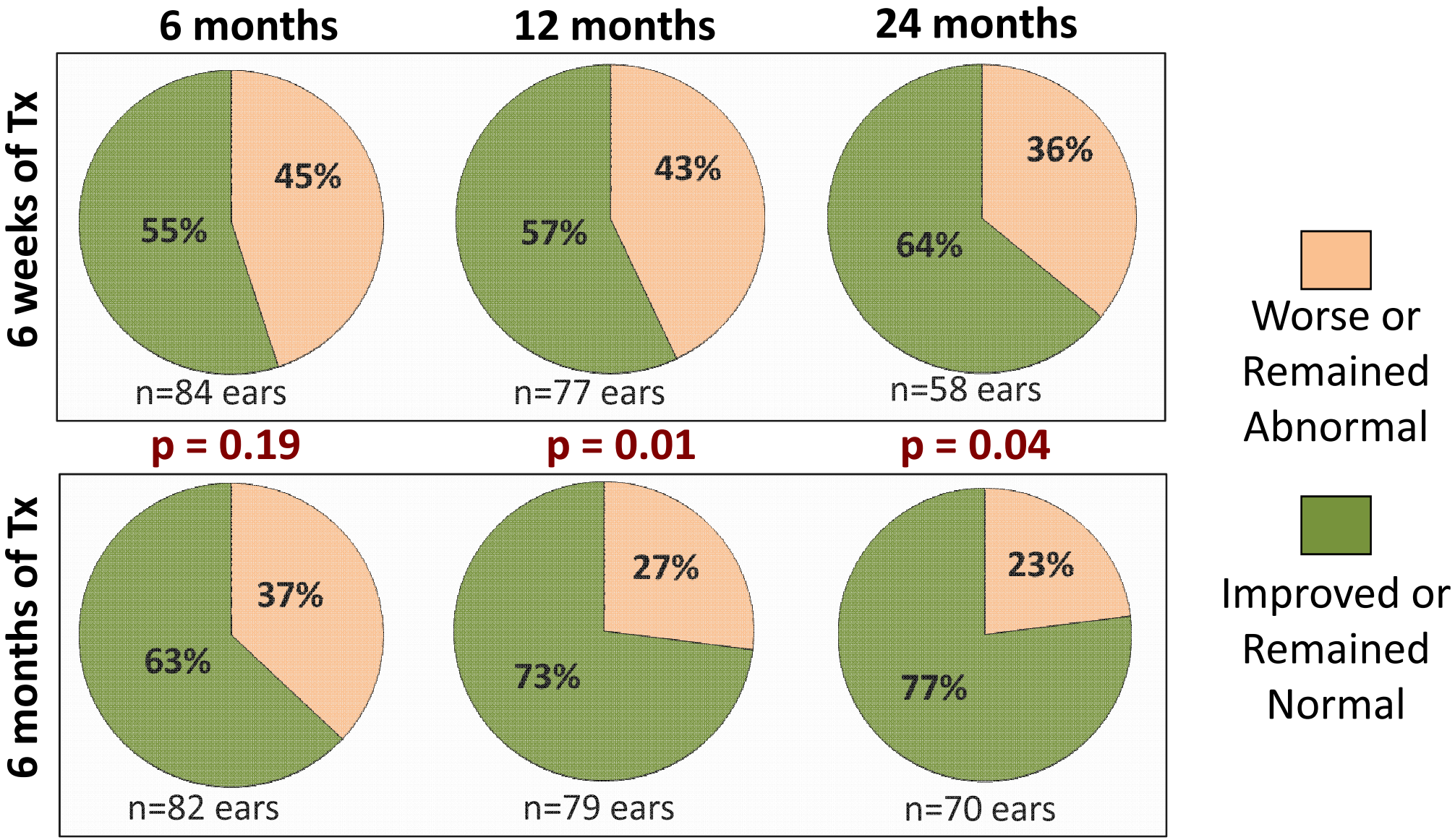
- 24 neonates (age ≤ 30 d; UTSW, 9 subjects)
- Birth weight ≥1200 g
- Gestational age ≥32 wk
- Population PK:
  - Valganciclovir syrup vs. ganciclovir IV (6 mg/kg/dose q 12 hr) x 6 wks
  - 16 mg/kg/dose q12 hr PO

VALGANCICLOVIR: 6 wks vs. 6 months?

Kimberlin et al. (CASG) NEJM 2015; 372:933

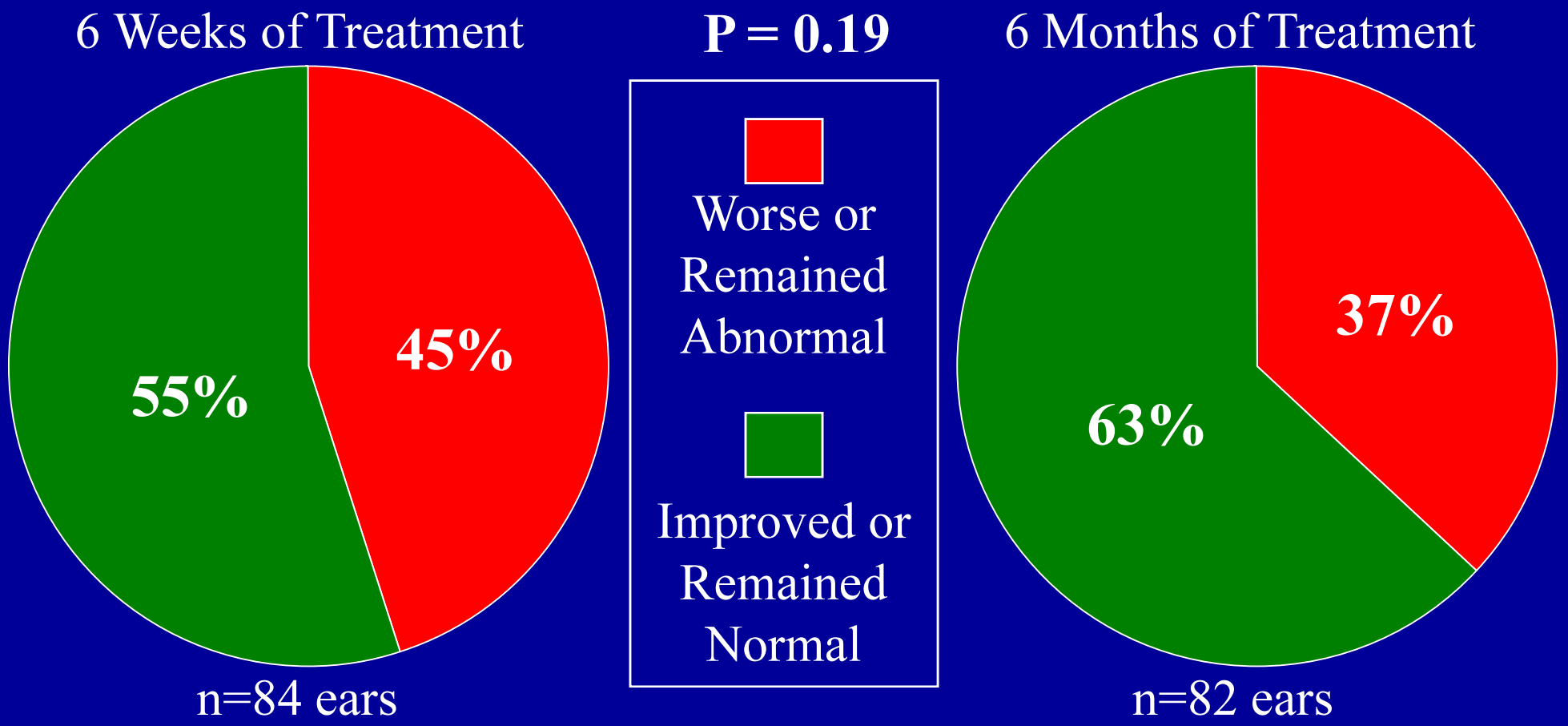
- Phase III trial, 6 wks of oral valganciclovir, then valgan or placebo for total of 6 months
- 109 infants (age ≤30 d; ≥32 wks GA, 1800 g):
  - "symptomatic" - with (63%) or without CNS disease
- Primary outcome: hearing at 6 months
- Bayley-III performed at 24 months

6 Weeks vs. 6 Months Oral Valganciclovir
Change in Hearing Between Birth and follow-up



6 Weeks vs. 6 Months Oral Valganciclovir Change in Hearing From Birth to 6 Months

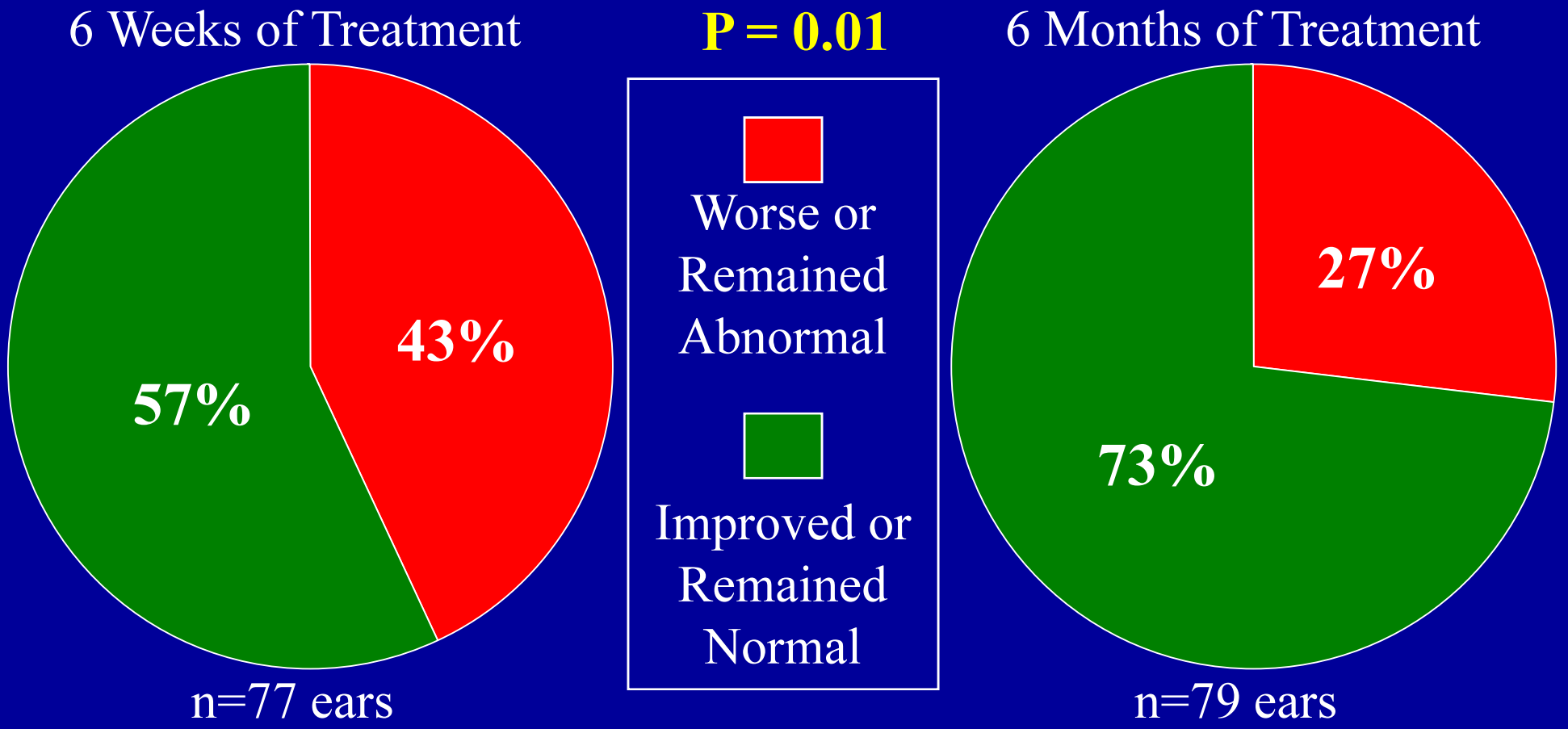
Kimberlin et al. NEJM 2015;372:933



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

6 Weeks vs. 6 Months Oral Valganciclovir Change in Hearing From Birth to 12 Months

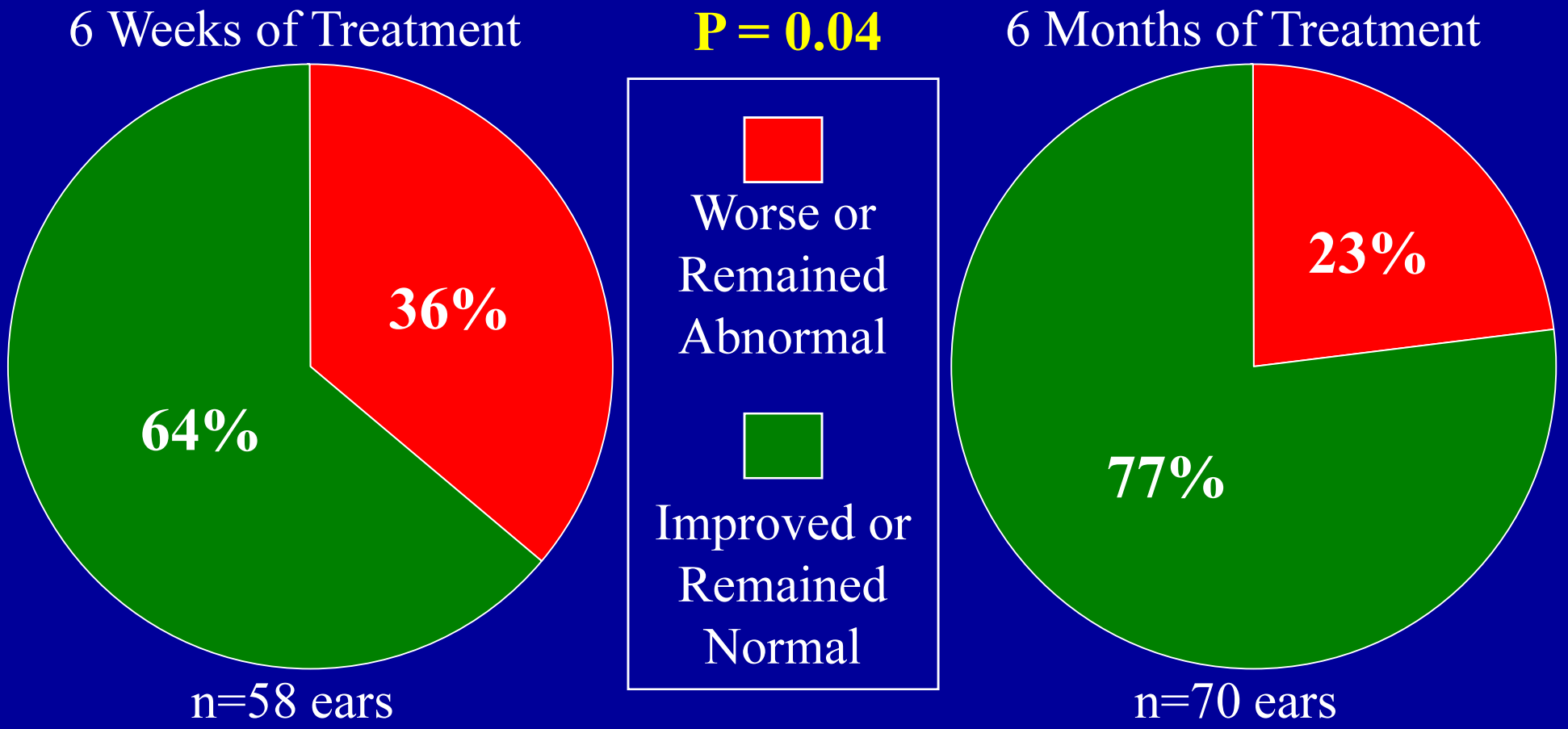
Kimberlin et al. NEJM 2015;372:933



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



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

6 Weeks vs. 6 Months Valganciclovir: BSID-III Results at 24 Months

	6 Week Therapy	6 Month Therapy	Adjusted P-value*
Cognitive Composite	76.0 ± 2.6	84.4 ± 2.6	0.024
Language Composite	72.5 ± 2.9	84.6 ± 2.9	0.004
Receptive Communication Scale	5.2 ± 0.5	7.3 ± 0.5	0.003
Expressive Communication Scale	5.5 ± 0.5	7.3 ± 0.5	0.016
Motor Composite	74.1 ± 3.2	85.5 ± 3.3	0.013
Fine Motor Scale	6.4 ± 0.6	8.0 ± 0.6	0.057
Gross Motor Scale	5.3 ± 0.5	7.0 ± 0.5	0.020

*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

Ronchi et al. Expert Review of Anti-Infective Therapy, 2017

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, rando[illegible], placebo[illegible]trolled, double-blind study
- Pregnant with prima[illegible] [illegible]ection diagnosed at <24 wks, or <28 wks [illegible]e CMV IgM, negative IgG screened before [illegible] but then have IgG seroconversion:
  - CMV-IGIV vs. p[illegible]o ([illegible])
- Primary outcom[illegible]al loss, [illegible]med fetal CMV infection from [illegible]ocentesis, [illegible]tal 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.


STOP CMV
IT'S TIME
TO ACT!
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