CMV: ¿cuándo y a quienes tratar?

Pablo J. Sánchez, MD

Nationwide Children's
When your child needs a hospital, everything matters.℠

The Ohio State University

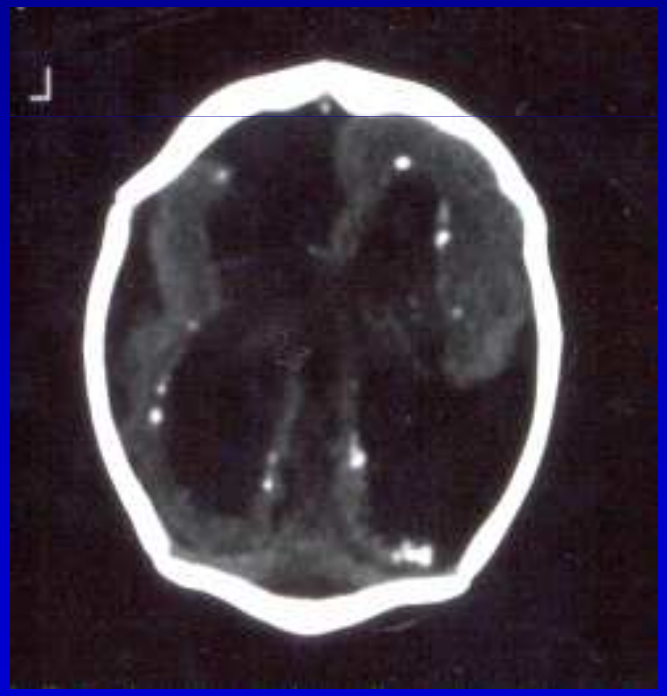
7˚ Congreso Argentino de Infectología Pediátrica
Córdoba, Argentina
April 3-5, 2014

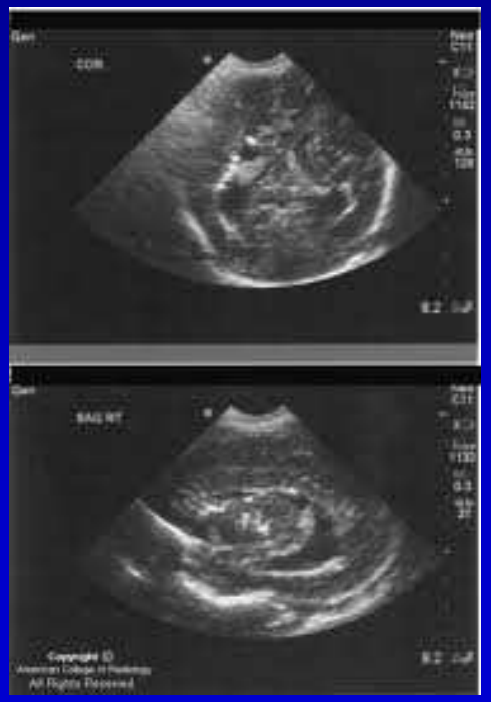
CONGENITAL CMV INFECTION

- Public health impact worldwide:
  - ~40,000 infants born infected each year in USA
  - >8000 with sequelae or fatal outcome

CONGENITAL CMV: SEQUELAE

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





CONGENITAL CMV AND NEURODEVELOPMENTAL OUTCOME

- Boppana et al., *Pediatrics* 1997;99:409:
  - Predictive value of ABN head CT scan in 56 children with SX congenital CMV infection:
    - Any sequelae: 90% (35/39) vs. 29% (5/17)
    - IQ<70: 59% vs. 11%
    - IQ<50: 48% vs. 0
    - Cerebral palsy: 70% vs. 12%
    - Hearing loss: 72% vs. 29%
  - Not possible to predict CT scan abnormalities using abnormal clinical, lab findings at birth

CONGENITAL CMV AND NEURODEVELOPMENTAL OUTCOME

- Williamson et al., *Pediatrics* 1992;90:862:
  - 59 infants with **ASX** congenital CMV infection: abnormalities on head CT scan (calcifications, periventricular radiolucencies) associated with:
    - Adverse developmental performance at 1 yr of age
    - Hearing loss: 5/16 (31%) vs. 2/40 (5%), p=0.03 (only factor)

SEQUELAE AFTER CONGENITAL CMV INFECTION

Sequelae	Symptomatic % (n=104)	Asymptomatic % (n=330)
Hearing loss:*		
Sensorineural	58	7
Bilateral	37	3
Mod-profound	27	2
Overall:+	22-65%	8-15%

*Stagno, 1994; +Fowler, Boppana, 2006

CONGENITAL CMV: SEQUELAE

- Sensorineural hearing loss:
  - Any clinical or laboratory abnormality at birth

PREDICTORS OF HEARING LOSS: SYMPTOMATIC CONGENITAL CMV

Rivera LB et al. Pediatrics 2002;110:762

- 190 children: 1966-1997
- 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: VIREMIA AND SENSORINEURAL HEARING LOSS

- "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

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: $\leq$ 1 mo, $\geq$ 32 wks GA, BW $\geq$ 1200 g
- CNS involvement: microcephaly, abnormal CT / HUS / CSF, chorioretinitis, hearing loss
- 47 evaluable infants
- Primary outcome: hearing
- No change in mortality (6% vs 12%)
- Neutropenia: 63%

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
- Current study: 6 weeks vs. 6 months of valganciclovir for "symptomatic" congenital CMV infection

VALGANCICLOVIR: 6 wks vs. 6 months? Inclusion Criteria

- CMV: urine/throat - culture, shell vial, or PCR
- "Symptomatic" congenital CMV disease:
  - Thrombocytopenia
  - Petechiae
  - Hepatomegaly
  - Splenomegaly
  - Intrauterine growth restriction
  - Hepatitis (↑ transaminases or bilirubin)
  - CNS disease: microcephaly, radiographic abnormalities, abnormal CSF indices, chorioretinitis, hearing deficits, or positive CSF CMV PCR
- ≤ 30 days of age and weight ≥ 1800 grams
- Gestational age ≥ 32 weeks

IDWeek 2013, Late Breaker Abstract #43178

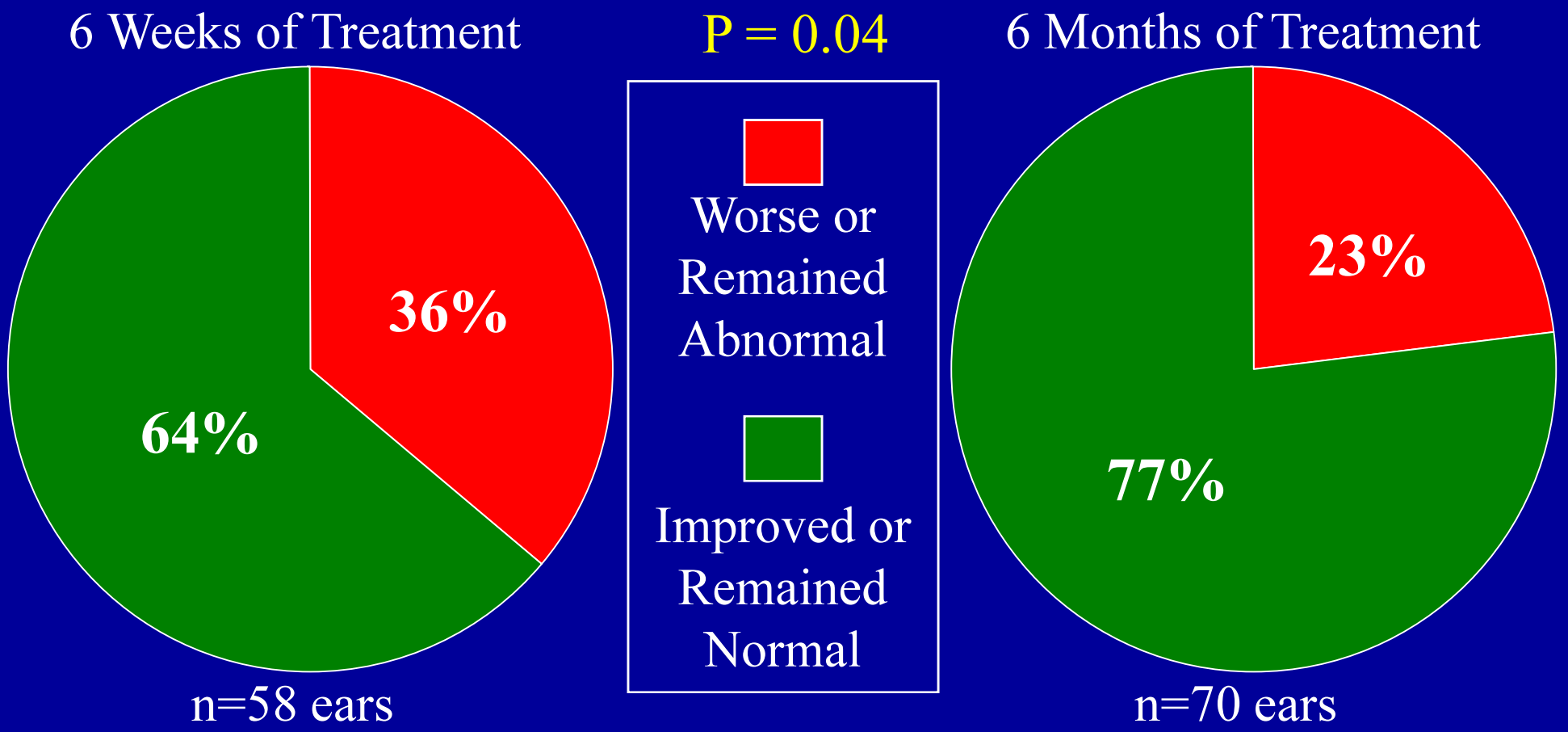
VALGANCICLOVIR: 6 wks vs. 6 months?

Kimberlin et al. (CASG) IDWeek, 2013

- Phase III trial, 6 wks of oral valganciclovir, then valgan or placebo for total of 6 months
- 109 infants (age ≤ 30 d); "symptomatic" with or without CNS disease
- Primary outcome: hearing; Bayley-III performed
- Hearing improved or remained normal:
  - 6 months: NS; 12 and 24 months: better outcomes with 6 months of rx (p=0.01, 0.04)
  - Language, receptive communication superior at 24 months in the 6 month rx group

IDWeek 2013, Late Breaker Abstract #43178

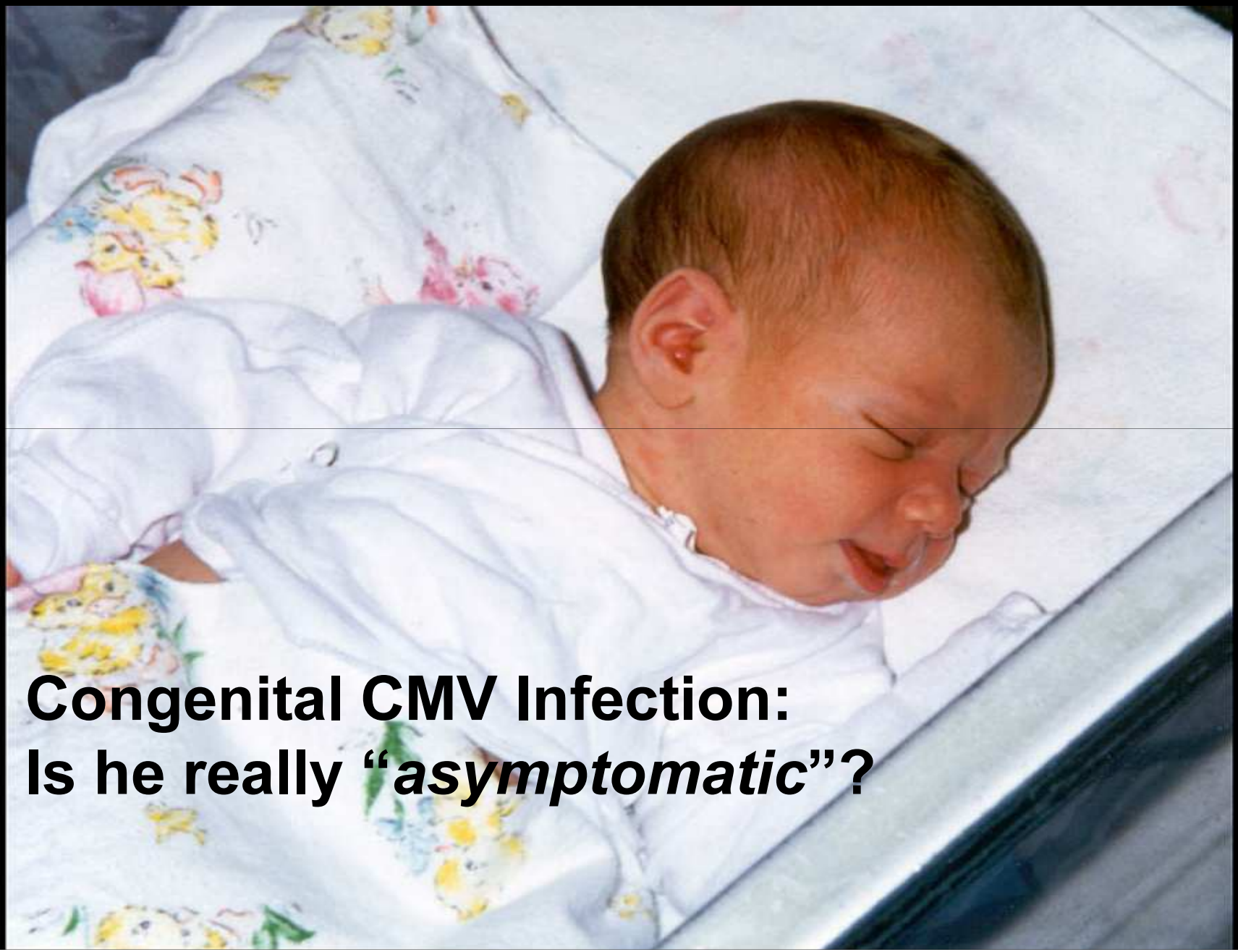
6 Weeks vs. 6 Months Oral Valganciclovir Change in Hearing Between Birth and 24 Mo



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

CONGENITAL CMV: CONCLUSIONS

- Is it time to treat?
  - CNS disease: YES
  - Clinically apparent disease ("symptomatic") but no documented CNS disease: wait for peer-reviewed publication, but likely yes and for 6 months
  - Clinically inapparent infection ("asymptomatic"); NO



Congenital CMV Infection: Is he really "*asymptomatic*"?

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

Ronchi et al. International CMV Conference, SF, 2012


STOP CMV
© David Clark, M
2005.03.14