

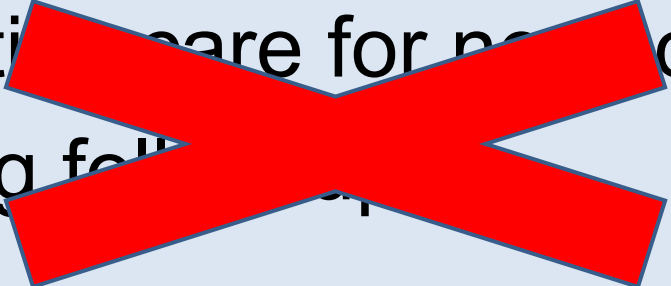


**ESCMID Postgraduate Education Course
Infectious Diseases in Pregnant Women, Fetuses and Newborns
Bertinoro, Italy 3 – 7 October 2010**

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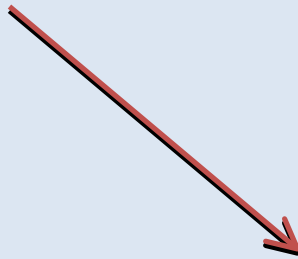
Disclosures: No competing interests related to this topic. “Off-label” use of antiviral drugs will be discussed.

Management of congenital CMV infection in the newborn: key issues

- Evaluation of the newborn
 - Counseling the family
 - Antiviral treatment decision
 - Supportive care for newborn disease
 - Planning follow-up
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How do newborns with congenital CMV infection come to attention?

Signs of congenital infection

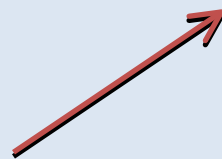


Maternal gestational CMV



+ test for CMV

Newborn screening for CMV



Evaluation of the newborn with congenital CMV infection

CONFIRM THE DIAGNOSIS

- Do not accept a single laboratory result as proof
- Requires detection of virus
 - Culture
 - PCR

Evaluation of the newborn with congenital CMV infection

DETERMINE THE EXTENT OF DISEASE

- Physical exam
- Laboratory assessment
- Imaging studies
- Hearing assessment
- Ophthalmological exam

Newborn with Symptomatic Congenital CMV Infection



Is the newborn “symptomatic?”

Understanding the jargon -

Original meaning:

- Clinically evident
- Microcephaly
- Petechiae/ecchymoses
- Dermal erythropoiesis
- Retinitis/optic atrophy
- Hepatosplenomegaly
- Jaundice
- Neurologic abnormalities
- Associated lab and imaging results

Expanded meaning:

- Hearing loss
- Small for gestational age
- Prematurity
- Ultrasound findings
- CT or MRI findings
- Others?

Counseling the family: Do not take away hope.

- Normal newborn
 - ~5-25% risk of sequelae
 - Mostly hearing loss
- Abnormal newborn
 - ~10% mortality in newborn period
 - ~50% CNS sequelae: hearing loss, cognitive impairment, cerebral palsy, impaired vision
- If treatment is considered, parents must be involved in decision

The outcome of congenital CMV is highly variable and cannot be predicted precisely by:

- Type of newborn symptoms
- Viral load in newborn blood or urine
- Imaging findings
- Type of maternal infection (primary or nonprimary)

To treat or not to treat?

- Which newborns merit treatment consideration?
- What antiviral agents are available for newborns?
 - ganciclovir
 - valganciclovir
 - Not recommended: acyclovir, valacyclovir, cidofovir, foscarnet
- Is there a benefit to treatment?
- What are the risks associated with treatment?

What evidence supports use of antiviral treatment for newborns with CMV?

Newborn disease	Evidence
CNS/hearing	Randomized trial; no placebo, not blinded
NonCNS signs (liver, spleen, petechiae, etc)	Case series (anecdote)
Imaging abnormalities	Anecdote
No disease	None*

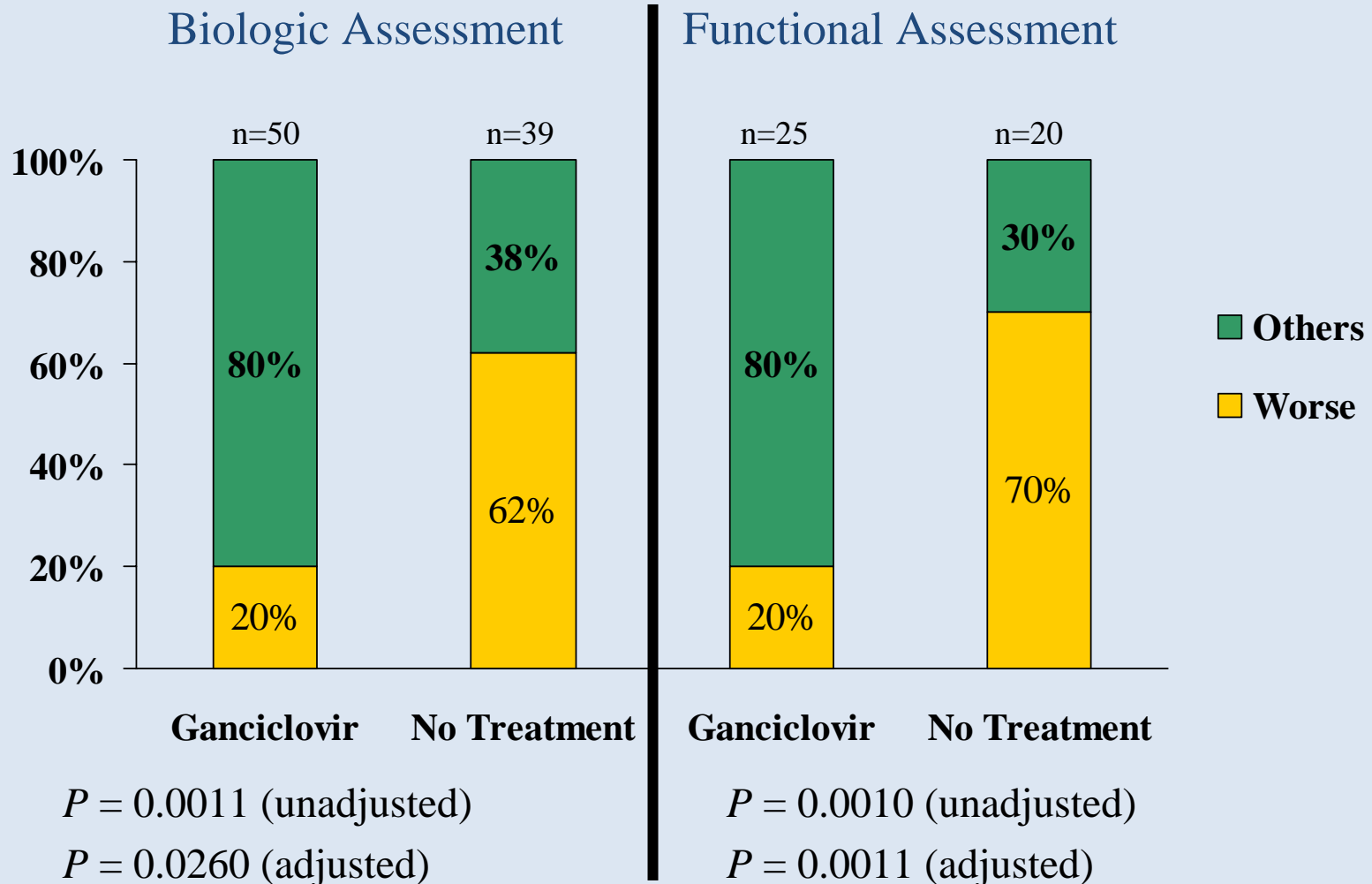
Treatment of newborns with severe symptomatic congenital CMV: ganciclovir vs no treatment

From Kimberlin et al, J Pediatr 143:16-25, 2003.

- Culture proven congenital CMV infection
- Evidence of CNS disease
- > 32 weeks gestation
- < 6 weeks of age
- A randomized, unblinded trial; GCV vs no treatment
- Treatment: 6 weeks of iv GCV, 12/mg/kg/day, divided bid

Ganciclovir treatment of symptomatic congenital CMV: Effect on Hearing Outcome (≥ 1 year)

From Kimberlin et al, J Pediatr 143:16-25, 2003.



GCV improves CNS outcome for treated newborns with CNS disease

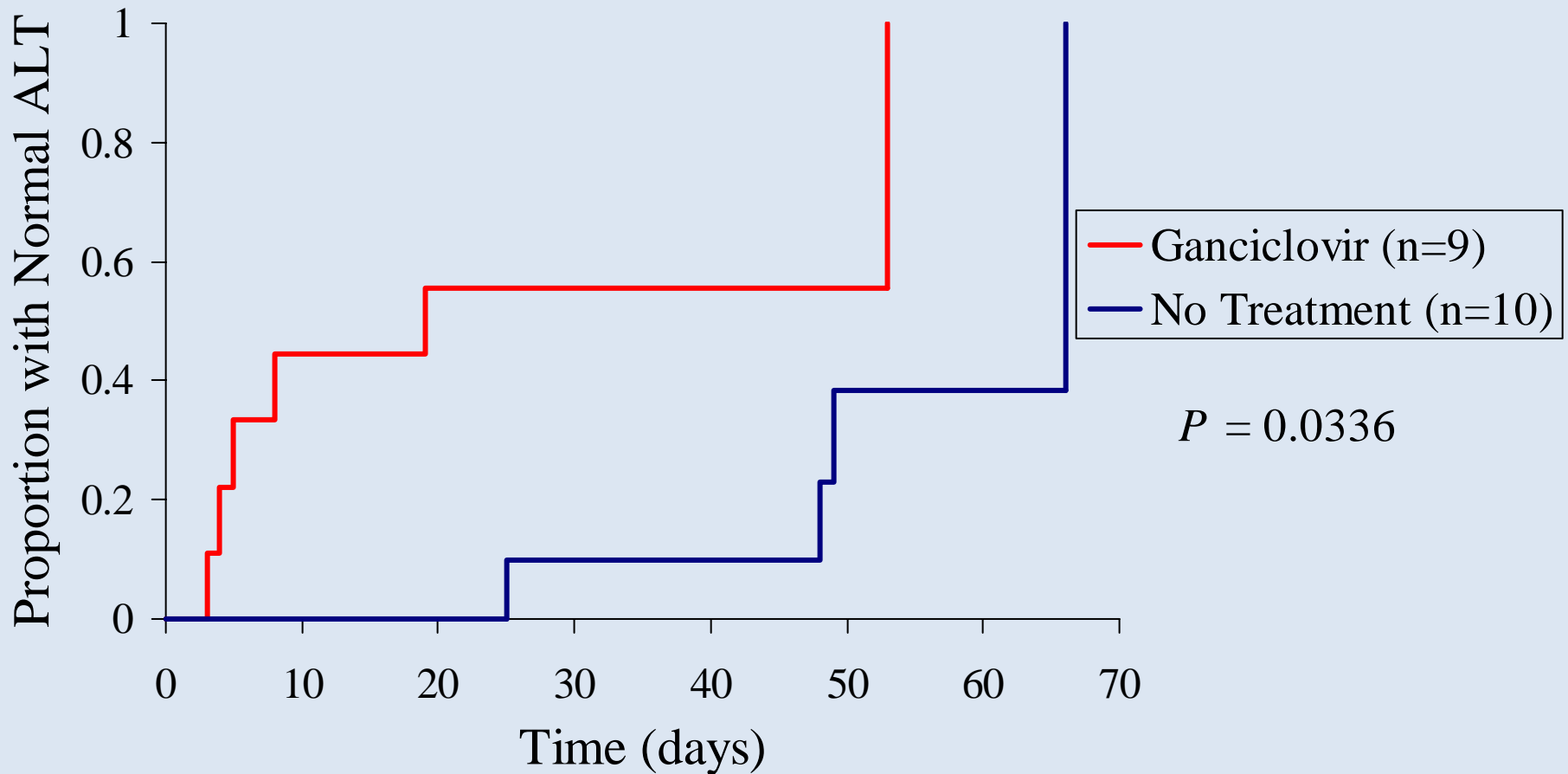
Oliver et al, J Clin Virol 46:822, 2009

- Newborns with CNS abnormalities
- Denver dev test at 6 weeks, 6 mo, 12 mo
- Delays = failure on milestone achieved by >90% of age peers

	Average number of delays	
Evaluation	Ganciclovir	No treatment
6 month	4.5 (35)	7.5 (39)
12 month	10.1 (35)	17.1 (36)

Differences were statistically significant

Time to First Normalization of ALT (SGPT)



Effect of 6 weeks of iv ganciclovir in severe symptomatic congenital CMV infection

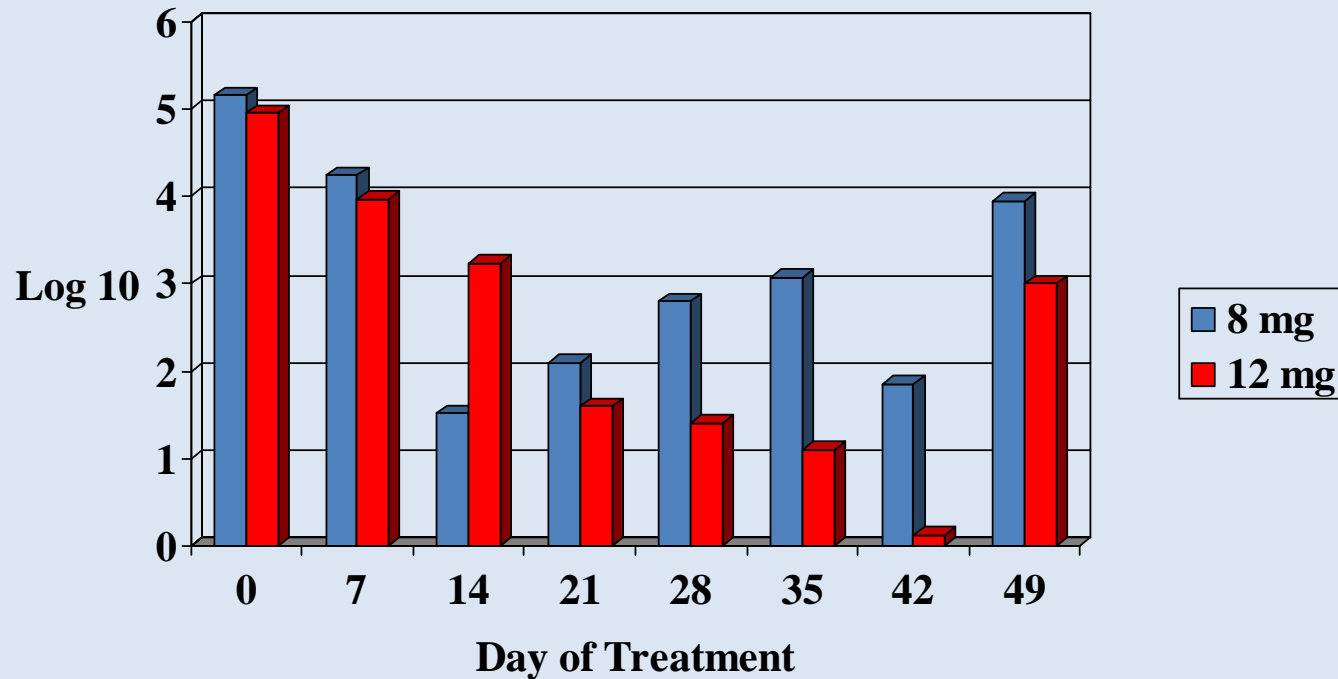
- GCV reduces the risk of worsening of hearing up to and beyond one year of age.
- GCV treated newborns had better developmental progress than untreated subjects
- GCV had little effect on the course of the acute illness (clinical or laboratory)
- ~ 2/3 of subjects had neutropenia
 - ~ half of them required interruption of treatment

Ganciclovir toxicity

- Humans: Dose dependent hematologic toxicity common at therapeutic doses
- Animal reproductive toxicity:
 - At ~1.7 the human drug exposure at 5mg/kg dose, ♀ mice have ↓ mating behavior and fertility and ↑ fetal loss.
 - At daily dose and systemic exposure < 0.1x that achieved in humans, ♂ mice and dogs had hypospermatogenesis
- Animal teratogenicity: at ~ 2x human drug exposure - cleft palate, anophthalmia/microphthalmia, aplastic organs (kidney and pancreas), hydrocephaly and brachygnathia, embryoletality, hypoplasia of the testes and seminal vesicles
- Animal carcinogenicity: at 0.1 to 1.4x human drug exposure, multiple tissues, especially reproductive

Quantity of CMV in Urine of Newborns by Dose of Ganciclovir

From Whitley et al, J Infect Dis, 175:1080, 1997.



6 weeks of iv GCV for newborns with CMV: Current limitations

- Randomized trial data available only for newborns with CNS disease
- Measured benefit is modest
- Toxicity
- Rebound viral shedding
- Requirement for iv, usually central line

Valganciclovir is being studied for congenital CMV infection

- Potential benefits
 - No iv line
 - Chronic therapy facilitated
- Liquid formulation approved by FDA 2009
 - For child transplant patients 4 mo to 16 years
 - Not approved for congenital CMV treatment

Pharmacokinetics of valganciclovir in newborns

- Galli et al, *Pediatr Infect Dis J*, 2007
 - 8 infants 4-90 d. of age, symptomatic cong CMV
 - Liquid compounded from tablets
 - 15 mg/kg, 2x per day achieved median GCV of 3.1 $\mu\text{g/ml}$

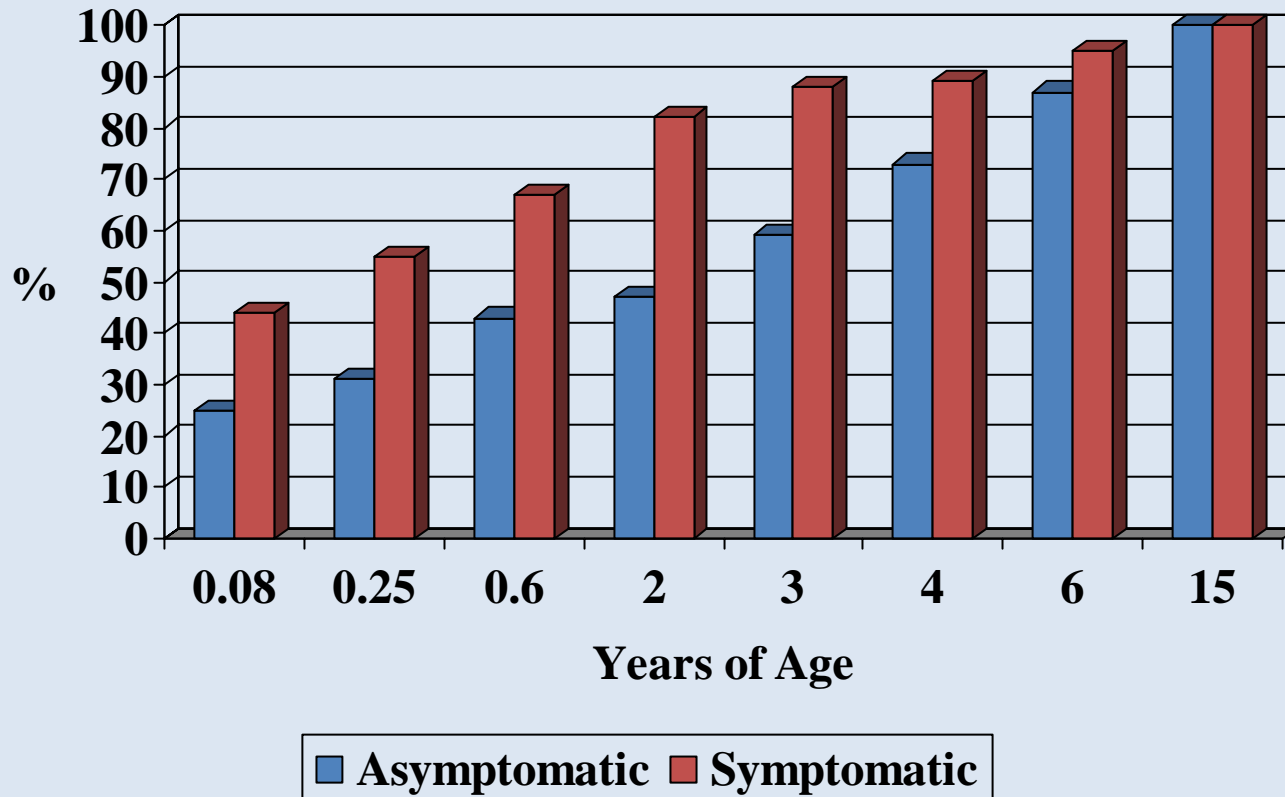
Valganciclovir pharmacokinetics and pharmacodynamics in newborns

- Acosta et al, Clin Pharm Therapeutics, 2007
 - 24 newborns, symptomatic cong CMV, 8-34 d. of age
 - iv GCV followed by liquid oral formulation VGCV from Roche
 - Studied 14, 16 and 20 mg/kg oral dose
 - VGCV 16 mg/kg 2x/day achieved similar AUC to GCV 6 mg/kg 2x per day iv
- Kimberlin et al, J Infect Dis, 2008
 - Same clinical trial as Acosta study
 - 7 subjects developed neutropenia (≤ 750); 1 discontin. drug at d. 38 and 1 interrupted treatment.
 - CMV viremia decreased by mean of 0.7 log; 6/18 cleared viremia

Valganciclovir pharmacokinetics in newborns

- Lombardi et al, Eur J Clin Microbiol, 2009
 - 13 newborns with symptomatic cong CMV
 - Oral preparation compounded locally from tabs
 - 15 mg/kg, 2x/day
 - GCV levels ranged from mean trough 0.5 ± 0.3 to mean peak 4.4 ± 1.3 $\mu\text{g/ml}$
 - Not all subjects cleared virus, but all had \downarrow quantity
 - 8 with hearing loss, none worsened up to 6 months

Cumulative % of hearing loss by age: Congenital CMV patients with hearing loss



Prolonged treatment of congenital CMV infection with ganciclovir

- Amir et al, Eur J Pediatr, 2010
 - Retrospective study
 - 23 newborns with CMV & CNS signs
 - VGCV compounded from tablets
 - iv GCV, 6 weeks; then oral VGCV (17-18 mg/kg) 2x/day for 6 weeks; then oral VGCV 1x/day to one year
 - 12/23 neutropenia; 2 had to interrupt drug
 - 18% psychomotor retardation at 1 year of age
 - Normal hearing in 54% ears at baseline, 76% at one year of age

Short-Term vs. Long-Term Valganciclovir Therapy for Symptomatic Congenital CMV Infections

This study is currently recruiting participants.

Last Updated: September 9, 2010

Sponsor: [National Institute of Allergy and Infectious Diseases \(NIAID\)](#)

Information provided by: National Institute of Allergy and Infectious Diseases (NIAID)

ClinicalTrials.gov Identifier: NCT00466817

- All subjects receive 6 weeks iv ganciclovir
- Then randomized to 6 months oral valganciclovir or placebo
- Followed for safety, hearing, development
- Currently ~75% of full enrollment

Antiviral treatment of congenital CMV infection:

Practical Considerations

- Treatment of newborns who are symptomatic and have evidence of CNS disease has merit based on RCT evidence.
- Insufficient evidence to support treatment of any other category.
- Oral valganciclovir will likely replace iv GCV as preferred treatment
- There is no convincing evidence to date that prolonged treatment will improve outcome, but study results are pending
- Neither GCV nor VGCV have FDA approval for treatment of newborns with congenital CMV