Management of Newborns with Congenital CMV Infection

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ESCMID Postgraduate Course

Centro Universitario Residenziale di Bertinoro

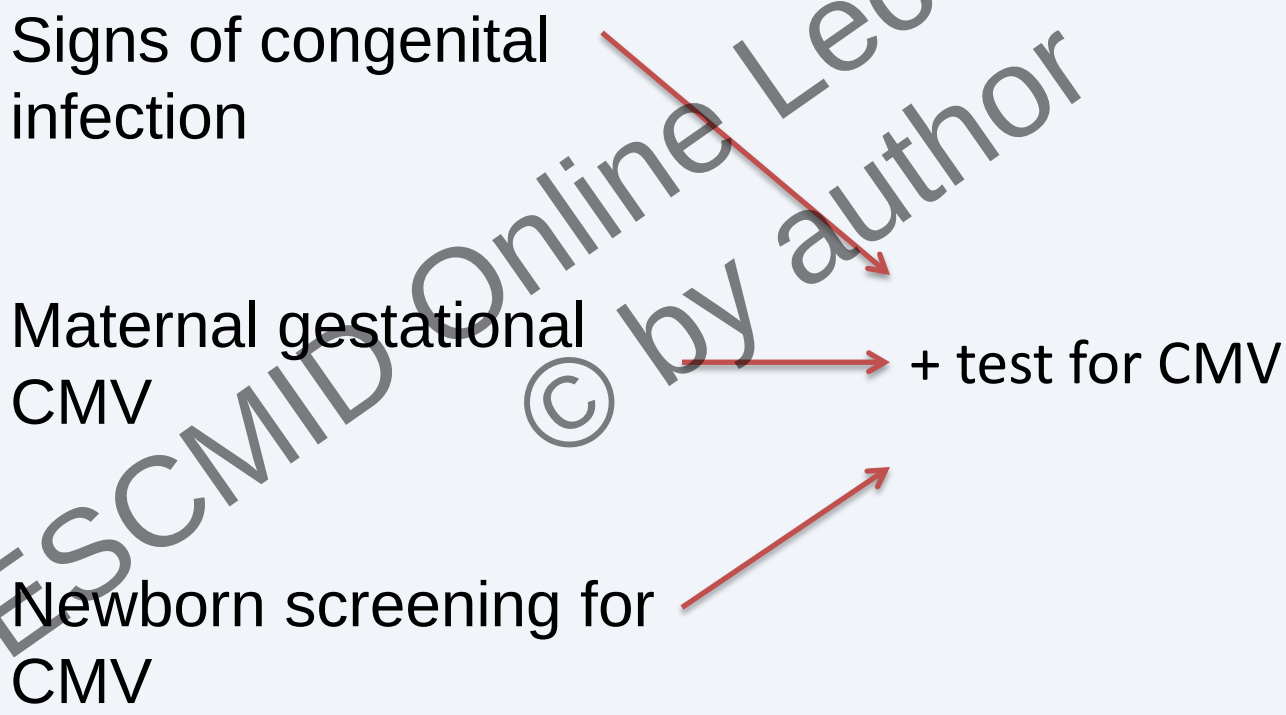
29 Sept 29 – 3 Oct 2013

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

Sources of Newborn CMV Infection

Route	Estimated Rate	Disease potential
Transplacental	0.7% (0.2 to >2%) of live births	Significant – congenital infection, CNS sequelae
Intrapartum	~ 10% of births to seropos. mother	VLBW or immunocompromised
Postpartum, breast milk	~50% breastfed by seropos mother (variable)	VLBW or immunocompromised
Postpartum, iatrogenic Blood products, banked human milk	Low and highly variable depending on local prevalence and practice	VLBW or immunocompromised

How do newborns with congenital CMV infection come to attention?



Newborn with Symptomatic Congenital CMV Infection

Is the newborn “symptomatic?” Understanding the jargon -

Original meaning:

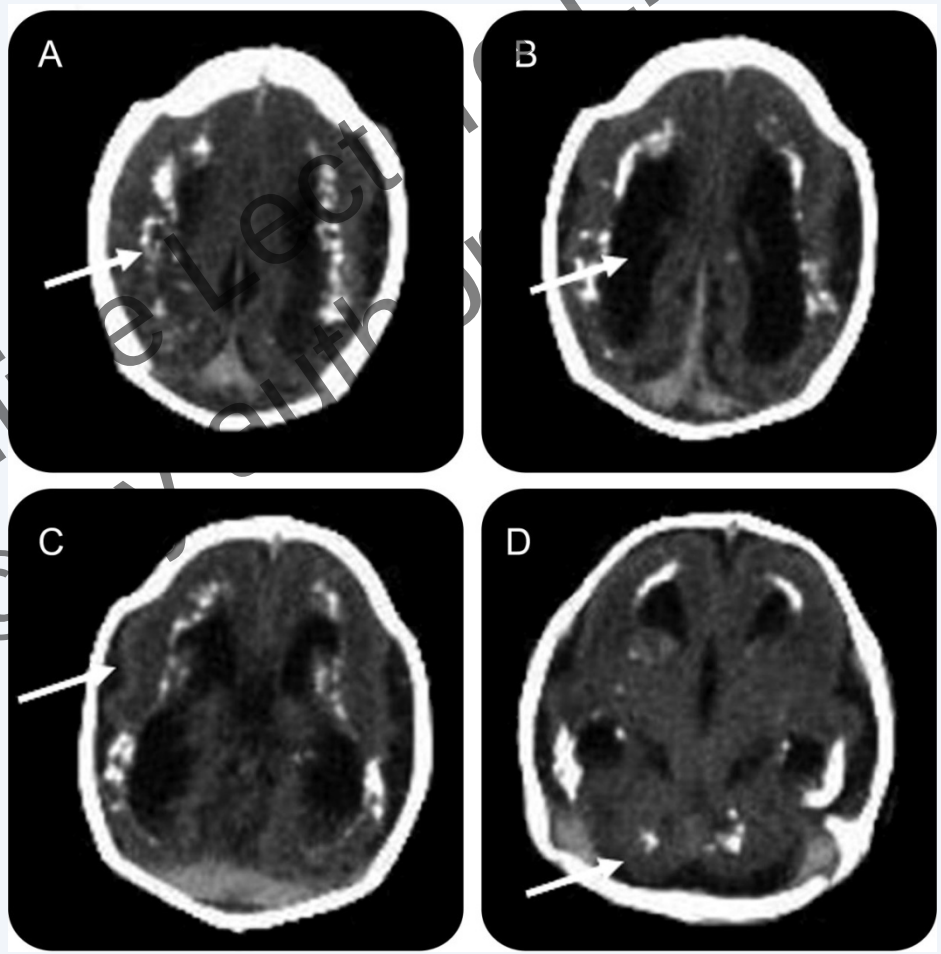
- Clinically evident
- Microcephaly
- Petechiae/ecchymoses
- Dermal erythropoesis
- Retinitis/optic atrophy
- Hepatosplenomegaly
- Jaundice
- Neurologic abnormalities
- Associated lab and imaging results

Expanded meaning:

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

Classic CT findings of brain involvement in symptomatic congenital CMV infection

Axial CT scan of the brain at day 1 of life shows
(A)extensive periventricular calcifications,
(B)ventriculomegaly,
(C)reduced cortical sulcation, and
(D)cerebellar hypoplasia.



From Dhamija & Keating, Neurology 76:e13, 2011.

Congenital CMV Infection Causes Newborn Disease and Lifetime Disability

Newborn Disease	CNS Sequelae
• ~10% of cases • Minor to severe illness • Prolonged hosp., 2-3 weeks • Mortality, ~10%	• 15-25% of cong. CMV • Hearing loss • Mental retardation • Cerebral palsy • Retinitis, optic atrophy

Rates of congenital infection from selected studies that screened >10,000 newborns for CMV

Study	N, screened	Cong CMV %	Sympt %
Saigal, Canada, 1973-1976	15,212	0.4	6.4
Ahlfors, Sweden, 1977-1986	16,474	0.5	18.4
Peckham, London, 1979-1982	14,200	0.3	4.8
Fowler, U.S., 1980-1990	17,163	1.3	7.4
Boppana, U.S., 1991-1997	20,885	1.2	19
Numazaki, Japan, 1997-2002	11,938	0.3	13.5
Yamamoto, Brazil, 2003-2009	12,195	1	10

Sequelae/disability from congenital CMV infection

- Symptomatic at birth: ~50-60% with permanent impairment
- Normal at birth: ~5-15% with disability, mostly hearing loss

Predictors of adverse outcome of congenital CMV infection

- Symptomatic at birth
  - Microcephaly, clinical encephalopathy
  - Chorioretinitis
  - Sensorineural hearing loss
  - SGA
- Abnormal brain imaging
- Type of maternal infection
  - Primary vs nonprimary
- Gestational age at maternal infection
- Viral load in the newborn

Management of the newborn with (symptomatic) congenital CMV infection

- Determine extent of disease
  - Physical exam
  - Audiometry
  - Ophthalmologic exam
  - Brain imaging (ultrasound)
- Supportive care – possibly for thrombocytopenia, respiratory difficulty, encephalopathy, seizures
- Antiviral treatment decision
- Counseling of family
- Transition to long-term follow-up

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	Case reports
No disease	None

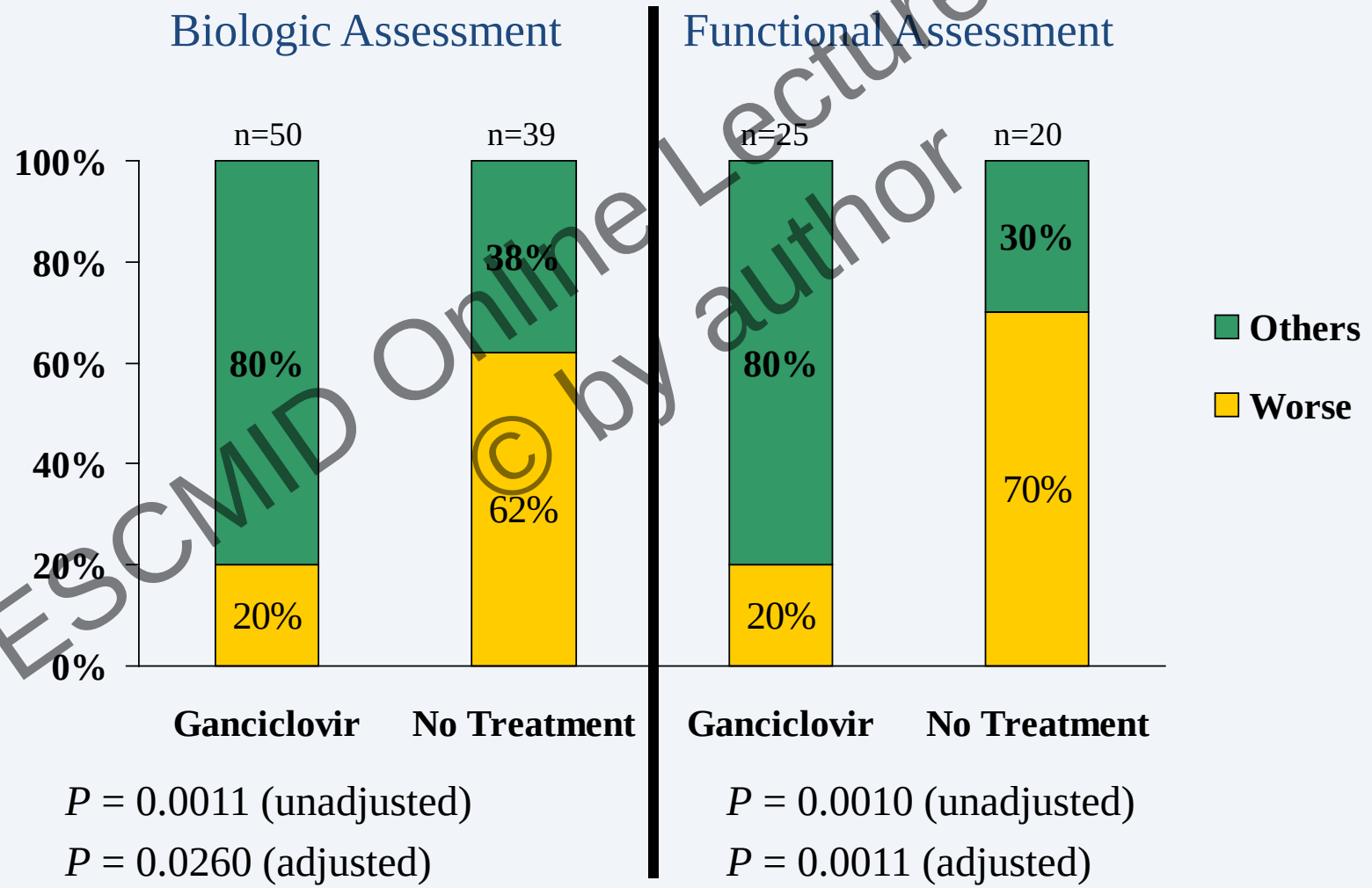
Treatment of newborns with severe symptomatic congenital CMV: ganciclovir vs no treatment

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 age	Ganciclovir (N)	No treatment (N)
6 month	4.5 (35)	7.5 (39)
12 month	10.1 (35)	17.1 (36)

Differences were statistically significant

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, embryolethality, hypoplasia of the testes and seminal vesicles
- Animal carcinogenicity: at 0.1 to 1.4x human drug exposure, multiple tissues, especially reproductive

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

Valganciclovir pharmacokinetics and pharmacodynamics in newborns

- VGCV 16 mg/kg 2x/day achieved similar AUC to GCV 6 mg/kg 2x per day iv
- VGCV decreased viral load or cleared viremia in some subjects
- Some subjects improved or did not have progressive hearing loss
- References
  - Galli et al, Pediatr Infect Dis J, 2007
  - Acosta et al, Clin Pharm Therapeutics, 2007
  - Kimberlin et al, J Infect Dis, 2008
  - Lombardi et al, Eur J Clin Microbiol, 2009
  - Amir et al, Eur J Pediatr, 2010

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

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
- Results to be reported at IDSA October, 2013

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 should replace iv GCV as preferred treatment
- Treatment for 6 months may become the standard (awaiting review and publication).
- Neither GCV nor VGCV have FDA approval for treatment of newborns with congenital CMV

Suggested long-term follow-up of infants with congenital CMV infection

- Serial audiometry to check for late onset or progressive hearing loss
  - 3-4 times during 1st year
  - 2 x during second year
  - Annually until school age
  - More often if abnormal or changing
- Eye examination at birth for all
  - Repeat exam for symptomatic or if abnormal
- Developmental and neurological assessments as part of routine health maintenance
  - Referral for neuropsychological assessment if indicated