NCHAM Webinar Series

Congenital CMV 101: From Prevention to Treatment

Presented by:
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Epidemiologist
Centers for Disease Control and Prevention
## Possible Outcomes of Congenital CMV Infection

### Transient outcomes
- Hepatomegaly
- Splenomegaly
- Jaundice
- Petechia and purpura
- Seizures
- Fetal growth retardation
- Pneumonitis

### Permanent outcomes
- Hearing loss
- Intellectual disability
- Vision loss
- Microcephaly
- Motor disabilities
- Seizures
- Death

Adapted from Stagno, 2001

- Child with cerebral palsy, hearing loss, and mental retardation
- Child with spastic quadraplegic cerebral palsy, vision loss, microcephaly, intracranial calcifications, and epilepsy
- Infant with microcephaly

Infant with microcephaly
US Estimated Annual Congenital CMV Disease Burden

- 30,000 congenital CMV infections
- 3,500 symptomatic infections
- 140 deaths
- \( \geq 5500 \) children with permanent sequelae

Long-term sequelae

Relative Burden of Congenital CMV

Costs > $1 billion in direct medical care each year

- Congenital CMV disease
- Fetal alcohol syndrome
- Down syndrome
- Spina bifida/anencephaly
- Pediatric HIV/AIDS
- Invasive Hib
- Congenital rubella syndrome

Annual Number of U.S. Children with Long-Term Sequelae

Adapted from Cannon & Davis, BMC Public Health, 2005
Congenital CMV is an Invisible Disease

- Mothers do not know when they are infected
- Many infected babies are asymptomatic at birth
- When babies have symptoms, they are often non-specific
- Congenital CMV usually cannot be diagnosed retrospectively

CMV Natural History

- Primary infection
- Latency
- Reactivation
- Recurrence or secondary infection

The Laboratory Vocabulary

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Labelled</th>
<th>Detects</th>
<th>Test format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever been infected</td>
<td>Seropositive</td>
<td>Antibody</td>
<td>ELISA</td>
</tr>
<tr>
<td>At risk for transmission</td>
<td>Shedding or excreting</td>
<td>Virus or viral DNA</td>
<td>PCR or culture</td>
</tr>
</tbody>
</table>
Seroprevalence is higher among:
- Older people
- Females
- Mexican-Americans
- Non-Hispanic Blacks

Bate, CID, 2010
Demographic Risk Factors for Seroconversion

- In the U.S., rates of new CMV infections in susceptibles are much higher in disadvantaged populations such as racial/ethnic minorities and persons of low SES.
Household Transmission Risk

CMV seroprevalence differences

- Seroprevalences among family members of seropositive children are 30-50 percentage points higher than among family members of seronegative children

Staras, J Clin Virol, 2008
### Summary CMV Annual Seroconversion

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Summary annual seroconversion rate (%)</th>
<th>95% confidence interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>2.2</td>
<td>2.1 - 2.4</td>
</tr>
<tr>
<td>Parents with child not shedding CMV</td>
<td>2.1</td>
<td>0.3 - 6.8</td>
</tr>
<tr>
<td>Healthcare workers</td>
<td>2.7</td>
<td>2.3 - 3.2</td>
</tr>
<tr>
<td>Day care providers</td>
<td>8.5</td>
<td>6.1 - 11.6</td>
</tr>
<tr>
<td>Women attending STD clinics</td>
<td>13</td>
<td>10 - 17</td>
</tr>
<tr>
<td>Parents with child shedding CMV*</td>
<td>24</td>
<td>18 - 30</td>
</tr>
</tbody>
</table>

*Annual infection rate of less 25% in this high risk group suggests that CMV is not easily transmitted.

Adapted from Hyde, Rev Med Virol, 2010
## Comparison of Models of Contagiousness

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Force of infection (100 p-y)</th>
<th>Basic reproductive rate</th>
<th>Age of infection (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles Mumps Rubella</td>
<td>Review Ages 11-17</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>Convenience Ages ≥10</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV Griffiths (2001)</td>
<td>Hospital-based Ages 16-40</td>
<td>3.1 and 3.5</td>
<td>2.4 and 2.7</td>
<td>29 and 32 (median)</td>
</tr>
<tr>
<td>CMV Colugnati (2007)</td>
<td>Pop.-based Ages 12-49</td>
<td>1.8</td>
<td></td>
<td>28.7 (mean)</td>
</tr>
<tr>
<td>HSV-2</td>
<td>Pop.-based Ages ≥12</td>
<td>0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Pop.-based Ages ≥10</td>
<td>0.2-1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Pop.-based Ages 6-39</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Colugnati, BMC Infect Dis, 2007
Among children, shedding prevalence peaks at ages 1-2 years.

These are the ages at which children are putting the most fluids into the environment.
CMV Viral Load Data

Viral loads higher in:
- Saliva than in urine
- Children than in adults
- Younger children than in older children

Cannon et al., unpublished data
Summary of CMV Transmission

- CMV is transmitted through direct contact with body fluids
- CMV is not transmitted easily
- Saliva and urine are important fluids for transmission
- Saliva has higher viral loads than urine
- Young children are a major source of infection
- CMV can be transmitted through intimate adult contact
Estimates of congenital CMV-related hearing loss in the United States

Note:
About 30% of HL is bilateral moderate to profound
About 70% of HL is unilateral or mild bilateral

Quality of evidence of benefit from newborn CMV screening
- Good evidence of benefit
- Fair evidence of benefit
- Poor evidence of benefit
- No presumed benefit

About 30% of HL is bilateral moderate to profound
About 70% of HL is unilateral or mild bilateral

Timing of Hearing Loss

Figure. Cumulative SNHL >20 dB thresholds in children with congenital CMV infection according to symptomatic and asymptomatic status at birth ($P < .0001$).

Fowler, J Peds, 1999
Bilateral Moderate to Profound Hearing Loss Attributable to Congenital CMV

18% Congenital CMV

82% Other Causes

Adapted from Grosse, J Clin Virol, 2008
Takeaway Points for Congenital CMV Infection and Outcomes

- Non-primary maternal infection is a major source of congenital infection
- Congenital infection occurs in 0.5%-1% of newborns in the U.S.
- Disabilities occur or develop in 15%-20% of infected newborns
- Congenital CMV is a major cause of childhood hearing loss
Potential Clinical and Public Health Interventions for Congenital CMV

Currently, none of these interventions is routine in the U.S.
<table>
<thead>
<tr>
<th>Probably satisfies</th>
<th>May not yet satisfy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Important health problem</td>
<td>• Suitable test available</td>
</tr>
<tr>
<td>• Recognizable latent or early symptomatic stage</td>
<td>• Test acceptable to population</td>
</tr>
<tr>
<td>• Natural history adequately understood</td>
<td>• Agreed on policy on whom to treat</td>
</tr>
<tr>
<td></td>
<td>• Facilities for diagnosis and treatment available</td>
</tr>
<tr>
<td></td>
<td>• Cost-effective</td>
</tr>
</tbody>
</table>

Grosse, J Clin Virol, 2009
# Laboratory Approaches to Newborn CMV Screening

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried blood spot</td>
<td>PCR from DBS</td>
<td>NBS program already in place</td>
<td>CMV viral load lower in blood, less available specimen</td>
</tr>
<tr>
<td>Saliva</td>
<td>PCR from cheek swab</td>
<td>CMV viral load higher in saliva</td>
<td>Not part of existing NBS program</td>
</tr>
<tr>
<td>Urine</td>
<td>PCR from bagged urine or diaper insert</td>
<td>CMV viral load higher in urine</td>
<td>Not part of existing NBS program</td>
</tr>
</tbody>
</table>

Dollard, J Inherit Metabol Dis, 2010
Pharmaceutical Treatment of Infants with Congenital CMV

- 42 symptomatic infants with central nervous system (CNS) deficits were evaluated for hearing loss.
- 6 weeks IV ganciclovir vs. no treatment
- Ganciclovir recipients were significantly less likely to experience worsening in hearing.
- Two thirds of treated infants had significant neutropenia during therapy.

- Current multi-site trial underway with oral valganciclovir
- Infants need not have CNS deficits to be enrolled

Estimates of congenital CMV-related hearing loss in the United States

- 4,248,000 Live births
- 4,222,512 Children born without congenital CMV infection
- 25,488 Children born with congenital CMV infection
  - 3,262 Children who are symptomatic at birth
    - 2,447 Symptomatic children not diagnosed clinically with congenital CMV
      - 670 Hearing loss at birth
      - 78a Delayed hearing loss < 9 months
      - 78a Delayed hearing loss 9-24 months
    - 75%
  - 222a Delayed hearing loss < 9 months
  - 178a Delayed hearing loss 9-24 months
- 815 Symptomatic children diagnosed clinically with congenital CMV
- 1,067a Delayed hearing loss 24-72 months
- 5.3%
- 222 a Delayed hearing loss < 9 months
- 178 a Delayed hearing loss 9-24 months
- 99.4%
- 0.6%
- 87.2%
- 87.8%
- 5.6%
- 1%
- 1%
- 1%

Note: About 30% of HL is bilateral moderate to profound
About 70% of HL is unilateral or mild bilateral

aBenefit would come from non-pharmaceutical treatment
bBenefit would come from pharmaceutical treatment

Quality of evidence of benefit from newborn CMV screening
- Good evidence of benefit
- Fair evidence of benefit
- Poor evidence of benefit
- No presumed benefit
Proportion of Respondents who Somewhat/Strongly Agreed by CMV Statement

- **I think CMV problems are too rare to worry about,** N=3,785
  - 33%

- **Would want to have baby tested for CMV even if doctor/hospital didn’t do it routinely,** N=3,832
  - 85%

- **Willing to pay $20 to have baby tested for CMV,** N=3,811
  - 87%

- **Would want to know if child has CMV even if he/she never develops problems,** N=3,820
  - 86%

- **Would worry that CMV test would lead to unneeded doctor visits and expenses,** N=3,803
  - 44%

Din, Pediatrics, 2011
Future Directions for Newborn CMV Screening

- Further assessments of DBS assays
- Development of point-of-care assays for saliva and urine
- Evaluation of saliva or urine collection on filter paper cards
- Assessments of psychosocial impacts of screening
- Develop protocols for monitoring and treatment of children who screen positive for CMV at birth
- Pilot studies for feasibility of universal screening
- Pilot studies of targeted CMV screening (e.g., infants who fail hearing screen)
Selected Additional References

- **Vaccines**
  - Krause et al., Vaccine, Vol. 32, p. 4-10 (2013)

- **Prenatal screening/prenatal diagnosis**

- **Behavioral intervention**

- **Prenatal treatment**
Go to cmv.usu.edu to register for the conference, view the conference agenda, and learn more about cmv.
Questions?

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For more information about CMV please visit www.cdc.gov/cmv

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