Controversies in the Diagnosis and Treatment of Cytomegalovirus Induced Hearing Loss

Albert Park, MD
Chief Pediatric Otolaryngology
Department Surgery and Pediatrics
University of Utah
Nondisclosure:

• NIH U01 PI CMV multi-institutional study
• NIDCD R01 co-I Cochlear Implantation
• Valganciclovir – not FDA approved for congenital CMV
Objectives:

• Convince you that CMV is an important topic yet awareness low
• Story of DD
• Epidemiology of cCMV induced hearing loss
• Rationale for diagnosis
• Treatment
• Changing landscape of screening
• What steps you can do
• One interesting research path
Acknowledge:

- ValEAR Team (UCSD)
- Daniela Carvalho (site PI)
- Julie Stickland (audio)
- Alice Dong (site co-PI)
- Jane Duong (Pharmacy)
- Hena Din (Research Coordinator)
Knowledge Amongst Hearing Specialists:

- Expect those who treat pediatric hearing loss should have high fund of knowledge
- Email list serve ASPO and AOS
- 70 respondents
- 100% familiar with CMV
- 83% evaluate and treat pediatric SNHL

Which of the following are routes of transmission for CMV? (Pick all that apply)

<table>
<thead>
<tr>
<th>Route</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kissing</td>
<td>42</td>
<td>61%</td>
</tr>
<tr>
<td>Changing diapers</td>
<td>32</td>
<td>46%</td>
</tr>
<tr>
<td>Breast milk</td>
<td>37</td>
<td>53%</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>43</td>
<td>61%</td>
</tr>
<tr>
<td>Sexual Intercourse</td>
<td>36</td>
<td>51%</td>
</tr>
<tr>
<td>Sharing food with children</td>
<td>33</td>
<td>47%</td>
</tr>
<tr>
<td>I do not know</td>
<td>20</td>
<td>29%</td>
</tr>
</tbody>
</table>

- 41% more than 80% correct
- 56% more than 50% correct
- 20% with 0 correct
<table>
<thead>
<tr>
<th>True</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 15% of children with asymptomatic cCMV can develop hearing loss</td>
<td>27</td>
<td>39%</td>
</tr>
<tr>
<td>Up to 75% children with symptomatic cCMV will develop hearing loss</td>
<td>21</td>
<td>30%</td>
</tr>
<tr>
<td>cCMV is the most common environmental cause of hearing loss</td>
<td>33</td>
<td>47%</td>
</tr>
<tr>
<td>False</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 30 % of children with asymptomatic cCMV can develop hearing loss</td>
<td>24</td>
<td>34%</td>
</tr>
<tr>
<td>Up to 95% of children with symptomatic cCMV will develop hearing loss</td>
<td>5</td>
<td>7%</td>
</tr>
<tr>
<td>I do not know</td>
<td>14</td>
<td>20%</td>
</tr>
</tbody>
</table>

- 23% had at least 75% correct answers
- 54% at least 50% correct
<table>
<thead>
<tr>
<th>True</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried blood spot CMV PCR at any age</td>
<td>23</td>
<td>33%</td>
</tr>
<tr>
<td>Dried blood spot (DBS) prior to 3 weeks of age</td>
<td>28</td>
<td>41%</td>
</tr>
<tr>
<td>Urine PCR/culture prior to 3 weeks of age</td>
<td>44</td>
<td>63%</td>
</tr>
<tr>
<td>Saliva CMV Culture with confirmation with Urine PCR/Culture prior to 3 weeks of age</td>
<td>44</td>
<td>63%</td>
</tr>
<tr>
<td>False</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serologic CMV IgG testing at any age</td>
<td>11</td>
<td>16%</td>
</tr>
<tr>
<td>Urine PCR/culture at any age</td>
<td>10</td>
<td>14%</td>
</tr>
<tr>
<td>Saliva CMV Culture at any age</td>
<td>6</td>
<td>9%</td>
</tr>
<tr>
<td>Serologic IgM testing at any age</td>
<td>7</td>
<td>10%</td>
</tr>
<tr>
<td>I do not know</td>
<td>14</td>
<td>20%</td>
</tr>
<tr>
<td>Question</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
<td>----</td>
</tr>
<tr>
<td>Which test(s) can definitively establish a diagnosis for cCMV in children &gt;3 weeks of age?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>True</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dried blood spot testing</td>
<td>25</td>
<td>36%</td>
</tr>
<tr>
<td><strong>False</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology for IgM and IgG for CMV</td>
<td>27</td>
<td>39%</td>
</tr>
<tr>
<td>Imaging studies including CT and MRI</td>
<td>9</td>
<td>13%</td>
</tr>
<tr>
<td>Urine PCR/culture for CMV</td>
<td>16</td>
<td>23%</td>
</tr>
<tr>
<td>Saliva culture for CMV</td>
<td>8</td>
<td>11%</td>
</tr>
<tr>
<td>I do not know</td>
<td>20</td>
<td>29%</td>
</tr>
<tr>
<td>Practice Patterns</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>--------</td>
<td>----</td>
</tr>
<tr>
<td>Do you incorporate any type of cCMV testing for children with SNHL?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>8</td>
<td>11%</td>
</tr>
<tr>
<td>Sometimes</td>
<td>22</td>
<td>31%</td>
</tr>
<tr>
<td>Rarely</td>
<td>20</td>
<td>29%</td>
</tr>
<tr>
<td>Never</td>
<td>20</td>
<td>29%</td>
</tr>
<tr>
<td>Do you offer DBS CMV PCR testing for your patients?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>23%</td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>76%</td>
</tr>
<tr>
<td>Do you offer antiviral therapy or refer to infectious disease specialist for antiviral therapy for cCMV infected children?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, only if they are symptomatic</td>
<td>15</td>
<td>21%</td>
</tr>
<tr>
<td>Yes, for symptomatic children and asymptomatic children that fail the hearing screen</td>
<td>28</td>
<td>40%</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td>I don't know</td>
<td>15</td>
<td>21%</td>
</tr>
</tbody>
</table>
The Story of DD and Hearing Targeted CMV Screening in Utah:

- 19 mo child progressively worsening hearing
- Failed newborn hearing screen and automated ABR
- Click ABR at 3 weeks: 30 dB nHL right and 25 dB nHL left
- Audiology recommended FU 9 mo.
- Enlarged ventricles 34 wks gestation in utero U/S
- U/S at birth- “germinolytic” cystic changes- in utero insult
Case History DD and Utah CMV Screening:

- Normal Otologic examination
- Repeat ABR right profound and left moderate SNHL
- Saliva Cytomegalovirus (CMV) PCR- positive
- Neonatal Dry Blood Spot CMV PCR- positive
- 6 week course of valganciclovir
- Left ear worsened to profound
- Bilateral Cochlear Implantation
- Explanted and reimplanted 2 years later
Public Health Impact of CMV

- Herpes virus
- Seroprevalence 50 – 90% of adults
- Increases with age
- Varies btw and within populations

Colugnati et al. BMC Infectious Diseases 2007 7:71
Public Health Impact of CMV

- Species specific (only infects humans)
- Most common congenital infection worldwide- 0.7% ALL live births
- Most common cause of nonhereditary SNHL
- May account up to 20% pediatric SNHL
- Cost C-CMV greater than $4 billion/year in US
Incidence of Congenital Conditions

“Higher risk of Congenital CMV infection that all 29 screened neonatal diseases combined”
Overall risk of CNS complications related to congenital infections

Congenital CMV

- LOW prevalence population - 1 / 1,000 live births
- HIGH prevalence population - 1 / 270 live births

Zika virus

- Brazil - 1 / 800 live births
- US - 1 / 71,684 live births
  (102 reported Zika cases to CDC out of 7.9 million live births 2016-2017)

US Congress funded $1.1 Billion for Zika Research and Prevention
Sept 2016
Transmission Mother to Fetus:

- Seronegative moms (Primary infection)
- Seropositive moms (Secondary infection)
- Infant presentation
  - Symptomatic (evident at birth)
  - Asymptomatic (silent at birth)
  - CHIP (CMV infected Hearing Impaired Person)
CMV: Symptomatic Congenital Infection

- Approximately 10%
- Fetal demise
- Prematurity
- Common features:
  - Hepatomegaly
  - Splenomegaly
  - Petechiae
  - IUGR
  - Jaundice
  - Microcephaly
  - Chorioretinitis
  - Sensorineural hearing loss (50%)
CMV: Asymptomatic Congenital Infection

- Approximately 70%
- No signs or symptoms
CHIP: CMV Hearing Impaired Only Person

- **CHIP**: 5–15% have sensorineural hearing loss that can be evident at birth or appear later in childhood
Transmission:

- Child with congenital CMV will shred virus for months or years—“contagious”
- Transmission body fluids
- Pregnant moms or immunocompromised patient at risk for cCMV
- Classic- toddler gets infection daycare then shares it with pregnant mom
- Hand washing, avoid kissing on lips, no sharing utensils
- 5000 seronegative pregnant women—behavioral intervention > 50% drop expected rate seroconversion

Vauloup-Fellous et al, 2009
Hysteria of CMV:

- Audiologists not want to test cCMV infected kids
- Daycare and Schools not wanting to allow cCMV infected kids to attend
- Not the recommendation National CMV Foundation!
- Any child or adult may be seropositive
- Academy position statement
Hearing Loss Disease Burden Symptomatic Asymptomatic CMV and CHIP in the US (annual):

- cCMV-infected newborns (19,600)
  - Symptomatic (2000/yr)
    - Hearing loss (1000/yr)
  - Asymptomatic (14,000/yr)
    - Normal Hearing (1000/yr)
  - CHIP (3600/yr)

Characteristics of CMV Induced Hearing Loss:

CMV Diagnosis:

- Best if testing when child less than 2-3 weeks of age
- Postnatal infection not associated with hearing loss
- Serology – confounding from maternal IgG and IgM-poor sensitivity
- Urine culture or PCR. Saliva- breastmilk contamination
- Positive DBS definite for CMV but poor sensitivity
Saliva vs Urine for CMV Screening:

• Two large studies indicate high false positive rate with saliva PCR testing
• Saliva obtained immediately after birth
• 26-41% false positive
• Associated with lower viral load BUT low viral load seen in both true positive and false positive samples
• If you obtain a positive saliva PCR result, you should obtain a confirmatory urine PCR before the child is 3 weeks of age
• Consider just ordering a urine CMV PCR

Puhakka et al. JPIDS 2018; Leruez-Ville et al. Clin Infect Dis 2017
What is the Sensitivity of DBS Testing?

- CHIMES March 2007-2008
- 7 US Medical Centers
- Compared saliva rapid culture to DBS CMV PCR (single and double primer)
- 92/20,448 infants CMV based on saliva cx
- Sensitivity DBS:
  - Single primer- 28.3%
  - Double primer- 34.4%
- Should have compared to urine culture or PCR testing?
- Schleiss and Dollard CDC study on DBS

Boppana S et al. JAMA 2010; 303(14): 1375-1382.
Role of CMV Testing in Pediatric Hearing Loss:

Role of CMV Testing in Pediatric Hearing Loss:

BACKGROUND

In the United States and other developed countries, approximately one to two children per 1,000 have moderate to profound bilateral sensorineural hearing loss (SNHL). SNHL can be broadly classified as hereditary, acquired, or idiopathic. Up to 35% of children with SNHL have a history suggestive of acquired environmental etiology. Physical examination can reveal dysmorphic features suggestive of syndromes that are associated with SNHL. However, in the majority of children, history and physical examination alone will not reveal the cause of SNHL. The practitioner is then faced with a plethora of diagnostic options to determine the etiology of the SNHL.

In addition to a complete history, physical examination, and audiometric testing, the evaluation of bilateral pediatric SNHL has typically included a comprehensive battery of laboratory tests, radiologic studies, electrocardiogram (ECG), and more recently, genetic testing, as well as ophthalmology evaluation and referral to a clinical geneticist. The necessity of exhaustive testing remains controversial, and recent studies have demonstrated that a sequential diagnostic algorithm is sensitive and clearly more cost-effective than a comprehensive testing approach.

LITERATURE REVIEW
Role of CMV Testing in Pediatric Hearing Loss:

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Chart and database review
- Children 3 yrs or younger
- May 2008-September 2013
- Sequential diagnostic paradigm

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

• Those with negative CMV testing underwent imaging, genetics evaluation +/- EKG

• Cost analysis of the diagnostic testing (Multihospital Standardized Cost Accounting System):
  
  MRI t-bone $1591
  
  GJB2 testing $611
  
  CMV PCR saliva or urine $66

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

SNHL Etiology Based on CMV, Imaging and Genetic Evaluation

Largest group with a known etiology 30%

N=83

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Breakdown of CMV Patients (n=25)
- Sixteen – confirmed CMV diagnosis
- Six of sixteen diagnosed via DBS testing
- Nine- probable CMV diagnosis

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- Characteristics of CMV Induced SNHL Patients:
- Average age initial evaluation 352 days (range 24-1387 days)
- Only 5 infants evaluated at one month of age or younger

Cost Estimates Using Different Approaches for SNHL Evaluation:

The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

• Conclusion:
• Diagnostic Paradigm incorporating early CMV testing has high yield (30%)
• DBS testing can diagnose infants > 3 weeks of age
• Average age of initial evaluation significant challenge for diagnosis
• Early CMV testing – lower cost than imaging or genetic testing
Role of CMV Testing in Pediatric Hearing Loss:

International Pediatric Otolaryngology Group (IPOG) consensus recommendations: Hearing loss in the pediatric patient

Bryan J. Liming, John Carter, Alan Cheng, Daniel Choo, John Curotta, Daniela Carvalho, John A. Germiller, Stephen Hone, Margaret A. Kenna, Natalie Loudon, Diego Preciado, Anne Schilder, Brian K. Reilly, Stephane Roman, Julie Strychowsky, Jean-Michel Triglia, Nancy Young, Richard J.H. Smith

PlumX Metrics
DOI: http://dx.doi.org/10.1016/j.ijpeds.2016.06.016

Abstract

Objective
To provide recommendations for the workup of hearing loss in the pediatric patient.

Methods
Expert opinion by the members of the International Pediatric Otolaryngology Group.

Results
Consensus recommendations include initial screening and diagnosis as well as the workup of sensorineural, conductive and mixed hearing loss in children. The consensus statement discusses the role of genetic testing and imaging and provides algorithms to guide the workup of children with hearing loss.

Conclusion
The workup of children with hearing loss can be guided by the recommendations provided herein.
*Single gene testing is not supported by the evidence in most cases. If comprehensive genetic testing is not available, then the genes selected for single gene testing should be guided by audiometric phenotype and ethnicity.
DD=Daisy Doutre

Sara Doutre
Board National
CMV Foundation

Former Representative
Ronda Menlove
Challenge of CMV testing in the “Older” (> 3 weeks) Hearing Impaired Child:

Without HT-CMV

With HT-CMV

Awareness of CMV:

- National survey 4184 participants (HealthStyles survey)
- 7% men and 13% women had heard of CMV

Utah Legislative Efforts:
Utah House Bill 81 (July 2013):

• DOH public education program to inform caregivers about CMV

• DOH education for providers and other organizations offering children’s programs

• Medical practitioners to test infants < 3 wks of age who fail two newborn screening tests for CMV and inform the parents cx and rx
National Map for Hearing Targeted Early CMV Screening (HT-CMV) 2013:
National Map for Hearing Targeted Early CMV Testing (HT-CMV) 2018:

Congenital CMV Legislation in the United States
May 16, 2018

Key: Law enacted = Law proposed = Law drafted = Stakeholder interest in legislation
AAP Newsletter:

- December 2015
- Department Practice and Division of Quality
- Response to legislative efforts on CMV Testing for newborns who fail an infant hearing test
AAP Newsletter:

• “No evidence ... supports treatment of newborns who test positive for CMV but are otherwise asymptomatic...”
AAP Newsletter:

• “Treatment currently is limited to off-label use of the antiviral drug valganciclovir which carries potential risks”
AAP Newsletter:

• “Clinicians practicing in the best, most up-to-date fashion ... face increased medical practice liability risk. If states continue down this path, it may threaten our ability to practice medicine in a manner consistent with the best available science...”
AAP Views:

• “These kinds of laws... may drive such treatment ...parents and providers often will feel that they must do something...In so doing, we may harm the children we are trying to help...”
What is Treatment?

- **treatment** [trēt´ment]
- 1. the management and care of a patient; see also **CARE**.
- 2. the combating of a disease or disorder; called also **therapy**.

Treatment Does Not Need to Mean Just Antiviral Therapy!
The Evidence for HT-CMV Screening is...

- Helps the family of hearing impaired child
- Increases Detection rate of **Symptomatic** CMV infected children
- Focuses attention on CMV infected infants for progressive hearing loss
- Improves time to diagnose hearing loss for all newborns who fail their hearing screen
- May improve hearing outcomes of CMV hearing impaired infants
Helping the Family:

“Blindness separates people from things; deafness separates people from people.”

Helen Keller
Helping the Family:

• Parental response – surprise, sadness and concern

• Questions- cause of the hearing loss, likely impact on new family member, options for treatment

Kurtzer-White & Luterman, 2003; Yoshinaga-Itano & DeUzcategui, 2001; Young & Tattersall, 2007
Helping the Family even if the child doesn’t present with hearing loss:

- “I would want to have my baby tested for CMV even if my doctor or hospital didn’t do it routinely.” (84%)
- “I would want to know if my child has CMV even if he or she never develops problems.” (84%)
- “I would be willing to pay $20 to have my baby tested for CMV.” (87%)

Helping the Family:

• CMV testing requires child must be less than 3 weeks of life!
• Unlike Genetic testing, you cannot decide to wait until the child is older to make the diagnosis
• Families want testing and are willing to pay for it.
Increasing the Detection Rate of the Symptomatic CMV Infected Infant:

- 10% fetal demise
- Prematurity
- Common features:
  - Hepatomegaly
  - Splenomegaly
  - Petechiae
  - Jaundice
  - Microcephaly
  - Chorioretinitis
  - Sensorineural hearing loss (50%)
Increasing the Detection Rate of the Symptomatic CMV Infected Infant:

- Minority symptomatic CMV cases diagnosed clinically!
- Vaudry et al., 2014; Townsend et al., 2011; McMullan et al. 2011
- <10% (Sorichetti et al. 2015)
Treating the Symptomatic cCMV Infected Infant:

• Symptomatic CMV is treatable!
• General consensus that this group would benefit from antiviral therapy (valganciclovir or VGCV)
Valganciclovir (VGCV):

- L-valyl ester prodrug of ganciclovir
- Blocks viral replication
- After oral administration, it is rapidly converted to ganciclovir by intestinal and hepatic esterases
- FDA approved to prevent CMV disease for pediatric patients receiving heart or kidney transplants
- Not FDA approved for treatment of cCMV
6 Weeks vs. 6 Months Valganciclovir Hearing Outcomes @ Two year Followup

6 Weeks of Treatment

- Improved or Remained Normal: 64%
- Worse or remained abnormal: 36%

P = 0.04

6 Months of Treatment

- Improved or Remained Normal: 77%
- Worse or remained abnormal: 23%

Kimberlin et al. NEJM 2015
### 6 Weeks vs. 6 Months Valganciclovir Bayley III Outcomes 24 mo.

<table>
<thead>
<tr>
<th></th>
<th>6 Week Therapy</th>
<th>6 Month Therapy</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Composite</td>
<td>76.0±2.6</td>
<td>84.4±2.6</td>
<td>0.0236</td>
</tr>
<tr>
<td>Language Composite</td>
<td>72.5±2.9</td>
<td>84.6±2.9</td>
<td><strong>0.0037</strong></td>
</tr>
<tr>
<td>Receptive Communication Scale</td>
<td>5.2±0.5</td>
<td>7.3±0.5</td>
<td><strong>0.0027</strong></td>
</tr>
<tr>
<td>Expressive Communication Scale</td>
<td>5.5±0.5</td>
<td>7.3±0.5</td>
<td>0.0158</td>
</tr>
<tr>
<td>Motor Composite</td>
<td>74.1±3.2</td>
<td>85.5±3.3</td>
<td>0.0130</td>
</tr>
<tr>
<td>Fine Motor Scale</td>
<td>6.4±0.6</td>
<td>8.0±0.6</td>
<td>0.0566</td>
</tr>
<tr>
<td>Gross Motor Scale</td>
<td>5.3±0.5</td>
<td>7.0±0.5</td>
<td>0.0198</td>
</tr>
</tbody>
</table>

P-values < 0.0071 (≈0.05/7) considered statistically significant using Bonferroni adjustment for multiple testing.
Outcomes HT-CMV Screening for Detecting sCMV Kids (Utah):

• Two years following implementation
• 5 sCMV infants diagnosed
• Would not have been diagnosed otherwise
Focusing Attention on CHIP and “Asymptomatic” at Risk for Progressive Hearing Loss:

• cCMV infected hearing impaired > 50% risk for progressive hearing loss
• “Asymptomatic” cCMV infected infants have a 4 fold greater risk for hearing loss than uninfected controls
• Identification of CHIP or asymptomatic CMV kids enables us to focus attention

Focusing on CHIP or “Asymptomatic” Infants:

• Example of Tracking hearing thresholds in a CMV infected child:
Impact HT-CMV Testing on Diagnostic Hearing Testing:

- Timely diagnostic hearing evaluation 56% (2 years prior) and 77% (2 years after law)!
- After the law, 86.6% diagnostic hearing evaluation among CMV screened vs 61.5% diagnostic hearing testing among non-CMV screened group
- HT-CMV benefits not just CMV infected but ALL children who fail their newborn hearing screen

Importance of Early Identification:

Average total language quotient for children with normal cognition by category of hearing loss and age of identification. Solid bars = by 6 mo; shaded = after 6 mo.

TABLE 1 Summary of Outcome Measures Reported by UNHSI Programs

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Weighted % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns screened before discharge</td>
<td>92 (25–100)</td>
</tr>
<tr>
<td>Newborns who did not pass screening before discharge</td>
<td>4 (1–34)</td>
</tr>
<tr>
<td>Newborns who were referred for a diagnostic evaluation</td>
<td>2 (1–7)</td>
</tr>
<tr>
<td>Infants who needed a diagnostic evaluation and received one</td>
<td>62 (15–95)</td>
</tr>
<tr>
<td>Infants who needed a diagnostic evaluation and received one by the age of 3 mo</td>
<td><strong>52 (5–93)</strong></td>
</tr>
<tr>
<td>Infants who did not pass the hearing screening who had a medical home</td>
<td>80 (5–100)</td>
</tr>
<tr>
<td>Infants with confirmed hearing loss linked to EI</td>
<td>68 (10–100)</td>
</tr>
<tr>
<td>Infants with confirmed hearing loss linked to family-to-family support</td>
<td>40 (5–100)</td>
</tr>
</tbody>
</table>

*States and territories reported estimated percentages, which are weighted by the number of live births reported by the state or territory. States did not report estimates for all measures.*

*This measure reflects the percentage of infants referred for diagnostic evaluation as a result of nonpass results in the hospital before discharge or nonpass results at an outpatient rescreening.*

*Some programs reported rates that reflect the percentage of children referred to EI or family-to-family support, whereas others reported rates that reflect the percentage of children who received services through EI or family-to-family programs. When both rates were reported, we recorded the percentage that received services.*

Utah Survey of Parental Awareness and Knowledge AFTER Utah CMV Law

- n = 356 parents in ENT clinic
- M:F 53%:47%
- Mean age child 27 months (2 weeks to 18 years)
- 65% children -24 months or younger
Attitudes about CMV Screening

“Would want to have my baby tested even if my doctor/hospital didn't do it routinely”

- Agree or Strongly Agree: 11%
- Neutral: 50%
- Disagree or Strongly Disagree: 39%

“Would want to know if my child has CMV even if he or she never develops problems”

- Agree or Strongly Agree: 9%
- Neutral: 20%
- Disagree or Strongly Disagree: 71%
Attitudes about CMV Screening

"Would be willing to pay $20 to have my baby tested for CMV"

- 70% Strongly Agree or Agree
- 22% Neutral
- 8% Strongly Disagree or Disagree

"Would be more worried about the stigma associated with a CMV diagnosis than about the health effects of CMV"

- 62% Strongly Disagree or Disagree
- 30% Neutral
- 8% Strongly Agree or Agree
Attitudes about CMV Screening

"would worry that the CMV test would lead to unneeded doctor visits and expenses"

- 55% Strongly Disagree or Disagree
- 31% Neutral
- 14% Strongly Agree or Agree
Parents’ Knowledge of CMV Law

Most parents were unfamiliar with the law

- **required by law in Utah if failed newborn hearing screen**
  - Correctly
  - Incorrectly
  - Not Sure

- **required by law of all newborns**
  - Correctly
  - Incorrectly
  - Not Sure
Parents’ Knowledge of CMV

CMV is not very contagious

CMV is a common virus that can infect almost anyone
Parents’ Knowledge of CMV

spread through contact with body fluids

- Correctly
- Incorrectly
- Not Sure
What about Antiviral Therapy of CHIP?

- 26 day old infant presented with CMV induced SNHL
- Failed NBHS
- Saliva CMV PCR @ 3 wks age- positive
- ABR- normal right and left profound SNHL
- Ophthalmology exam- normal
- HUS-normal
Rationale for Antiviral Therapy for CHIP:

- VGC x 6 weeks
- FU audio 2+ yrs after rx-stable hearing
- Speech progressing normally
The Controversy with VGCV for CHIP:

“Antiviral therapy is not the standard of care of infants with cCMV infection who have isolated SNHL as there are insufficient data to support the safety or efficacy of treating these infants.”

Joseph Bocchini, Jr., M.D.
Professor and Chairman
Department of Pediatrics, LSU
NIH Valganciclovir Ear Trial:

- **Aim 1:** Compare the hearing and language outcomes of cCMV-infected with isolated hearing loss treated with VGCV to untreated infants via a multi-institutional double-blinded placebo controlled clinical trial.

- **Aim 2:** To evaluate the safety of antiviral VGCV therapy for cCMV-infected infants with isolated hearing loss.

- **Aim 3:** Evaluate the pharmacokinetics of valganciclovir using pharmacometric modeling to develop a population pK model.
Study Design:

Screening
Key Inclusion Criteria:
CMV Positive Hearing Impaired Only Infants (1-6 months)

Randomization
Arm 1: VGC
Arm 2: Placebo

Primary Endpoint (Maximal Worsening Ear Change in Hearing)

Day 0

8 mo post-randomization

cCMV Hearing Impaired Only (CHIP) Infants Randomized to Valganciclovir (VGC) or Placebo
Current Status:

- FDA approved May 2017
- UU IRB approved May 2017
- NIDCD- LOA July 2017 as U01
- Genetech- subcontract Nov. 2017
- Budget approved by NIDCD Feb 2018
- Training June 2018
- Sites contracts -finalizing
- Enrollment- soon
Over Thirty Institutions Starting HT-CMV Screening!
Take Home Message:

• “No There is evidence ... supports “treatment” of newborns who test positive for CMV but are otherwise asymptomatic...including those w HL”

  a. Provides providers and parents etiology for SNHL
  b. Increases opportunity to dx Sx cCMV patient
  c. Focus at risk patients (asymptomatic or CHIP) for progressive loss
  d. Improves time to diagnose hearing loss for ALL infants who failed their newborn hearing screen
  e. Role of antiviral rx- pending (ValEAR Trial)
<table>
<thead>
<tr>
<th>Practice Patterns</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you incorporate any type of cCMV testing for children with SNHL?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>8</td>
<td>11%</td>
</tr>
<tr>
<td>Sometimes</td>
<td>22</td>
<td>31%</td>
</tr>
<tr>
<td>Rarely</td>
<td>20</td>
<td>29%</td>
</tr>
<tr>
<td>Never</td>
<td>20</td>
<td>29%</td>
</tr>
<tr>
<td>Do you offer DBS CMV PCR testing for your patients?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>23%</td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>76%</td>
</tr>
<tr>
<td>Do you offer antiviral therapy or refer to infectious disease specialist for antiviral therapy for cCMV infected children?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, only if they are symptomatic</td>
<td>15</td>
<td>21%</td>
</tr>
<tr>
<td>Yes, for symptomatic children and asymptomatic children that fail the hearing screen</td>
<td>28</td>
<td>40%</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>17%</td>
</tr>
<tr>
<td>I don't know</td>
<td>15</td>
<td>21%</td>
</tr>
</tbody>
</table>
Hearing Targeted Early CMV Screening:

Should Infants Who Fail Their Newborn Hearing Screen Undergo Cytomegalovirus Testing?

Albert H. Park, MD; Angela Shoup, PhD

**BEST PRACTICE**

Given the current evidence available, it is recommended that infants who fail their newborn hearing screening should undergo CMV testing.

Screening all Newborns in California?

• Universal almost 500,000 vs HT-CMV 5000 annually in California

• Logistical challenge- personnel costs, transport, laboratory infrastructure, insurance coverage

• Educating parents/personnel- approx. 85% asymptomatic
What About Universal CMV Screening?

Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy

William D Rawlinson, Suresh B Boppana, Karen B Fowler, David W Kimberlin, Tiziana Lazzarotto, Sophie Alain, Kate Daly, Sara Doutré, Laura Gibson, Michelle L Giles, Janelle Greenlee, Stuart T Hamilton, Gail J Harrison, Lisa Hui, Cheryl A Jones, Pamela Palasanthiran, Mark R Schleiss, Antonia W Shand, Wendy J van Zylen

The group recommended that consideration should be given to universal neonatal cytomegalovirus screening to enable early detection of congenital cytomegalovirus-infected infants, facilitating early detection and intervention for sensorineural hearing loss

Universal cCMV vs HT-CMV Approaches:

• Ontario using universal DBS cCMV screening as standard of care
• Several states and multiple institutions implementing HT-CMV
• Cost and logistics
• “Normal” cCMV infants difficult to manage—one-third in HT-CMV cohort
Are We Missing a Lot of CHIP Kids with HT-CMV Screening?

A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening

Karen B. Fowler, DrPH, a Faye P. McCollister, EdD, b Diane L. Sabo, PhD, c Angela G. Shoup, PhD, d Kris E. Owen, AuD, d Julie L. Woodruff, AuD, e Edith Cox, AuD, f Lisa S. Mohamed, AuD, f Daniel I. Choo, MD, g Suresh B. Boppana, MD, h on behalf of the CHIMES Study

Fowler et al. Pediatrics 2017
Are We Missing a Lot of CHIP Kids with HT-CMV Screening?

- NBHS identified 57% infants who had CMV-related SNHL in newborn period
- **43%** cCMV infants not identified via HT-CMV
- Used saliva for cCMV screening
- Newborn hearing screening methodology not presented
- Not clear methodology diagnostic ABR testing
- Need validation of newborns diagnosed with ABR testing with behavioral testing

Fowler et al. Pediatrics 2017
Are We Missing a Lot of CHIP Kids with HT-CMV Screening?

• 4/178 cCMV from HT-CMV with hearing loss-no significant difference from those identified from universal screening (Roth et al. Arch Dis Child Fetal Neonatal Ed 2017)

• 11,861 Brazilian newborns universal CMV screening AND hearing screening- 8 diagnosed with cCMV and SNHL. HT-CMV screening detected 7/8. No later onset of progressive SNHL FU 18 mo (Yamamoto et al. CMV Public Policy Meeting, 2018)
Cost Effectiveness of Early CMV Screening:

Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection

Soren Gantt, MD, PhD, MPH; Francois Dionne, PhD; Fred K. Kozak, MD; Oran Goshen, MD; David M. Goldfarb, MD; Albert H. Park, MD; Suresh B. Boppana, MD; Karen Fowler, DrPH
Cost Effectiveness Universal or HT-CMV Approaches:

Table 4. Estimated Mean Incremental Costs per Newborn to Identify Cases of cCMV Infection and Related Hearing Loss

<table>
<thead>
<tr>
<th>Screening Strategy, $a</th>
<th>Universal</th>
<th>Targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/Test</td>
<td>2000</td>
<td>566</td>
</tr>
<tr>
<td>50/Test</td>
<td>10,000</td>
<td>2,832</td>
</tr>
<tr>
<td>Cost to identify 1 cCMV infection</td>
<td>27,460</td>
<td>975</td>
</tr>
<tr>
<td>Cost to identify 1 cCMV-related hearing loss</td>
<td>40,641,572</td>
<td>3,916</td>
</tr>
<tr>
<td>Cost to prevent 1 cochlear implantb</td>
<td>12,620,277</td>
<td>271,947</td>
</tr>
</tbody>
</table>

Abbreviation: cCMV, congenital cytomegalovirus.

a All costs are in 2016 US dollars.
b Assumes valganciclovir hydrochloride treatment of only symptomatic newborns, calculated as the number of newborns who needed to be screened to prevent 1 cochlear implant case multiplied by the incremental cost of screening, follow-up, and valganciclovir per newborn screened.

Gantt et al. JAMA Pediatrics 2017

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Selective</th>
<th>Universal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs (2001 US dollars)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cost of detection of deafness in cohort†</td>
<td>$69,200</td>
<td>$671,200</td>
<td>$2,122,780</td>
</tr>
<tr>
<td>Cost per infant whose deafness is diagnosed by 6 mo</td>
<td>$2,230</td>
<td>$10,100</td>
<td>$44,300</td>
</tr>
<tr>
<td>Lifetime costs of all care related to deafness and lost productivity</td>
<td>$116,980,800</td>
<td>$115,520,600</td>
<td>$114,648,300</td>
</tr>
<tr>
<td>Cost per deaf child with normal language outcomes</td>
<td>$2,215,500</td>
<td>$1,978,100</td>
<td>$1,769,300</td>
</tr>
<tr>
<td>Incremental cost or saving (2001 US dollars)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incremental cost per infant whose deafness is diagnosed 6 mo†</td>
<td>$16,400</td>
<td>$44,300</td>
<td></td>
</tr>
<tr>
<td>Incremental total savings over lifetime of deaf cohort†</td>
<td>$1,460,200</td>
<td></td>
<td>$872,300</td>
</tr>
</tbody>
</table>

Keren et al. Pediatrics 2002
What About Targeted Screening Beyond Just Hearing Screening?

- Benefit from antiviral
- N=349 patients
- Targeted Screening
- 19/349 (5.4%) cCMV +
- IUGR (47.1%)
- NBHS fail (11.8%)
- Thrombocytopenia (11.8%)
What Can You Do?

• Start HT-CMV and NICU/newborn testing
• Talk to your Colleagues, Audiologists, Pediatricians and Newborn Medical Directors
• Almost 100 hospitals performing HT-CMV testing
• Implement DBS CMV PCR testing
• Every state has DBS that can be tested for CMV
What about Surveillance?

If any of the following present:
1) Mother positive for CMV infection during pregnancy
2) Abnormal head size (OFC <10th %ile OR >90th %ile at birth)
3) Intrauterine growth restriction (weight <10th %ile for gestational age)
4) Unexplained hydrops
5) Intracranial OR intraabdominal calcifications on first imaging exam
6) Unexplained hepatomegaly OR splenomegaly (>1 cm below the right or left costal margin)
7) AST or ALT >100 U/L OR unexplained direct bilirubin >1.0 mg/dL
8) Petechial rash or blueberry muffin rash at any time
9) Leukomalacia, polymicrogyria, lissencephaly, pachygyria, schizencephaly
10) Unexplained persistent thrombocytopenia (platelets < 100k/mm3)
11) Failed hearing screen

Send urine CMV PCR (obtain by 21 days of life when possible)

If CMV +, perform all of the following tests:
- CBC + differential
- CMP
- Ophthalmology (inpatient or outpatient) within 2 weeks of test
- Head ultrasound
- Hearing: Diagnostic ABR, OAE (Tympanometry and Bone if indicated)
- Refer to Early Intervention

ASYMPTOMATIC if all of:
- Normal ophthalmology exam
- Normal ABR*
- Normal head ultrasound
- Normal platelet count
- No hepatosplenomegaly
- Normal liver function

*Normal ABR ≤25 dBHL at all test frequencies (500, 1k, 2k, and 4k whenever possible) with present OAE

By 4 weeks of age:
- Consult Pediatric ID to discuss antiviral treatment
- Contact Pediatric Neurology if abnormal HUS or microcephaly

At 3 months of age:
Follow-up with audiology and ENT

Isolated Sensorineural Hearing Loss

SYMPTOMATIC if ≥ one of:
- Thrombocytopenia
- Hepatomegaly
- Splenomegaly
- IUGR/SGA
- Microcephaly
- Abnormal HUS
- Hepatitis
- Sensorineural hearing loss (if also ≥ one of above)
Hearing Surveillance?

• How frequent and for how long?

**Asymptomatic** - if no hearing loss by age 5 yrs no greater risk for progressive hearing loss later compared to uninfected controls

**CHIP** - progressive HL continues thru 18 yrs

Lanzieri et al. Pediatrics 2017
CHIP Hearing Surveillance?

• Best or worse ear? Worse ear thru 1\textsuperscript{st} yr
  Fraction develop worsening hearing in the better ear and no change in worse ear. 0/8
  \textbf{Fraction develop worsening hearing in the worse ear and no change in best ear. 5/8}
  Fraction develop worsening in both ears 1/8
  Fraction develop no change in either ear 1/8
  Fraction develop improvement in either ear 1/8

• Worse ear tends to worsen more frequently than better ear

  Torrecillas, Lanzieri, Demmler, et al. pending
Hearing Surveillance?

• Which frequencies are most likely to worsen?
• 1,2,4k Hz over 18 years
• No specific frequency

Torrecillas, Lanzieri, Demmler, et al. pending
Hearing Surveillance?

• Do symptomatic, asymptomatic or CHIP behave differently? Yes

Hearing Surveillance

- N=16 sCMV all underwent VGC treatment
- 14/16 clinically worsening hearing
- Worse vs better ear (n=11)
  - No change (2/11)
  - Both ears worse (3/11)
  - Better ear worse (3/11)
  - Worse ear worse (3/11)

McCrary et el. Int J Peds Oto in press
Recommendations for Hearing Surveillance:

• Evolving
• Risk higher with CHIP, sCMV infected
• Every 3 months x 3 years then every 6 months through 18 years
• Both ears need to be tested
Future Directions:

• Loss of synaptic connections of the spiral ganglion cells without elevated audiometric thresholds
• Studied age and noise induced SNHL
• Can a similar effect be seen in CMV?

Kujawa and Liberman 2008
Study Design:

P3 days old IC injection mCMV 200 pfu C57BL/6

ABR thresholds, Amplitude and Ribbon synapse Counts 4,6 and 8 weeks
ABR Thresholds:

- Uninfected (4 wks)
- CMV (4 wks)
- CMV (6 wks)
- CMV (8 wks)
Suprathreshold Responses:

(A) 12 kHz
(B) 32 kHz

Wave I Amplitude (µV)

Tone Level (dB SPL)
Ribbon Synapse Counts:
Summary:

- Synaptopathy occurs in murine model for CMV
- Does this occur in children with CMV?
Clinical Study:

• A retrospective study design
• 4 groups: hearing impaired (HI) patients without CM and with cCMV, and normal hearing patients with and without cCMV (A, B, B’ and C respectively)
• Ages of 14 days - 17 years who obtained ABRs at Primary Children’s Hospital between 2014-2018
• ABR waveforms -Integrity Vivisonic ABR equipment
• ABRs (45-90 dB nHL) using click and 4 kHz toneburst stimuli
• Outcomes used for analysis: I/V amplitude ratio
• The following additional data was taken into consideration when analyzing data: intensity, rate, polarity, gender and patient chronological age
### Patient Demographics:

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group B'</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HI without cCMV</td>
<td>cCMV Positive</td>
<td>cCMV with normal hearing</td>
<td>Normal Hearing</td>
</tr>
<tr>
<td><strong>Age (standard deviation)</strong></td>
<td>21.9 months (35.34)</td>
<td>14.37 months (13.48)</td>
<td>14.75 months (14.29)</td>
<td>22.45 months (35.34)</td>
</tr>
<tr>
<td><strong>Gender (Male/Female)</strong></td>
<td>10/10</td>
<td>7/13</td>
<td>4/7</td>
<td>20/14</td>
</tr>
<tr>
<td><strong>Intensity (click) Right/Left dB nHL</strong></td>
<td>80.79/78</td>
<td>75.56/67.63</td>
<td>73.57/62.5</td>
<td>67.35/65.61</td>
</tr>
<tr>
<td><strong>Intensity (4kHz) Right/Left dB nHL</strong></td>
<td>77.89/77.89</td>
<td>62.81/60</td>
<td>55.71/52.86</td>
<td>61.92/60.45</td>
</tr>
</tbody>
</table>
Summary:

• Synaptopathy may occur in cCMV infected children
• Limitations- retrospective, not all underwent suprathreshold stimuli
• Need prospective study
• Implications- help identify cCMV children postnatally
Conclusion:

• Convince you that CMV is an important topic
• Awareness low- caregivers AND providers
• Rationale for targeted screening but not universal
• ValEAR trial – role of universal or targeted screening
• What steps you can do
• Future research needed
Cytomegalovirus Clinical Group:

James Bale  
Neurology

Stephanie McVicar  
DOH

Marissa Diener  
Family Studies

Angela Shoup  
UTSW

John Carey  
Genetics

Krow Ampofo  
Infectious Disease

Liz O’Brien  
Lonnie Miner  
Mariana Baserga  
Roger Faix  
Shrena Patel  
Melanie Boogaard

Tom Greene  
Epidemiology

Sean Redmond  
Speech and Lang.

Soren Gantt  
Univ. BC  
Infectious Disease

Mike Dean  
Clinical Trials

Betsy Ostrander  
Angela Shoup  
Bradley Yoder  
Elizabeth Knacksteadt  
Emily Thorell  
Xiaoming Sheng  
Shannon White  
Claudia Fruin  
Cathleen Zick  
Jill Boettger
ValEAR Team:

Training session at Salt Lake City June 6, 2018
Finis: