Newborn Hearing Screening, Congenital CMV, and Statutorily Mandated Care

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Disclosures

+ Perry Brown: none
+ Joe Hilinski: none
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• Thank you to Sherry Iverson for acquiring statutes and proposed statutes for us

Goals

• Review newborn hearing screening in Idaho: laws, algorithms, and accuracy of screening
• Discuss causes of congenital hearing loss, focusing on CMV
• Summarize the epidemiology and diagnosis of congenital CMV
• Define symptomatic vs. asymptomatic congenital CMV
• Outline the prognosis of asymptomatic and unexpected congenital CMV, and potential treatment
• Introduce current and proposed legislation related to congenital CMV, and potential challenges of such legislation
Background

2013: Utah became 1st state in US to enact law requiring requiring each newborn that fails the newborn hearing screening to be tested for congenital CMV

Since then:

- Connecticut and Iowa have passed similar laws
- Illinois requires that a CMV test be offered to the parents of every child who fails newborn hearing screening
- The balance of benefits vs. risks and costs make screening and even education controversial
- Statutes mandating specific medical care can be problematic

2017: CMV legislation in Idaho proposed and brought forward, and passed (more on this in a bit...)

Utah Congenital CMV Legislation

Enacted by Chapter 45, 2013 General Session
2/2/2018

(2) The department shall establish and conduct a public education program to inform pregnant women and women who may become pregnant regarding:

- (a) the incidence of CMV;
- (b) the transmission of CMV to pregnant women and women who may become pregnant;
- (c) birth defects caused by congenital CMV;
- (d) methods of diagnosing congenital CMV; and
- (e) available preventative measures.

(3) The department shall provide the information described in Subsection (2) to:

- (a) child care programs licensed under Title 26, Chapter 39, Utah Child Care Licensing Act, and their employees;
- (b) a person described in Subsection 26-39-403(1)(c), (f), (g), (h), (j), or (k);
- (c) a person serving as a school nurse under Section 53A-11-204;
- (d) a person offering health education in a school district;
- (e) health care providers offering care to pregnant women and infants; and
- (f) religious, ecclesiastical, or denominational organizations offering children's programs as a part of worship services.

CONCERN: Can education prevent congenital CMV? If it cannot or only has mild efficacy, does this primarily just increase anxiety and potential testing and cost?

(4) If a newborn infant fails the newborn hearing screening test(s) under Subsection 26-10-6(1), a medical practitioner shall:

- (a) test the newborn infant for CMV before the newborn is 21 days of age, unless a parent of the newborn infant objects; and
- (b) provide to the parents of the newborn infant information regarding:
  - (i) birth defects caused by congenital CMV; and
  - (ii) available methods of treatment.

Questions / concerns:

- What percent of failed newborn hearing screens actually represent true hearing loss?
- Who is the responsible physician to do this? The newborn nursery physician or the follow-up PCP? And how is communication and responsibility of this managed?
- Are primary care pediatricians and family physicians expert enough to complete congenital CMV treatment counseling and management? If no, who does, and is there enough clinical access?
- Does treatment of otherwise asymptomatic congenital CMV accomplish anything? Is it worth the costs and risks?
Newborn Hearing Screening in Idaho

- No Idaho statute requiring newborn hearing screening
- General algorithm: screen in hospital; if fail, then re-screen before discharge; if still failing, then audiology follow-up by 3 months of age (ideally earlier, by 4 weeks of age)
- 2017 Idaho statistics:
  - 19,810 births
  - 99.1% screened for hearing
  - 3.1% failed screening = 614 newborns
    - 37.9% of these lost to audiological follow-up
- ~ 0.2% of newborns are born with true hearing loss
- Calculated rate of false positives newborn hearing screens in Idaho: 93.5%

Causes of Congenital Hearing Loss

- Congenital CMV = 3.2% of all failed newborn hearing screens (99,945 babies screened; 961 failed screen; 31 CMV+)
- A review estimates that congenital CMV infection accounts for approximately 21 - 25% of all true hearing loss at birth.

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital CMV</td>
<td>- Birth of a child with a congenital anomaly</td>
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<td></td>
<td>- Presence of a congenital anomaly at birth</td>
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<td></td>
<td>- Genetic factors (e.g., Down syndrome)</td>
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<td></td>
<td>- Environmental factors (e.g., noise exposure)</td>
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<td></td>
<td>- In utero drug exposure (e.g., salicylates)</td>
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<tr>
<td></td>
<td>- In utero infection (e.g., toxoplasmosis)</td>
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<tr>
<td></td>
<td>- In utero ischemia (e.g., hypoxia, strokes)</td>
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<tr>
<td></td>
<td>- In utero metabolic disorders (e.g., PKU)</td>
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<td></td>
<td>- In utero viral infection (e.g., CMV)</td>
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<td></td>
<td>- In utero immune response (e.g., HIV)</td>
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<td></td>
<td>- In utero radiation exposure (e.g., CT scans)</td>
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<td></td>
<td>- In utero infection (e.g., herpes simplex)</td>
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<td>- In utero exposure to drugs (e.g., amphetamines)</td>
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<td>- In utero exposure to sedatives (e.g., barbiturates)</td>
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<td>- In utero exposure to other medications (e.g., antibiotics)</td>
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<tr>
<td></td>
<td>- In utero exposure to toxic substances (e.g., alcohol)</td>
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<tr>
<td></td>
<td>- In utero exposure to physical trauma (e.g., birth asphyxia)</td>
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</tbody>
</table>

Fetal hearing loss

- Congenital CMV, rubella, toxoplasmosis, and other viral infections can affect fetal hearing loss.
Non-correlation between newborn hearing screening, CMV status, and hearing loss

- Study of 99,945 newborns routinely screened for both hearing loss and CMV: 93% of CMV+ babies passed their newborn hearing screen.
- Utah Department of Health study of 509 infants who failed hearing screening:
  - 234 were screened for congenital CMV within 21 days of age
  - 14 were diagnosed with congenital CMV (6%)
  - 6 had true hearing loss
  - Additional 80 patients were screened after 21 days of age for CMV
    - 7 tested positive for CMV (8.8%)
    - 3 had true hearing loss.
- With 57% of the CMV+ patients having false positive newborn hearing screens and normal hearing in the newborn period, how many asymptomatic CMV+ newborns are out there with normal hearing at birth and who go untested for CMV?
- Statistical analysis suggests there were an estimated 400 to 700 infants with congenital CMV during the study period, most of whom were not detected.

Epidemiology of Congenital CMV

- Incidence of congenital CMV infection: 0.2% - 2.2%, with 0.5% - 1.0% of all newborns in the United States infected with CMV in the prenatal period.
- Congenital CMV infection at birth may manifest symptomatically, but 90-95% of infants with congenital CMV infection will have no clinically apparent symptoms (present asymptomatically) at birth.
- Both symptomatic and asymptomatic infants may later develop sequelae, with more severe and frequent sequelae occurring in the symptomatic infants. Sequelae following congenital CMV infection include sensorineural hearing loss (SNHL), retinitis, mental retardation, microcephaly, seizures, and cerebral palsy. The most common sequelae following congenital CMV infection is SNHL.
- Approximately 8-12% of children without clinically apparent (asymptomatic) congenital CMV infection will develop SNHL.
- Less than half of the hearing loss due to CMV infection is present at birth. Other CMV infected children may go on to develop late onset loss during the preschool and early school years. Approximately 33 to 50% of SNHL due to congenital CMV infection is late onset loss.
My conclusions about hearing screening and congenital CMV

✦ A small minority of newborns who fail their newborn hearing screen have congenital CMV (3 - 8%)
✦ The great majority of newborns with congenital CMV pass their newborn hearing screen (93%)
✦ Hearing screening is a terrible screening test for CMV — poor sensitivity and specificity
✦ “Targeted newborn screening” for CMV is a mess!

Universal Newborn Screening for CMV

✦ Has been proposed by many CMV experts, audiologists, otolaryngologists, and public health officials
✦ Main goal is to identify asymptomatic infected infants in order to provide careful monitoring for delayed-onset hearing loss.
✦ Antiviral treatment is generally not recommended for infected infants who pass the newborn hearing screen and are otherwise asymptomatic
✦ If delayed-onset hearing loss is identified, educational accommodations, speech/language therapies, and other appropriate interventions can be initiated at an early stage in order to optimize the child’s language development and learning
✦ Universal newborn screening appears to be cost effective
✦ Not yet included on the national Routine Universal Screening Panel.
ID Statutes Related to Congenital CMV

…but is a statute mandating CMV testing forthcoming?

Diagnosis – Prenatal Infection

- Routine maternal serology not recommended by ACOG – screening should be done only for clinical suspicion:
  - CMV serology with IgM/IgG
  - Follow up with CMV IgG avidity assay if IgM positive
    - Positive maternal IgM with low IgG avidity is consistent with primary/recent infection
  - Serology has no role in diagnosis of congenital CMV in infant
  - CMV PCR on amniotic fluid is recommended test for fetal infection
Lab Diagnosis – Congenital Infection

- Requires confirmation of virus detection in body fluids within first 3 weeks of life:
  - Urine most commonly used (can be bag specimen, cath not required)
  - Saliva/Buccal swab also acceptable
  - Culture for CMV is gold standard (infants shed in very high titer with congenital infection)
  - PCR for CMV more rapid turn around, now more widely available and used
    - Caveat that viral PCR titers may not be helpful with prognosis or serially monitored
  - Viral isolation or detection beyond 3 weeks of life cannot be used to establish diagnosis of congenital CMV
  - Peri- or Post-natal acquisition may lead to a positive result > 3 weeks

Additional Studies for Suspected Symptomatic Congenital CMV

- CBC with differential to look for thrombocytopenia or leukopenia
- Chemistry panel to look for elevated transaminases, direct hyperbilirubinemia
- Dilated eye exam by ophthalmologist looking for retinitis
- Head ultrasound to look for calcifications or large structural defects
- U/S is imaging modality of choice for congenital CMV and findings have been shown to correlate with outcome
Symptomatic vs Asymptomatic Infection

- More than 90% of congenitally infected infants appear normal at birth:
- Only 7% of infected infants in large screening study had signs noticeable at birth
- The main sequela of inapparent, asymptomatic infection is sensorineural hearing loss (10-15%)

Symptomatic Congenital CMV

- Symptomatic infection is associated with mortality! 12% by 6 weeks of age
- CNS involvement occurs in 2/3 of infants who are symptomatic at birth
  - Mental retardation
  - Cerebral palsy
  - Sensorineural hearing loss
  - Vision loss
### Symptomatic Congenital CMV

<table>
<thead>
<tr>
<th>Clinical or Lab Abnormality</th>
<th>Percentage Reported in Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>34</td>
</tr>
<tr>
<td>IGA</td>
<td>30</td>
</tr>
<tr>
<td>Petechiae</td>
<td>36</td>
</tr>
<tr>
<td>Purpura</td>
<td>13</td>
</tr>
<tr>
<td>HSM</td>
<td>60</td>
</tr>
<tr>
<td>Jaundice</td>
<td>67</td>
</tr>
<tr>
<td>Neurologic abnormality (any):</td>
<td>68</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>63</td>
</tr>
<tr>
<td>Lethargy/Hypotonia</td>
<td>27</td>
</tr>
<tr>
<td>Poor suck</td>
<td>19</td>
</tr>
<tr>
<td>Seizures</td>
<td>7</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>83</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>77</td>
</tr>
<tr>
<td>Direct Hyperbilirubinemia</td>
<td>81</td>
</tr>
</tbody>
</table>

### Asymptomatic Congenital CMV

- Most infants with asymptomatic congenital CMV have no long term deficits
- Sensorineural hearing loss is the main sequela:
  - 10-15% of asymptotically infected newborns
  - May be present at birth, or develop over time even after age 2 yrs
  - Can be progressive
- Lopez et al, Pediatrics 2017:140 established that asymptatically infected infants with normal hearing by 2 years of age do not appear to have differences in IQ, vocabulary, or academic achievement in childhood or adolescence.
Treatment

**Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease**


Randomized placebo controlled trial of 6 weeks Valganciclovir (VGC) vs 6 months in infants with **SYMPTOMATIC** congenital CMV:

- Best ear hearing at 6 months similar in both groups
- Total ear hearing more likely to stay normal or improve at 12/24 months in 6 month treatment group
- Better neurodevelopmental scores at 24 months in 6 month treatment group
- Grade 3-4 neutropenia occurred in ~25% of subjects
- Conclusion: 6 months of VGC did not improve hearing in short term, but improved hearing and developmental outcomes modestly in longer term
Treatment: AAP Recs

- Treatment is indicated for neonates with symptomatic congenital CMV with or without CNS disease
- Must be started within first 4 weeks of life
- Valganciclovir 16 mg/kg/dose PO BID x 6 months
  - IV Ganciclovir 6 mg/kg/dose q12 can be substituted if PO not possible
- ANC and additional labs should be measured frequently during therapy
- Antiviral therapy is NOT indicated for asymptomatic infection or isolated sensorineural hearing loss

Treatment: Practical Issues

- Therapy effect may be mild or moderate – primary endpoint of study was not actually improved
- Significant risk of neutropenia or severe bone marrow suppression if not followed closely and adjusted
- VGC has been shown to be teratogenic, carcinogenic, and potentially cause sterility in animals at similar dosages to those used in humans
- There is zero long term follow up data on prolonged use of VGC in infants and above toxicity issues
- Should be done by practitioner experienced in use and prescription of the drug
Treatment: Practical Issues

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 2]).
Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016). Assess risk to determine appropriate containment strategy (USP-NF 2017).

Prevention:

- Transmission requires direct contact with body fluids
- Standard precautions are the official isolation and recommendation to prevent transmission:
  - Should assume that all body fluids from all sources are potentially infectious with CMV
  - Asymptomatic shedding throughout life is common in all infected individuals
Prevention:

- Education of pregnant women about risks and hygiene measures to prevent CMV infection can result in reduced rates in pregnancy
- Largely include hand washing, avoiding direct contact with toys or objects that may be contaminated by saliva
- Avoiding direct saliva contact with young children
- Education will not be effective in preventing non-primary infections (may account for up to half of overall infections)
- CMV-IG during pregnancy for primary maternal infection to prevent fetal CMV has not been shown to be effective, and is not generally recommended
CMV: The Future

- Development of less toxic drugs:
  - Brincidofovir on the horizon (not currently licensed)

- Development of CMV vaccine:
  - Several candidate vaccines in development that may have efficacy – none are close to licensure