Objective: Cytomegalovirus infection from breastmilk: should we be worried?

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Disclosures

• I have no financial disclosures to report.

Objectives

At the end of this presentation, you should know the:

1. Risk of developing postnatal cytomegalovirus (CMV) infection from maternal breastmilk
2. Potential consequences of postnatal cytomegalovirus infection

Overview

• Incidence of postnatal CMV infection
• Maternal and infant risk-factors for postnatal CMV infection
• Postnatal CMV infection and outcomes:
  – Sepsis-like syndrome
  – Bronchopulmonary dysplasia
  – Necrotizing enterocolitis
  – Long-term neurodevelopmental and hearing impairment
• Discuss prevention and treatment

Cytomegalovirus

• Cytomegalovirus (CMV) is a herpesvirus
• After initial infection, CMV becomes latent, residing in cells without causing illness.
• Can establish lifelong latency.
• By 5 years of age, 1/3 of children have been infected
• By 40 years of age, 1/2 of adults have been infected

Source: CDC

Cytomegalovirus

• Most infected people have no or mild symptoms:
  – Fever
  – Sore throat
  – Fatigue
• However, CMV can cause severe infection in immunocompromised patients
  – Preterm infants
  – Patients on immunosuppressants
  – Recipients of bone marrow transplants

Source: CDC
Effects of CMV infection

- CMV can target multiple cell types
- **Congenital** CMV infection can cause
  - intracerebral calcifications
  - chorioretinitis
  - hepatitis
  - neurodevelopmental impairment
  - Hearing loss

Methods of CMV transmission

- CMV is shed in multiple body fluids and infection can be acquired in the following ways:
  - Direct contact with urine or saliva from children
  - Blood transfusions
  - Breast milk
  - From mother to child during pregnancy
  - Sexual contact
  - Transplanted organs
- Currently, handwashing only routinely recommended approach to decrease CMV transmission

Source: CDC

Postnatal CMV infection

- Postnatal acquired CMV infection in very low birth weight infants can cause a sepsis-like syndrome
- However, most infants have no overt symptoms
- The two major sources of postnatal CMV infection (onset after 2 weeks of life) are:
  - Breast milk
  - Blood transfusions

Risk and sources of postnatal CMV

Source: CDC

Study Flow Diagram

Assessed for eligibility
(n=1455)

n=415

Met enrollment criteria
(n=1102)

n=499

Enrolled
(n=541 infants)
(n=462 mothers)

Followed for 90 days or until hospital discharge or death
(n=539)

n=2

Did not meet inclusion criteria:
- birthweight (n=327)
- age ≤ 5d (n=58)
- Met exclusion criteria:
- Not expected to survive >7d (n=96)
- Congenital anomaly (n=11)
- Transfusion before screening (n=2)

Did not meet enrollment criteria
- did not meet enrollment criteria

Testing for CMV infection

100% of infants evaluated for CMV by nucleic acid testing at least 2 times and 98% 3 or more times

Source: Josephson et al., JAMA Pediatrics 2014
Testing for sources of CMV infection

- CMV NAT: 93% (882/954) units tested for CMV
- Residual WBC: 92% (878/954) units tested for residual WBCs

91% of milk tested at least 1 time for breast feeding mothers and 69% tested at least twice

Incidence of postnatal CMV infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion Infected</th>
<th>Cumulative Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV infection</td>
<td>29/539</td>
<td>6.9%</td>
<td>4.2 - 9.2%</td>
</tr>
<tr>
<td>- infants born to CMV (-) mothers</td>
<td>0/127</td>
<td>0.0%</td>
<td>0.0 - 2.1%</td>
</tr>
<tr>
<td>- infants born to CMV (+) mothers</td>
<td>29/412</td>
<td>9.1%</td>
<td>5.6 - 12.3%</td>
</tr>
<tr>
<td>- CMV disease or mortality</td>
<td>5/539</td>
<td>0.9%</td>
<td>0.3 - 1.9%</td>
</tr>
</tbody>
</table>

Source of postnatal CMV infection

<table>
<thead>
<tr>
<th>Source</th>
<th>Proportion Infected</th>
<th>Cumulative Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk-transmitted</td>
<td>27 / 221</td>
<td>15.3%</td>
<td>9.3 - 20.2%</td>
</tr>
<tr>
<td>Transfusion-transmitted</td>
<td>0 / 310</td>
<td>0.0%</td>
<td>0.0 - 0.9%</td>
</tr>
<tr>
<td>Unknown source</td>
<td>1 / 539</td>
<td>0.2%</td>
<td>0.0 - 1.0%</td>
</tr>
</tbody>
</table>

Breast milk CMV shedding

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency</th>
<th>Cumulative Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV in breast milk in CMV seropositive mothers</td>
<td>189 / 255</td>
<td>74%</td>
<td>70% - 80%</td>
</tr>
<tr>
<td>CMV in breast milk in CMV seronegative mothers</td>
<td>0 / 81</td>
<td>0%</td>
<td>0% - 5%</td>
</tr>
</tbody>
</table>

Risk factors for postnatal CMV infection (univariate)

<table>
<thead>
<tr>
<th>CMV Risk Factor</th>
<th>CSHR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (per 100g increase)</td>
<td>0.97</td>
<td>0.85-1.11</td>
<td>0.62</td>
</tr>
<tr>
<td>Leukopenia at birth (WBC &lt;5000)</td>
<td>1.54</td>
<td>0.62-3.84</td>
<td>0.35</td>
</tr>
<tr>
<td>Late onset sepsis</td>
<td>0.56</td>
<td>0.15-2.21</td>
<td>0.42</td>
</tr>
<tr>
<td>Breast milk feeding days (per 7 day increase)</td>
<td>1.68</td>
<td>1.21-2.34</td>
<td>0.002</td>
</tr>
<tr>
<td>CMV in breast milk in CMV seropositive mothers</td>
<td>0.53</td>
<td>0.22-1.30</td>
<td>0.16</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>0.90</td>
<td>0.31-2.62</td>
<td>0.84</td>
</tr>
<tr>
<td>Premature rupture of membranes</td>
<td>3.14</td>
<td>1.46-6.73</td>
<td>0.003</td>
</tr>
<tr>
<td>ROM &gt; 18 hour</td>
<td>1.83</td>
<td>0.86-3.90</td>
<td>0.12</td>
</tr>
<tr>
<td>Breast milk CMV viral load (per 1 log10 IU)</td>
<td>2.71</td>
<td>2.20-3.35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.50</td>
<td>0.23-1.07</td>
<td>0.07</td>
</tr>
<tr>
<td>SNAP score (per 1 unit increase)</td>
<td>1.02</td>
<td>0.95-1.09</td>
<td>0.56</td>
</tr>
<tr>
<td>Repeal of antenatal steroids</td>
<td>0.96</td>
<td>0.37-2.46</td>
<td>0.93</td>
</tr>
</tbody>
</table>
### Risk factors for postnatal CMV infection (multivariate)

<table>
<thead>
<tr>
<th>CMV Risk Factor</th>
<th>CSHR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature rupture of membranes</td>
<td>3.21</td>
<td>1.43 - 7.23</td>
<td>0.005</td>
</tr>
<tr>
<td>Breast milk CMV viral load (per 1 log10 IU increase)</td>
<td>1.87</td>
<td>1.48 - 2.35</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Josephson et al. JAMA Pediatrics 2014

### CMV transmission by maximum breast milk CMV viral load

<table>
<thead>
<tr>
<th>Maximum breast milk CMV viral load</th>
<th>Probability of CMV transmission (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 IU</td>
<td>9% (5% - 14%)</td>
</tr>
<tr>
<td>10,000 IU</td>
<td>17% (11% - 25%)</td>
</tr>
<tr>
<td>100,000 IU</td>
<td>30% (20% - 42%)</td>
</tr>
</tbody>
</table>

Josephson et al. JAMA Pediatrics 2014

### Breastmilk and CMV

![Image of Breastmilk and CMV](http://example.com/breastmilk_cmv)

Hamprecht K et al. Lancet. 2001

### Current recommendations in US

“There are no recommendations against breastfeeding by mothers who are CMV-seropositive. However, premature infants (born <30 weeks gestational age and <1500g) who acquire CMV from breast milk may be at risk of developing a late-onset sepsis-like syndrome. The potential benefits of human milk versus the risk of CMV transmission should be considered when making a decision about breastfeeding of very low birth weight infants (birth weight <1500 g) by mothers known to be CMV-seropositive.”

-Centers for Disease Control and Prevention (2016)

Source: https://www.cdc.gov/cmv/clinical/features.html

### AAP Policy Statement

“Decisions about breastfeeding of very low birth weight infants (birth weight < 1500 g) by mothers known to be CMV-seropositive should be made with consideration of the potential benefits of human milk versus the risk of CMV transmission.”

-American Academy of Pediatrics

Section on Breastfeeding (2005)

### Updated AAP Policy Statement

“There is no contraindication to breastfeeding for a full-term infant whose mother is seropositive for cytomegalovirus. There is a possibility that CMV acquired from mother’s milk may be associated with a late-onset sepsis-like syndrome … The value of routinely feeding human milk from seropositive mothers to preterm infants outweighs the risks of clinical disease, especially because no long-term neurodevelopmental abnormalities have been reported.”

-American Academy of Pediatrics

Section on Breastfeeding (2012)
Incidence of postnatal CMV infection in VLBW infants in the US

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk among infants fed untreated breast milk (95% CI)</th>
<th>Number of cases based on 2008 US data</th>
</tr>
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<tbody>
<tr>
<td>Postnatal CMV infection</td>
<td>19% (11-32%)</td>
<td>2000</td>
</tr>
</tbody>
</table>

Lanzieri TM et al. /Pediatrics 2013

What is the relationship between postnatal CMV and adverse neonatal outcomes?

Postnatal CMV and outcomes

- Sepsis-like syndrome
- Bronchopulmonary dysplasia
- Necrotizing enterocolitis
- Long-term neurodevelopmental outcomes

Sepsis-like syndrome

Manifestations could include:
- thrombocytopenia
- neutropenia
- petechiae
- respiratory distress syndrome
- sepsis-like syndrome
- hepatopathy

Incidence of postnatal CMV sepsis-like syndrome

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<th>Risk among infants fed untreated breast milk (95% CI)</th>
<th>Number of cases based on 2008 US data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal CMV sepsis-like syndrome</td>
<td>4% (2-7%)</td>
<td>600</td>
</tr>
</tbody>
</table>

Lanzieri TM et al. /Pediatrics 2013

Breastmilk acquired CMV and outcome

CROSS-CONTROL STUDY OF SYMPTOMS AND NEONATAL OUTCOME OF HUMAN MILK-TRANSMITTED CYTOMEGALOVIRUS INFECTION IN PREMATURE INFANTS

Objective: Prevent infections in high-risk premature infants by breast milk.

1. Risk of CMV infection in premature infants who received breast milk and were untreated.
2. Risk of CMV infection in premature infants who received breast milk and were treated with intravenous ganciclovir.
3. Risk of CMV infection in premature infants who received breast milk and were treated with oral valganciclovir.

Results: The risk of CMV infection was significantly lower in the treated groups compared to the untreated group. The risk of CMV infection was highest in the untreated group, and lowest in the treated group.

Conclusion: Breast milk can be a source of CMV infection in premature infants. Treatment with intravenous ganciclovir or oral valganciclovir can significantly reduce the risk of CMV infection in premature infants who receive breast milk.

Lanzieri TM et al. /Pediatrics 2013

Children's Healthcare of Atlanta | Emory University
CMV and NEC?

Postnatal CMV and NEC

Symptomatic Postnatal Cytomegalovirus Testing among Very Low-Birth-Weight Infants: Indications and Outcomes

Sapna Malhotra et al.

- Among 2,132 VLBW infants, 7% evaluated for postnatal CMV infection and 27 (19%) positive
- NEC incidence among postnatal CMV infants 21% vs. 10% in uninfected/untested infants (P=0.11)

N=61 infants
(70 specimens)

Postnatal CMV and BPD

Symptomatic Postnatal Cytomegalovirus Testing among Very Low-Birth-Weight Infants: Indications and Outcomes


- Among 2,132 VLBW infants, 7% evaluated for postnatal CMV infection and 27 positive
- NEC incidence among postnatal CMV infants 73% vs. 34% in uninfected/untested infants (P<0.001)

CMV and BPD?

- Of 101,111 infants, 328 (0.3%) had postnatal CMV infection
- Postnatal CMV infection associated with increased risk for BPD
  - RR, 1.33 (95%CI 1.19-1.50)
Postnataally acquired cytomegalovirus infection via breast milk: effects on hearing and development in preterm infants

Background. In preterm infants there is a high risk of transmission of cytomegalovirus (CMV) via breast milk from a mother with manifesting of the virus during lactation. There is little information about the long-term sequelae of early postnatally acquired CMV infection in preterm infants. This study aimed to investigate whether there was an increased frequency of hearing loss and cognitive impairment in the long term in preterm infants with postnatally acquired CMV infection through transmission by CMV-positive breast milk.

Methods. Twenty-nine preterm infants (median birth weight, 40.7 ± 10.8% in kilograms; gestational age, 28.4 ± 5.2 weeks [range, 22.8 to 30.9 weeks]) with early postnatally acquired CMV infection (defined by breast feeding [mainly] or carry-
**Postnatal CMV and NEC**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>pCMV+ (n=33)</th>
<th>pCMV- (n=563)</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>9.1%</td>
<td>5.0%</td>
<td>1.78 (0.64, 4.94)</td>
<td>0.27</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>24.2%</td>
<td>22.7%</td>
<td>1.02 (0.57, 1.80)</td>
<td>0.95</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>12.0%</td>
<td>13.5%</td>
<td>0.85 (0.34, 2.09)</td>
<td>0.72</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>15.2%</td>
<td>10.5%</td>
<td>1.36 (0.68, 2.74)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Association between postnatal CMV and necrotizing enterocolitis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>pCMV No pCMV Unadjusted RR / HR (95% CI)</th>
<th>Adjusted RR / HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>18% 7%</td>
<td>2.23 (0.54-9.20)</td>
</tr>
<tr>
<td>Approach 1</td>
<td>- -</td>
<td>2.23 (0.54-9.20)</td>
</tr>
<tr>
<td>Approach 2</td>
<td>- -</td>
<td>4.95 (1.08-22.6)</td>
</tr>
</tbody>
</table>

**Current recommendations in US**

“Freezing and pasteurization of breast milk can decrease the risk of transmission; however, freezing does not eliminate the risk of transmission.”

-CDC (2016)

“Freezing of milk reduces but does not eliminate CMV.”

-AAP (2012)

Source: [https://www.cdc.gov/cmv/clinical/features.html](https://www.cdc.gov/cmv/clinical/features.html)

Eidelman et al. Section of Breastfeeding. AAP. Pediatrics. 2012
Estimates of incidence of pCMV infection in VLBW infants in the US

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Infants fed untreated breast milk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal CMV infection</td>
<td>19% (11-32%)</td>
</tr>
<tr>
<td>- Infants fed frozen milk</td>
<td>13% (7-24%)</td>
</tr>
<tr>
<td>Postnatal CMV sepsis-like syndrome</td>
<td>4% (2-7%)</td>
</tr>
<tr>
<td>- Infants fed frozen milk</td>
<td>5% (2-12%)</td>
</tr>
</tbody>
</table>

Lanzieri TM et al. | Pediatrics 2013

Pasteurization

Effects of Different CMV-Heat-Inactivation-Methods on Growth Factors in Human Breast Milk

Short (5 s) pasteurization vs.
Long (30 min) Holder pasteurization at 63°C.

Irradiation

Antiviral treatment

- No guidance currently available on when to treat postnatal CMV infection
- Medications include ganciclovir and valganciclovir


Take home points

- Postnatal CMV infection occurs in 7-13% of VLBW infants born to CMV seropositive mothers.
- Freezing of breastmilk decreases but does not prevent transmission.
- Further studies needed to understand the potential effects of CMV exposure from breast milk and NEC, BPD and long-term outcome.
- Currently, there is not enough data to guide prevention strategies or routine testing of VLBW infants.

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