Children's Healthcare of Atlanta

EMORY UNIVERSITY

MOM for Neonates When CMV is a Concern

Andi L. Shane, MD, MPH, MSc
Chief, Division of Pediatric Infectious Disease and Marcus Professor of Hospital Epidemiology and Infection Prevention
Emory University and Children's Healthcare of Atlanta
15 April 2025

1

Disclosures

- Emory University has received funds from the Bill & Melinda Gates Foundation and the National Institutes of Health, that have been applied to my salary for research-related activities
- Two NIH-funded RDCRN projects relate to congenital CMV but neither to breastfeeding nor human milk
- I receive a stipend from the Pediatric Infectious Disease Society to serve as the Deputy Editor of *The Journal of the Pediatric Infectious Diseases Society (JPIDS)*

2

2

Objectives

At the conclusion of this presentation, participants will be able to:

1. Discuss the epidemiology, transmission, and clinical presentation of cytomegalovirus (CMV) in the neonatal period
2. Describe the role of human milk in the transmission of CMV in the neonatal period
3. Identify strategies to reduce or eradicate CMV from human milk
4. Apply options for management of human milk feeding in a neonate with CMV infection

3

3

Objectives

At the conclusion of this presentation, participants will be able to:

1. Discuss the epidemiology, transmission, and clinical presentation of cytomegalovirus (CMV) in the neonatal period, with a focus on human milk
2. Describe the role of human milk in the transmission of CMV in the neonatal period
3. Identify strategies to reduce or eradicate CMV from human milk
4. Apply options for management of human milk feeding in a neonate with CMV infection

4

4

CMV 101

- Human CMV (human herpesvirus) ds DNA; species-specific, ubiquitous, extensive genetic diversity, no seasonal predilection
  - Horizontal transmission: person-to-person
  - Vertical transmission: birth parent to infant before, during, or after birth, transfusion, solid organ transplantation
  - Infants: commonly transmitted through human milk ingestion
- CMV becomes dormant in leukocytes and tissue cells after a primary infection
  - intermittent shedding
  - symptomatic reinfection (immunosuppression)
  - reinfection with different strains of CMV
  - risk for infection/reinfection: early childhood, adolescence, childbearing years

5

5

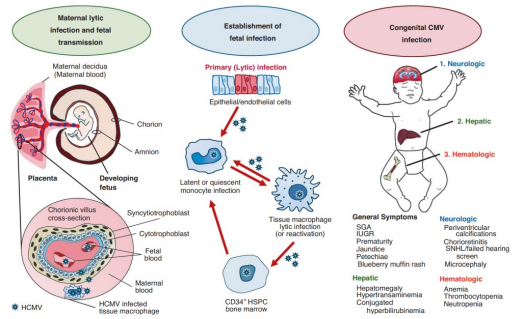
Vertical Transmission of CMV

1. in utero (congenital) through transplacental transmission
   - 5/1,000 liveborn infants
   - Black newborns (9.5/1,000 live births) disproportionately infected
   - most common congenital viral infection in the United States
   - primary infection: (infection in person without pre-existing immunity)
   - non-primary infection: acquisition of a different viral strain or by reactivation of a strain from a previous infection
   - sequelae greatest when infection occurs during the first trimester; likely similar risk with primary and nonprimary infections
2. at birth (perinatal) passage through a CMV-infected genital tract
3. ingestion of CMV-containing human milk

6

6

Pathophysiology of Congenital CMV

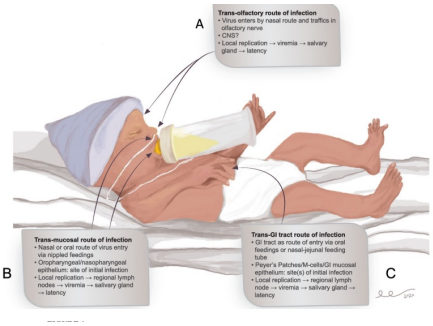


7

Pediatric Research (2024) 95:532–542; https://doi.org/10.1038/s41390-023-02957-9

7

Pathophysiology of Acquired CMV



Rev Med Virol. 2020 November ; 30(6): 1–11. doi:10.1002/rmv.2117

8

8

Congenital vs. Acquired CMV

- **Preterm infants (<32 weeks GA and birthweight < 1500g) at greatest risk for sequelae when exposed to CMV**
- **Diagnosis of congenital CMV infection requires detection of CMV DNA from CSF, blood, urine, saliva (confirmed with urine PCR) within 21 days of life**
- **Differentiation between congenital and peri/post-natal infection difficult beyond 21 days of life**
- **Antiviral management differs for congenital and perinatal acquisition**

9

9

Strategies to Reduce/Eradicate CMV from Human Milk

At the conclusion of this presentation, participants will be able to:

1. Discuss the epidemiology, transmission, and clinical presentation of cytomegalovirus (CMV) in the neonatal period
2. **Describe the role of human milk in the transmission of CMV in the neonatal period**
3. Identify strategies to reduce or eradicate CMV from human milk
4. Apply options for management of human milk feeding in a neonate with CMV infection

10

10

CMV and Human Milk Association and Clinical Outcomes

- **Early 1970's, human milk identified as a potential source of CMV exposure in 18 infants**
- **Short term outcomes:**
  - **Danish study with 26 preterm infants who received MOM found a higher CMV viral load in MOM ingested by CMV-infected versus CMV-uninfected infants**
  - **4 acquired CMV, 2 with sepsis-like symptoms**
- **Medium term outcomes:**
  - **No sensorineural hearing loss and speech/motor differences in CMV-infected infants via human milk acquisition**
    - **even among those who had a sepsis-like syndrome with initial infection, risk low for sequelae**
- **Long term outcomes:**
  - **School-aged and older children with postnatal CMV infection had lower scores on visual and spatiotemporal processing tests and different fMRI grey matter volumes**

11

CMV in Human Milk

- **CMV DNA detected in colostrum in 20-60% of lactating persons**
- **90% of preterm infants of seropositive persons acquire CMV via lactation and human milk ingestion; a minority of these develop signs and symptoms of CMV infection**
  - **cytokines, lactoferrin, CD8+ T-cell phenotypes modulate viral shedding**
- **After human milk CMV exposure, the median time to onset of CMV viruria is 7 weeks (range 3-24 weeks)**
- **Higher CMV viral loads in human milk and exposures to increased volumes of CMV positive human milk are associated with greater likelihood of transmission**

12

12

VLBW Acquisition of CMV in the NICU

- 302 NICUs from 2002-2016, 75,000 infants Pediatrix Medical Group
- 304 (0.4%) infants with postnatal CMV identified
- 273 (90%) matched to control infants without postnatal CMV
- Newborn hearing screen failure among 45 (16%) with postnatal CMV compared with 25 (9%) infants without postnatal CMV (p=0.01)
- Association between postnatal CMV and BPD, but no association found between postnatal CMV and NEC
- Those with postnatal CMV infection had slower weight gain and prolonged hospitalizations than those without postnatal CMV infection

JAMA Pediatrics Feb 2020; 174(2):133 13

13

CMV + Human Milk and NEC

- Secondary analysis of a multicenter, observational cohort
- Human milk and infant serum/urine serially evaluated for CMV DNA
- Three NICUs in Atlanta
- Infants with birth weight < 1500 grams
- Infants with cCMV excluded
- Evaluated relationship between human milk CMV exposure or postnatal CMV infection and NEC
- Outcome: NEC Bell II or greater
- 596 enrolled, 457 (77%) CMV-positive birth parent; 33 developed postnatal CMV infection
  - 6/33 (18%) NEC incidence with CMV infection vs. 37/563 (7%) NEC incidence without CMV infection
  - higher human milk CMV viral load associated with higher risk for NEC

Arch Dis Child Fetal Neonatal Ed 2020; 105:F259-F265 14

14

Objectives

At the conclusion of this presentation, participants will be able to:

1. Discuss the epidemiology, transmission, and clinical presentation of cytomegalovirus (CMV) in the neonatal period
2. Describe the role of human milk in the transmission of CMV in the neonatal period
3. **Identify strategies to reduce or eradicate CMV from human milk**
4. Apply options for management of human milk feeding in a neonate with CMV infection

15

15

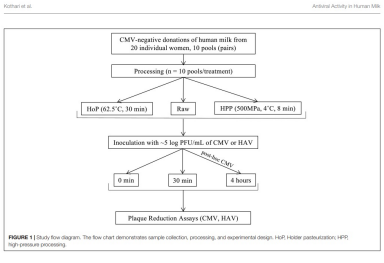
CMV and Human Milk Processing

- Pasteurization of human milk can decrease the likelihood of CMV transmission via human milk by inactivating CMV
  - Holder pasteurization (62.5°C /144.5°F) for 30 minutes
  - Short-term pasteurization (72°C / 161°F) for 15 seconds
  - Alternative short-term heat inactivation (62°C) for 5 seconds
- Freezing human milk at -20°C (-4°F) does not reduce the risk of CMV-sepsis syndrome and reduces the bioactivity of human milk
- CMV-antibody negative human milk donors may be considered for infants born to CMV-negative birth parents if feasible
- For infants infected with CMV (congenital or peri/postnatally), benefits of human milk from their birthing parents outweighs the risk of additional CMV exposure

16

16

Preservation of Anti-CMV Activity Human Milk: High Pressure Processing (HPP) vs. Holder Pasteurization (HoP)



Front. Nutr. 9:918814. doi: 10.3389/fnut.2022.918814

- [CMV] declined in all pools after 30 minutes of incubation
- HPP-treated milk inactivated CMV to a degree intermediate between raw and HoP milk at 30 min
- Anti-CMV activity in human milk preserved following HoP and HPP for 4 hours at room temp
- HPP preserves bile salt stimulated lipase, lactoferrin, lysozyme, and microbiological safety, compared to HoP, flash heating, UV-C radiation

17

17

Infants with Severe Combined Immunodeficiency (SCID)

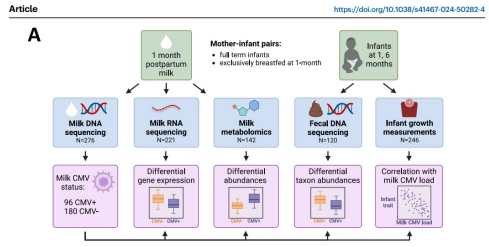
- Controversy: breastfeeding by CMV seropositive parents of neonates with SCID
  - shedding CMV into human milk
  - if premature → contracting disease
  - auto-immune cytopenia and poor transplant outcome after CMV infection
- Guidance: no breastfeeding until CMV status of breastfeeding parent confirmed and CMV seropositive parents should not breastfeed
- Retrospective study 19 years (1997-2016) 43 children SCID at Texas Children's Hospital
  - 72% birth parents seropositive CMV
  - 61% continued breastfeeding their infants
  - Two developed CMV, one BF and one non-BF of seropositive birth parents; both engrafted after transplantation; one with GVHD; both alive 5 years post transplant
  - CMV transmission rate 1/19 (5%) in patients with SCID who received human milk from CMV+ birthparent

18

J Allergy Clin Immunol Pract 2019;7:2863-6

18

CMV Associated with Milk Composition and Infant Gut Microbiome and Growth in Full Terms



- Upregulation of indoleamine 2,3-dioxygenase tryptophan-to-kynurenine pathway in CMV + human milk
- Decreased *Bifidobacterium* in infants who received CMV + human milk
- Kynurenine positively associated with growth; CMV viral load negatively correlated with infant weigh-for-length at 1 month of age

19

Nature Communications (2024)15:6216

19

Objectives

At the conclusion of this presentation, participants will be able to:

1. Discuss the epidemiology, transmission, and clinical presentation of cytomegalovirus (CMV) in the neonatal period
2. Describe the role of human milk in the transmission of CMV in the neonatal period
3. Identify strategies to reduce or eradicate CMV from human milk
4. **Apply options for management of human milk feeding in a neonate with CMV infection**

20

20

Antivirals for CMV

- Congenital CMV: intravenous ganciclovir or oral valganciclovir (off-label) to prevent additional hearing loss and optimize developmental outcomes
  - AAP recommends valganciclovir be initiated within the first 13 weeks for 6 months following birth for infants with:
    - moderate to severe symptomatic congenital cytomegalovirus isolated cCMV associated sensorineural hearing loss (SNHL)
    - longer-term therapy (6 months vs. 6 weeks) has been shown to improve outcomes, especially when CNS involvement is present
- Acquired CMV: intravenous ganciclovir and oral valganciclovir approved for induction and maintenance treatment of CMV retinitis in immunocompromised adults, prophylaxis and treatment of CMV disease in adult transplant recipients, pediatric kidney transplant recipients 4 months and older and for pediatric heart transplant recipients 1 month and older.
  - treat CMV infections of other sites (esophagus, colon, lungs)
  - preemptive treatment of immunosuppressed adults with CMV antigenemia or viremia
- Adverse effects: myelosuppression, renal and hepatic toxicity, teratogenic in animals

21

AAP Committee on Infectious Diseases *Red Book, 2025-2027*

21

Future Research Questions for CMV and MOM

1. Are minimally symptomatic or asymptomatic infants who acquire CMV from human milk at similar risk for long term sequelae as symptomatic neonates?
2. Consensus on maternal sero-screening in lactating persons
3. Mechanisms of CMV infection donor/targets; understanding cell to cell spread of virus
4. Point-of-care testing of human milk to identify situations where treatment of human milk or receiving infant may be beneficial
5. Understanding why some, but not all, human milk fed infants become CMV-infected
6. Serial testing of VLBW infants for CMV viremia/viuria
7. Antiviral therapy for asymptomatic/minimally symptomatic neonates; new agents
8. Strategies to decrease CMV infectivity of human milk without impacting the beneficial properties
   a. anti-CMV immunoglobulins
   b. leukofiltration

JAMA Pediatrics Feb 2020; 174(2):121-3

22

22