

Recommendations for Minimizing Cytomegalovirus (CMV) Exposure in Breastmilk-Fed Very Low Birth Weight (VLBW) Preterm Infants

Background:

Human milk is the preferred feeding for all infants, including premature and sick newborns, with rare exceptions.¹ The benefits include improved digestion and absorption of nutrients, gastrointestinal function, neurodevelopment, host defenses and maternal psychological well-being.^{2,3} Studies also show a possible long-term protective effect against later childhood and adult diseases.¹ Preterm infants fed their own mothers' milk reach full enteral feedings sooner and tend to be discharged sooner, saving NICU costs.^{4,5} Despite the significant demonstrated benefits of human milk, potentially pathogenic infectious agents can be transmitted via breastmilk to the infant.

There is considerable evidence that shedding of CMV into breastmilk is a major source of CMV infections in early life⁶⁻⁸ with reported transmission rates of 6-76% for infants fed CMV-positive breastmilk.⁹⁻²⁰ Term infants with acquired CMV infections usually remain asymptomatic,²¹⁻²⁷ with the exception of immunocompromised patients.²⁸ Infants who do not acquire transplacental antibody to CMV develop symptomatic infections more frequently.²¹

Transfusion-acquired CMV infections cause serious or fatal symptoms in 50% of infected premature infants who had seronegative mothers.^{23,24} No serious symptoms were attributed to transfusion-acquired infections in preterm infants who had seropositive mothers. In one study³⁰ 17% of the preterm infants of seropositive mothers acquired CMV infection, despite receiving packed red blood cell transfusions from seronegative donors and banked human milk, as well as their own mother's fresh breastmilk. These premature infants demonstrated hepatosplenomegaly, thrombocytopenia, neutropenia and pulmonary morbidity. The authors postulated that loss of passively acquired antibody to CMV through catabolism and iatrogenic blood loss may predispose to a higher incidence of symptomatic infections in premature infants than would be expected in term infants. However, intravenous immunoglobulins failed to prevent maternal and nosocomial CMV transmission from occurring in premature neonates.^{31,32}

Protection from disease has been attributed to passively transferred maternal CMV antibody as well as to other nutritional and immunological factors in the breastmilk.²⁹ However, very premature infants appear to be more susceptible to CMV disease since they are born before the major transfer of protective immunoglobulin (~28 weeks), and have very immature immune systems.

A 1998 study identified infected breastmilk as the sole source of transmission of CMV in a cadre of preterm infants (less than 32 weeks, less than 1500 grams) of seropositive

mothers.¹⁴ The study involved serologic testing of mother and infant and viral culture and CMV PCR of breastmilk and infant urine. The transmission rate was 59% (17 of 29 exposed infants). Early onset (4-7 weeks), acute symptomatic illness, similar to that previously described^{30, 32, 33} occurred only in 5 extremely immature (24.4 ± 0.5 weeks) preterm infants. Expansion of this cohort to 170 VLBW infants in 2 subsequent papers^{32,34} from the same group revealed a transmission rate of 38% of infants of sero-positive mothers with 48% of those infected having at least 1 symptom (neutropenia, hepatopathy, thrombocytopenia, sepsis-like deterioration) and 12% of those infected having sepsis-like symptoms. Two infants (6%) of those infected required reintubation. The smallest, most immature infants had the highest rate of symptomatic infection, and there were 2 pairs of twins who were discordant for CMV transmission. CMV has also been implicated in gastrointestinal illness and necrotizing enterocolitis.³⁴⁻³⁶

Four more recent studies have found lower rates of transmission and clinical symptoms. Yasuda et al¹³ found 3 of 30 preterm infants (< 34 wks or < 2000 gm) exposed to CMV-DNA-positive breastmilk with confirmed infection; none were symptomatic. They found that most breastmilk became positive for CMV 2 weeks after delivery with viral DNA copy numbers peaking at 4-6 weeks postpartum. They explained their lower transmission rate on the fact their infants were slightly older and that all the breastmilk was frozen prior to thawing and feeding.

Jim et al¹⁷ found that the risk of infection was highest when mothers shed viable virus in their milk. Although 35 mothers had milk that was PCR-DNA positive, virolactia, as demonstrated by positive viral culture, was present in only 6 (17%). Overall transmission from CMV positive mothers was 15%, and more likely when the mothers had high CMV IgG levels. Maternal milk was routinely frozen at -18°C overnight or for several days before feeding. Mussi-Pinhata et al¹⁸ studied CMV transmission in a high CMV prevalence maternal population (98.4%) and in an NICU with no screening of blood for CMV. Under these circumstances they found a transmission rate of 22.1% with infection rates higher if the infant received natural expressed breastmilk at < 30 days of age, or for > 30 days. Clinical findings of possible CMV infection were found in 1 (4.8%) of 21 infected infants.

Finally, Miron et al,¹⁹ in a prospective study of 70 premature infants < 32 weeks and/or < 1500 gm, found 4 of 70 (5.6%) infants of CMV seropositive mothers who received expressed breastmilk acquired CMV infection between the age of 3-7 weeks. Breastmilk was refrigerated at -2 to -8°C and fed within 24 hours of expression. Only 1 infant had "severe" CMV disease with complete recovery and no sequelae at 2 year follow-up.

Long-term sequelae of CMV infection occurring in the first two months of life are also of concern, but difficult to separate from the complications of prematurity itself. In contrast to congenital CMV, perinatal infection has not been found to cause sensorineural hearing loss.^{30, 38} Increased risk of moderate to severe neurologic impairment was seen one,³⁷ but not the most recent follow-up study.³⁸

Several methods of killing the virus in milk have been studied, including freezing, pasteurization and rapid heating.³⁹⁻⁴³ CMV seronegative preterm infants who were fed banked human milk that was either pasteurized or frozen did not develop evidence of infection.³⁰ Short-term high temperature (72° C for 10 seconds) left no trace of infectious virus in cell tube cultures.¹⁴ Holder pasteurization and freezing (-20°C for 3 days) are known to inactivate CMV in naturally infected raw human milk.³⁹⁻⁴¹ Freezing and thawing (-20°C for 12 hours) has been shown to prevent vertical transmission of HTLV-I infection to breastmilk-fed babies as well.⁴⁴

Simmer et al⁴⁵ studied the effect of freezing for from 1-14 days in EBM from 19 CMV-seropositive women. CMV PCR was only positive in 12, and CMV actually cultured in 5, of the 19 women. After 7 days of freezing, CMV could not be cultured in any of the samples. In another study⁴⁶ of CMV seronegative mothers, fresh breastmilk was spiked with CMV with a fluorescent protein marker and cultured fresh or after freezing at -20°C and -70°C for 1 and 7 days. Viral recovery was greater (~100 fold) when the spiked milk samples were diluted 1:10 prior to plating. Freezing milk at -20°C dramatically reduced (93.5% at day 1 and 99% at 7 days), but did not completely eliminate CMV. There were no reductions in viral recovery at -70°C.

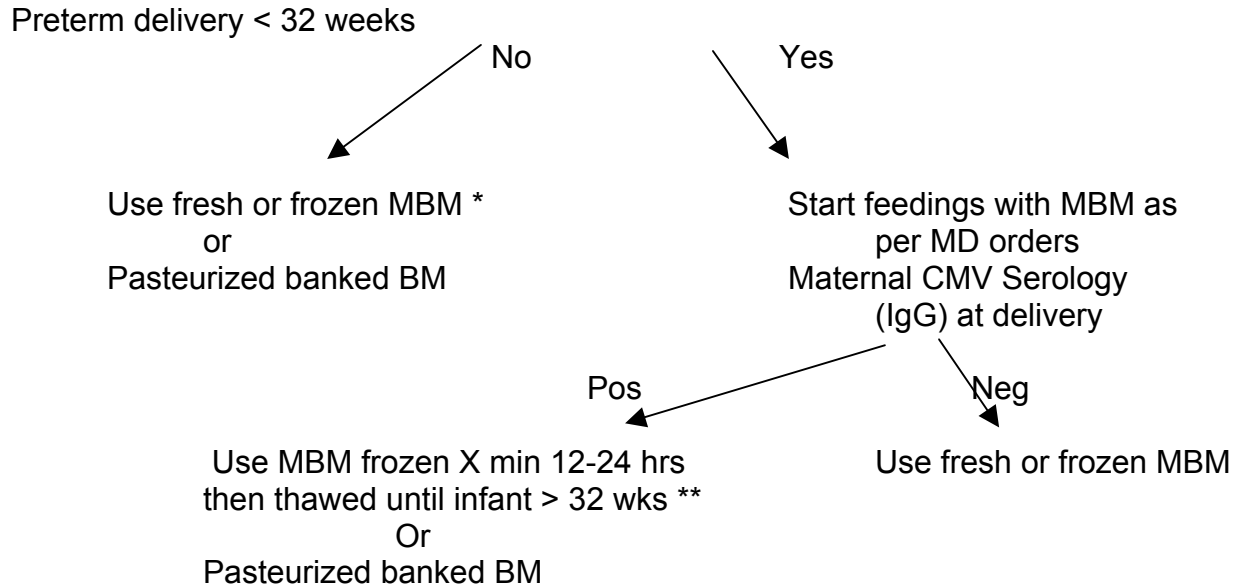
The authors of the largest CMV cohort study re-evaluated methods of eliminating CMV infectivity from human milk.⁴⁷ Holder pasteurization (62.5°C X 30 min) and a new short term high-temperature pasteurization (72°C X 5 seconds) were both able to destroy viral infectivity completely. The success of freeze-thawing strongly depended on the level of cell-free viro lactia at the time of inactivation. Freezing was not sufficient to kill CMV during maximum viro lactia, and was not able to completely destroy viral infectivity as viral load decreased. They concluded that DNA PCR was not appropriate to evaluate the success of CMV inactivation methods, as even high high viral loads may reflect only replication-incompetent virus particles.

These results indicate that there is a risk for serious disease in the very preterm infant by feeding even mothers' own expressed breastmilk. While the rate appears low and the risk for long-term sequelae limited, elimination of CMV from mothers' milk without damaging the nutritional and protective components should be the goal. Pasteurization removes infectivity and should be used for donated milk. For the mother's own milk, freeze storage, while less than the perfect solution, appears to lower the rate of transmission.⁴⁸ A recent review concluded that changes in practice could not be recommended without further studies.⁴⁹

Until a reliable method of removing viral infectivity is universally available, one approach would be to use pasteurized donor human milk or to heat-treat mothers' own milk. Such treatment currently alters the milk and is not readily available. Given the demonstrated risk of symptomatic CMV disease in extremely preterm infants, and the effectiveness of freezing in reducing viral load, we recommend freezing expressed human milk from seropositive women, before giving it to extremely immature infants. As a margin of

safety we recommend screening mothers for CMV seropositivity who deliver at < 32 weeks (~ < 1600 gms, AGA). Given the peak time of viro lactia of 3-4 weeks,¹⁴ the lower isolation rate from colostrum,^{8,9} and the likelihood that ELBW infants will not be fed in the first 12 hours of life, we believe initiating breastmilk feedings while maternal CMV screening studies are in progress is appropriate.

Recommended Procedure/Protocol:



* MBM = maternal breastmilk

** Some clinicians may choose to use frozen MBM until infant is nursing directly from the mother.

Evaluation

Infants greater than 3 weeks of age with signs and symptoms consistent with CMV (severe respiratory deterioration, leukopenia, thrombocytopenia, hepatitis) should be evaluated for CMV with saliva culture or urine shell vial culture for CMV and quantitative plasma PCR for CMV. If the culture or PCR is CMV positive the infection could be acquired, perinatal or congenital. If mother's CMV cultures are negative, blood transfusion records should be reviewed. As part of routine continuous quality improvement efforts we recommend data collection on these symptomatic infants and correlation with maternal screening results above.

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February 2005

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