Imported food risk advice

Cytomegalovirus in human milk and human milk products

Context of this risk advice

- Human milk means expressed milk collected from lactating women to be fed to infants that are not the biological infants of the women supplying the milk.
- Human milk products means products derived from human milk that have been specially formulated to meet the specific nutritional needs of infants such as fortifiers and formula.
- The level of risk for this hazard in human milk and human milk products was determined assuming that the most vulnerable category of infants (preterm infants in hospital neonatal intensive care units) would be receiving the products.

Nature of the hazard

Human cytomegalovirus (CMV) belongs to the *Herpesviridae* family of viruses. It is an enveloped virus with a DNA genome and icosahedral capsid (Mocarski et al. 2013; Pellett and Roizman 2013). CMV is sensitive to heat and is inactivated by pasteurisation (Hamprecht et al. 2004). Like all viruses, CMV can multiply in living host cells but cannot replicate in food (Codex 2012). In preterm infants CMV can infect many organs, causing incapacitating and potentially life threatening illness.

Transmission

CMV can be transmitted sexually, via mother-to-infant transmission (predominantly *in utero* or through human milk) or through contact with infected body fluids (Meier et al. 2005; Mocarski et al. 2013; Stowell et al. 2014). CMV can be transmitted through human milk to infants; a systematic review identified the transmission rate of CMV to preterm infants through human milk ranged from 5.6-58.6% (Kurath et al. 2010). Studies have demonstrated that infants that did not acquire CMV congenitally (negative for CMV at birth) acquired CMV infection postnatally after receiving CMV positive human milk (Capretti et al. 2009; Hayashi et al. 2011; Narvaez-Arzate et al. 2013).

CMV has been detected in human milk. A systematic review found that 52-97% of mothers analysed in the studies assessed were CMV-seropositive, with 66-96% of these seropositive mothers shedding CMV in their milk (Kurath et al. 2010). CMV infection is never completely cleared and remains latent for the life of the host (Mocarski et al. 2013). CMV can be reactivated in latently infected mothers and shed in their milk (Meier et al. 2005; Schleiss 2006).

Disease severity

In most cases CMV infection in full-term infants is asymptomatic. However, in postnatally infected premature neonates CMV is a serious hazard as it can cause incapacitating and potentially life threatening illness. Limited studies suggest that although at two years of age there appeared to be no neurodevelopmental effects, later in life there may be longer term cognitive consequences of postnatally acquired CMV infection in preterm infants (Hamprecht and Goelz 2017; Jim et al. 2015; Okulu et al. 2012). In preterm infants CMV infection can be asymptomatic, with a systematic review showing symptomatic disease developed in 0-83% of CMV infected preterm infants (Kurath et al. 2010). Symptoms of disease can include pneumonia, sepsis-like symptoms and multiple organ involvement, neutropenia[1], thrombocytopenia[2], cholestasis[3] and hepatitis with hepatosplenomegaly[4]. In rare cases the infection can be fatal (Jim et al. 2015; Lombardi et al. 2012; Lopes et al. 2016).

[1] An abnormally low count of neutrophils which leads to increased susceptibility to infection
[2] Low blood platelet count that can lead to bleeding problems
[3] Reduced bile flow from the liver
[4] Enlargement of the liver and spleen

Infectivity

CMV is moderately infectious, with transmission more common in human milk with higher viral loads. Viral shedding in human milk peaks around 4-8 weeks after birth and then declines during weeks 9-12. There is uncertainty around the viral load required to cause infection, with some reported cases of infection occurring at a peak viral load of 1500 DNA copies/ml of human milk, whereas other infants receiving a similar viral load did not become infected (Hamprecht et al. 2008; van der Strate et al. 2001; Wakabayashi et al. 2012). A study by van der Strate et al. (2001) has reported viral loads of over 7000 DNA copies/ml were required for transmission of CMV. Another study states that the majority of non-transmitters have a viral load of 1000-20,000 DNA copies/ml, and report a viral load of over 65,000 DNA copies/ml in human milk associated with transmission (Hamprecht et al. 2008).

Risk mitigation

Controls are needed to minimise contamination of human milk with CMV, including pasteurisation of the milk. An early study by Friis and Andersen (1982) showed that low temperature pasteurisation (63^{o}C) for 8 minutes killed all viable CMV in human milk. Holder pasteurisation (62.5^{o}C, 30 min) has been demonstrated to completely eliminate CMV infectivity and CMV-RNA in artificially inoculated human milk (Hamprecht et al. 2004). International human milk banks, including those in Australia, routinely perform Holder pasteurisation on human milk to ensure the microbiological safety of donor human milk (Bharadva et al. 2014; Hartmann et al. 2007; HMBANA 2015; UKAMB 2003).

Evaluation of uncertainty

There is uncertainty around the infectivity of CMV in human milk, with the viral load required for transmission of infection varying. There is also uncertainty around potential sequelae of CMV infection when acquired as a preterm infant.

Pooling of human milk from multiple donors is common practice amongst many human milk banks and would dilute the viral load from a single donor, however some milk banks only pool milk from individual donors (Haiden and Ziegler 2016). The Australian Red Cross milk bank pasteurises human milk in single donor batches (Australian Red Cross 2018).

Risk characterisation

There is evidence that CMV can be present in human milk and can be transmitted to infants via human milk. CMV is moderately infectious, with higher viral loads in the human milk associated with transmission. There is a very high likelihood of exposure due to the high incidence of mothers that are CMV seropositive and the high proportion of these CMV seropositive mothers that shed the virus in their milk. In preterm infants CMV causes serious disease. CMV in imported human milk and human milk products presents a potential medium or high risk to public health and safety.

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References

Australian Red Cross (2018) Milk bank media release. Australian Red Cross Blood Service, Melbourne. https://www.donateblood.com.au/milk-bank-media. Accessed 2 July 2019

Bharadva K, Tiwari S, Mishra S, Mukhopadhyan K, Yadav B, Agarwal RK, Kumar V, Infant and Young Child Feeding Chapter, Indian Academy of Pediatrics (2014) Human milk banking guidelines. Indian Pediatrics 51:469–474

Capretti MG, Lanari M, Lazzarotto T, Gabrielli L, Pignatelli S, Corvaglia L, Tridapalli E, Faldella G (2009) Very low birth weight infants born to cytomegalovirus-seropositive mothers fed with their mother's milk: A prospective study. The Journal of Pediatrics 154:842–848

Codex (2012) Guidelines on the application of general principles of food hygiene to the control of viruses in food (CAC/GL 79-2012). Codex Alimentarius, Rome. http://www.fao.org/fao-who-codexalimentarius/codex-texts/guidelines/en/. Accessed 22 May 2018

Friis H, Andersen HK (1982) Rate of inactivation of cytomegalovirus in raw banked milk during storage at -20 degrees C and pasteurisation. British Medical Journal 285:1604–1605

Haiden N, Ziegler EE (2016) Human Milk Banking. Annals of Nutrition & Metabolism 69:8–15

Hamprecht K, Goelz R (2017) Postnatal cytomegalovirus infection through human milk in preterm infants: Transmission, clinical presentation, and prevention. Clinics in Perinatology 44:121–130

Hamprecht K, Maschmann J, Müller D, Dietz K, Besenthal I, Goelz R, Middeldorp JM, Speer CP, Jahn G (2004) Cytomegalovirus (CMV) inactivation in breast milk: Reassessment of pasteurization and freeze-thawing. Pediatric Research 56:529–535

Hamprecht K, Maschmann J, Jahn G, Poets CF, Goelz R (2008) Cytomegalovirus transmission to preterm infants during lactation. Journal of Clinical Virology 41:198–205

Hartmann BT, Pang WW, Keil AD, Hartmann PE, Simmer K (2007) Best practice guidelines for the operation of a donor human milk bank in an Australian NICU. Early Human Development 83:667–673

Hayashi S, Kimura H, Oshiro M, Kato Y, Yasuda A, Suzuki C, Watanabe Y, Morishima T, Hayakawa M (2011) Transmission of cytomegalovirus via breast milk in extremely premature infants. Journal of Perinatology 31:440–445

HMBANA (2015) Guidelines for the establishment and operation of a donor human milk bank. Human Milk Banking Association of North America, Fort Worth

Jim WT, Chiu NC, Ho CS, Shu CH, Chang JH, Hung HY, Kao HA, Chang HY, Peng CC, Yui BH, Chuu CP (2015) Outcome of preterm infants with postnatal cytomegalovirus infection via breast milk: A two-year prospective follow-up study. Medicine 94:e1835-e1835

Kurath S, Halwachs-Baumann G, Müller W, Resch B (2010) Transmission of cytomegalovirus via breast milk to the prematurely born infant: A systematic review. Clinical Microbiology & Infection 16:1172–1178

Lombardi G, Garofoli F, Manzoni P, Stronati M (2012) Breast milk-acquired cytomegalovirus infection in very low birth weight infants. Journal of Maternal-Fetal & Neonatal Medicine 25:57–62

Lopes AA, Belhabri S, Karaoui L (2016) Clinical findings and autopsy of a preterm infant with breast milk-acquired cytomegalovirus infection. American Journal of Perinatology Reports 6:e198-e202

Meier J, Lienicke U, Tschirch E, Krüger DH, Wauer RR, Prösch S (2005) Human cytomegalovirus reactivation during lactation and mother-to-child transmission in preterm infants. Journal of Clinical Microbiology 43:1318–1324

Mocarski E, Shenk T, Griffiths PD, Pass RF (2013) Cytomegaloviruses. In: Knipe DM, Howley PM (eds) Fields virology, 6th edition, Ch 62. Lippincott Williams & Wilkins, Philadelphia, pp 1960–2014

Narvaez-Arzate RV, Olguin-Mexquitic L, Lima-Rogel V, Noyola DE, Barrios-Compean LM, Villegas-Alvarez C (2013) Cytomegalovirus infection in infants admitted to a neonatal intensive care unit. Journal of Maternal-Fetal & Neonatal Medicine 26:1103–1106

Okulu E, Akin IM, Atasay B, Çiftçi E, Arsan S, Tümen T (2012) Severe postnatal cytomegalovirus infection with multisystem involvement in an extremely low birth weight infant. Journal of Perinatology 32:72–74

Pellett PE, Roizman B (2013) Herpesviridae. In: Knipe DM, Howley PM (eds) Fields virology, 6th edition, Ch 59. Lippincott Williams & Wilkins, Philadelphia, pp 1802–1822

Schleiss MR (2006) Acquisition of human cytomegalovirus infection in infants via breast milk: Natural immunization or cause for concern? Reviews in Medical Virology 16:73–82

Stowell JD, Forlin-Passoni D, Radford K, Bate SL, Dollard SC, Bialek SR, Cannon MJ, Schmid DS (2014) Cytomegalovirus survival and transferability and the effectiveness of common hand-washing agents against cytomegalovirus on live human hands. Applied and Environmental Microbiology 80:455–461

UKAMB (2003) Guidelines for the establishment and operation of human milk banks in the UK. United Kingdom Association for Milk Banking, London. https://www.rcpch.ac.uk/sites/default/files/asset_library/Research/Clinical%20Effectiveness/Endorsed%20guidelines/Milk%20Banks/donor%20guidelines%203rd%20ed%20FINAL.pdf. Accessed 8 February 2018

van der Strate B, Harmsen MC, Schafer P, Swart PJ, The TH, Jahn G, Speer CP, Meijer D, Hamprecht K (2001) Viral load in breast milk correlates with transmission of human cytomegalovirus to preterm neonates, but lactoferrin concentrations do not. Clinical and Diagnostic Laboratory Immunology 8:818–821

Wakabayashi H, Mizuno K, Kohda C, Negoro T, Maekawa C, Sawato S, Tanaka K, Nakano Y, Murayama J, Taki M, Miyazawa T, Murase M, Aizawa M, Sakurai M, Takahashi K, Itabashi K (2012) Low HCMV DNA copies can establish infection and result in significant symptoms in extremely preterm infants: A prospective study. American Journal of Perinatology 29:377–382