Imported food risk advice

Herpes simplex virus 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

The two distinct types of herpes simplex virus (HSV)—type 1 (HSV-1) and type 2 (HSV-2) (Schneweis 1962)—belong to the *Herpesviridae* family of enveloped viruses with linear double-stranded DNA genomes and icosahedral capsids (Roizman et al. 2013).

HSV-1 typically causes oral herpes ('cold sores') and can also cause genital herpes. HSV-2 infections typically cause genital herpes (James et al. 2014; Looker and Garnett 2005).
In newborns, both HSV-1 or HSV-2 infections can cause a range of symptoms, including severe illnesses with chronic neurologic sequelae (James et al. 2014; Whitley et al. 1980).

Transmission

Transmission of HSV most often occurs through intimate person-to-person contact. The virus must come in contact with mucosal surfaces or damaged skin for infection to occur (Gutierrez et al. 2011; Roizman et al. 2013).

Approximately 67% of the world population under the age of 50 are infected with HSV-1 (Looker et al. 2015). Infection rates in children by five years of age range from 20% to 33% (higher to lower socioeconomic statuses, respectively) (Chayavichitsilp et al. 2009).

Neonatal HSV infection can occur via mother-to-infant transmission in utero (approximately 5% of cases), during birth (85% of cases) or postnatally (10% of cases). In Australia, the estimated incidence of neonatal herpes is 3.27 cases per 100,000 live births (Jones et al. 2014). In the United States, estimates range from 12 to 60 neonatal cases per 100,000 live births (Corey and Wald 2009). Postnatal acquisition usually involves someone in close contact with the infant shedding HSV from the mouth; exposure to HSV from a breast lesion; or exposure to a herpetic finger lesion in the nursery (Kimberlin 2007).

Case reports have documented severe HSV-1 infections in infants associated with HSV-positive breast lesions in the mothers (Field 2016; Sullivan-Bolyai et al. 1983). However, these were attributed to direct contact of the infant with the lesions, rather than transmission through human milk. There are no reports on expressed human milk being contaminated with HSV via shedding from herpetic breast lesions.

There is limited literature documenting the presence of HSV in human milk derived from mothers without herpetic lesions on their nipples/breast, and human milk has not been confirmed as a route of HSV transmission:

- (Dunkle et al. 1979) describe a case of possible postnatal HSV-1 infection via human milk, where virus was culturable from milk expressed 9 days postpartum. Serology confirmed the mother's prior infection with the virus, although she had no history of symptomatic disease, and virus was not culturable from oral or genital sources or from milk expressed a further 10 days later. Although transmission to the infant might have occurred via human milk, perinatal transmission could not be ruled out.

- (Kotronias and Kapranos 1999) showed that HSV DNA could be detected in human milk samples from 47% (n=34) of new mothers exhibiting no clinical signs of HSV infection. HSV-1 and HSV-2 were found concurrently in some milk samples, and HSV-2 was found alone in others, demonstrating that both HSV types can be shed in human milk. However, the authors acknowledge that their results do not indicate whether the virus was in latent or replicating (hence infectious) state, and they could not be certain that neonatal illness resulted from its presence.

Both (Chayavichitsilp et al. 2009) and (James et al. 2014) assert that HSV is not transmitted through human milk, but provide no supporting evidence or references.

Disease Severity

HSV is a severe hazard in newborns. Both types of HSV can cause potentially life threatening illness with chronic sequelae (CDC 2018). However, because of the increasing incidence of HSV-1 genital infections in the general population, the majority of neonatal HSV infections are now caused by HSV-1 (James et al. 2014).

Neonatal HSV infections acquired postnatally are usually classified as:

- disease limited to the skin, eyes, and/or mouth (SEM disease)
- central nervous system disease, with or without skin lesions (CNS disease)
- disseminated HSV disease involving multiple visceral organs, including lung, liver, adrenal glands, skin, eye, and/or the brain (disseminated disease) (Kimberlin 2007).

SEM disease is most common in neonates (approximately 45–60% of neonatal HSV infections), followed by CNS disease (30%) and disseminated disease (25–40%) (James et al. 2014; Jones et al. 2014). Patients with disseminated disease commonly present with viral sepsis, including respiratory collapse, liver failure and disseminated intravascular coagulopathy[1] (James et al. 2014). CNS disease manifests with symptoms like lethargy, irritability, tremors, poor feeding and temperature instability. Other symptoms more indicative of underlying encephalitis can also be present, including a bulging fontanelle and focal or generalised seizures (James et al. 2014). Cutaneous lesions can be a diagnostic clue, but up to 40% of infants with disseminated disease and 35% of infants with CNS disease do not develop a vesicular rash during the course of their illness (James et al. 2014).

The most significant sequela of neonatal HSV disease is neurological impairment. Approximately 17% of survivors of disseminated disease and 69% of survivors of CNS disease have chronic neurologic conditions (e.g. seizures, psychomotor retardation, spasticity[2], blindness, and learning disabilities) (Kimberlin 2007; Sukhbir 2013). In contrast, fewer than 2% of SEM disease patients who receive antiviral therapy experience developmental delay (Thompson and Whitley 2011). Although not of the same significance, cutaneous recurrences are also a common sequela (Kimberlin 2007). With the use of retroviral therapy, disseminated disease and CNS disease have a fatality rate of 29% and 4%, respectively (Kimberlin 2007).

Infectivity

The infective dose of HSV in human milk or any other transmission route is not known. Mathematical modelling predicts that HSV-2 transmission through sexual contact is unlikely at viral loads less than 10^4 HSV DNA copies (Schiffer et al. 2014), implying that the virus is only mildly infectious.

Risk mitigation

In experimental culture media, heat treatment has been shown to be effective at inactivating HSV. For example:

- (Croughan and Behbehani 1988) reported a 2-log reduction in titre of both HSV-1 and HSV-2 after 5 minutes at 56°C, and showed that treatment at 56°C for 30 minutes reduced the viral titres of HSV-1 and HSV-2 from 6.5 log and 5.5 log, respectively, to <1 log.
- (Moriuchi et al. 2000) reported 95-99% reduced infectivity of HSV-1 and HSV-2 after 30 minutes at 56°C, and loss of measurable infectivity after 1 hour.
- Extrapolation from the thermal inactivation curves of (Kabuta et al. 1969; Plummer and Lewis 1965) implies that Holder pasteurisation (62.5°C for 30 min) should inactivate HSV.

[1] Condition in which blood clots form throughout the body, blocking small blood vessels, contributing to organ failure. The concomitant exhaustion of factors and platelets, along with high levels of fibrin degradation products affecting platelet function and fibrin cross-linking, potentially result in profuse bleeding from various sites.

[2] Condition in which certain muscles are continually contracted.

International human milk banks, including those in Australia, routinely perform Holder pasteurisation to ensure the microbiological safety of donor human milk (Bharadva et al. 2014; Hartmann et al. 2007; HMBANA 2015; UKAMB 2003).

Suitable hygiene controls are needed in human milk banks to minimise contamination of human milk with HSV. International human milk banks follow guidelines for the storage, processing, and handling of human milk and train staff in health, hygiene, and quality and safety controls to ensure the safety of donor milk (Haiden and Ziegler 2016; PATH 2013).

Evaluation of uncertainty

There is uncertainty around the transmissibility of HSV through human milk. The US Centers for Disease Control and Prevention (CDC) recommend against feeding expressed milk from breasts with active herpetic lesions due to the potential for contamination, whereas the American Academy of Pediatrics state that expressed milk from breasts with herpetic lesions is safe and there is no concern for transmission to the infant (CDC 2018; Eidelman and Schanler 2012). Postnatal transmission of HSV can occur from mothers with infectious lesions on their breast or nipple (Field 2016; Sullivan-Bolyai et al. 1983), and direct contact is a major route of transmission, but the number of infectious particles required to cause infection is unknown. If assumed to be the same as estimated for HSV-2 transmission through sexual contact, very large quantities of the virus would be required for illness.

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).

There is limited literature documenting the presence of HSV in human milk derived from mothers without herpetic lesion on their nipples/breast, and transmission of the virus to infants through this route has not been unequivocally demonstrated.

Risk characterisation

Neonatal HSV infection causes severe, life-threatening disease with likelihood of substantial chronic sequelae. However, viral infectivity is very low and the likelihood of exposure is very low. While viral DNA has been detected in human milk, there is limited evidence for the presence of viable, infective HSV virions. There is limited evidence of neonatal illness arising from the presence of virus in human milk. Documented cases of postnatal mother-to-infant transmission have involved direct contact with skin lesions or have not ruled out perinatal exposure as possible routes of transmission.

In imported human milk and human milk products HSV does not present a potential medium or high risk to public health and safety.

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