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Prevention of Cytomegalovirus (CMV) Transmission via Maternal Breast Milk to an Infant with Severe Combined Immunodeficiency (SCID) using Kimie: New Compact Breast Milk Pasteurizer

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Keywords
Pasteurization, Pasteurizer, SCID, CMV, Breast Milk.

Abbreviations
BM: Breast milk, CMV: Cytomegalovirus, DBM: Donor breast milk. DBMB: Donor breast milk bank, EBM: Expressed breast milk. GA: Gestational AG, HSCT: Hematopoietic stem cell transplantation, MBM: Maternal breast milk, NBS: Newborn screening, NICU: Neonatal Intensive Care Unit, PBM: Pasteurized breast milk, PDBM: Pasteurized donor breast milk, SCID: Severe Combined Immuno-Deficiency, TREC: T-cell recombination excision circle.

Case History
Our patient was born to a 27-years old G1P0 mother at 39 weeks of gestational age (GA) by spontaneous onset vaginal delivery. His mother had appropriate prenatal care and an otherwise normal pregnancy. His Apgar scores were 8 and 9 at 1'and 5' of life. He was appropriate for GA; weighed 3.55 kg (50 %). Head circumference 33 cm (55 %) and the length 51 cm (85 %). Shortly after birth he developed mild respiratory distress and required supplemental oxygen for 36 hours. Because of respiratory distress he was evaluated for bacterial sepsis and treated with antibiotics for two days. During the hospital stay he received colostrum plus maternal breast milk (MBM) and supplemental formula. After negative blood culture results, he was discharged home on the second day of life.

Newborn screening (NBS) demonstrated low T cell recombination excision circles (TREC) of 6 copies /µL Additional screening is recommended if TREC copies are less than 17 /µL [1]. At 7 days of age his lymphocyte count was 335 cells / cmm, slightly higher than threshold (300) for the diagnosis of classical Severe Combined Immunodeficiency (SCID [1]. Nonetheless, he was severely lymphopenic and concerning for SCID [1]. Recommendations for infants with SCID include cessation of MBM at the time of possible diagnosis of SCID, and to assess maternal status for CMV status [1,2]. Patient evaluation for CMV demonstrated that he did not have an active CMV infection (negative serum CMV RT-PCR). Maternal testing was positive for serum CMV IgG antibodies, negative for CMV IgM antibodies and negative for CMV RT-PCR. These results imply she did not have active CMV viremia. However, these results are consistent with prior maternal CMV infection with a high possibility for reactivation and transmission of CMV to our patient via MBM [2-5]. Preventing CMV infection in infants with SCID is crucial [1-3]. When there is evidence of prior maternal CMV infection, the options for infant nutrition are to withhold MBM, use infant formula or pasteurized donor breast milk (PDBM) because Holder pasteurization (heating to 62.5* C) inactivates CMV [2,5-10].

Natural MBM is the best feeding option for all neonates. It's importance for the overall well-being of the infant is well established. Whenever natural MBM is not available, insufficient or not suitable, DBM is the second-best option. However, this approach is not ideal since PDBM is donated by several women who are few months post-partum, is pooled before pasteurization [11,12]. PDBM is also expensive, current cost $ 6-7 / oz plus shipping. Therefore, it would be ideal if natural mother's BM could be pasteurized safely, efficiently and would be cost effective. Kimie is a new, compact, portable, automated Holder device capable of pasteurizing 5 to 500 ml of expressed breast milk (EBM) during each cycle [13,14]. We had recently imported Kimie from Pune, India. Parents were informed about the feeding option of using infant formula, PDBM obtained from a commercial donor breast milk bank (DBMB) or his mother's EBM pasteurized using Kimie. They chose to utilize pasteurized MBM.

The patient is currently 15 months old and is followed by primary care and pediatric immunology. While receiving baby food and his own mother's PEBM his lymphocyte counts have remained low (between 300 and 1500) but stable (Table 1). Genetic testing showed a lack of pathogenic gene associated with classical SCID. Therefore, his initial diagnosis of presumed SCID was later adjusted to non-SCID lymphopenia. At his recent check at 15 months of age, his urine and blood CMV tests have remained negative. His growth and development have been totally appropriate for age: weight 14 kg (99.9 %) HC 47cm (80%) and length 79.5 (85%). He has not suffered from any major infection. He had an episode of immune mediated hemolytic anemia at 10 months of age which resolved after red blood cell transfusions, corticosteroid and intravenous immunoglobin therapy. He has undergone initial evaluation for hematopoietic stem cell transplant (HSCT), but thus far the decision has been made to continue closely monitoring T cell lymphopenia without HSCT.

Table 1: T cell counts (cells / cmm): Consistently low at various ages.

Age	Total T (CD3+)	Helper (CD4+)	Cytotoxic (CD8+)
1 week	335	235	144
2 months	832	622	132
3 months	351	255	52
5 months	453	312	70
6 months	611	432	91
10 months	602	353	153
12 months	449	291	83

Materials and Methods

The technical details of Kimie (Shreeyash Electro Medical, Pune, India) flown in by air under the commodity code number 84198998 have been described [13,14]. In the USA, a BM pasteurizer is considered a catering device not requiring FDA approval. Members of the Centinela Hospital Executive Medical Board had approved the use of Kimie. The Neonatal Intensive Care Unit (NICU) at Centinela Hospital possesses a Tissue Bank License (State of California, CTB 00082083) necessary for using any DBM. There are no other state regulations when biological mother's BM is pasteurized for her own baby [15]. All precautions and standards established by the Human Milk Banking Association of North America (HMBANA) regarding the use of PBM including data collection and documentation were strictly followed [11,12]. After obtaining informed written consent, parents were educated about the importance of personal hygiene, expression, collection, handling, storage and transportation of BM [11,12]. Before pasteurization, frozen EBM was thawed using Waterless Milk Warmer (Madela, McHnery, Illinois, USA) already in use in the NICU. Thawed BM was pasteurized using Kimie according to the written instructions and the video provided [16]. The stainless-steel cylinders and the plastic lids were mostly sterilized using Sterrad hydrogen peroxide plasma based low temperature device, or at times by immersing in hot water as recommended by the manufacturer [16]. PBM collected in plastic bottles was stored at 4* C. A parent, mostly the dad, had to drive ~ 80 miles in a day in busy Los Angeles traffic to deliver frozen EBM and to collect PBM from the hospital. The volume of EBM ranged from 30 to 1400 ml/day. It was collected and kept frozen at home prior to transfer on ice packs to the hospital. Generally, BM was pasteurized every day or every other day. At times it was necessary to run the pasteurization cycle three times a day. The pasteurization cycle took 2 to 2½ hours. The mother was able to express BM till our patient was about fourteen months age.

Discussion

SCID encompasses multiple genetic disorders characterized by impaired T-cell development and function with an inability to produce antibodies [1,2,17,18]. NBS for SCID was first piloted in 2008 in Wisconsin. At present all states in USA are screening for SCID [2,17,18]. Therefore, most cases are diagnosed before the onset of symptoms mostly related to infection. The overall incidence of SCID is 1/50000 live births [1-3,17,18]. SCID is treatable by enzyme replacement or gene therapy or HSCT [1,2,17,18]. While waiting many children acquire infection which has a significant negative impact on the 5-year survival and success of the HSCT [1-3,17,18]. Our patient did not have a pathogenic variant in a gene known to cause SCID or have < 300 lymphocyte count [1]. Thus, he did not meet the criteria for the diagnosis of classical SCID [1]. However, he had abnormal TRECs and consistently low (<1500) lymphocyte count. Therefore, the diagnosis of non-SCID lymphopenia. These patients are a heterogenous group. Some may resolve lymphopenia and have normal immune function, others may worsen and may need HSTC transplant or some may have sub-normal immune function not to the severity of needing HSTC transplant.

Other conditions with non-SCID T-cell lymphopenia include Di George syndrome, TBX1intragenic mutation, ataxia telangiectasia, CHARGE and Down syndrome, VACTERL and Noonan syndrome, Kabuki makeup and Jacobsen syndrome, CLOVES and Fryns syndrome, immune-osseous dysplasia, gastroschisis and Thrombocytopenia absent radii syndrome [2]. If the mother of a baby with any of these conditions is seropositive for CMV and the baby is lymphopenic, pasteurization of mother's BM may be indicated. With the availability of Kimie it should be easy to do so.

Kimie 500

Kimie 3000

Among infections, CMV is of major concern because of high prevalence of seropositive mothers (~ 70 %) and early shedding of CMV into the BM (~ 20 %) [19]. In infants with SCID, the incidence of maternal to neonatal transmission of CMV was 5% and 6 % [1,3]. While exact data was not provided, all patients out of 59 with SCID who developed CMV were fed BM [20]. In a cohort of 100 patients, maternal to neonatal transmission of CMV was a major contributor to mortality [21]. In a review of 240 patients who received HSCT, 7 % were diagnosed with CMV infection [22]. Five-year survival in infants more than 3.5 months old with active or resolved infection was 50 % and 82 % respectively which is less than 94 % in those without infection [22]. Therefore, preventing CMV infection in these children is of highest priority. Holder pasteurization completely eliminates CMV [6-9]. Therefore, use of PDBM is suggested when the mother is CMV seropositive and the baby has SCID [1,2]. Preventing CMV infection from natural mother's BM without decreasing its immunologic or nutritional benefits would be an important strategy in protecting immuno-comprised infants. Holder pasteurization decreases sIgA, lactoferrin, lysozyme, the number and function of cells [23]. However, it is unclear if these findings are clinically relevant. While freezing of EBM at -20* C for varying period (3-20 days) does not decrease sIgA, lysozyme, lactoferrin, nutritional composition or the number of functional cells, it does not completely eliminate CMV infection [23]. Therefore, this approach is generally not practiced.

Beyond a doubt natural mother's BM is the best feeding option for all neonates. It's importance for growth, development and overall wellbeing of the infant is well established. Therefore, American Academy of Pediatrics recommends exclusive BM feeding until six months of age with continued BF until one year while introducing other foods [24]. While ~ 85 % of infants in the USA are breast fed at birth, ~ 60 % are breast fed at 6 months of age (range 38-75 %) [24]. Our patient's mother was dedicated to provide EBM for 14 months.

Kimie is user friendly, needs limited space and training, does not require special plumbing or electrical connections, water is recycled and is inexpensive compared to other pasteurizers (Figure 1). While we pasteurized EBM in the hospital setting, it can be easily done at home. In addition to the machine, a refrigerator preferably with a freezer, a sink, sterile and non-sterile gloves, sterile 5-10 ml syringe, mask, soap and water, large plastic or metal container, plastic bottles to store milk and defined space will be needed. While we used low temperature gas sterilization in the hospital setting, stainless steel cylinders and plastic lids can be sterilized using hot water at home [16]. Initially both parents can be trained in the hospital setting before using Kimie at home. Leasing Kimie for home installation will not be only cost effective and convenient but it will eliminate the need to freeze EBM and the hassle of driving many miles in a metropolitan city. A parent can use the machine at his convenience especially if it is necessary to run multiple cycles.

After we used Kimie for about three months, we recognized there was a need to have a machine with a larger capacity. Kimie-3000 is the genesis of our request (Figure 2).

In summary, our patient is the first infant with non-severe SCID at risk of acquiring CMV infection from his mother's BM who received his own mother's PEBM. Not only he has remained CMV free but has grown and developed appropriately. More infants need to be treated similarly to establish the safety and efficacy of this approach.

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References

1. Dorsey MJ, Dvorak CC, Cowan MJ, et al. Treatment of infants identified as having severe combined immunodeficiency by means of newborn screening. J Allergy Clin Immunol. 2017; 139: 733-742.
2. Verbsky J, Routers J. Screening for and treatments of congenital immunodeficiency diseases. Clinics in Perinatology. 2014; 41: 1001-1015.
3. Kelty WJ, Beatty SA, Wu S, et al. The role of breast-feeding in cytomegalovirus transmission and hematopoietic stem cell transplant outcomes in infants with severe combined immunodeficiency. J Allergy Clin Immunol Pract. 2019; 7: 2863-2865.
4. Qasim W, Davies EG, Rao K, et al. How I treat combined immune- deficiency. Blood. 2013; 122: 3749-3758.
5. Thaker MS, Hintermeyer MK, Gries MG, et al. A practical approach to newborn screening for severe combined immunodeficiency using the T cell receptor excision circle assay. Front Immunol. 2017; 8: 1470.
6. Lawrence RM. Cytomegalovirus in human breast milk: Risk

to the premature infant. Breastfeeding Medicine. 2006; 1.

7. Forsgren M. Cytomegalovirus in breast milk: reassessment of pasteurization and freeze-thawing. Pediater Res. 2004; 56: 526-528.
8. Friis H, Andersen HK. Rate of inactivation of cytomegalovirus in raw banked milk during storage at -20 ° C and pasteurization. BMJ (Clin Res Ed). 1982; 285: 1604-1605.
9. Hamprecht K, Goelz R. Postnatal cytomegalovims infection through human milk in preterm infants transmission, clinical pres¬entation, and prevention. Clin Perinatal. 2017; 44: 121-130.
10. Bialas KM, Swamy GK, Permar SR. Perinatal CMV and varicella zoster virus infections. Epidemology, prevention and treatment. Clin Perinatal. 2015; 42: 61-75.
11. Jones F. Best practice for expressing, storing, and handling human mil in hospitals, homes and child care settings. 4th Edition, 2019.
12. HMBNA. Guidelines for the establishment and operation of a donor human milk bank. 2018.
13. Waghmare SP, Kharche A, Kalane SU, et al. KIMIE: New human breast milk pasteurizer: fully automated, user friendly, cost effective device for universal application. Research Square. 2020.
14. Devaskar UP, Waghmare SP. Human donor breast milk bank: What is on the horizon?. BJSTR. 2020; 30: 23750-23753.
15. https://www.cdph.ca.gov/Programs/OSPHLD/LFS/Pages/FacilityLicensingHome.aspx
16. www.shryeesh.india.com
17. Routes JM, Grossman WJ, Verbsky J, et al. Statewide newborn screening for severe T-cell lymphopenia. JAMA. 2009; 302: 2465-2470.
18. Vora SB, Englund JA. Cytomegalovirus in immunocompromised children. Current opinion in infectious diseases. 2015; 28: 323-329.
19. Walter JE. Heimall J. CMV-seropositive mothers of SCID: To breast-feed or not?. J of allergy and clinical immunology. 2019; 7: 2866-2867.
20. Gasper HB, Qasim W, Davies EG, et al. How I treat severe combined immunodeficiency. Blood. 2013; 122: 3749-3758.
21. Heimall J, Logan BR, Cowan MJ, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. Blood. 2017; 130: 2718-2727.
22. Pai SY, Logan BR, Griffith LM, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med. 2014: 371: 434-446.
23. Bardanzellu F, Fanos V, Reali A. Human breast milk acquired cytomegalovirus infection: Certenties, doubts and perspectives. Curr Pediatr Rev. 2019; 15: 30-41.
24. www.cdc.gov/breastfeeding