Office of Evidence Based Practice (EBP) – Critically Appraised Topic: Use of Donor Breastmilk

Special Care Question
Use of Donor Breast Milk and Donor Milk Derived Human Milk Fortifier In the ICN: Summary of the Evidence

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Significance and importance of the question:
Mother's own milk (MOM) is the ideal milk for infants. For mothers of infants born preterm, initiating and sustaining a milk supply can be difficult. Donor human milk (DHM) is a source of nutrition when MOM is not available and bovine protein formula is not desired.

Although feeding MOM has been shown to improve neurodevelopment (Lucas & Cole, 1990), protect against necrotizing enterocolitis (Huston et al., 2014) and late onset infections (Patel et al., 2013) it is not clear if DHM confers the same benefits. DHM adds to the cost of an infant's ICN stay, but the balance between the cost of DHM and the savings incurred by decreasing length of stay by reducing the complications of prematurity, especially necrotizing enterocolitis (NEC) is not clear.

Since 2013, human milk fortifier derived from human milk (HUM) rather than human milk fortifier derived from bovine milk (BOV) is commercially available. It is unknown HUM derived fortifier added to MOM or DHM is beneficial. Three very low quality cohort studies (Assad, Elliott, & Abraham, 2016; Hair et al., 2016; Huston et al., 2014) are included in this synthesis.

Clinical Bottom Line:

Based on very low quality evidence we make a weak recommendation to use DHM and HUM derived fortifiers. Three factors support the recommendation:
(a) Agreement with the American Academy of Pediatrics Policy on Breastfeeding and the Use of Human Milk (Eidelman, 2012). However when studies that used strong research methods are separated from studies that had high risk of bias, the occurrence of NEC was not different between the feeding groups.
(b) The non-inferiority of an exclusive HUM milk diet (Quigley & McGuire, 2014). Although for short term growth, infants fed formula have shorter time to regain birthweight, and significantly greater incremental weight (g/kg/d) and length (mM/wk) gains. Only two of the studies included in Quigley & McGuire, 2014) reported upon long-term growth, and neither study reported differences in weight, length, or head circumference at nine months, 18 months, or 7.5-8 years post term. (Lucas & Cole, 1984; Morely & Lucas, 2000)
(c) The potential cost savings by potentially decreasing the incidence of NEC (See Figure 1). Further research is likely to have an important influence on our confidence in the estimate of effect, and is likely to change the effect.

Synthesis of the Literature by Outcome:

Donor Human Milk versus Preterm Formula when MOM is not available-

A Cochrane systematic review and meta-analysis (CDSR) on this question was published by Quigley & McGuire (2014). Only studies that from Quigley & McGuire (2014) that used preterm infant formula as a comparison are included in this synthesis. Since then, two studies have been published and have been added to the analysis (Sullivan et al., 2010; Corpelejin et al., 2012).

NEC

Seven studies that included 1382 subjects are included in the meta-analysis. The addition of two studies to the CDSR does not change the estimate of the effect (See Figure 1). When donor breast milk is fed the odds of NEC are lower than when preterm formula is fed OR= 0.54, 95% CI [0.35, 0.85]. In absolute terms, when donor milk is fed there are 35 fewer cases of NEC per 1000 infants with a range of 11-50 fewer occurrences of NEC. However, when the included research is separated by studies with low risk of bias and those with moderate to high risk of bias, the studies with low risk of bias report the odds of NEC to be no different in infants fed donor milk versus those fed preterm formula OR= 0.61, 95% CI [0.36, 1.05] or 5 more to 71 fewer per 1000 infants. Three of the four studies with high risk of bias were published in the 1980s (See Table 1 and Figure 1).

Confidence in the data remains very low. The range of publication dates in the included studies is concerning. Changes in neonatal care have evolved from the 1980s to the present and influence our confidence on the estimate of effect. Like the studies in the CDSR, NEC was not the primary outcome variable in Corpelejin et al (2016) or Sullivan et al (2010), therefore the studies may not have been powered to detect a difference in the occurrence of NEC. Further research, if performed, is likely to have influence on our confidence in the in the estimate of the effect, and likely will change the estimate.

Growth and Development

Five studies that included 366 subjects reported on incremental weight and length gains reported that infants fed donor breast milk had

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Plain Language Summary: Although mother's own milk is the ideal milk for infants, for mothers of infants born preterm providing breast milk can be difficult. Mother's own milk has been shown decrease infections and necrotizing enterocolitis (NEC). Donor milk banks are able to pasteurize donated human milk and maintain the beneficial qualities of human milk. Pasteurization increases the cost over the cost of infant formula. However, if donor human milk can be shown to decrease the infections and NEC in preterm infants, it may be the best way to provide nutrition to preterm infants.

There is reduced occurrence of NEC in infants fed human milk, either mother's own milk, donor human milk, or human milk derived fortifiers.. A cost study showed an expected cost savings of approximately $8000 per infant fed donor milk. Those fed donor milk also had shorter stays in the hospital. Further studies that compare the two milks are needed to increase our confidence in these findings.

Search Strategy and Results:
PubMed search performed on November 3 2016: Search was perform to locate research published since the publication of the (Quigley & McGuire, 2014) CDSR.

("human milk"[tw] OR "breast milk"[tw]) AND ("Milk Banks"[Mesh] OR "donor breast milk"[tw] OR "milk bank*"[tw] OR "donor milk"[tw]) AND ("2014/01/01"[PDat] : "2017/12/31"[PDat]) 146 results

CINAHL search performed on November 3 2016:

S1-(MH "Milk Banks") OR "donor milk" OR "milk bank*" OR "donor breast milk"- 330 results
S2- (MH "Milk, Human") OR "breast milk" OR "human milk" 4009 results
S3- S1 AND S2 288 results
S4- S1 AND S2 with Limiters - Published Date: 20140101-20161231 0 results

(Quigley & McGuire, 2014) included studies that compared term infant formula or preterm infant formula to DHM. For this review, studies that compared term human milk to term formula are excluded. Since (Quigley & McGuire (2014), one randomized control trial was identified (Corpelejin et al., 2016). Therefore, six studies that included 1175 subjects are included in this review, and there were 68 events of NEC (5.8%).

Excluded articles and reason for exclusion:

First Author	Year	Reason for exclusion
(Colaizy, 2014)	2014	Narrative review
(Kair, Colaizy, Hubbard, & Flaherman, 2014)	2014	Donor Milk
(Meier, Patel, & Esquerra-Zwiers, 2017)	2017	Narrative review
(Panczuk, Unger, O'Connor, & Lee, 2014)	2014	Narrative review
(Unger, Gibbins, Zupancic, & O'Connor, 2014)	2014	Protocol only
(Williams, Nair, Simpson, & Embleton, 2016)	2016	Does not answer the question, answers the effect of availability of DHM on maternal breast feeding rates

Method Used for Appraisal and Synthesis:
The Team Leader identified the following outcomes for review: NEC, Infection, Growth and Development, and Cost.
The Evidence Based Scholars used the Review Manager 5.3 software to analyze single studies.

EBP Team Member Responsible for Reviewing, Synthesizing, and Developing this Document: Nancy H. Allen, MS, MLS, RD,LD

Figures

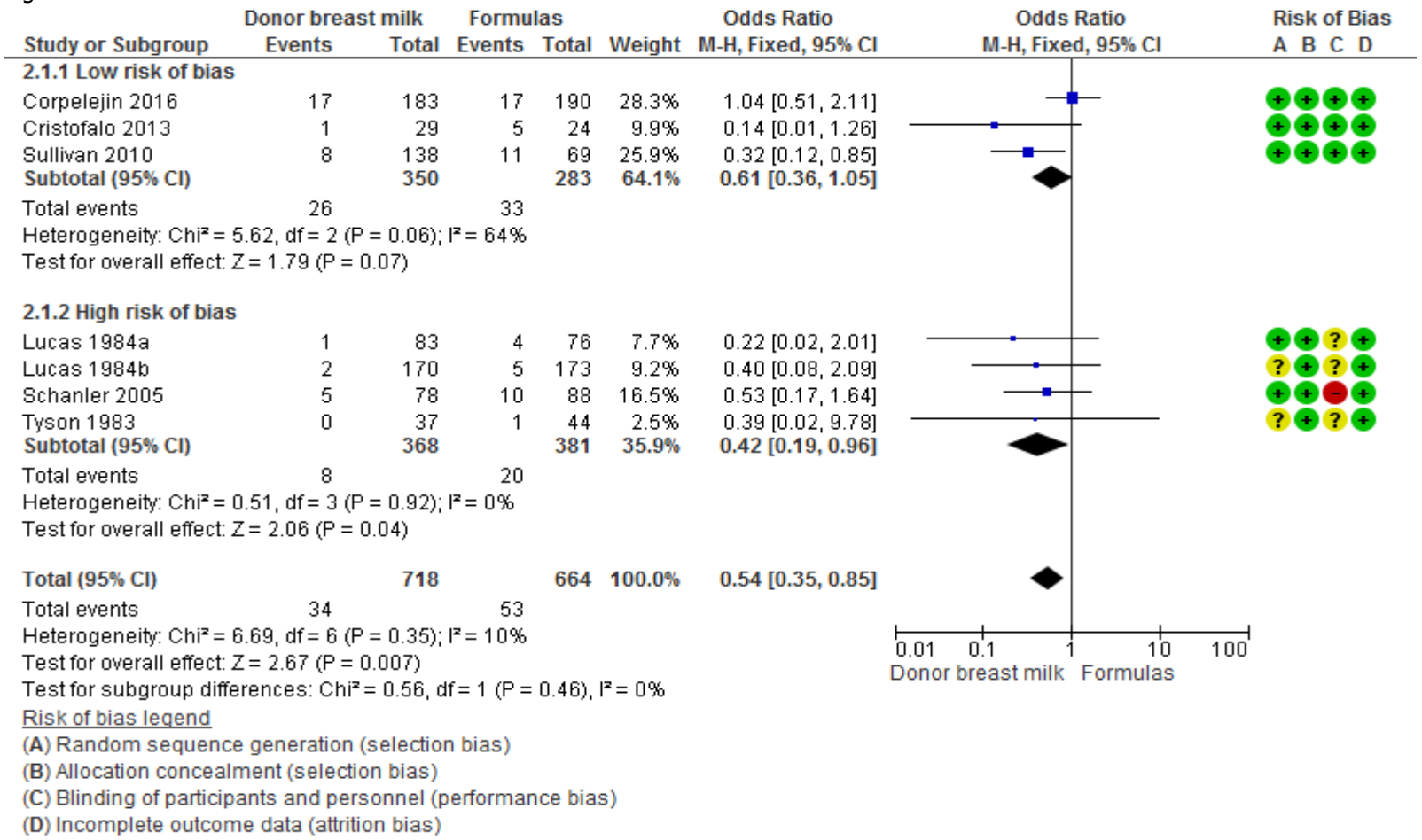

Figure 1. Donor Human Milk vs. Preterm Formula used as primary nutrition, or supplemental nutrition when MOM was not available, Outcome: Necrotizing Enterocolitis (NEC). Overall, infants in the group that used supplemental donor breast milk had lower odds of NEC. However, when studies with low risk of bias are analyzed separately from those with high risk of bias, there is no difference in the odds of NEC. (for the MOM/ donor milk group, either BOV or DHM was used as fortifier).

GRADE Tables

Table 1.

GRADE Analysis: Donor Human Milk versus Preterm Formula in the Intensive Care Nursery
Bibliography: (Quigley and McGuire 2014) and (Corpeleijn, de Waard et al. 2016)

№ of studies (95% CI) (95% CI)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients Donor Breast	Effect Formula	Quality	Relative	Importance	
Weight change (g/kg/d)												
5	randomized trials	serious [a]	very serious [b]	not serious	very serious [c]	none	228	240	-	MD **3.71 gm/kg/d lower** (4.63 lower to 2.79 lower)	⨁◯◯◯ VERY LOW	
Change in Length MM/week												
5	randomized trials	serious [a]	very serious [b]	not serious	not serious [c]	none	180	186	-	MD **2.02 mM/wk lower** (2.68 lower to 1.36 lower)	⨁◯◯◯ VERY LOW	
Necrotizing Enterocolitis (NEC)												
7	randomized trials	serious [a]	not serious	not serious	very serious [c,d]	none	34/718 (4.7%)	53/664 (8.0%)	**OR 0.54** (0.35 to 0.85)	**35 fewer per 1,000** (from 11 fewer to 50 fewer)	⨁◯◯◯ VERY LOW	
Necrotizing Enterocolitis (NEC) - Low risk of bias												
3	randomized trials	not serious	not serious	not serious	very serious [c]	none	26/350 (7.4%)	33/283 (11.7%)	**OR 0.61** (0.36 to 1.05)	**42 fewer per 1,000** (from 5 more to 71 fewer)	⨁⨁◯◯ LOW	
Necrotizing Enterocolitis (NEC) - High risk of bias												
4	r randomized trials	serious [a]	not serious	not serious	very serious [c, d]	none	8/368 (2.2%)	20/381 (5.2%)	**OR 0.42** (0.19 to 0.96)	**30 fewer per 1,000** (from 2 fewer to 42 fewer)	⨁◯◯◯ VERY LOW	

Note. **CI:** Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations:

a. Two of the included studies did not report random sequence generation, three did not report if the participants and personnel were blinded to the intervention. One study did not blind participants and personnel.

b. There is wide variation in the confidence intervals, and the I2 statistic > 50%. The I2 statistic is an indicator of heterogeneity, and < 50% is desired.

c. There is a low number of subjects in the included studies. Studies with small number of subjects are subject to greater sampling variation and precision is reduced.

d. Individual studies have wide confidence intervals. Imprecision is graded higher when there is a low number of events. For this outcome, there are 68 cases of NEC reported. For low risk of imprecision, events should be greater than 300.

References:

Assad, M., Elliott, M. J., & Abraham, J. H. (2016). Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. J Perinatol, 36(3), 216-220. doi:10.1038/jp.2015.168

Colaizy, T. T. (2014). Donor human milk for preterm infants: what it is, what it can do, and what still needs to be learned. Clin Perinatol, 41(2), 437-450. doi:10.1016/j.clp.2014.02.003

Corpeleijn, W. E., de Waard, M., Christmann, V., van Goudoever, J. B., Jansen-van der Weide, M. C., Kooi, E. M. W., . . . van Zoeren-Grobben, D. (2016). Effect of Donor Milk on Severe Infections and Mortality in Very Low-Birth-Weight Infants. JAMA Pediatrics, 170(7), 654-661. doi: 10.1001/jamapediatrics.2016.0183

Corpeleijn, W. E., Kouwenhoven, S. M., Paap, M. C., Van Vliet, I., Scheerder, I., Muizer, Y., . . . Vermeulen, M. J. (2012). Intake of own mother's milk during the first days of life is associated with decreased morbidity and mortality in very low birth weight infants during the first 60 days of life. Neonatology, 102(4), 276-281.

Eidelman, A. I. (2012). Breastfeeding and the use of human milk: an analysis of the American Academy of Pediatrics 2012 Breastfeeding Policy Statement. Breastfeed Med, 7(5), 323-324. doi:10.1089/bfm.2012.0067

Ganapathy, V., Hay, J. W., & Kim, J. H. (2012). Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. Breastfeed Med, 7(1), 29-37. doi:10.1089/bfm.2011.0002

Hair, A. B., Peluso, A. M., Hawthorne, K. M., Perez, J., Smith, D. P., Khan, J. Y., . . . Abrams, S. A. (2016). Beyond Necrotizing Enterocolitis Prevention: Improving Outcomes with an Exclusive Human Milk-Based Diet. Breastfeed Med, 11(2), 70-74. doi:10.1089/bfm.2015.0134

Huston, R. K., Markell, A. M., McCulley, E. A., Pathak, M., Rogers, S. P., Sweeney, S. L., . . . Gardiner, S. K. (2014). Decreasing necrotizing colitis and gastrointestinal bleeding in the neonatal intensive care unit: The role of donor human milk and exclusive human milk diets in infants </= 1500 g birth weight. ICAN: Infant, Child & Adolescent Nutriton. doi:10.1177/1941406413519267

Kair, L. R., Colaizy, T. T., Hubbard, D., & Flaherman, V. J. (2014). Donor Milk in the Newborn Nursery at the University of Iowa Children's Hospital. Breastfeeding Medicine, 9(10), 547-550.

Lucas, A., & Cole, T. J. (1990). Breast milk and neonatal necrotising enterocolitis. Lancet, 336(8730), 1519-1523.

Meier, P., Patel, A., & Esquerra-Zwiers, A. (2017). Donor Human Milk Update: Evidence, Mechanisms, and Priorities for Research and Practice. J Pediatr, 180, 15-21. doi:10.1016/j.jpeds.2016.09.027

Morely, R., & Lucas, A. (2000). Randomized diet in the neonatal period and growth performance untils 7.5-8 y of age in preterm children. American Journal of Clinical Nutrition, 71, 822.

Panczuk, J., Unger, S., O'Connor, D., & Lee, S. K. (2014). Human donor milk for the vulnerable infant: a Canadian perspective. International breastfeeding journal, 9(1), 1.

Patel, A. L., Johnson, T. J., Engstrom, J. L., Fogg, L. F., Jegier, B. J., Bigger, H. R., & Meier, P. P. (2013). Impact of early human milk on sepsis and health-care costs in very low birth weight infants. J Perinatol, 33(7), 514-519. doi:10.1038/jp.2013.2

Quigley, M., & McGuire, W. (2014). Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev(4), CD002971. doi:10.1002/14651858.CD002971.pub3

Sullivan, S., Schanler, R. J., Kim, J. H., Patel, A. L., Trawoger, R., Kiechl-Kohlendorfer, U., . . . Lucas, A. (2010). An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr, 156(4), 562-567 e561. doi:10.1016/j.jpeds.2009.10.040

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