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

**Team Members:** Steve Olsen, MD

**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 Corpeleijn 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 less incremental weight gain and incremental length MD = -3.71 gm/kg/d, 95% CI [-4.63, -2.79] and MD -2.02 MM/week, 95% CI [-2.68, -1.36], respectively, than infants fed preterm formula (See Figures 2 and 3). Corpeleijn et al. (2016) did not include data on growth and development and Sullivan et al (2010) reported their as data as medians, with interquartile ranges.

Cost
A cost study reported the mean net savings in hospital costs for each extreme preterm infant owning to the exclusive HUM arm (MOM, DHM and HUM derived fortifier) compared to BOV milk supplements and fortifiers as $8,167.00, 95% CI [$4,405, $11,930] (Ganapathy, Hay, & Kim, 2012). The average cost per unit of the feedings used:

<table>
<thead>
<tr>
<th>Product</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor human milk</td>
<td>$0.10/ml</td>
</tr>
<tr>
<td>Preterm infant formula</td>
<td>$0.03/ml</td>
</tr>
<tr>
<td>Donor human milk fortifier</td>
<td>$6.25/ml</td>
</tr>
<tr>
<td>Bovine human milk fortifier</td>
<td>$1.30/packet</td>
</tr>
</tbody>
</table>

Human Milk Derived Fortifier vs Bovine Milk Derived Fortifier
Three retrospective chart review papers have been published on this question (Assad et al., 2016; Hair et al., 2016; Huston et al., 2014). (See Table 2) The overall quality of the evidence is very low. By design, the included studies did not randomize patients into treatment groups. The treatments occurred as a before vs. after the availability of human milk derived fortifier at the hospitals. Although the rate of NEC was lower in the groups fed EHM, only an association can be implied. Moreover, since the included studies are not RCTs, it is unknown if there are enough
subjects to determine a difference. Further research, if performed will is likely to have an important influence on our confidence on the estimate of effect.

**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.

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:**

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

**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.
**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).
Figure 2. Donor Human Milk vs. Preterm Formula, Outcome: Incremental Weight Gain (g/kg/d). Daily weight gain an indicator of growth is desired in the ICN. Infants fed donor milk had significantly less weight gain than those fed formulas.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Donor breast milk</th>
<th>Formulas</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Cristofalo 2013</td>
<td>15</td>
<td>5.8</td>
<td>29</td>
<td>17</td>
<td>7.1</td>
</tr>
<tr>
<td>Lucas 1984a</td>
<td>12.8</td>
<td>2.6</td>
<td>28</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Lucas 1984b</td>
<td>14.3</td>
<td>3.1</td>
<td>59</td>
<td>16.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Schanler 2005</td>
<td>17.1</td>
<td>5</td>
<td>78</td>
<td>20.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Tyson 1993</td>
<td>12.4</td>
<td>4.8</td>
<td>34</td>
<td>24.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>228</td>
<td>240</td>
<td>100.0%</td>
<td>-3.71 [-4.63, -2.79]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 38.06, df = 4 (P < 0.00001); I² = 89%

Test for overall effect: Z = 7.91 (P < 0.00001)

Risk of bias legend:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Incomplete outcome data (attrition bias)
Figure 3. Donor Human Milk vs Preterm Formula, Outcome: Incremental Length gain (MM/week). Increases in length, an indicator of growth is desired in the ICN. Infants fed donor milk had significantly less incremental gains in length than those fed formulas.
# 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)

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No. of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Weight change (g/kg/d)</td>
<td>5 randomized trials</td>
<td>serious a</td>
<td>very serious a</td>
<td>not serious</td>
</tr>
<tr>
<td>Change in Length MM/week</td>
<td>5 randomized trials</td>
<td>serious a</td>
<td>very serious a</td>
<td>not serious</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (NEC)</td>
<td>7 randomized trials</td>
<td>serious a</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (NEC) - Low risk of bias</td>
<td>3 randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (NEC) - High risk of bias</td>
<td>4 randomized trials</td>
<td>serious a</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

**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.

Table 2.

GRADE Analysis: Human milk derived fortifier compared to bovine milk derived fortifier for pre-term infants

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>NEC</td>
<td>observational studies</td>
<td>very serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

CI: Confidence interval; OR: Odds ratio

a. There is heterogeneity across the three studies, two include infants with birthweights < 1250 grams, while the third studies uses birthweight < 1500 grams as the cutoff
b. There is heterogeneity across the three studies for type of feeding. Exclusive human milk diet (EHM) for all studies was mother's own milk (MOM), donor human milk (DHM) and human milk derived human milk fortifier (HUM). However, in the comparison group, two of the studies included infants fed preterm formula (PTF) along with infants fed MOM or DHM with bovine derived human milk fortifier (BOV).
References:


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.


Updated: 3/1/2011, 11/30/2016, 1/31/2017