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ORIGINAL ARTICLE

Quality indicators for human milk use in very low-birthweight infants: are we measuring what we should be measuring?

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OBJECTIVE: The objective of this study was to compare the currently used human milk (HM) quality indicators that measure whether very low-birthweight (VLBW; <1500 g birthweight) infants 'ever' received HM and whether they were still receiving HM at discharge from the neonatal intensive care unit (NICU) to the actual amount and timing of HM received.

STUDY DESIGN: This study used data from a large NIH-funded cohort study and calculated whether VLBW infants ever received HM (HM-Ever) and of these infants, the percentage who were still receiving HM at NICU discharge (HM-DC). Then, the HM-DC indicator (exclusive, partial and none) was compared with the amount and timing of HM feedings received by these same infants.

RESULT: Of the 291 VLBW infants who met inclusion criteria, 285 received some HM (HM-Ever = 98%). At NICU discharge (HM-DC), 24.2, 15.1 and 60.7% were receiving exclusive, partial and no HM, respectively. Of the 60.7% infants with no HM-DC, some had received higher amounts of HM during the NICU hospitalization than infants categorized as exclusive and partial for HM-DC. Of the infants with no HM-DC, 76.8 and 59.7% had received exclusive HM during the days 1–14 and days 1–28 exposure periods, respectively.

CONCLUSION: The average daily dose (HM-DD; in ml kg^{-1} d^{-1}) and cumulative percentage (HM-PCT; as % of cumulative enteral intake) of HM feedings were sufficient to significantly reduce the risk of multiple morbidities, including late-onset sepsis, necrotizing enterocolitis, neurocognitive delay and rehospitalization, in the majority of the VLBW infants who were discharged with no HM-DC. Quality indicators that focus on the amount and timing of HM feedings in the NICU should be added to the HM-Ever and HM-DC measures.

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INTRODUCTION

Human milk (HM; milk from the infant's own mother) feedings during the neonatal intensive care unit (NICU) hospitalization reduce the risk of prematurity-related morbidities in a dose-response manner for very low birth weight (VLBW; <1500 g birth weight; includes extremely low birth weight; ELBW; <1000 g birth weight) infants.[1] These morbidities, which include late-onset sepsis, necrotizing enterocolitis, chronic lung disease and retinopathy of prematurity, prolong the NICU hospitalization, increase health-care costs and predispose the infant to long-term health and educational problems.[1–8] A dose-response relationship between the amount of HM feedings received during the NICU hospitalization and a reduction in the risks of neurodevelopmental delay and re-hospitalization at 18 and 30 months of age, corrected for prematurity, has also been demonstrated for this population.[9,10] These clinical outcomes have led individual NICUs and care networks to establish quality improvement programs focused on increasing the use of HM during the NICU hospitalization for VLBW infants.[11,12]

A first step in this quality improvement process is the identification of measurable HM quality indicators that reflect the latest evidence. For HM feedings in the NICU, recent research has consistently linked the amount and timing of HM feedings with a reduction in the risk of morbidities during and after the NICU hospitalization in VLBW infants.[1] However, the current quality indicators for HM feeding in the NICU do not measure the amount or timing of HM feeding. Instead, these indicators measure two simple characteristics of HM feeding: (1) whether the infant ever received any HM milk during the NICU stay, regardless of the amount or timing of the milk and (2) whether the infant was receiving exclusive, partial and no HM feedings on the day of NICU discharge.[11–13] Although calculations based on the use of the current HM quality indicators are simple and easy to perform, the indicators are imprecise and do not reflect the amount and timing of actual human milk feedings that impact health outcomes during and after the infant's NICU hospitalization.

The purpose of this study was to compare the currently used HM quality indicators to the actual amount and timing of HM received by VLBW infants during the NICU hospitalization to determine whether the quality indicators provide adequate information about HM feeding in the NICU. Specifically, we described the amounts of HM received during critical periods of the NICU hospitalization (days 1–14 and days 1–28 post-birth) as well as throughout the NICU stay, and then compared these data with the currently used HM quality indicators of ever receiving HM and still receiving HM at the time of NICU discharge.

METHODS

Sample

This study is part of a larger ongoing prospective cohort study examining health outcomes and cost of HM feedings for VLBW infants conducted in a 57-bed tertiary NICU in Chicago.[14] For the larger study, all eligible infants and their mothers were offered enrollment, and data were collected from

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the time of the infant's NICU admission through NICU discharge. Eligibility criteria for the larger study included the following: birth weight <1500 g; gestational age $\leqslant 35$ weeks; absence of severe congenital anomalies; negative maternal drug screen at birth; admitted to the study NICU within 24 h of birth; infant under legal custody of birth mother; and feedings initiated before day 14 of life. Maternal initiation of lactation was not an inclusion criterion for enrollment. In the case of multiple births, one infant from each set of multiples was selected randomly for inclusion in the study. For the research reported here, additional exclusions included infants who did not survive were transferred to another institution before NICU discharge, or whose length of stay was over 180 days. This study was approved by the Rush University Institutional Review Board, and signed informed consent was obtained from parents or guardians of all enrolled subjects.

Measures

All measures were extracted from the database for the larger study and included maternal and infant demographic and clinical data, as well as the following daily measures for each infant: weight, intake (ml) of clear intravenous fluids, parenteral nutrition fluids, HM and formula.

Human milk quality indicators. The two current HM quality indicators are (1) whether an infant had ever received HM (HM-Ever) and (2) whether the infant was receiving HM at the time of NICU discharge (HM-DC). These variables were calculated for each infant in the following manner. If any HM feedings had been documented in the database for the infant, regardless of the amount or timing, the HM-Ever was classified as 'yes'. If only formula feedings were documented, the HM-Ever was classified as 'no'. HM-DC was calculated by examining the infant's type of feedings on the last full day of hospitalization before NICU discharge (12A–12A), and classifying infants into three mutually exclusive categories: exclusive HM (only fortified or unfortified HM, and no formula); partial HM (some HM and some formula); and no HM (only formula; no HM). During the study period, no human donor milk was used; hence, the infants received only their own mother's milk. This milk was fortified with proprietary powdered bovine additives following a standardized procedure.

Amount of HM feedings. The amount of HM feedings received by infants was measured both as a weight-adjusted daily dose (ml kg^{-1} d^{-1}) and as a percentage of total enteral feedings that consisted of HM. These measures were selected because several studies have demonstrated either a reduction in the risk or the incidence of a specific morbidity as a function of receiving either a threshold dose[2,6,9,10,15,16] or percentage of HM feedings.[3–5,8]

Daily dose of human milk (HM-DD). The HM-DD was calculated for each infant for each day of the NICU hospitalization as follows. The total number of ml of HM (fortified and unfortified) received by the infant during a 24 h period from 12AM to 12AM was summed, and then divided by the infant's measured weight for that day, and expressed as ml kg^{-1} d^{-1}.

Daily percentage of enteral feedings consisting of HM (HM-PCT). The HM-PCT was calculated to determine the relative amounts of human milk and formula received by each infant for each day of the NICU hospitalization as follows. For a 24 h period from 12AM to 12AM, the total number of ml of HM and formula were calculated. Then, the ml of HM was divided by the sum of the ml of HM and formula and then multiplied by 100 ({ml HM/[ml HM + ml formula]} $\times$ 100).

Timing of HM feedings. The timing of HM feedings was measured by creating three post-birth exposure period variables that have been linked to a reduction in the risk and/or incidence of morbidities in VLBW infants as a function of the amount of HM received: the first 14 days post-birth (days 1–14);[3–5,8] the first 28 days post-birth (days 1–28; includes the first 14-days post-birth);[2,6,16] and the total NICU hospitalization.[9,10,16] For each of these exposure periods, the average daily dose of HM (average HM-DD) and the cumulative percentage of HM (Cumulative HM-PCT) were calculated.

Average HM-DD. The average HM-DD was calculated for each infant for the exposure period of interest by summing the individual HM-DDs for each infant for the days within the exposure period and then dividing this sum by the number of days in the exposure period. Average HM-DD was calculated for days 1–14, days 1–28 and the total NICU hospitalization.

Cumulative HM-PCT. The Cumulative HM-PCT was calculated as the percentage of enteral intake that consisted of HM over the specific exposure period, rather than being calculated as a daily measure and then summed. Specifically, for the exposure period of interest, the ml of HM and formula for the days within the exposure period were summed. Then, the sum of the ml of HM was divided by the sum of ml of HM plus the sum of the ml of formula, and this figure was multiplied by 100 ({sum of ml HM/[sum of ml HM + sum of ml formula]} $\times$ 100]. Cumulative HM-PCT was calculated for days 1–14, days 1–28 and the total NICU hospitalization.

Data analyses

Data were analyzed using Excel (Redmond, WA, USA) and SPSS 15.0 (Chicago, IL, USA). Descriptive statistics were used to summarize the demographic characteristics of infants and the HM feeding variables and for all dose and exposure period measures.

RESULTS

A total of 324 VLBW infants were enrolled into the larger cohort study between February 2008 and August 2012. Of these 324 subjects, 291 infants met the inclusion criteria for this analysis. Of the 33 ineligible subjects, 26 infants were transferred to a different institution before NICU discharge, hence HM-DC could not be verified. An additional three infants did not survive, and four had a length of stay that exceeded 180 days.

Quality indicator #1: ever received HM during the NICU hospitalization (HM-Ever)

Of the 291 infants in the study, 285 received some HM during the NICU hospitalization, corresponding to a value of 98% for the HM-Ever quality indicator. The characteristics of the infants who ever and never received HM are reported in Table 1. For the 285 infants who received HM during the NICU hospitalization, the average HM-DD and cumulative HM-PCT are summarized in Table 2. For the 285 infants, the actual fed volume of HM during the NICU hospitalization ranged from 3 to 28 229 ml. For the days 1–14 and 1–28 exposure periods, 63.2 and 44.8%, respectively, of these infants received exclusive HM feedings. The median cumulative HM-PCT for days 1–14 and days 1–28 were 100 and 98%, respectively.

Table 1. Characteristics of the sample ($n = 291$)

	HM-Ever = Yes *n = 285*	*HM-Ever = No* *n = 6*
Gestational age (weeks)[a]	28.5 ± 2.3	30.6 ± 2.3
Birth weight (grams)[a]	1063.8 ± 252.4	1266.2 ± 173.8
Maternal age (years)[a]	27.7 ± 6.5	25.2 ± 7.8
Maternal race/ethnicity[b]		
White	53/285 (18.6%)	0/6 (0.0%)
Black	147/285 (51.6%)	5/6 (83.3%)
Hispanic	80/285 (28.1%)	1/6 (16.7%)
Other	5/285 (1.8%)	0/6 (0.0%)
Male gender[b]	156/285 (54.7%)	2/6 (33.3%)
Multiple gestation[b]	41/285 (14.4%)	5/6 (83.3%)
% WIC eligible[b]	136/261 (65.3%)	6/6 (100%)
Length of hospitalization (days)[a]	71.4 ± 31.0	41.7 ± 13.1
PMA at discharge (weeks)[a]	38.7 ± 2.9	36.6 ± 1.3
Weight at discharge (grams)[a]	2616.7 ± 623.3	2220.0 ± 452.1

Abbreviations: HM, human milk; PMA, postmenstrual age; WIC, Women, Infants, and Children food assistance program.
[a]Data are presented as either mean ± s.d.
[b]Frequency (%).

Table 2. Amount of HM feedings received during three NICU exposure periods for infants categorized as receiving exclusive, partial, or no HM at the time of discharge from the NICU ($n = 285$)

HM-DC	*n (%)*	*Average HM-DD (ml kg^{-1} d^{-1})*		*Cumulative HM-PCT (%)*	
		Median	*25–75 percentile*	*Median*	*25–75 percentile*
Exclusive HM					
Days 1–14	69 (24.2%)	44.9	16.4–71.6	100	100–100
Days 1–28	64 (23.7%)[a]	84.2	58.9–108.8	100	100–100
NICU hospitalization	69 (24.2%)	120.6	108.7–133.4	100	99.6–100
Partial HM					
Days 1–14	43 (15.1%)	28.7	17.0–62.1	100	72.3–100
Days 1–28	40 (14.8%)[a]	71.1	37.5–91.3	97.8	62.3–100
NICU hospitalization	43 (15.1%)	88.7	68.0–115.2	73.5	49.9–90.9
No HM					
Days 1–14	173 (60.7%)	14.6	4.8–37.3	100	58.4–100
Days 1–28	166 (61.5%)[a]	26.6	9.2–61.4	68.3	20.4–100
NICU hospitalization	173 (60.7%)	18.0	6.5–52.9	11.7	3.9–39.7
Total sample					
Days 1–14	285 (100%)	21.9	7.2–48.9	100	84.1–100
Days 1–28	270 (100%)[a]	45.7	14.4–84.7	98.0	38.6–100
NICU hospitalization	285 (100%)	58.3	13.0–109.3	45.0	9.0–95.4

Abbreviation: HM, human milk.
[a]Total reflects infants that were discharged home prior to 28 days post-birth.

Quality indicator #2: human milk feeding at NICU discharge (HM-DC)

Of the 285 infants who ever received HM, the HM-DC status was 69 (24.2%) of the infants were receiving exclusive HM feedings, 43 (15.1%) were receiving partial HM feedings and 173 (60.7%) were receiving no HM. Table 2 summarizes the medians of average HM-DDs and medians of cumulative HM-PCTs for each category of HM feeding at discharge (exclusive, partial or no HM), during the critical periods (days 1–14 and 1–28) and for the entire NICU hospitalization.

Table 2 reveals that of the 173 infants categorized as receiving no HM at NICU discharge, many of the infants had received significant amounts of HM, especially during the early post-birth exposure periods of days 1–14 and days 1–28. Of these infants receiving only formula at the time of NICU discharge, 44 (25.4%) of the infants received an average HM-DD $\geqslant 50$ ml kg^{-1} d^{-1} for the entire NICU hospitalization, and 29.6% of NICU days consisted of exclusive HM feedings. In addition, for the no HM at NICU discharge infants, 76.8 and 59.7% received exclusive HM during days 1–14 and days 1–28, respectively. The median cumulative HM-PCTs for days 1–14 and days 1–28 were 100% and 68.3%, respectively.

Figures 1a and b show graphically that some infants categorized as no HM at NICU discharge had actually received higher amounts of HM and higher cumulative proportions of HM than did infants categorized as partial or exclusive HM feedings at NICU discharge during the first 28 days of life.

DISCUSSION

The findings from this study illustrate the limitations in using HM-Ever and HM-DC as the only quality indicators for evaluating the use of HM for VLBW infants in the NICU. Of the 291 infants enrolled in our study, 285 (98%) were categorized as receiving some HM, using the HM-Ever quality indicator, and 112 (39.3%) of these infants were categorized as still receiving some HM at the time of NICU discharge using the HM-DC measure. Thus, the HM-DC quality measure was not met for 173 (60.7%) infants, all of whom were grouped into a single 'no HM' category, regardless of the actual amount and timing of HM feedings that were received during the NICU hospitalization. It is easy to conclude that the NICU did not achieve quality HM use for 60.7% of the infants in this study.

However, a closer look at the data for the 285 infants who ever received HM reveals that irrespective of the HM-DC status, the amount of HM they received was sufficient to reduce the risk of many morbidities during and after the NICU hospitalization.[1–10,16] For example, the median of average HM-DDs for the NICU hospitalization was 58.3 ml kg^{-1} d^{-1}, an amount of HM that exceeds the <50 ml kg^{-1} d^{-1} threshold dose that has been linked to a reduction in the risk of several morbidities during the NICU hospitalization.[2,6,16] Furthermore, even smaller amounts of HM received during the NICU hospitalization have been shown to impact morbidities in the post-NICU period in a dose-response manner.[2–5,8–10] In one large multi-site study of 1034 ELBW infants, each 10 ml kg^{-1} d^{-1} of HM during the NICU hospitalization translated into points gained in neurodevelopmental and behavioral scores and in a reduction in the risk of rehospitalization at 18 and 30 months of age, corrected for prematurity.[9,10] Thus, even the infants in our study who received <50 ml kg^{-1} d^{-1} of HM during the NICU hospitalization would be at lower risk for these post-NICU morbidities than infants who never received HM, regardless of the HM-DC quality measure.

Our findings about the extremely high amounts of HM received during days 1-14 and days 1-28 for this cohort further exemplify the limitations in the currently used HM-DC quality indicators. Several outcome studies have addressed the impact of HM feedings in the reduction in the risk, incidence and severity, and cost of NEC and late-onset sepsis in VLBW infants, and these studies form the scientific basis for prioritizing the use of HM in this population.[1–5,5–8,15,16] However, these prematurity-specific morbidities are not affected by whether or not the infant is still receiving HM at the time of NICU discharge; they are mediated by the amount of HM received in days 1–14 and days 1–28. For example, Johnson *et al.*[8] demonstrated a threefold increase in the

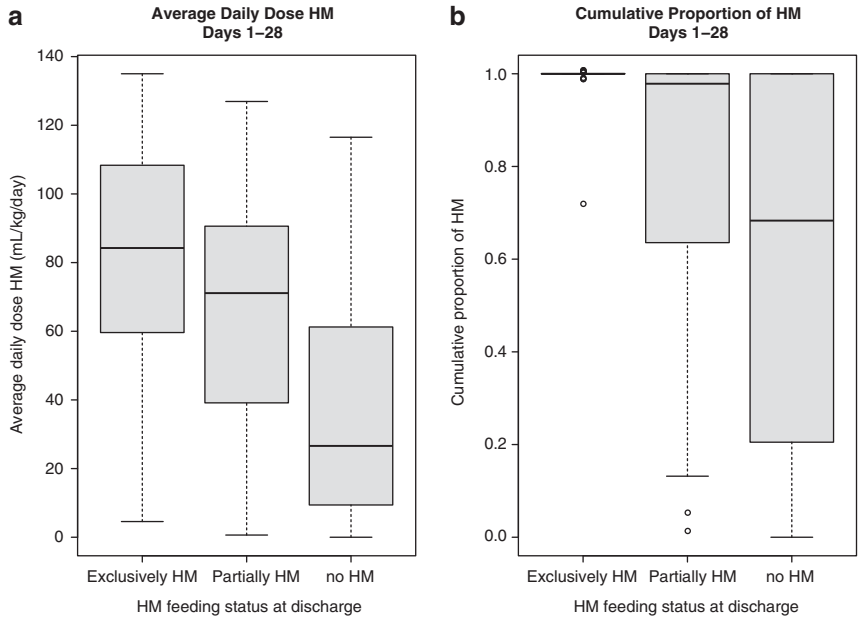

Figure 1. HM intake over the first 28 days of life. (**a**) Dose of HM expressed as average daily dose (ml kg^{-1} d^{-1}); (**b**) cumulative proportion of HM to enteral feedings. Both panels demonstrate that some infants categorized as no HM at NICU discharge had actually achieved cinically important amounts of HM during the first month of life.

risk of NEC in VLBW infants as a function of receiving any formula (for example, < 100% cumulative HM-PCT) during days 1–14, and Sisk *et al.*[3] reported a sixfold reduction in the risk of NEC when VLBW infants received a cumulative HM-PCT ⩾50% during this same days 1–14 exposure period. Similarly, Patel *et al.*[2] demonstrated a dose-response relationship between average HM-DD and the risk of late-onset sepsis and its associated costs in VLBW infants, such that each additional 10 ml kg^{-1} d^{-1} of HM during days 1–28 reduced the risk of sepsis by 19%. In our study, the 173 infants who received no HM at NICU discharge would have been at significantly less risk for the development of NEC and late-onset sepsis due to the high amounts of HM received in the early post-birth period. For this group of infants, the median of average HM-DDs and the median cumulative HM-PCTs for days 1–14 were 14.6 ml kg^{-1} d^{-1} and 100%, respectively, for days 1–28 they were 26.6 ml kg^{-1} d^{-1} and 68.3%, respectively. These amounts of early HM feedings were sufficient to reduce the risk, incidence/severity and costs associated with NEC and late-onset sepsis, although the infants were considered 'failures' with respect to the HM-DC quality indicator.

The importance of adding quality indicators that measure the amount of HM received by VLBW infants during days 1–14 and 1–28 is underscored by a solid body of mechanistic research that details 'why' high amounts of HM are essential for the reduction in risk of morbidities in VLBW infants. It is well-established that high-dose (and in some instances, 100%) early HM feedings, especially colostrum, promote the growth, maturation and protection of the gut epithelial border.[17–27] HM feedings have been shown to stimulate healthy gut microflora, reduce intestinal permeability, and interfere with the translocation of bacteria from the gut lumen to the mucosa, and appear to be the most critical as VLBW infants transition from intrauterine (for example, swallowing amniotic fluid) to extrauterine nutrition in the early post-birth period.[1,17–23,26–33] There is also evidence that commercial formulae may have a separate detrimental impact on these processes during these early post-birth exposure periods, via upregulation of inflammatory processes, GIT epithelial cell toxicity and other mechanisms.[1,2,8,18,19,23,27] Although the combination of the clinical outcomes and mechanistic research about the impact of HM in the early post-birth period for VLBW infants is compelling, as yet it has not been integrated into HM quality improvement measures.[1]

It is likely that the currently used NICU quality indicators were adapted from national goals for the initiation and duration of breastfeeding that were first proposed in 1984 and continue today.[34–38] Although intended primarily for healthy populations of mothers and infants, their use with VLBW infants was appropriate when NICU lactation care was prioritized primarily to sustain lactation in mothers who wanted to feed at the breast after discharge. However, in the last decade, research has linked specific amounts and timing of HM use with a reduction in the risk of morbidities in VLBW infants.[1] With the evolution of this evidence, our findings reveal that these current HM quality indicators do not adequately measure the amount and timing of HM feedings received by VLBW infants. Additional HM quality indicators should include the average DD-HM and the cumulative PCT-HM for three critical exposure periods: days 1–14, days 1–28 and the NICU hospitalization.

The strengths of our study include the large sample size, prospectively collected feeding data and the variability in the actual amounts of HM received by the sample of infants. Our study findings are limited in that the actual volumes of HM were clustered into either very high or very low categories and were not normally distributed. This was especially true for HM-PCT during days 1–14, when the median value was 100% for the 285 infants. In addition, our study focused on currently used quality indicators for VLBW infants in th NICU rather than the Joint Commission Perinatal Core Measure for exclusive breastfeeding during the maternity hospitalization, as the latter initiative focuses primarily on healthy term infants.[39,40]

We conclude that average HM-DD and cumulative HM-PCT during days 1–14, 1–28 and the entire NICU hospitalization should be added to the existing HM-Ever and HM-DC quality indicators for measuring the use of HM in VLBW infants. With the widespread use of electronic medical records, these and other quality indicators based on the amount and timing of HM feedings (for example, percentage of NICU fed-days equal to exclusive HM) are simple to perform and easily linked to clinical outcome measures, cost of care and other quality improvement initiatives.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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