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Impact of Early Human Milk on Sepsis and Health Care Costs in Very Low Birth Weight Infants

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Abstract

Objective—To study the incidence of sepsis and neonatal intensive care unit (NICU) costs as a function of the human milk (HM) dose received during the first 28 days post-birth for very low birth weight (VLBW) infants.

Study Design—Prospective cohort study of 175 VLBW infants. Average daily dose of HM (ADDHM) was calculated from daily nutritional data for the first 28 days post-birth (ADDHM-Days1-28). Other covariates associated with sepsis were used to create a propensity score, combining multiple risk factors into a single metric.

Result—The mean gestational age and birth weight were 28.1 ± 2.4 wk and 1087 ± 252 g, respectively. The mean ADDHM-Days1-28 was 54 ± 39 mL/kg/d (range 0-135). Binary logistic regression analysis controlling for propensity score revealed that increasing ADDHM-Days1-28 was associated with lower odds of sepsis (OR .981, 95%CI .967-.995, p=.008). Increasing ADDHM-Days1-28 was associated with significantly lower NICU costs.

Conclusion—A dose-response relationship was demonstrated between ADDHM-Days1-28 and a reduction in the odds of sepsis and associated NICU costs after controlling for propensity score. For every HM dose increase of 10 mL/kg/d, the odds of sepsis decreased by 19%. NICU costs were lowest in the VLBW infants who received the highest ADDHM-Days1-28.

Keywords

premature infant; breast milk; infection; economics; health care costs

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Conflict of interest The authors declare no conflict of interest.

INTRODUCTION

Late-onset sepsis (sepsis) occurs in approximately 22% of very low birth weight (VLBW; birth weight <1500 g) infants in the United States, making it one of the most common morbidities in this population.[1] In addition to predisposing the infant to other morbidities,[2] and subsequent neurodevelopmental disability,[3] sepsis significantly increases NICU costs,[2,4] and translates into higher societal and educational costs for VLBW infants who survive sepsis with neurodevelopmental disability.[5] Thus, interventions to decrease the risk of sepsis are a high priority for VLBW infants.

Several small studies have demonstrated that human milk (HM) feedings reduce the incidence and/or the risk of developing sepsis in extremely preterm and VLBW infants.[6-8] Furthermore, studies and research reviews[7,9-11] suggest that the early post-birth period may represent a “critical period” for the feeding of high doses of HM to reduce the risk of sepsis and other morbidities in premature infants. This critical period has been variably defined as the first 14 or 28 days of life (DOL). We selected the first 28 DOL since most VLBW infants are receiving full enteral nutrition by that time, as opposed to the first 14 DOL when 55% of our infants were still receiving parenteral nutrition (PN). Furthermore, the cost of treating sepsis is high, due to increased ventilation use and longer lengths of NICU stay. Recent research has demonstrated that sepsis is associated with $10 055 in additional costs to the hospital.[2] The purpose of this study was to determine the relationships among sepsis, hospital costs and the dose of HM feedings during the NICU hospitalization in a prospective cohort of VLBW infants.

METHODS

Subjects

This is an ongoing prospective cohort study of VLBW infants admitted to Rush University Medical Center NICU since February 2008 who survived to receive enteral feedings by DOL 14.[12] Exclusion criteria included the following: birth weight (BW) >1500g, birth gestational age (GA) >35 weeks, initiation of enteral feedings after DOL 14, onset of sepsis before initiation of feedings, major congenital anomalies or chromosomal disorders, maternal conditions that precluded HM provision or use for the infant (e.g., maternal cocaine use), and death before NICU discharge because the costs of care for these infants would likely be lower and not comparable for these subjects due to early death.[13,14] Of the three subjects excluded due to death before NICU discharge, none had sepsis. Subjects were excluded after enrollment if they were transferred to a lower level NICU because complete cost data for the hospital stay would not be available. This study was approved by the Rush University Institutional Review Board. Signed informed consent was obtained from parents/guardians of all enrolled subjects.

RUMC Nutritional practices for VLBW infants

In 2008, all VLBW infants received PN upon NICU admission, and mothers were strongly encouraged to provide HM for their infants. Colostrum was administered oropharyngeally once available, even if the infant was not receiving enteral feedings.[15] When the

neonatologist deemed an infant stable (e.g., no longer receiving inotropic support or indomethacin), enteral feedings were started at 20mL/kg/day and advanced daily by 20mL/kg as tolerated and PN was decreased in a complimentary manner. Except for the 14 subjects who received donor milk products (donor milk and human milk-based fortifier) through a separate ongoing clinical trial in 2008,[16] feedings were initiated in all other infants with unfortified HM or 20 calorie preterm formula. HM was fortified with bovine human milk fortifier when feeding volumes reached 100ml/kg/day. Formula-fed infants were switched from 20 to 24 calorie preterm formula when feeding volumes reached 140ml/kg/day. Thereafter, the caloric content and feeding volumes were adjusted based on the infant's growth and tolerance. Hindmilk was given for a maximum of 14 days to a small subset of infants (6/175 = 3%) for slow growth with exclusive HM feedings at the neonatologist's discretion.[17] Infants received fresh HM if it was available; otherwise they received previously frozen HM. Starting Dec. 1, 2009, a BW-based enteral feeding protocol, which did not alter the PN or oropharyngeal colostrum provisions, was instituted for all VLBW infants. This protocol consisted of a minimal enteral feeding period (3-4 days) during which time feedings were not advanced, and then a BW-based advancement period which lasted 9-17 days. HM was fortified with bovine human milk fortifier when feeding volumes reached 140ml/kg/day. Formula-fed infants were switched from 20 to 24 calorie preterm formula when feeding volumes reached 140ml/kg/day. Infants were discharged once they achieved satisfactory weight gain with full oral feedings, thermal stability, and resolution of acute medical conditions.

Data Collection and Clinical Outcomes

Prospectively collected data included daily weight, occurrence of sepsis, maternal and neonatal clinical factors, daily intake (mL) of clear intravenous fluids, PN, HM, and formula, and timing of HM fortifier supplementation. Sepsis was defined as a positive blood culture after DOL 3 and with antibiotic treatment ≥5 days. Daily dose of HM was calculated as follows: the total number of mL of HM (fortified and unfortified) received by the infant during each 24 hour period from 12AM to 12AM was summed. This summed value was divided by the infant's measured weight for that day and expressed as mL/kg/d. These individual daily measures were then summed and divided by the number of days to create the average daily dose of HM (ADDHM) for the first 28 days post-birth or until discharge from the NICU if the infant was discharged before DOL 28 (ADDHM-Days1-28). Although it would be ideal to calculate the HM dose received by each infant prior to onset of sepsis, the resulting variation in the study interval would make comparisons among sepsis and non-sepsis infants difficult to interpret. The first 28 days post-birth has been used by previous investigators[7] in a prospective observational study of VLBW infants and was selected as the exposure period for HM dose calculations for this study. ADDHM-Days1-28 was subdivided into 3 dose categories for analysis based on prior literature (<25 mL/kg/day, 25-49.99 mL/kg/day and ≥50 mL/kg/day).[6,7] Daily dose of HM was also calculated as the proportion of total enteral intake over a 24 hour period that consisted of HM (fortified and unfortified) and compared with ADDHM.

Economic Data

RUMC's system-wide cost accounting system provided the direct cost of care for each chargeable item (e.g., room and board, all clinical and non-clinical personnel time with the exception of physician time) used during each infant's hospital stay. The direct costs for each chargeable item were summed to calculate the hospital direct cost for each NICU hospitalization. Direct costs included only costs incurred by the hospital, because the physicians used a separate billing system. Direct costs were adjusted to 2010 dollars using the Bureau of Labor Statistics Consumer Price Index for all items.[18]

Data Analysis

Descriptive statistics included mean ± SD (minimum-maximum), median (minimum-maximum) and number (percent). Categorical data were analyzed using chi square or Fischer's exact test as appropriate, ordinal data were analyzed using the Mann-Whitney U test, and continuous data were analyzed using t-test or analysis of variance (ANOVA) to assess differences between subjects with sepsis and subjects without sepsis. Variables with data that were not normally distributed were logarithmically transformed before analysis to produce normal distributions.

Due to the fact that there were a relatively small number of events and a relatively large number of potential covariates, a propensity score[19] was created to account for variables that were statistically and clinically associated with sepsis. Statistically, the propensity score allowed the assignment of a proxy value for the likelihood that each infant in the data set would develop sepsis. Pearson correlation coefficients were used to assess the correlation of potential covariates with sepsis. Initially we examined 9 risk factors (GA, BW, gender, race, receipt of surfactant, steroid post birth, DOL of enteral feeding initiation, receipt of PN on DOL 10, and mechanical ventilation on DOL 10) that were potentially associated with sepsis either due to correlation at $p<0.1$ or clinical plausibility. DOL 10 preceded the onset of sepsis for all infants, thus avoiding the potential effect of reverse causality in which the occurrence of sepsis would prolong PN or mechanical ventilation duration. Multiple binary logistic regression analysis was used to obtain the optimal combination of risk factors which resulted in retention of 5 risk factors in the final propensity score: BW,[20] receipt of surfactant, receipt of PN on DOL 10,[21] white race, and DOL of enteral feeding initiation.[20] Collinearity between these five variables was less than 7% of the variance in the predictor variance-covariance matrix. ADDHM-Days1-28 was excluded from the propensity analysis because this was our primary predictor variable of interest.

For the current study, the outcome of sepsis was considered as both a dichotomous and a time-to-event outcome. Multiple binary logistic regression analysis, controlling for the propensity score, was used to evaluate the effect of ADDHM-Days1-28 on the occurrence of sepsis. The results of the logistic regression analysis were cross-validated with a Cox regression analysis using ADDHM-Days1-28 and propensity score as predictors. The dependent variable in the Cox regression was the hazard of sepsis.

A generalized linear regression model was fit to evaluate the relationship between direct cost and ADDHM-Days1-28 (<25 mL/kg/day, 25-49.99 mL/kg/day and ≥50 mL/kg/day),

controlling for the propensity score and presence of sepsis. The generalized linear model was fit with a gamma distribution and log link function. The distribution was selected using a modified Park test, which identifies the appropriate distribution for the mean-variance relationship.[18,22] We re-estimated the regression model excluding sepsis to test whether its omission impacted the relationship between ADDHM and costs. Average predicted costs were computed for the three ADDHM categories. One-way ANOVA was used to test for differences in actual costs and predicted costs from the regression models across the three categories, and Tukey and Bonferroni's methods for post-hoc comparisons were conducted. Analyses were performed using SPSS 15.0 (Chicago, IL) and SAS Version 9.2 (Cary, NC). Statistical significance was set at $p<0.05$ for all analyses.

RESULTS

Subjects

During 2008-2010 285 VLBW infants were enrolled (Figure 1) in this study; 175 infants for whom data collection was complete comprise the study cohort. Demographic, maternal and neonatal characteristics for the study sample and each subgroup (with and without sepsis) are reported in Table 1. Of the 175 infants, 171 (97.7%) received at least some HM and the ADDHM-Days1-28 for the entire cohort was 53.6 ± 39.2 mL/kg/d (mean ± SD; min-max 0-135 mL/kg/d). Figure 2 depicts the average daily HM intake, both as ADDHM-Days1-28 (ml/kg/d) and as the daily dose of HM as the proportion of total enteral intake for each ADDHM-Days1-28 dose category. After the first 5 DOL, infants in the highest HM dose group consistently received more HM on a day-by-day basis than infants in the middle group who received more than the lowest HM dose group. In contrast, infants in all 3 HM dose groups received at least 50% of enteral intake as HM for the first 10 DOL, with a subsequent gradual decline during the remaining 18 days for the lower 2 HM dose groups.

Clinical Outcomes

The occurrence of sepsis and other morbidities, survival, growth, and duration of NICU hospitalization are shown in Table 1. Sepsis occurred in 23 (13%) infants at a mean postnatal age of 30 ± 18 days (median 24 days, min-max 12-77). The organisms isolated from sepsis cases were coagulase negative staphylococci (17%), *Staphylococcus aureus* (17%), other gram positive bacteria including group B *Streptococcus* and *Enterococcus* species (9%), *Escherichia coli* (17%), *Klebsiella* species (13%), *Enterobacter* species (9%), *Pseudomonas* species (9%), and *Serratia* species (9%).

After correcting for propensity score, results of the binary logistic regression analysis demonstrated an independent protective effect of ADDHM-Days1-28 on sepsis with a 19% reduction in the odds of developing sepsis for every 10mL/kg/d increase in ADDHM-Days1-28 (OR .981, 95% CI .967-.995, p=.008) (Table 2). Cox regression analysis correcting for propensity score revealed the same protective effect of ADDHM-Days1-28 on sepsis with a significant reduction in the hazard ratio (HR 0.982, 95% CI .968-.995, p=.009). Figure 3 demonstrates this dose-response effect of ADDHM-Days1-28 on sepsis after correcting for propensity score using ADDHM dose categories based on prior literature.[6,7]

Economic Impact

Table 3 reports the mean costs by ADDHM-Days1-28. Correcting for propensity score and sepsis did not significantly alter the adjusted costs. However, after correcting for propensity score and sepsis, average costs were $31 514 lower for infants with ADDHM-Days1-28 ≥50mL/kg/d and $20 384 lower for infants with ADDHM-Days1-28 25-49.99mL/kg/d, when compared to infants with ADDHM-Days1-28 <25mL/kg/d ($p<0.001$). Tukey and Bonferroni's methods for post-hoc comparisons indicated significant differences in costs for infants with ADDHM-Days1-28 < 25mL/kg/day compared to infants with 25-49.99mL/kg/d and ≥50mL/kg/d. The comparison between 25-49.99mL/kg/d and ≥50mL/kg/d was not significant.

DISCUSSION

In this study, we report a dose-response relationship between the amount of HM feedings received during the first 28 days post-birth and a reduction in sepsis risk and mean hospital costs for a prospective cohort of VLBW infants. Even after adjusting for several covariates that predicted risk of sepsis, Cox regression analysis revealed that ADDHM-Days1-28 was a stronger predictor of sepsis than was the combination of variables in the propensity score (results not shown). The impact of ADDHM-Days1-28 was such that each 10 mL/kg/d increase in HM received over the first 28 days post-birth translated into a 19% reduction in the odds of sepsis and increases in ADHHM-Days1-28 were associated with significantly lower NICU costs. While our findings are consistent with those of previous studies that reported a protective effect of HM feedings for sepsis,[6-8] our study is the first to report an economic impact of ADDHM-Days1-28 that is attributable to a reduction in the odds of sepsis and hospital costs of care for VLBW infants. Increasing ADDHM-Days1-28 from < 25mL/kg/day to ≥50mL/kg/day decreased NICU costs by $31 514. Even moderate increases in HM dosage from < 25mL/kg/day to 25-49.99 mL/kg/day were associated with significantly lower costs. This decrease in NICU costs was independently associated with increasing ADDHM-Days1-28, even after taking infant risk factors and occurrence of sepsis into account.

Our choice of specific doses of 25 mL/kg/d and 50mL/kg/d for ADDHM-Days1-28 was based on previous research by Schanler[6] and Furman.[7] Consistent with our findings they demonstrated a protective effect of HM for sepsis at threshold doses of ≥50 mL/kg/d. However, a major difference in our studies and those of Schanler and Furman is that both of these investigators examined the rates of sepsis as a function of dose, whereas our primary outcome measure was the odds of developing sepsis. Unlike Furman, who reported no beneficial effect of ADDHM-Days1-28 between doses <25 mL/kg/d and 25-49 mL/kg/d, our findings were dose-responsive for these thresholds (Figure 3). Multiple methodological differences between the studies could explain these disparate findings for lower threshold doses.

Several lines of inquiry support the importance of ADDHM-Days1-28 in reducing the risk of sepsis and other acquired morbidities in premature infants.[11] While it is widely accepted that the bioactive components in HM, including secretory IgA, lactoferrin, and oligosaccharides,[23,24] provide direct protection from sepsis, the indirect protection afforded

by HM during the transition from intrauterine to extrauterine nutrition may be equally important. This is especially true for premature infants, whose gastrointestinal tracts receive less exposure to the gestation-dependent growth factors and protective cytokines provided by swallowed amniotic fluid.[25] During the early post-birth period, the immature gut is extremely sensitive to the initial luminal contents.[26,27] Human colostrum has high concentrations of anti-infective and anti-inflammatory components, growth factors and protective cytokines that rapidly grow, mature and protect the immature gut.[28] As colostrum transitions to mature milk, high doses of HM facilitate the closure of these paracellular pathways, reducing the risk for translocation of potential pathogens.[11,27] These processes are time-dependent, in that they occur during the critical early post-birth period which is reflected in ADDHM-Days1-28.

Of the 175 infants in this study, 57 (33%) received ADDHM-Days1-28 < 25mL/kg/d. Our results suggest a substantial cost savings associated with increasing ADDHM-Days1-28, demonstrating a dose-response relationship between ADDHM-Days1-28 and onset of sepsis. The incremental cost of sepsis is likely due to several factors. First, infants with sepsis stay longer in the NICU than infants without sepsis. Our results demonstrated that infants with sepsis stayed an average of 28 days longer than those without. In addition to longer NICU stays, treatment of sepsis is resource intensive, due to increased likelihood of ventilation use, which is costly. We estimate that moderately increasing ADDHM to 25-49.99mL/kg/d could have reduced hospital costs by decreasing the odds of sepsis for the infants in this study by $1.2 million ($20 384 cost savings multiplied by 57 infants), while increasing ADDHM for these infants to ≥50mL/kg/d could have potentially reduced hospital costs by $1.8 million ($31 514 cost savings multiplied by 57 infants).

Our results are somewhat higher than the increase in costs due to sepsis in a study by Payne, et al of 2,809 infants born in 17 NICUs.[4] Payne found that sepsis was associated with a 12% increase in NICU hospitalization costs for infants <1500g. Our results (not shown), demonstrated that sepsis was associated with a 31% increase in NICU hospitalization costs. The study by Payne, however, was based on data from 1998-1999. The relative cost of services and supplies used during the NICU hospitalization are likely to have changed over the past decade, hence making comparisons difficult.

The cost savings associated with HM during the NICU hospitalization underestimate the overall impact of HM on societal costs due to the potential for long term health and neurodevelopmental problems[3] which require ongoing health care and special education services. Future work should extend this line of work to quantify the multiplier effect of cost savings throughout childhood due to a reduction in sepsis during the initial NICU hospitalization. This research team is currently examining this relationship in an economic modeling study.

A potential limitation of our study included the selection of DOL 28 for HM dose assessment, which was at the mean onset of sepsis in our subjects. Although it would be ideal to calculate the HM dose received by each infant prior to onset of sepsis, the resulting variation in study interval would make comparisons among sepsis and non-sepsis infants difficult to interpret. Additionally, DOL 28 is a reasonable interval to measure HM dosing

since others have also demonstrated a protective effect of HM received during this time interval[7] as well as the majority of our infants (84%) had achieved full enteral feedings by DOL 28.

Another potential limitation was that this was a single center study, which may limit the generalizability of our results. Due to the many lactation initiatives at our NICU, the vast majority of mothers provide at least some HM for their VLBW infants, especially in the early post-birth days (Figure 2). Thus, very few VLBW infants receive only formula and our HM proportion of enteral intake data are skewed to higher proportions than most NICUs. Therefore, although we did not find a significant difference in HM proportions between sepsis and non-sepsis infants, this may have been due to the high rate of HM feedings at our institution.

The strengths of our study include its prospective design, highly accurate HM dosing data, and sample diversity. Our sample reflected the racial and ethnic diversity of VLBW infants cared for in United States NICUs,[29] and included a representative proportion (47%) of African American infants, a population group that is under-represented in HM research in the United States because, the mothers are statistically less likely to provide milk and/or breastfeed.[30]

In conclusion, our data demonstrate that HM provision of at least 25ml/kg/d over the first 28 DOL was significantly associated with a decrease in sepsis, which is associated with long-term and costly outcomes in VLBW infants.[3] The substantial NICU hospital cost savings associated with increased dosages of HM is likely to offset the maternal and institutional costs of HM provision and feeding, such as breast pump rental, lactation care providers and milk storage. This speculation is currently under empirical investigation by this research team.

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Abbreviations

ADDHM	Average daily dose of human milk
ADDHM-Days1-28	Average daily dose of human milk for the first 28 days post-birth
BW	birth weight
DOL	days of life
GA	gestational age
HM	human milk
NICU	neonatal intensive care unit
PN	parenteral nutrition

VLBW very low birth weight

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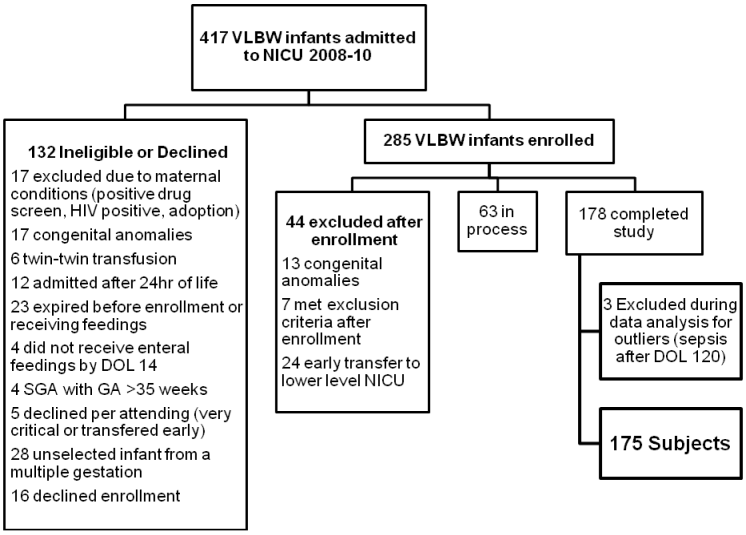

Figure 1.
Flow diagram of subject recruitment

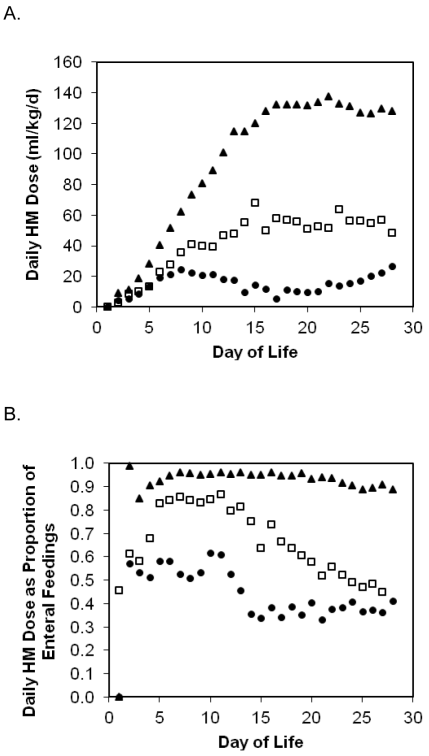

Figure 2.

Daily mean HM intake in three different ADDHM-Days1-28 dosing groups: • Less than 25mL/kg/d, n 57; □ 25-49.99,mL/kg/d, n 32; ▲ 50mL/kg/d or greater, n 86.

Panel A. HM dose expressed as ADDHM (ml/kg/d).

Panel B. HM dose expressed as a proportion of total enteral intake.

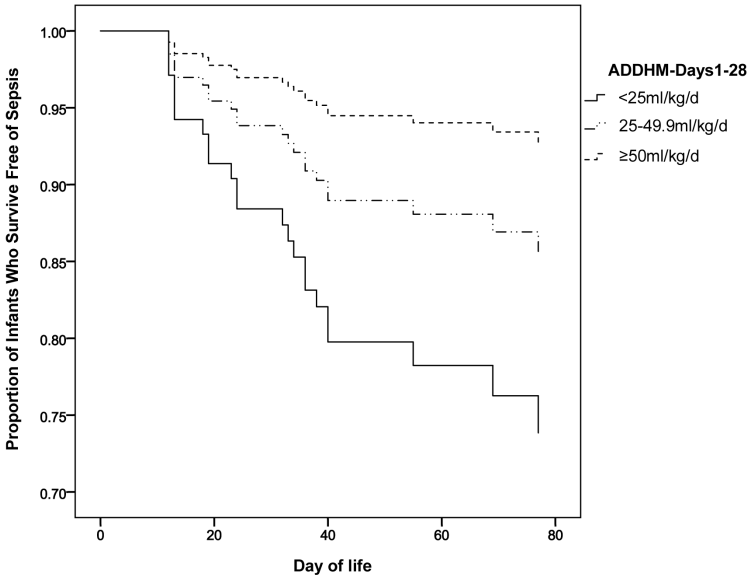

Figure 3.

Adjusted survival curves for sepsis by ADDHM-Days1-28 over the first 28 days of life. Survival curves adjusted for propensity score.

Table 1

Subject Characteristics and Outcomes

Data are presented as mean ± SD (min-max), median (min-max) or frequency (%). GA, gestational age; BW, birth weight; SGA, small for gestational age; ADDHM-Days-1-28, average daily dose of human milk for the first 28 days post-birth; DOL, day of life; PDA, patent ductus arteriosus; PMA, post menstrual age.

	Total Sample (n 175)	Late Onset Sepsis (n 23)	No Late Onset Sepsis (n 152)	p value[a]
GA (week)	28.1 ± 2.4 (23-34)	26.4 ± 1.6 (23-29)	28.4 ± 2.4 (23-34)	<0.001
BW (g)	1087 ± 252 (515-1495)	913 ± 221 (535-1446)	1114 ± 247 (515-1495)	<0.001
SGA at Birth	28 (16%)	2 (9%)	26 (17%)	NS
Maternal race / ethnicity				0.049
% African American/ Black	83 (47%)	7 (30%)	76 (50%)	
% Hispanic	56 (32%)	9 (39%)	24 (16%)	
% non-Hispanic Caucasian	33 (19%)	7 (30%)	49 (32%)	
% Other or Unknown	3 (2%)	0 (0%)	3 (2%)	
Male gender	94 (54%)	13 (57%)	81 (53%)	NS
Antenatal steroids–2 doses (n 174)	120 (69%)	14 (64%)	106 (70%)	NS
Chorioamnionitis	31 (18%)	6 (26%)	25 (16%)	NS
Cesarean section	109 (62%)	13 (57%)	96 (63%)	NS
Multiple gestation	26 (15%)	4 (17%)	22 (15%)	NS
5 minute APGAR	8 (2-10)	8 (5-9)	8 (2-10)	NS
ADDHM-Days 1-28 (ml/kg/d)	54 ± 39 (0-135)	31 ± 33 (0.4-111)	57 ± 31 (0-135)	0.001
DOL enteral feeding initiation (d)	5.6 ± 4.0	6.7 ± 4.5	5.4 ± 4.0	NS
DOL full enteral feedings (d)	19.6 ± 13.0	32.3 ± 24.2	17.7 ± 9.1	0.009
Receiving PN on DOL 10	126 (72%)	21 (91%)	105 (69%)	0.026
Surfactant	126 (72%)	23 (100%)	103 (68%)	0.001
Mechanical ventilation (days)	10.6 ± 16.0	19.4 ± 20.9	9.3 ± 14.7	0.034
PDA	73 (42%)	10 (44%)	63 (41%)	NS
Necrotizing enterocolitis	23 (13%)	6 (26%)	17 (11%)	NS
Chronic lung disease	46 (26%)	12 (52%)	34 (22%)	0.002
Retinopathy of prematurity ≥ 3	2 (1%)	0 (0%)	2 (1%)	NS
NICU Hospitalization (days)	71 ± 35	95 ± 33	67 ± 34	<0.001
Discharge weight (g)	2574 ± 620	2982 ± 824	2512 ± 561	0.001
Discharge PMA (week)	38.5 ± 3.3	40.3 ± 4.3	38.2 ± 3.1	0.005

[a] p values reflect comparisons between infants with and without late onset sepsis.

Table 2

Logistic Regression Analysis of Sepsis

Variable	Adjusted OR (95% CI)	p value
Propensity Score[a]	1.252 (1.019-1.537)	.032
ADDHM-Days 1-28 (ml/kg/d)	.981 (.967-.995)	.008

[a]Propensity score – a single metric composed of BW, receipt of surfactant, receipt of parenteral nutrition on day of life 10, white race, and day of life of enteral feeding initiation

Table 3
Mean Cost by Average Daily Dose of Human Milk, Days 1-28

ADDHM-Days-1-28, average daily dose of human milk for the first 28 days post-birth

	ADDHM-Days 1-28			
	Less than 25 mL/kg/day (n 57)	**25-49.99 mL/kg/day (n 32)**	**50 mL/kg/day or more (n 86)**	**p-value**
Uncorrected cost	148 094 ± 86 129 [c]	124 628 ± 63 022	113 732 ± 65 768 [a]	0.023
Cost corrected for propensity score	146 270 ± 30 778 [b,c]	125 338 ± 22 404 [a]	115 168 ± 23 860 [a]	<0.001
Cost corrected for propensity score and sepsis	146 384 ± 38 998 [b,c]	126 000 ± 27 055 [a]	114 870 ± 24 782 [a]	<0.001

[a] Significantly different from ADDHM less than 25 mL/kg/day

[b] Significantly different from ADDHM 25-49.99 mL/kg/day

[c] Significantly different from ADDHM 50 mL/kg/day or more.