ORIGINAL RESEARCH

Donor vs Maternal Breast Milk and Factors Associated with Hyponatremia in Preterm Infants

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Abstract

Background: Premature infants fed pasteurized mature donor human milk (DHM) from milk banks have been documented to be at higher risk of developing hyponatremia. Premature infants with a history of hyponatremia have been noted as at a higher risk of suboptimal growth and neurodevelopmental outcomes. In this study, we compared infants with documented hyponatremia vs matched controls to identify the clinical risk factors of low serum sodium (Na) levels and discharge growth parameters.

Materials and methods: In this retrospective study, preterm infants with hyponatremia (plasma Na < 135 mEq/L) were compared with a control group of matched gestational age. Demographics, details of the clinical course during their hospital stay, and growth parameters (weight, head circumference, and length) at discharge were recorded.

Results: Sixty infants with hyponatremia, including 32 who received supplemental Na and 28 who did not, were compared with 29 controls with normal Na levels. Hyponatremic infants were more often male (70 vs 44.8%), Caucasian (81.4 vs 62.1%), received assisted ventilation (21.7% vs none), received more mother's own milk (49.2 vs 17.9%), had a later Na nadir (14 vs 5 days), and had a longer length of hospital stay (56 vs 43 days). After controlling for length of stay, infants who received supplemental Na did not differ from matched controls in *Z*-scores for weight, length, or head circumference.

Conclusion: Contrary to our assumptions, most infants with hyponatremia had received more MOM, not DHM. Na chloride supplementation did not improve the growth parameters at discharge.

Clinical significance: Human milk feedings may not always provide recommended Na intake in preterm infants even after fortification. In our small cohort, NaCl supplementation did not always correct serum Na levels or correct the growth parameters. Current protocols for the addition of NaCl to human milk do not consistently enhance serum Na levels and growth; further studies are needed.

Keywords: Neonatal hyponatremia, Preterm growth, Preterm infant, Preterm nutrition.

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Introduction

Hyponatremia is frequently seen in newborn infants, a manifestation of a myriad of fluid and electrolyte shifts. Preterm infants show low serum sodium (*natrium*, Na) levels even more frequently because of immature renal reabsorption and low dietary sodium intake from human milk that is not adequate to compensate for these losses.[1,2]

Preterm, term, and donor human milk (DHM) may not contain sufficient Na to maintain serum levels in newborn infants even after the addition of milk fortifiers.[3–6] Not surprisingly, premature infants frequently develop hyponatremia in the postnatal period; documented low serum Na levels have been associated with medium/long-term suboptimal growth and neurodevelopmental outcomes such as decreased motor and sensory quotients, memory and learning, language, executive skills, and behavior.[2,7–11] Many studies have shown a positive impact of Na supplementation on growth and neurodevelopmental outcomes, but the best timing for this intervention is still unclear.[12–15] The differences between the incidence of hyponatremia in infants fed mother's own milk (MOM) and others who received pasteurized mature DHM are also not known. In this study, we sought to determine the characteristics of preterm infants and the type of feedings associated with hyponatremia. Additionally, we compared growth outcomes between infants fed Human milk (HM) supplemented with Na chloride (NaCl) vs controls.

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Materials and Methods

This retrospective study was performed after approval by the Institutional Review Board during the period June 2019–August 2022 at a level III NICU where preterm infants born at ≥26 weeks'

gestation with a birth weight (BW) > 750 gm are treated. Preterm infants who developed hyponatremia (laboratory-measured serum Na ≤ 135 mEq/L), were compared with gestation-matched controls who were born immediately after the subjects of interest.[14,16,17] We excluded infants who had congenital malformations, required diuretics, or had kidney injury, were transferred to an outside hospital, or did not survive.

Demographic information and data regarding factors that could influence Na balance, such as medications, metabolic acidosis, and type of respiratory support, were recorded. Special emphasis was placed on growth parameters because of the reported association between hyponatremia and growth failure.[10,13] Weight, length, and head circumference (HC) were recorded at admission and discharge, as were weight 14 days after birth and when the infant regained BW.

We cautiously start HM feedings shortly after birth in all infants born at <34 weeks gestation. If MOM is not readily available in the initial few days after birth, the infants are started on DHM and then switched to maternal milk once the supply improves. As our outcome of interest was hyponatremia, data regarding the type of milk used in feedings were manually recorded for each infant, and the final type of feeding was defined as the infant consuming >50% of a specific type of milk during the entire hospitalization. Per unit practice, once infants reach an enteral HM feeding volume of 120 mL/kg/day, HM fortifier (HMF) is added to increase the caloric content to 24 kcal/oz. Typically, infants remain on fortified HM feeds until close to discharge, when HMF is replaced by powder preterm formula to enrich the feeds for caloric content.

NaCl Management

To identify the factors associated with hyponatremia, we first compared infants with low serum Na levels with those who showed normal serum chemistries. To evaluate how treatment affected discharge growth parameters, infants with hyponatremia group were further divided into those who received supplemental NaCl vs others who did not. The initiation and discontinuation of NaCl supplementation is determined by the treating team based on growth parameters and the level of hyponatremia. We typically start NaCl supplementation at 2 mEq/kg/day and then titrate it up or down based on serum Na levels. NaCl is discontinued once the required dose is less than the starting amount to maintain serum Na levels ≥ 135 mEq/L.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (released 2023, Version 29.0.2.0; IBM Corporation, Armonk, NY). In all analyses, an alpha value of 0.05 was considered significant. We aimed for a moderate-to-large effect size with $f = 0.33$; for differences between k means of equal-sized samples compared by one-way analysis of variance (ANOVA), the effect size index f is the standard deviation (SD) of the k means divided by the pooled within-population SD. Here, an $f = 0.10$ would be considered small, medium at 0.25, and large at 0.40. With the aforementioned alpha value of 0.05, 80% power, two numerator degrees of freedom, three independent groups, one covariate, and the estimated effect size = 0.33, a total of $n = 87$ participants ($n = 29$ in each group) would be needed for adequate statistical power.

The demographic and clinical characteristics of the sample and its subgroups were described using frequency and percentage statistics such as inter-quartile ranges (IQRs). The categorical parameters of independent groups were compared using Chi-squared analysis. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the chi-square analyses. Logistic regression was used to generate adjusted odds ratios (AORs) with 95% CIs when controlling for confounding variables.

For continuous parameters, we first performed Shapiro–Wilk tests to check for the statistical assumption of normality. When a set of continuous data did not fail on the assumptions of normality and homogeneity of variance, these were assumed to be parametric and described using means ± SDs. Independent subgroups were compared using the Student's *t*-test or ANOVA depending on the number of subgroups. If one or more assumptions were seen as violated, the groups were described with medians and interquartile ranges, and compared using the Mann–Whitney *U* or the Kruskal–Wallis *R* tests. When a significant difference was detected, further *post hoc* testing was performed via Dunn's test. Finally, analysis of covariance (ANCOVA) was performed to control for length of stay when comparing groups in terms of continuous variables (weight, length, and HC); marginal means with 95% CIs were reported and interpreted.

Results

A total of 60 infants met our eligibility criteria and were included in the study; 32 were treated with NaCl and 28 were not. Additionally, 29 matched infants were included as a control group. The characteristics of the infants are shown in Table 1. Hyponatremia was seen more frequently in males (70 vs 44.8%) and Caucasians (81.4 vs 62.1%); these infants had the lowest Na levels (132 vs 137 mEq/L) later after birth (14 vs 5 days), received most of their feeds with MOM (49.2 vs 17.9%), and had a longer length of stay (56 vs 43 days).

The 2 groups showed no difference in GA, birth parameters (weight, length, and HC), days of parenteral nutrition, postnatal day when feeds were started or full feeds (>120 mL/kg/day) were achieved, or fortification was initiated. Infants treated with NaCl received supplementation for an average of 19 days (IQR 11.39). Concurrent medications included caffeine (65%), multivitamins with iron (65%), and antibiotics (10% with either ampicillin, vancomycin, gentamicin, or cefepime). None of the infants in the cohort were receiving intravenous fluids.

For the level of respiratory support, most infants with hyponatremia were on room air (53.3 vs 44.8%) compared with those with normal serum Na levels. Among those on support, there was a statistically significant difference between those who were intubated (21.7% vs none) and those on noninvasive support (25 vs 55.2%) for infants with and without hyponatremia, respectively ($p = 0.003$). To assess the presence of metabolic acidosis at the time of diagnosis, serum bicarbonate levels were recorded; the two groups showed no differences.

Even though most infants admitted to the study were exposed to MOM (75.3%) and/or DHM (88.9%) during their hospitalization, the majority of those who developed hyponatremia primarily received MOM compared with those who did not (49.2 vs 17.9%, $p = 0.01$). The use of DHM was protective against hyponatremia, which persisted after controlling for other variables (AOR = 0.22, 95% CI: 0.06–0.72, $p = 0.013$) (Table 2). The progression of weight gain was assessed serially; there was no significant difference between BW, weight on postnatal day 14, or when the infant's weight returned to BW. There was a significant difference in discharge weight, HC, and length

Table 1: Characteristics and outcomes of infants with and without hyponatremia

	Hyponatremia	*Control group*
Number of infants	60	29
Birth gestational age (weeks and days)	30 2/7	30 4/7
Birth weight (grams)	1,415	1,450
Birth weight percentile	48	56
Birth weight *Z*-score	0	0.24
Birth length (cm)	40	40.6
Birth head circumference (cm)	27	27.9
Birth head circumference *Z*-score[a]	−0.13	0.36
Male sex (%)[a]	42 (70)	13 (44.8)
Parenteral nutrition (days)	5 (4, 9)	6 (4, 7)
First enteral feed (days)	1 (0, 1)	1 (0, 1)
First fortification (days)	7 (3, 11)	7 (3, 10)
First full enteral feed (days)	7 (6,11)	7 (6, 10)
Infants who used MOM (%)[a]	49.2	17.9
Weight at 14 days old (grams)	1407	1560
Return to birth weight (days)	12 (7, 17)	11 (6, 16)
Lowest Na (mEq/L)[a]	132 (131, 133)	137 (136, 140)
Day of life for lowest Na[a]	14 (11, 20)	5 (4, 11)
Length of stay (days)[a]	57 (31, 76)	43 (28, 47)
Weight gain day 14 until discharge (grams)	36	32.2
Discharge weight (grams)[b]	2,789	2,350
Discharge weight percentile	28	26
Discharge weight *Z*-score	−0.75	−0.82
Weight delta *Z*-score[a]	−0.76	1.06
Discharge head circumference (cm)[b]	33	32
Discharge head circumference *Z*-score[a]	−0.46	−0.58
Head circumference delta *Z*-score[a]	−0.33	−0.94
Discharge length (cm)[b]	48	45

Values are expressed in means and the interquartile range, *Z*-score is a statistical measure of the distance between a data point and the mean of a dataset, expressed as the number of standard deviations from the mean of the distribution, MOM: Mother's own milk; DHM: donor human milk; LOS: length of stay; IQR: inter-quartile range; [a]Statistically significant difference ($p < 0.05$) when comparing infants with hyponatremia (treated and not) vs infants without hyponatremia; [b]Discharge weight, head circumference, and length were statistically significant; however, after controlling for LOS, there was no significant difference

between the groups; but these differences were not seen after controlling for length of stay (LOS; $p = 0.23$, $p = 0.82$, and $p = 0.17$, respectively). The discharge weight percentile was not significantly different between the groups ($p = 0.44$).

To evaluate the influence of Na supplementation on growth outcomes, we compared the group that was treated with NaCl with infants who did not receive this supplementation (Table 3). The birth parameters were similar between the groups. Among those treated with NaCl, the majority were on caffeine (78 vs 50%),

Table 2: Type of enteral feed that was predominantly given

	Hyponatremia% (n)	*No hyponatremia% (n)*	*UnORs (95% CIs)*
MOM	49.2 (29)	17.9 (5)	
DHM	44.1 (26)	78.6 (22)	0.20 (0.07, 0.62)
Formula	6.8 (4)	3.6 (1)	0.69 (0.06, 7.51)
Logistic regression model predicting for hyponatremia			
Variable	*Adjusted ORs*	*95% CI*	*p-value*
DHM	0.22	0.06–0.72	0.013
Male sex	2.49	0.85–7.24	0.093
African–American race	0.53	0.16–1.73	0.293
Respiratory support	0.48	0.16–1.47	0.440

Odds ratios were calculated using MOM as the reference category. After controlling for other factors, DHM use was significantly associated with less odds of hyponatremia; *Z*-score is a statistical measure of the distance between a data point and the mean of a dataset, expressed as the number of standard deviations from the mean of the distribution; MOM, Mother's own milk; DHM, donor human milk

received antibiotics (12.5 vs 7%), had lower sodium levels (130 vs 133, $p < 0.0001$) and longer lengths of stay (65 vs 50, $p = 0.006$) than did those not treated. Nevertheless, there were no statistically significant differences in the *Z*-scores for discharge weight (−0.62 vs −0.9, $p = 0.19$), HC (−0.22 vs −0.74, $p = 0.052$), or delta *Z*-score s for the weight (−0.66 vs −0.86, $p = 0.27$) and HC (−0.3 vs −0.37, $p = 0.81$). Daily weight gain was calculated from day 14 of hospitalization (to allow for infant hemodynamic stabilization) until discharge, and those who were treated had a significantly greater mean daily weight gain than those who were not (35.8 g/m/day vs 30.2 g/day, $p = 0.01$).

Discussion

Hyponatremia is a frequent occurrence in preterm infants and has correlated with inadequate weight gain and deleterious neurodevelopmental consequences. In our study, late hyponatremia was more common in white, male preterm infants and was associated with the predominant use of MOM. Treatment with NaCl did not correct discharge growth parameters after controlling for LOS.

Na Requirements

Preterm infants are born with immature renal function and sodium reabsorption mechanisms.[18] After birth, there is a physiological contraction of the extracellular fluid compartment and as renal function matures, Na reabsorption also improves.[19,20] However, a negative Na balance has been well described in the literature.[2,19,21] In a disbalanced neonatal transition, the length and degree of immaturity have been correlated with prolonged adverse respiratory effects and subsequent inadequate adaptation of the cardiorespiratory system of the neonate.[22,23] Most authors link early hyponatremia (<7 days after birth) to inadequate fluid balance and late hyponatremia (≥7 days) to inadequate Na intake.[17,19]

In preterm infants, the optimal Na intake has not been clearly defined. Term infants should ideally receive 1–2 mEq/kg/day, which seems to be extrapolated from the Na content in term HM.[16]

Table 3: Characteristics and outcomes of infants with hyponatremia comparing those treated vs not

	Treated	*Not treated*
Number of infants	32	28
Birth gestational age (weeks and days)	30	30 5/7
Birth weight (grams)	1,380	1,540
Birth weight percentile	51	47
Birth weight Z-score	0.04	−0.04
Birth length (cm)	39.4	40.8
Birth head circumference (cm)	27.3	27.6
Birth head circumference Z-score	0.09	−0.37
Male sex (%)[a]	23 (71.9)	19 (67.9)
Parenteral nutrition (days)	6 (4, 9)	5 (2, 8)
First enteral feed (days)	1 (0, 1)	0 (0, 1)
First fortification (days)	7 (5, 11)	6 (2, 10)
First full enteral feed (days)	8 (5, 11)	7 (3, 11)
Infants who used MOM (%)	48.4	50
Weight at 14 days old (grams)	1,414	1,575
Return to birth weight (days)	12 (7, 17)	12 (8, 16)
Lowest Na (mEq/L)[a]	130 (127, 133)	133 (132, 134)
Day of life for lowest Na	15 (11, 21)	16 (10, 22)
Length of stay (days)[a]	65 (45, 85)	50 (30, 62)
Weight gain day 14 until discharge (grams)[a]	35.8	30.2
Discharge weight (grams)[b]	3,090	2,610
Discharge weight percentile	32	24
Discharge weight Z-score	−0.62	−0.9
Weight delta Z-score	−0.66	−0.86
Discharge head circumference (cm)[b]	34	32.3
Discharge head circumference Z-score	−0.22	−0.74
Head circumference delta Z-score	−0.3	0.37
Discharge length (cm)[b]	49	47

Values expressed in means and IQR; *Z*-score is a statistical measure of the distance between a data point and the mean of a dataset, expressed as the number of standard deviations from the mean of the distribution; MOM: Mother's own milk; [a]Statistically significant difference ($p < 0.05$) when comparing infants treated vs those not; [b]Discharge weight, head circumference, and length were statistically significant; however, after controlling for LOS, there was no significant difference

For growing preterm infants, once the BW has been regained, the American Academy of Pediatrics recommends an intake of 3–5 mEq/kg/day.[16,24] The European Society of Pediatric Gastroenterology, Hepatology and Nutrition has recommended 3–8 mEq/kg/day.[10] These guidelines are still contested as the renal losses during the early neonatal period and the changes in the maturing kidney do not seem to have received due consideration.[16,15] Even though serum Na levels may appear to be normal, several reports show low urinary Na excretion, and hence, low total Na volumes.[20,24]

In our study, infants within the three groups had similar birth growth parameters. However, those who did not meet the criteria for hyponatremia had their lowest Na level within the first 7 days after birth, consistent with the initial postnatal fluid shifts. There were no statistically significant differences in the number of days to return to BW, weight at 14 days of age, or mean daily weight gain. Those who developed hyponatremia were on more respiratory support, specifically invasive ventilation. Late-onset hyponatremia has been associated with adverse respiratory status, possibly indicating that cardiorespiratory adaptation is still in process.[7–9]

Maternal vs Donor Human Milk

Human milk is the gold standard for infant nutrition, especially in preterm infants.[1] DHM has evolved into a valuable adjuvant for the nutrition of preterm infants; however, its nutritional content is somewhat inferior to that of MOM.[25] Although DHM provides multiple short- and long-term benefits for preterm infants, growth has been reported to be affected by its use, and a detailed analysis of its composition continues to be elusive.[25,26] However, both MOM and DHM do not carry adequate macronutrients needed for growing preterm infants.[25,26] Moreover, DHM also shows greater variation in its composition, mostly due to processing factors.[5,26]

Like macronutrients, the mineral composition of HM does not fulfill the recommended intake reported in preterm infants.[27] Specifically, the amount of Na present in HM (term, preterm, or DHM) is insufficient.[3,5,10,26] Recent reports suggest that even after fortification, the amount of Na provided does not meet the recommended daily intake requirements.[2,6,10] Neither MOM, DHM (fortified or plain), nor preterm formula provides the minimum recommended amount of Na even with enteral feeding volumes of 160 mL/kg/day (Table 4). This effect has been recognized and the Na content in some HMFs has been increased from 5 mg to 7.5 mg/5 mL for better alignment with current recommendations (Table 4).

To our knowledge, this is the first study to look specifically at the type of feeding and its influence on hyponatremia. In our cohort, DHM was the primary source of enteral feeds for our preterm infants during hospitalization (53.9 vs 38.2%). Contrary to expectations, hyponatremic infants in our cohort were more likely to have received MOM as the primary source of enteral nutrition. Infants fed MOM or DHM showed no difference when NaCl supplements were added (48.4 vs 45.2% and 50 vs 42.9%, $p = 0.06$). Conversely, a large portion of infants without hyponatremia received DHM as the primary source of nutrition. Although we anticipated DHM to increase the risk of hyponatremia, the Na content is not significantly lower than in MOM (Table 4). Based on these findings, we can infer that hyponatremia might not be related to the type of milk given but rather to a lack of adequate Na intake and decreased reabsorption by the preterm neonatal kidney.[10,17]

Hyponatremia and its Effect on Weight Gain or Growth

Several studies have investigated the correlation between hyponatremia and inadequate growth.[10] Al-Dahhan et al.[12] supplemented 22 infants from days 4–14 after birth and detected increased weight as well as decreased hyponatremia in control infants, with no adverse effects. These groups were subsequently evaluated for neurodevelopmental outcomes, and the results demonstrated that the supplemented group had better test scores.[11] Vanpee et al.[13] randomized 20 infants to receive Na supplementation during postnatal days 4–14 and found enhanced weight gain; interestingly, their control group had normal serum Na levels. Hartnoll et al.[23,28] randomized 24 preterm infants to receive Na supplementation on postnatal day 2 and 22 infants to receive it after they had lost 6% of BW. Early supplementation led to increased

Table 4: European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommendations and different enteral feeding preparations

	Volume (ml/kg/day)	*Calories (kcal)*	*Protein (g)*	*Fat (g)*	*Sodium (mg)*	*Chloride (mg)*
ESPGHAN (daily requirements)	135–200	110–135	3.5–4	4.8–6.6	69–115	105–177
MOM[a]	160	108	2.3	6.2	40	88
DHM	160	108.8	1.7	6.2	28.3	67.5
MOM[a] + Similac HMF to 24 kcal/oz	160	127	4.5	6.3	51.3	126
MOM[a] + Similac HMF to 24 kcal/oz (new formulation)	160	127	4.5	6.3	73	142
MOM[a] + Enfamil Standard Protein HMF to 24 kcal/oz	160	127.3	3.2	7.5	57.1	90.3
DHM + Similac HMF to 24 kcal/oz	160	128	4	6.3	50.3	126
DHM + Similac HMF to 24 kcal/oz (new formulation)	160	128	4	6.3	63.5	126
DHM + Enfamil Standard Protein HMF to 24 kcal/oz	160	128	3.3	8	56	90
Enfacare to 24 kcal/oz	160	128	3.6	6.8	47.4	99.9
Neosure to 24 kcal/oz	160	128	3.6	7	42.2	96

Values obtained from WebNova by Abbott® and PENS by Timeless®; MOM, Mother's own milk; DHM, donor human milk; HMF, human milk fortifier; [a]Since MOM has variable nutrient content, we present the reported values of preterm milk in this table

oxygen requirements, altered water composition, and no difference in time to regain BW or weight at 36 weeks and 6 months.[22] Isemann et al.[14] randomized 27 preterm infants to receive sodium supplementation from 7 to 35 days of life rather than a placebo and reported improved weight gain and no adverse effects. Segar et al.[15] used calculated urine Na concentrations to identify 50 infants with Na deficiency to received Na supplementation after 2 weeks of postnatal age. There was a significant improvement in weight gain compared with historical controls, although the accuracy of measurement of urinary Na losses has been questioned.[16] Notably, none of these authors reported adverse effects while receiving additional enteral Na. Still, the safety of early Na administration due to cardiovascular and fluid adaptation due to Na shifts needs confirmation.[10,17,19,22,29]

We did not treat some infants with a laboratory diagnosis of hyponatremia with NaCl supplements. Those treated had significantly lower Na levels, which can explain the providers' decision to start treatment (Table 3). In contrast, the discharge parameters in our cohort were similar among the three groups after controlling for LOS.

Infants who did not develop hyponatremia showed better outcomes; there was a significant difference in the delta *Z*-score for discharge weight and no infants diagnosed with moderate malnutrition (delta *Z*-score < 1.2) at discharge compared with seven infants in the treated group and six infants from those not treated. On the other hand, the *Z*-scores for HCs (approaching significance, $p = 0.052$) favored the group that received treatment. Considering that a negative Na balance can negatively affect the neurodevelopmental outcomes of preterm infants, these subtle changes are impactful.

The strengths of our study include the quasi-experimental design allowing for the comparison of Na supplementation in two groups diagnosed with hyponatremia and its effects on growth. The matched control group helped us determine factors associated with the development of hyponatremia and the effects of treatment. Limitations of our study include its retrospective nature, not having an analyzer to determine the amount of daily enteral Na intake received from HM, not determining the urinary Na losses between groups, and the limited neurodevelopmental follow-up after discharge.

Conclusions

- Na supplementation should be cautiously started once the postnatal fluid contraction has been achieved. Initiating Na supplementations very early after birth could negatively impact the cardiorespiratory adaptation. We need to closely evaluate the preterm kidney function and fine-tune the Na supply at various corrected gestational ages.
- Inadequate Na intake could negatively impact growth and neurodevelopmental outcomes; we must ensure that a minimum amount of Na, at least 3–5 mEq/kg/day, should be provided to all growing preterm infants. Most of our current recommendations are not clearly defined by gestation and weight.
- Late-onset hyponatremia was seen more frequently in white, preterm male infants who were on invasive respiratory support, were fed predominantly MOM, and stayed longer in the NICU.
- Enteral intake of Na is not sufficient with current feeding preparations, including fortified MOM/DHM. Aside from inadequate supply, there are no other clearly identified predisposing factors for hyponatremia.

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