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ORIGINAL ARTICLE

Improved outcomes with a standardized feeding protocol for very low birth weight infants

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Objective: The objective of this study was to evaluate the impact of a standardized enteral feeding protocol for very low birth weight (VLBW) infants on nutritional, clinical and growth outcomes.

Study Design: Retrospective analysis of VLBW cohorts 9 months before and after initiation of a standardized feeding protocol consisting of 6–8 days of trophic feedings, followed by an increase of 20 ml/kg/day. The primary outcome was days to reach full enteral feeds defined as 160 ml/kg/day. Secondary outcomes included rates of necrotizing enterocolitis and culture-proven sepsis, days of parenteral nutrition and growth end points.

Result: Data were analyzed on 147 VLBW infants who received enteral feedings, 83 before ('Before') and 64 subsequent to ('After') feeding protocol initiation. Extremely low birth weight (ELBW) infants in the After group attained enteral volumes of 120 ml/kg/day (43.9 days Before vs 32.8 days After, $P = 0.02$) and 160 ml/kg/day (48.5 days Before vs 35.8 days After, $P = 0.02$) significantly faster and received significantly fewer days of parenteral nutrition (46.2 days Before vs 31.3 days After, $P = 0.01$). Necrotizing enterocolitis decreased in the After group among VLBW (15/83, 18% Before vs 2/64, 3% After, $P = 0.005$) and ELBW infants (11/31, 35% Before vs 2/26, 8% After, $P = 0.01$). Late-onset sepsis decreased significantly in the After group (26/83, 31% Before vs 6/64, 9% After, $P = 0.001$). Excluding those with weight <3rd percentile at birth, the proportion with weight <3rd percentile at discharge decreased significantly after protocol initiation (35% Before vs 17% After, $P = 0.03$).

Conclusion: These data suggest that implementation of a standardized feeding protocol for VLBW infants results in earlier successful enteral feeding without increased rates of major morbidities.
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Keywords: enteral nutrition; practice guidelines; necrotizing enterocolitis; very low birth weight

Introduction

Extrauterine growth restriction is a significant problem for premature infants, with 28 to 97% of very low birth weight (VLBW) infants reported to fall below the 10th percentile for weight at 36-weeks postmenstrual age (PMA) or discharge from the neonatal intensive care unit (NICU).[1–3] How, when and what these infants are fed influence somatic growth, brain growth and ultimately neurodevelopmental outcome.[4–6] Wide variations exist in the initiation and advancement of enteral feedings, and concerns of provoking necrotizing enterocolitis (NEC) continue to influence nutritional management decisions among providers.[7,8]

Adoption of a standardized enteral feeding protocol has been suggested as a 'potentially better practice' for nutritional management of the VLBW infant.[9] Previous studies of the implementation of standardized feeding protocols have shown improvement in nutritional outcomes, such as time to reach full enteral feedings, as well as decreased variability in these outcomes.[9,10] Although many studies have presented analyses of nutritional outcomes and NEC rates,[11–13] other clinical outcomes and growth effects have not been as well characterized.

The aim of our study was to evaluate the impact of a standardized feeding protocol for VLBW infants implemented as a quality improvement project in our NICU. Our hypothesis was that a standardized protocol would lead to improved nutritional outcomes, decreased rates of major morbidities and better growth for VLBW infants.

Methods

This study was a retrospective comparative analysis of VLBW cohorts from the Level IIIC[14] NICU at Lucile Packard Children's Hospital at Stanford before and after implementation of a feeding protocol. Infants included in this analysis had birth weights ⩽1500 g and were inborn or transferred to Lucile Packard Children's Hospital by day of life (DOL) 3. Exclusion criteria were major congenital anomalies and known gastrointestinal abnormalities.

A standardized feeding protocol was developed through a mechanism of monthly clinical consensus conferences, which had been established previously at our institution. The Lucile Packard

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Feeding Guidelines

≤1000 grams or ≤27+0/7 weeks:			1001-1500 grams or ≤31+0/7 weeks:		
Feeding day	Total feed volume/kg/day	Feed frequency	Feeding day	Total feed volume/kg/day	Feed frequency
1	10 ml/kg/day	÷ q 6 hrs	1	20 ml/kg/day	÷ q 3 hrs
2	10 ml/kg/day	÷ q 6 hrs	2	20 ml/kg/day	÷ q 3 hrs
3	10 ml/kg/day	÷ q 6 hrs	3	20 ml/kg/day	÷ q 3 hrs
4	10 ml/kg/day	÷ q 6 hrs	4	20 ml/kg/day	÷ q 3 hrs
			5	20 ml/kg/day	÷ q 3 hrs
5	20 ml/kg/day	÷ q 3 hrs	6	20 ml/kg/day	÷ q 3 hrs
6	20 ml/kg/day	÷ q 3 hrs			
7	20 ml/kg/day	÷ q 3 hrs	7	40 ml/kg/day	÷ q 3 hrs
8	20 ml/kg/day	÷ q 3 hrs	8	60 ml/kg/day	÷ q 3 hrs
			9	80 ml/kg/day	÷ q 3 hrs
9	40 ml/kg/day	÷ q 3 hrs	10	100 ml/kg/day	÷ q 3 hrs
10	60 ml/kg/day	÷ q 3 hrs	11	120 ml/kg/day	÷ q 3 hrs
11	80 ml/kg/day	÷ q 3 hrs	12	140 ml/kg/day	÷ q 3 hrs
12	100 ml/kg/day	÷ q 3 hrs	13	160 ml/kg/day	÷ q 3 hrs
13	120 ml/kg/day	÷ q 3 hrs			
14	140 ml/kg/day	÷ q 3 hrs			
15	160 ml/kg/day	÷ q 3 hrs			

Figure 1 Feeding protocol for VLBW infants.

Children's Hospital protocol was established by consensus of the faculty on the basis of a review of the literature and other centers' feeding protocols. The major aims of the protocol were to (1) advance enteral feeds in a safe, standardized manner; (2) advocate the use of human milk as the definitive first choice for feeds; and (3) use colostrum, by oral administration, to promote immunological protection and intestinal colonization and maturation in neonates. These aims were put into clinical practice by the use of standardized order sets.

The standardized feeding protocol in Figure 1 was initiated in the Lucile Packard Children's Hospital NICU on 1 April 2007. The 'Before' cohort consisted of infants meeting inclusion criteria who were admitted during the 9 months before feeding protocol initiation, from 1 July 2006 to 31 March 2007. The 'After' cohort consisted of infants admitted during the 9 months after initiation, from 1 April 2007 to 31 December 2007. The feeding protocol consisted of 6 to 8 days of trophic feedings, followed by an advance of 20 ml/kg/day to reach a goal of 160 ml/kg/day. The duration of trophic feeding and the rate of advancement were different for infants with birth weights $\leqslant$1000 g (extremely low birth weight, ELBW) versus those with birth weights between 1001 and 1500 g. The feeding protocol promoted the start of trophic feedings by DOL 3 and suggested guidelines for withholding or discontinuing feeds, but these decisions were ultimately at the discretion of the clinical team.

Baseline demographic and perinatal data were collected through chart review, including gestational age, birth weight, small for gestational age (birth weight <10th percentile for gestational age on the Fenton premature growth curve[15]) or large for gestational age (birth weight >90th percentile for gestational age on the Fenton curve), gender, delivery mode, multiple gestation, antenatal steroid treatment, 5-min Apgar score, maximum level of delivery room resuscitation and death before hospital discharge. Rates of respiratory distress syndrome (including surfactant administration), patent ductus arteriosus and treatment, use of vasopressors or hydrocortisone for hypotension in the first 28 days, early-onset sepsis (at $\leqslant$3 days of age), intraventricular hemorrhage, cystic periventricular leukomalacia, retinopathy of prematurity and bronchopulmonary dysplasia were also noted. Respiratory distress syndrome was defined as the need for oxygen or positive pressure support for more than 6 h in the first 24 h. Bronchopulmonary dysplasia was defined as the physiological need for oxygen or positive pressure support at 36-weeks PMA, by the criteria of Walsh *et al*.[16]

The primary outcome was days to reach full enteral feeds, defined as a volume of 160 ml/kg/day. The hypothesis was that a standardized feeding protocol would lead to faster attainment of full enteral feeds. Other nutritional outcomes included DOL that enteral feeds were started, DOL that total parenteral nutrition (TPN) was started, total days of TPN administration, DOL to 120 ml/kg/day enteral feeds and DOL that birth weight was regained. Use of human milk (maternal and donor breast milk) and formula in the first 28 days, as well as oral colostrum administration (fresh breast milk 0.5 to 1 ml every 6 h to buccal pouch of mouth in the first 7 days of life), were noted. For the first 28 days of life, daily enteral feeding volumes and number of feedings held were also recorded.

Secondary outcomes included NEC (Bell's Stage 2 or greater[17]) and culture-proven late-onset sepsis (at $\geqslant$3 days of age). Other clinical outcomes examined were the number of central line days (umbilical venous, umbilical arterial and peripherally inserted central catheter (PICC)), spontaneous GI perforation (without NEC) and length of hospital stay. Growth outcomes included weight, length and head circumference at birth, 28 days of age, 36-weeks PMA and hospital discharge.

Statistical analyses, by the χ^2-or Fisher's exact test for categorical variables, by Student's *t*-test (with equal or unequal variances as appropriate) for continuous variables and by folded F-test for equality of variance, were conducted using SAS Enterprise Guide 4.1 (2006 SAS Institute, Cary, NC, USA). Analyses were also stratified by birth weight ($\leqslant$1000 g, 1001 to 1500 g), given the different rates of feeding advancement for these groups in the protocol. Institutional Review Board approval was granted by the Stanford University Panel on Medical Human Subjects.

Results

Charts from 189 infants were initially reviewed, 96 in the Before group and 93 in the After group. Figure 2 describes study flow. More infants in the After group died before being fed (3 Before vs 12 After, $P = 0.01$). There was no significant difference between the Before and After groups among infants who died before being fed with regard to average gestational age (25 weeks Before and After, $P = 0.69$), birth weight (760 g Before vs 741 g After, $P = 0.85$) or DOL at death (DOL 1 (range 1 to 2) Before vs DOL 2 (range 1 to 8)

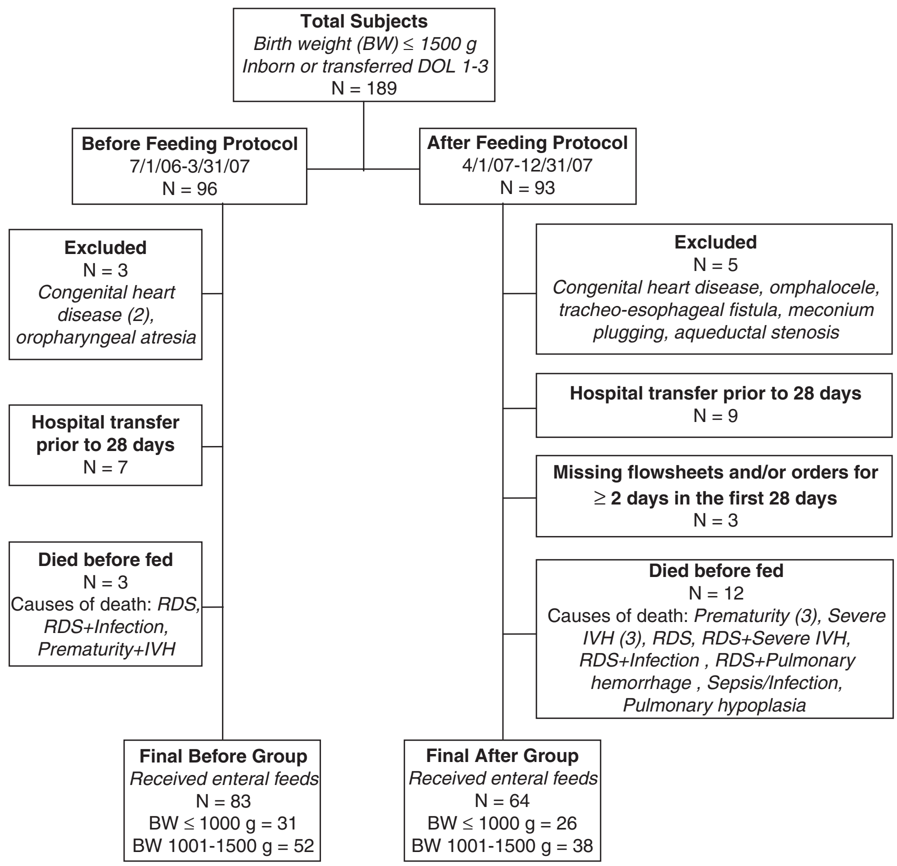

Figure 2 Study flow.

After, $P = 0.39$). A total of 83 infants (86%) in the Before group and 64 (69%) in the After group were included in the final analyses. In the After period, the standardized feeding protocol was formally ordered for 61 of 64 infants (95%); data from the remaining three infants were included in the After group analyses.

As seen in Table 1, no significant differences were detected between the groups in baseline demographic, perinatal and neonatal characteristics. Causes of death in the Before group included NEC (three infants), methicillin-resistant *Staphylococcus aureus* infection and sepsis; in the After group, causes of death were severe intraventricular hemorrhage and severe intraventricular hemorrhage plus infection.

Major nutritional outcomes are shown in Table 2. Overall, the After group attained 120 and 160 ml/kg/day of enteral feeds faster, although differences between the Before and After groups were not statistically significant. However, ELBW infants in the After group reached these feeding goals significantly faster and also received significantly fewer days of TPN. Although mean days to 120 ml/kg/day, days to 160 ml/kg/day and days of TPN for the overall VLBW cohort did not reach statistical significance, there was significantly less variability in these outcomes in the After group; this was also true for the 1001 to 1500 g cohort.

The number of days to regain birth weight was not different between groups (12 days Before and After, $P = 0.63$). Among the infants who received any formula in the first 28 days (19 infants Before and 11 infants After), the average number of days per patient on which any formula was administered was significantly less in the After group (10 days Before vs 3 days After, $P = 0.003$). The proportion of infants receiving banked donor breast milk was significantly higher in the After group (15/83 (18%) Before vs 22/64 (34%) After; $P = 0.03$). Among the infants who received any breast milk in the first 28 days (80 infants Before and 64 infants After), the average number of days per patient on which any breast milk was received was not different between groups (18 days Before vs 19 days After, $P = 0.23$). No infant in the Before group received oral colostrum, as this policy began with the new feeding protocol in April 2007. A total of 23 infants, or 36%, in the After group received oral colostrum, starting at an average of DOL 4.

Major clinical outcomes are also presented in Table 2. NEC rates were significantly decreased in the overall VLBW cohort and in ELBW infants. There were three surgical NEC cases in the Before group and none in the After group ($P = 0.10$). Late-onset sepsis was significantly decreased in all cohorts. The average number of PICC line days per patient was not statistically different between groups. However, the variability in the number of PICC line days was significantly decreased in the After group. Average DOL at hospital discharge (DOL 75 Before vs DOL 71 After, $P = 0.45$) was not different between groups.

Table 1 Baseline demographic, perinatal and neonatal characteristics of infants who received enteral feeds before and after initiation of a standardized feeding protocol for VLBW infants

	Before (N = *83*)	*% or* *(range)*	*After* (N = *64*)	*% or* *(range)*	P-*value*
Mean gestational age at birth (weeks)	28.8	(24–34.3)	28.6	(24–35.1)	0.59
Mean birth weight (g)	1054	(470–1470)	1076	(560–1490)	0.64
AGA (#)	55	66%	47	73%	0.48
SGA (#)	27	33%	17	27%	—
LGA (#)	1	1%	0	0%	—
Male (#)	43	52%	31	48%	0.68
Cesarean delivery (#)	58	70%	44	69%	0.88
Multiple births (#)	31	37%	18	28%	0.24
Twins (#)	28	34%	15	23%	0.18
Triplets (#)	3	4%	3	5%	0.88
Antenatal steroids (#)	72	87%	58	91%	0.47
Mean 5-min Apgar	7.4	(2–9)	7.4	(1–9)	0.96
Deaths (#)	5	6%	2	3%	0.40
Mean DOL at death	42	(16–117)	12	(10–14)	0.40
RDS (#)	69	83%	52	80%	0.77
PDA (#)	39	47%	35	55%	0.35
IVH grade 3 or 4 (#)	12	14%	12	19%	0.49
BPD (#)	19	23%	12	19%	0.54

Abbreviations: AGA, appropriate for gestational age; BPD, bronchopulmonary dysplasia; DOL, day of life; IVH, intraventricular hemorrhage; LGA, large for gestational age; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; SGA, small for gestational age; VLBW, very low birth weight.

Average daily enteral feeding volumes on the first 28 days of life are presented in Figure 3. For ELBW infants, enteral volumes were not significantly different in the Before and After groups, except on DOL 10. For infants 1001 to 1500 g, however, enteral volumes were significantly lower in the After group on 6 days. The average percentage of feedings held on each of the first 28 days was not significantly different in the Before and After groups.

Growth velocity[18] from birth to 36-weeks PMA was not statistically different between groups (13 g/kg/day Before vs 12 g/kg/day After, $P = 0.05$). Excluding infants who were small for gestational age at birth, rates of extrauterine growth restriction or weight less than the 10th percentile for gestational age on the Fenton curve, were not significantly different in the Before and After groups at 28 days, 36-weeks PMA or hospital discharge. Severe growth restriction was defined as weight less than the third percentile for gestational age on the Fenton curve. Excluding infants who were less than the third percentile at birth, severe growth restriction was significantly reduced in the After group at 28 days (36% Before vs 11% After, $P = 0.002$), 36-weeks PMA (39% Before vs 20% After, $P = 0.03$) and hospital discharge (35% Before vs 17% After, $P = 0.03$).

Discussion

We found that implementation of a standardized feeding protocol was associated with significantly faster achievement of full enteral feeds and reduced TPN use for ELBW infants. Rates of infection, NEC and severe extrauterine growth restriction were also lower after implementation.

These results are consistent with previous studies outlining the benefits of feeding protocols in premature infants.[9,10,19] Kuzma-O'Reilly *et al*.[9] described a set of potentially better practices for NICU nutrition, including early initiation of enteral nutrition within the first week, consistent systematic advancement of feeds, definitions and guidelines for withholding feeds and the use of breast milk as the preferred nutritional substrate. After implementing these potentially better practices, centers reported decreased time to start and reach full enteral feeds, increased use of breast milk as the first feed and decreased length of hospital stay.

In another study, Street *et al*.[10] noted that implementation of feeding guidelines for infants <2000 g led to decreased variability in feeding-related outcomes, with significantly decreased variance in the DOL of first feed, TPN days and DOL to 100 kcal/kg/day. Our results are consistent with these findings. Although the overall VLBW cohort and the 1001 to 1500 g cohort did not reach statistical significance in average time to start enteral feeds, in time to reach full enteral feeds or in TPN days, the variability in these outcomes was significantly decreased after protocol initiation.

In addition to improvement in feeding-related outcomes, standardized feeding protocols have also been associated with decreased NEC rates.[11–13] Patole and de Klerk[19] reported a meta-analysis of six studies from 1978 to 2003 of infants with birth weight <2500 g, looking at rates of Stage II or greater NEC. With the presence of any standardized feeding regimen, the pooled risk ratio for NEC was 0.13 (95% confidence interval 0.03 to 0.50), indicating a reduced incidence of NEC by 87%. In their VLBW subgroup analysis of three studies from 2000 to 2003, the incidence of NEC was reduced by 29% (pooled relative risk 0.71, 95% confidence interval 0.52 to 0.97).

In our study, NEC rates among infants who survived to receive enteral feeds were significantly decreased after implementation of a standardized feeding protocol in both the overall VLBW cohort, from 18% Before to 3% After, as well as in the ELBW cohort, from 35% Before to 8% After. Although the ultimate etiology of NEC remains unknown, studies have shown that certain feeding practices may be associated with decreased NEC rates. Although trophic feedings, or the provision of small volume, nutritionally insufficient feeds, have not been statistically associated with decreased NEC rates in systematic reviews,[20,21] they have been shown to stimulate gastrointestinal development[22–25] and promote gut motility[26] in premature infants. Studies have also shown a benefit to the use of human milk as the primary nutritional substrate for premature infants, with significant decreases in NEC rate associated with increased use of breast milk, both mother's own and donor.[27–29]

Our feeding protocol included a 6- to 8-day period of trophic feedings for VLBW infants and promoted the use of breast milk,

Table 2 Nutrition and clinical outcomes before and after initiation of a standardized feeding protocol for VLBW infants

	Before VLBW = 83, ELBW = 31, 1001–1500 g = 52	*% or (range)*	*After VLBW = 64, ELBW = 26, 1001–1500 g = 38*	*% or (range)*	P-*value*
Mean DOL enteral feeds started					
All VLBW	7.8	(2–45)	7.0	(2–23)	0.49 *Variance*[a] *0.01*
ELBW	11.1	(2–45)	9.8	(3–23)	0.56 *Variance 0.06*
1001–1500 g	5.8	(2–25)	5.2	(2–21)	0.48 *Variance 0.04*
Mean DOL enteral 120 ml/kg/day					
All VLBW	29.2	(6–86)	24.5	(6–66)	0.09 *Variance <0.0001*
ELBW	43.9	(12–81)	32.8	(17–66)	0.02 *Variance 0.03*
1001–1500 g	20.9	(6–86)	19.2	(6–38)	0.53 *Variance <0.0001*
Mean DOL enteral 160 ml/kg/day					
All VLBW	34.9	(8–113)	28.4	(9–69)	0.05 *Variance <0.0001*
ELBW	48.5	(15–102)	35.8	(17–69)	0.02 *Variance 0.01*
1001–1500 g	27.2	(8–113)	23.6	(9–58)	0.32 *Variance <0.001*
Mean days TPN					
All VLBW	30.2	(6–117)	24.1	(2–66)	0.06 *Variance <0.0001*
ELBW	46.2	(12–117)	31.3	(2–66)	0.01 *Variance 0.07*
1001–1500 g	20.6	(6–91)	19.2	(4–43)	0.62 *Variance <0.0001*
NEC (#)					
All VLBW	15	18%	2	3%	0.005
ELBW	11	35%	2	8%	0.01
1001–1500 g	4	8%	0	0%	0.08
Culture-proven late-onset sepsis (#)					
All VLBW	26	31%	6	9%	0.001
ELBW	17	55%	6	23%	0.01
1001–1500 g	9	17%	0	0%	0.01
Mean PICC days per patient					
All VLBW	24.4	(3–117)	21	(4–61)	0.21 *Variance <0.0001*
ELBW	35.5	(10–117)	26.3	(4–61)	0.07 *Variance 0.02*
1001–1500 g	16.7	(3–72)	17.1	(5–35)	0.87 *Variance 0.002*

Abbreviations: DOL, day of life; ELBW, extremely low birth weight; NEC, necrotizing enterocolitis; PICC, peripherally inserted central catheter; TPN, total parenteral nutrition; VLBW, very low birth weight.
[a]Folded F-test of equality of variance.

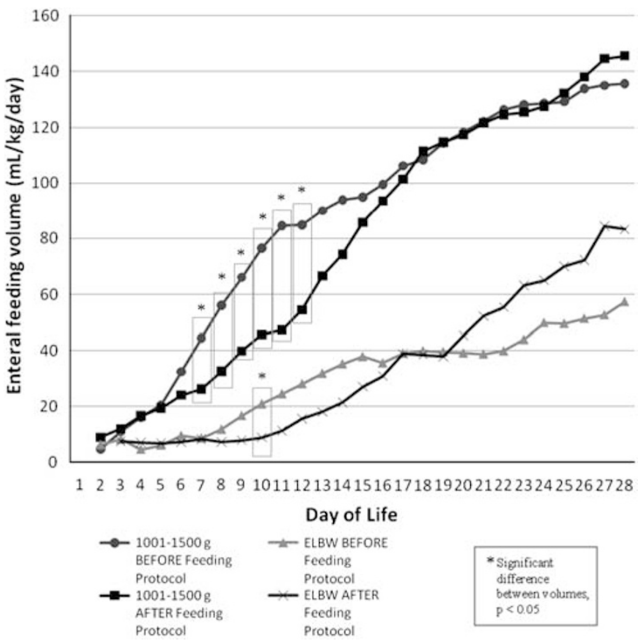

Figure 3 Average daily enteral feeding volumes during the first 28 days of life before and after implementation of a standardized feeding protocol for VLBW infants.

including donor milk when mother's milk was unavailable. In the period after protocol initiation, we observed a decreased use of formula and an increase in the proportion of infants receiving banked donor breast milk. Standardization of these practices likely contributed to the decreased NEC rates observed after protocol implementation. Moreover, as evidenced by the Patole and de Klerk meta-analysis,[19] the reduction in practice variation among providers when a standardized protocol is implemented may be more influential on the reduction of NEC than the specific details of the feeding volumes and advancement rates of the protocol.

Culture-proven late-onset sepsis rates also significantly decreased in our unit after beginning a standardized feeding protocol. With faster attainment of full enteral feeds and decreased time on TPN, especially among ELBW infants, decreased sepsis rates might be explained by a decrease in central line days. Although the average number of PICC line days was not significantly different in the Before and After groups, a significant decrease in the variability of PICC line days was evident. Colostrum administration, which began with the new feeding protocol and has anti-infective and immune-priming properties,[30,31] may also have contributed to the decreased sepsis and NEC rates.

A potential limitation in interpreting the differences in these clinical outcomes is that this was a retrospective analysis before and after a change in unit practice. Other interventions may have been occurring in the NICU at the same time as the new feeding protocol was being introduced, and may have influenced the results. A prospective, randomized trial of the feeding protocol would be needed to control for these other influences. Although causality has traditionally been established in the context of a randomized study, there is value in analyzing the results of a quality improvement project, such as ours, which 'uses the existing evidence-based knowledge to improve immediately health care delivery in particular settings.'[32] Analyzing practice changes that are applied to a whole unit, rather than randomized, recognizes that the context (the medical culture and social setting of a NICU) in which a change is made is as important as the mechanism of that practice change (a standardized feeding protocol).[33] This allows a complete, integrated study of a complex, multicomponent (or bundle) intervention[33] and the opportunity to continually improve that intervention.

Results of this study allowed us to make changes to our standardized feeding protocol to improve nutrition for our VLBW infants. For example, because enteral feeding volumes in the 1001 to 1500 g cohort were significantly lower in the After group on six of the first 28 days of life, without an accompanying significant decrease in the time to full enteral feeds or in NEC rates, we altered the protocol to speed up the feeding advance from 13 days (from initiation to full enteral feeds) to 10 days in this subset of VLBW infants.

Our protocol also left decisions regarding the start of trophic feedings and the discontinuation of feeds at the discretion of the clinical team, which still leaves room for variation. Days to start enteral feeds were not significantly different between the Before and After groups, and future interventions could include standardizing the start of enteral feeds, as well as creating more definitive guidelines for evaluating feeding intolerance and withholding feeds. In addition, our protocol did not specify guidelines for fortifying breast milk, and this has historically been carried out in our unit after establishment of full enteral feeds. Lack of standardization of early fortification may partly explain why rates of EUGR did not improve, although we did see a decrease in the rates of severe growth restriction or weight less than the third percentile for gestational age.

Another intervention has been the continued promotion of breast milk and colostrum administration. Although our use of formula decreased after protocol implementation and approximately one-third of patients received oral colostrum, we felt these numbers could be improved even further, and have aimed to increase awareness through nursing staff and provider education.

As this quality improvement project progresses, and we continue to make changes to our standardized feeding protocol, future studies will be needed to determine the impact of these changes on nutritional and clinical outcomes. Analysis of the data collected in this and future feeding protocol studies could also be analyzed to determine the predictors of extrauterine growth restriction, helping to prevent poor growth and potentially improve neurodevelopmental outcomes.

Conclusion

As a quality improvement project in our NICU, we implemented a standardized feeding protocol for VLBW infants. Our results demonstrate that infants attained earlier feeding tolerance after protocol initiation, and suggest decreased rates of major short-term morbidities. Although causality cannot be established in the context of a retrospective analysis, quality improvement efforts in the NICU can be associated with improved outcomes. Future studies will be needed to optimize the standardized protocol to attain the best nutritional, clinical and growth outcomes, and to determine whether improved short-term outcomes are associated with better neurodevelopmental outcomes for these high-risk infants.

Conflict of interest

SH has received Advisory Board payments from Genentech for the Joint Pregnancy Registry, Raptiva and Xolair.

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