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Reducing Necrotizing Enterocolitis in Very Low Birth Weight Infants Using Quality Improvement Methods

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Abstract

Objective—Due to a rise in necrotizing enterocolitis (NEC, stage 2) among very low birth weight (VLBW, birth weight <1500g) infants from 4% in 2005-6 to 10% in 2007-8, we developed and implemented quality improvement (QI) initiatives. The objective was to evaluate the impact of QI initiatives on NEC incidence in VLBW infants.

Study Design—In September 2009 we developed a NEC QI multidisciplinary team that conducted literature reviews and reviewed practices from other institutions to develop a feeding protocol, which was implemented in December 2009. The team tracked intervention compliance and occurrence of NEC stage 2. In May 2010 we reviewed our nasogastric tube practice and relevant literature to develop a second intervention that reduced nasogastric tube indwelling time. The infants were divided into three groups: baseline (Jan 2008-Nov 2009, n219), QI phase 1 (Dec 2009-May 2010, n62), and QI phase 2 (June 2010-Nov 2011, n170).

Result—The NEC incidence did not decrease after implementation of the feeding protocol in QI phase 1 (19.4%), but did decline significantly after changing nasogastric tube management in QI phase 2 (2.9%). Multivariable logistic regression analysis demonstrated a significant relationship between QI phase and the incidence of NEC.

Conclusion—QI initiatives were effective in decreasing NEC incidence in our high human milk-feeding NICU. Nasogastric tube bacterial contamination may have contributed to our peak in NEC incidence.

Keywords

infant; preterm; enterocolitis; necrotizing; quality improvement; enteral nutrition

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Conflict of interest

Drs. Patel and Meier have been funded by the NIH. The remaining authors declare no potential conflict of interest.

INTRODUCTION

Background Knowledge

Necrotizing enterocolitis (NEC) affects approximately 5-10% of very low birth weight (VLBW, birth weight <1500g) infants¹⁻³ and is associated with a mortality rate of 30%.⁴ The mortality rate is even higher among VLBW infants who require surgical intervention for NEC, as is the incidence of short and long-term morbidities including short gut, growth failure and neurodevelopmental delay.⁵⁻¹⁰

NEC is a multifactorial disease, representing the common end-point of multiple predisposing conditions.¹ Frequently associated risk factors that have been postulated in the pathogenesis of NEC include inappropriate colonization of the neonatal intestinal tract,¹¹⁻¹³ an excessive inflammatory response by the immature intestinal epithelial cells,¹⁴ anemia and transfusion related gut injury,¹⁵⁻¹⁸ prolonged exposure to antibiotics,^{19,20} patent ductus arteriosus,^{21,22} aggressive advancement of enteral feedings,¹⁷ absence of enteral feedings,²³ non-human milk feedings,²⁴⁻²⁶ reduced gastric acid production,²⁷ and reduced gut motility.²⁸ Of these many factors, human milk has been shown to decrease the risk of necrotizing enterocolitis,^{24,29,30} yet despite a very high rate of human milk feeding in VLBW infants at Rush University Medical Center (Rush) neonatal intensive care unit (NICU),³¹ the incidence of NEC stage 2 began to increase in 2007.

Local Problem

In June 2009, a sustained increase in the incidence of NEC stage 2 for 2007-8 (VLBW NEC incidence 9.2% in 2007 and 11.8% in 2008) was noted in comparison to previous years (VLBW NEC incidence 4.4% in 2005 and 4.1% in 2006). We retrospectively investigated potential risk factors for stage 2 NEC, focusing on feeding practices in our NICU including the transition from human milk to formula and/or addition of human milk fortifier (HMF). We included 44 VLBW infants diagnosed with NEC (Bell's criteria stage 2)³² from January 2005 through December 2008 and 44 randomly selected VLBW control infants, matched for birth year, gestational age, and birth weight. Infants were assigned to one of two groups based on birth year (2005-6 Low rate of NEC and 2007-8 High rate of NEC). During 2007-8 infants with NEC received HMF at an earlier postnatal age than controls (12.8 d NEC vs. 17.8 d control, $p=0.04$) and reached full feedings earlier than controls (15.7 d NEC vs. 19.8 d control, $p=0.03$). We considered these empirical findings in combination with the fact that we were not using a standardized feeding advancement protocol, and as a result the feeding practices in our NICU varied with individual health care providers. Additionally, we became aware that our feeding advancement practices for VLBW infants appeared somewhat more aggressive than at other US and Canadian centers (daily advancement by 20-30ml/kg/d without a minimal enteral nutrition or trophic feeding phase).

Intended Improvement

The data from that retrospective study were subsequently used as the basis for developing and implementing quality improvement (QI) initiatives in the Rush NICU, consisting of short-cycle improvement work and are still ongoing. We are reporting the outcomes for the

first 24 months after implementation of QI interventions, which consisted of two plan-do-study-act (PDSA) cycles.

METHODS

Ethical Issues

The sustained increase in rates of necrotizing enterocolitis in our unit was concerning to the medical team. To ensure our patients' well-being, we needed to investigate potential sources and develop strategies to address them. In implementing the quality initiatives, privacy was maintained throughout the whole process. Any physical intervention was not out of the scope of an ordinary procedure utilized in a NICU.

Population/Setting

Rush University Medical Center NICU is an urban 57-bed tertiary care NICU in Chicago, IL that cares for approximately 130 VLBW infants annually. The demographic and clinical data reported here reflect VLBW infants born at Rush or admitted to the Rush NICU within the first week of life. We excluded from this report VLBW infants who were transferred to Rush after this time, had significant congenital anomalies, died within 14 days due to causes unrelated to stage 2 or 3 NEC, or were transferred out of Rush within 14 days after admission due to circumstances unrelated to NEC. Prior to implementation of quality initiatives, VLBW infants typically were started on enteral feedings at the attending neonatologist's discretion and when maternal human milk was available with no minimal enteral nutrition phase. Feedings were advanced by 20-30ml/kg/day based on the infant's stability. On average, powdered human milk fortifier (HMF) was introduced by DOL 13 and infants reached full enteral feeds by DOL 15. If supplementation was required, preterm formula was given since donor human milk was not routinely available in our NICU until 2013. Each feeding was prepared by the nurse at the infant's bedside.

NEC stage 2 or 3 was defined as presence of at least 1 clinical sign (bilious gastric aspirate or emesis, abdominal distention, or blood in the stool) and radiographic findings of pneumatosis intestinalis or portal venous gas.^{7,32} Cases of stage 3 NEC were verified by surgical pathology or radiographic findings of pneumatosis or portal venous gas in addition to pneumoperitoneum. A diagnosis of spontaneous intestinal perforation (SIP) was determined based on early postnatal onset and pneumoperitoneum without associated pneumatosis or portal venous gas.³³ All cases of NEC and/or SIP were personally reviewed by a single neonatologist to verify the diagnosis using the above criteria. Unfortunately, no SIP data was available for the baseline cohort due to the retrospective nature of the data. Data from infants born after the quality initiatives were implemented were collected either prospectively for infants that were enrolled in a separate ongoing study during the years 2008-12³⁴ or retrospectively through abstraction of the medical record for infants who were not enrolled in the ongoing study.

Planning the Interventions

Quality improvement phase 1—Based on these findings from the case-control study of 88 infants, we developed a NEC QI multidisciplinary team in September 2009 with the

intent of initiating PDSA cycles to address this problem. Our goal was to develop and implement QI initiatives to reduce the incidence of NEC in VLBW infants while monitoring infant growth and side effects of interventions (Table 1).^{35, 36} The team consisted of the neonatologist team leader, NICU medical director, two NICU dietitians, one advanced practice nurse (APN), NICU clinical nurse coordinator, and the director of NICU lactation services.

Literature searches were conducted to collect information in regards to HMF as well as the introduction and advancement of feedings in VLBW infants.³⁷⁻⁵¹ Review of nutritional practices that were available from a range of other institutions across the US and Canada were conducted by team members. Using published research data and guidelines/protocols from other NICUs, a Rush VLBW infant feeding protocol was developed.^{37-39,44,45,47-49,51} Next, this protocol was presented to a larger multidisciplinary group consisting of all neonatologists, NICU APNs and several NICU nurses for review and comment. After revisions, the final feeding protocol (version 3) was disseminated to all NICU care providers, and implemented on December 1, 2009.

Quality improvement phase 2—We began to investigate other potential contributors to NEC such as human milk handling and NG tube care as a result of information presented at the 2010 Pediatric Academic Societies meeting.⁵² We also conducted another literature review⁵³⁻⁵⁶ which revealed that gram negative bacterial colonization increased with duration of NG tube placement⁵⁶ and that this gram negative colonization of feeding tubes was subsequently associated with NEC.⁵³ Upon investigation of Rush NICU practices, we found that a new NG feeding tube system and accompanying tube maintenance practice changes had been introduced in November 2009. Specifically, the new system included additional extension tubing that was not being flushed consistently after feedings, leaving residual fluid in the lumen. Additionally, the manufacturer's recommendation for NG tube integrity specified that the tubes could be maintained in place for up to 30 days. At this time, parental education about hygienic handling of human milk included a verbal description of pump cleaning methods.

Parental education about hygienic handling and cleaning of breast pumps was expanded to include a demonstration and provision of dishwashing soap and a basin for each mother. These changes were accompanied by a revision in the feeding protocol to emphasize feeding initiation with colostrum by DOL 2 due to concerns of gut atrophy and increased permeability with prolonged NPO status.^{57,58} Rapid in-services were conducted for NICU nurses during May 2010 to institute the practice changes of 1) reducing NG tube indwelling time to a maximum of 7 days, identifying "Tube Tuesdays" as the weekly time to replace NG tubes, and 2) changing the extension tubing between each feeding. The NG tube handling changes, parental education reinforcement and increased emphasis on earlier feedings of colostrum were implemented by early June 2010. We continued to revise the feeding protocol (Figure 1) in order to achieve full enteral feedings sooner, thus decreasing the durations of TPN and central catheter use. Through increased dietitian participation in daily rounds we aggressively adjusted feeding volumes to maintain growth targets.

Planning the Study of the Interventions

Process measures (compliance with feeding protocol rate of advancement for each BW group was categorized as compliant, faster than recommended rate of advancement, or slower than recommended rate of advancement), outcome measure (NEC), and balancing measures (TPN duration, postnatal growth velocity^{59,60} postnatal growth restriction defined as birth weight 10th percentile but discharge weight <10th percentile.^{61,62} and culture-proven late onset sepsis unrelated to NEC were collected.

Analysis

Descriptive statistics included mean $\pm$ SD, median (IQR), and number (percent). Categorical data were analyzed using chi square or Fisher's exact test, ordinal data were analyzed using the Kruskal-Wallis test, and continuous data were analyzed using analysis of variance (ANOVA). Post-hoc analyses were conducted using Tukey's HSD. Factors significantly associated with NEC in bivariate analyses at $p \leq .1$ were entered with QI phase (*Baseline*, *QI phase 1* or *QI phase 2*) into a multivariable logistic regression model. Analyses were performed using SPSS 21.0 (Chicago, IL). Statistical significance was set at $p < 0.05$. The monthly proportion of patients who developed NEC and surgical NEC was plotted on statistical process control charts using Microsoft Excel 2007 with Control Charts Add-in (Microsoft, Redmond, WA).⁶³ These control charts were chosen because they permit tracking of changes in data over time and allow the differentiation between normal variation due to randomly occurring factors inherent to a process and variations that fall outside of expected variation of the process.⁶⁴

RESULTS

The baseline demographics and clinical outcomes for 451 VLBW infants are presented in Table 2. These infants are divided into the following groups: *Baseline* period (January 1, 2008-Nov. 30, 2009, 219 infants), *QI phase 1* (Dec 1, 2009- May 31, 2010, 62 infants), and *QI phase 2* (June 1, 2010- Nov 30, 2011, 170 infants). There were significant differences among the groups for gestational age, birth weight, race/ethnicity, small for gestational age at birth (SGA) status, and postnatal steroids.

Outcome measure

No decrease in NEC or surgical NEC was noted between the baseline period and after *QI phase 1* (implementation of the feeding protocol), whereas a sharp decline in NEC incidence was noted after addition of the NG tube handling changes in *QI phase 2* (Table 2 and Figure 2). The rate of surgical NEC cases progressively declined from 5% in the *Baseline* phase to 4.8% in *QI phase 1* to 1.2% in *QI phase 2*. Multivariable logistic regression analysis controlling for potentially confounding factors associated with NEC in bivariate analyses (birth weight, sex, race/ethnicity, antenatal antibiotics) demonstrated a significant effect of QI phase on NEC (OR 0.46, 95%CI 0.31-0.68, $p < .001$). Other statistically significant factors that predicted NEC in the final model included male sex (OR 2.85, 95%CI 1.48-5.50, $p = .002$), birth weight (OR 0.999, 95%CI 0.998-1, $p = .046$) and receipt of antenatal antibiotics (OR 2.01, 95%CI 1.08-3.96, $p = .028$).

Process measures

Table 3 reports data about feeding initiation, advancement, fortification, type, and protocol compliance for the three groups of infants. Compliance with QI measures improved with time. Of noncompliant feeding practices, 52% of infants received feeding advancement at a faster rate than recommended in *QI phase 1* and 21% in *QI phase 2*, 43% at a slower rate than recommended in *QI phase 1* and 16% in *QI phase 2*.

Balancing measures

Balancing measures are reported in Table 4. During *QI Phase 1*, the standardization of the feeding protocol, especially slowing the advancement and fortification of feedings, had an adverse effect on postnatal growth, duration of TPN and the incidence of late onset sepsis. These balancing measures were addressed by progressively altering the feeding protocol to increase the feeding advancement rate during *QI Phase 2*. Additionally, the increase in the sepsis rate during *QI Phase 1* led to increased attention on infection control policies for central catheter insertion and maintenance and to the formation of a second QI committee in the NICU. Subsequently, the rate of late onset sepsis decreased to below baseline values.

DISCUSSION

Through use of quality improvement methodologies, including PDSA cycles, we successfully targeted a NEC epidemic in our NICU.(Figure 3) Whereas, our findings may not serve as the solution to NEC-related outbreaks in other institutions, the QI process by which we addressed this problem is generalizable to other centers when they evaluate their own practices that may potentially be related to NEC in their institutions. For example, previous findings have demonstrated the effectiveness of standardized feeding regimens in reducing NEC rates,^{49,65} and we anticipated that our *QI phase 1* standardized feeding protocol would reduce the incidence of NEC in our NICU. However, when our NEC incidence did not decline between *Baseline* and *QI phase 1*, we searched for additional risk factors. We found that the new NG feeding tube system had been initiated approximately one month prior to the introduction of the standardized feeding protocol in *QI phase 1*, and likely confounded the impact of the standardized feeding protocol. This highlights the unintended consequences that can result from a seemingly unrelated decision that was felt to be cost effective and would decrease handling of infants, and the importance of multidisciplinary communication. Attention to the potential impact of the new NG tube change procedure on NEC rates occurred as a result of multiple unrelated situations: attendance at a PAS 2010 seminar, neonatologists' bedside observations of residual fluid in NG extension tubing, and review of relevant literature. We quickly implemented quality initiatives which included more frequent NG tube changes and expanded parental education about hygienic handling and cleaning of breast pumps. By the end of *QI phase 2*, these combined changes resulted in a reduction in NEC rates. These processes illustrate the importance of multidisciplinary collaboration in QI processes in the NICU.

Experts have suggested that NEC incidence could be decreased by 50% by implementing a standardized feeding regimen and providing human milk to VLBW infants.^{28,66} Despite strong lactation support and human milk feeding rates over 90% in VLBW infants at our

institution, we had a NEC epidemic. Others have demonstrated similar epidemics, which led to investigations for a common infectious etiology and heightened infection control measures.⁶⁷ Using multivariable regression models we attempted to control for the differences in patient population. While we could not adjust for all potential covariates, we did adjust for birth weight, gender, race/ethnicity, and antenatal antibiotics. Of note, the postnatal steroid rate in *QI phase 1* was extremely high and reflected the institutional practice at the time to use postnatal steroids (primarily hydrocortisone) to facilitate extubation and/or prevent bronchopulmonary dysplasia. This had been a long-standing practice in our unit that existed even during the historically low NEC phase of 2005-6. The increased prevalence of postnatal steroid use during *QI phase 1* likely reflected the lower gestational age and small N (62) of this group. While there is an association between postnatal steroid use and SIP,⁶⁸ the cases of NEC were closely examined to distinguish NEC from SIP. Although one large network study has reported an association between postnatal steroid use and NEC,⁶⁹ no causality was demonstrated. Additionally, a review of postnatal steroid practices across three large networks did not demonstrate any impact of steroid practices on incidence of NEC.⁷⁰ Our results, while dramatic, may reflect targeted practices specific to our NICU that are not generalizable to other NICUs.

CONCLUSIONS

This quality improvement project led to a unified multidisciplinary approach for managing enteral feeding and monitoring postnatal growth in VLBW infants. Agreement and buy in evolved over a number of months after the feeding protocol was initiated. Although our initial approach was to advance feedings slowly, we found that we could progressively tailor the feeding protocol and improve growth while still achieving our primary outcome, reducing NEC rates. Even though growth velocities for VLBW infants did not change significantly over time, postnatal growth restriction improved and TPN days significantly decreased. These measures continue to be evaluated in our NICU as this is an ongoing process with additional PDSA cycles planned to continue to attempt to further lower our NEC rates.

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A. Initial Feeding protocol for infants with birth weight 400-1800 grams (version 1)

BIRTH WEIGHT	TROPIC FEEDING	DAILY ADVANCEMENT	GOAL FEEDING AMOUNT at 140ml/kg/d	Days from feeds initiation to 140ml/kg/d	FORTIFICATION	FORMULA
400-750g	1ml q4hr x 4 days	Day 5 of feedings: 1ml q2hr for 36 hr, THEN advance by 1ml q36hr (will increase amount by 1 ml/feed every 18 feedings)	6-9ml q2	12-16	↑	↑
751-1000g	1ml q2hr x 4 days	Day 5 of feedings: advance by 1ml/feed once q24hr	9-12ml q2	12-15	1. If at least 12 days old and feedings at 140ml/kg/day then Fortify - 1packet:50ml human milk.	20 calorie formula until at full feedings (140ml/kg/day). Then switch to 24 calorie/oz Formula
1001-1250g	1ml q2hr x 3 days	Day 4 of feedings: advance daily by 15ml/kg/day	12-15ml q2	12	2. If at least 14 days old and feedings at 140ml/kg/day then Fortify - 1packet:25ml human milk.	↓
1251-1500g	3ml q3hr x 3 days	Day 4 of feedings: advance daily by 15ml/kg/day	22-26ml q3	12		
1501-1800g	Start at 20 ml/kg/d	Advance daily by 20 ml/kg/d	26-32ml q3	8	↓	

B. Final Feeding protocol for infants with birth weight 400-1500 grams (version 8)

BIRTH WEIGHT	TROPIC FEEDING	DAILY ADVANCEMENT	GOAL FEEDING AMOUNT at 140ml/kg/d	Days from feeds initiation to 140ml/kg/d
400-750g	1ml q4hr x 5 days	Day 6 of feedings: 1ml q2hr for 24 hr, THEN advance by 1 ml/feed once q24hr	6-9ml q2	11-14
751-1000g	1ml q2hr x 4 days	Day 5 of feedings: advance by 2ml/feed once q24hr	9-12ml q2	9-11

1001-1250g	1ml q2hr x 3 days	Day 4 of feedings: advance daily by 20ml/kg/day	12-15ml q2	10
1251-1500g	3ml q3hr x 3 days	Day 4 of feedings: advance daily by 20ml/kg/day	22-26ml q3	9

FORTIFICATION

If at least 11 days old and feedings at 140ml/kg/day then Fortify - 1packet:50ml human milk.

THEN, if stable on the next day - Fortify 1packet:25ml human milk.

FORMULA

Start with 20 calorie formula until at full feedings (140ml/kg/day).

THEN, if stable next day, change to 24 calorie/oz Formula.

Figure 1.

Initial (version 1) and Final feeding protocols (version 8) used for feeding advancement in VLBW infants

Figure 2.

Control chart (p-chart) presenting the proportion of VLBW infants that developed NEC stage 2 or 3 (A) and surgical NEC (B). Major QI initiatives were implemented in December 2009 and June 2010 as delineated by the dotted lines. The solid black lines represent the monthly observed proportion of VLBW infants that developed NEC stage 2 or 3 (A) and surgical NEC (B). The solid grey lines represent the center line or the mean proportion of infants that developed NEC stage 2 or 3 or surgical NEC for each phase. The dashed grey lines represent the upper control limits (UCL), corresponding to 3SD from the mean. The lower control limits are at 0. A downward trend (6 consecutive data points below center line) in NEC (A) and a significant shift (8 consecutive points below the center line) in surgical NEC (B) were observed in QI phase 2; however, a special cause variation (above

the UCL) was noted in October 2011 for surgical NEC. Tests were performed with unequal sample sizes.

NEC, necrotizing enterocolitis; QI, Quality improvement; UCL, upper confidence limit.

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Figure 3.

The incidence of NEC stage 2 or 3 and surgical NEC in VLBW infants from January 2005 - December 2011. The solid black line represents the observed percentage of VLBW infants that developed NEC stage 2 or 3. The dashed black line represents the observed percentage of VLBW infants that developed surgical NEC. NEC, necrotizing enterocolitis; VLBW, very low birth weight

Table 1
Summary of Process Changes

DATE	ACTION
Baseline Data Acquisition and Team Development	
6/2009 – 8/2009	Conducted case control review of NEC cases and identified risk factors: Rapid introduction of fortifier Variable feeding regimens Overall rates of feeding advancement faster than other centers
Quality improvement phase 1 (9 months)	
9/01/2009	Established multidisciplinary NEC QI team Reviewed retrospective study findings Reviewed literature Developed feeding protocols for very low birth weight infants (versions 1, 2 &3) Completed data collection for baseline period (Jan-Nov 2009 infants not included in case-control study)
12/01/2009	Implemented feeding protocol version 3
1/21/2010	No substantial changes - updated feeding protocol version 4 to improve clarity
5/11/2010	NEC rate remained elevated - Evaluate other processes: Human milk handling, NG tubes, timing of feeding initiation
Quality improvement phase 2 (18 months)	
5/25/2010	Discontinued practice of prolonged NG tube dwell duration by implementing: Change NG tubes every Tuesday. Change extension tubing between each feeding Reeducation for breast pump handling and cleaning
6/08/2010	Prioritized initiation of colostrum trophic feedings at Day 2 (feeding protocol version 5)
7/13/2010	Focus on growth and TPN duration: shortened feeding protocol (version 6) Birth weight <1000g: Advance feedings faster after reach 100ml/kg/d Birth weight >1000g: Advance faster than prior protocol version
12/07/2010	Focus on growth and TPN duration, noted improvement in NEC rates: shortened feeding protocol (version 7) Birth weight <1000g: Advance feedings faster Birth weight >1000g: no changes
10/04/2011	Focus on protein intake: changed feeding protocol (version 8) Shorten interval between partial to full fortification of human milk (22kcal/oz to 24kcal/oz)

NEC, necrotizing enterocolitis; NG, nasogastric; QI, quality improvement; TPN, total parenteral nutrition

Table 2
Sample Characteristics

	Baseline Jan 1, 2008 - Nov. 30, 2009 (n 219)	QI phase 1 Dec 1, 2009 - May 31, 2010 (n 62)	QI phase 2 June 1, 2010 - Nov 30, 2011 (n 170)
Gestational age (wk) *	28.1±2.5 ^b	27.2±2.1 ^{a,c}	28.4±2.8 ^b
Birth weight (g) *	1070±270 ^b	972±267 ^a	1053±272
Male gender **	109 (49%)	34 (55%)	84 (49%)
Maternal race / ethnicity **			
African American	104 (48%) ^c	28 (45%)	92 (54%) ^a
Hispanic	65 (30%)	15 (24%)	30 (18%)
Non-Hispanic Caucasian	44 (20%)	17 (27%)	35 (21%)
Other	6 (2%)	2 (3%)	13 (8%)
SGA at birth **	41 (19%) ^c	8 (13%) ^c	56 (33%) ^{a,b}
Antenatal steroids (complete course) **	156 (72%)	49 (86%)	139 (82%)
Antenatal antibiotics **	116 (54%)	35 (67%)	91 (54%)
Multiple gestation **	47 (22%)	16 (26%)	44 (26%)
Inborn **	188 (86%)	48 (77%)	152 (89%)
C-section delivery **	151 (69%)	39 (63%)	118 (69%)
Apgar 5 min ***	8 (7-9) n 215	8 (6.75-9) n 62	8 (7-9) n 170
Postnatal steroid **	61 (28%) ^b	29 (47%) ^{a,c}	45 (27%) ^b
PDA **	92 (42%)	35 (57%)	81 (48%)
SIP **	NA	4 (7%)	8 (5%)
NEC stage 2 or 3 **	35 (16%) ^c	12 (19%) ^c	5 (3%) ^{a,b}
Surgical NEC **	11 (5%)	3 (5%)	2 (1%)

* Mean ± SD;

** n (%);

*** Median (IQR);

PDA, patent ductus arteriosus; QI, Quality improvement; SGA, small for gestational age; SIP, spontaneous intestinal perforation; NEC, necrotizing enterocolitis.

^a p<0.05 compared to Baseline.

^b
p<0.05 compared to QI phase 1.

^c
p<0.05 compared to QI phase 2.

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Table 3
Process Measures

	Baseline Jan 1, 2008 -Nov. 30, 2009 (n 219)	QI phase 1 Dec 1, 2009 - May 31, 2010 (n 62)	QI phase 2 June 1, 2010 - Nov 30, 2011 (n 170)
DOL feeding initiation (d) *	4 (3-7) n 210	5.5 (4-9) ^c n 62	4 (2-5) ^b n 169
Fed by DOL 3 **	93 (43%) ^b	12 (19%) ^{a,c}	84 (49%) ^b
DOL fortifier started (d) *	13 (8.75-18) ^{b,c} n 58	29 (18-38.5) ^{a,c} n 61	18 (14-25) ^{a,b} n 166
DOL formula introduced (d) *	11 (3-18) ^b n 43	18.5 (12.25-37.5) ^a n 48	16 (7.5-22.5) n 117
DOL full feedings (d) *	15 (11-22) ^b n 206	25.5 (17-37) ^{a,c} n 62	17 (13-23) ^b n 168
Interval start feedings-fortifier (d) *	7.5 (5-11.25) ^{b,c} n 58	20 (13-32) ^{a,c} n 61	12.5 (10-18.25) ^{a,b} n 166
Interval start-full feedings (d) *	9.5 (7-15) ^b n 206	18.5 (12-31) ^{a,c} n 62	11 (9-17) ^b n 168
Human milk – any **	201(99%) ^c n 202	60 (97%) n 62	157 (92%) ^a n 170
Compliance with feed advancement **	NA	36 (58%) ^c	133 (78%) ^b
Compliance with fortification **	NA	49 (80%)	121 (75%)

* Median (IQR);

** n (%);

DOL, day of life; IQR, interquartile range; QI, Quality improvement.

^a p<0.05 compared to Baseline.

^b p<0.05 compared to QI phase 1.

^c p<0.05 compared to QI phase 2.

Table 4
Balancing Measures

	Baseline Jan 1, 2008 - Nov. 30, 2009 (n 219)	QI phase 1 Dec 1, 2009 - May 31, 2010 (n 62)	QI phase 2 June 1, 2010 - Nov 30, 2011 (n 170)
Discharge PMA (wk) *	38.3 ± 4.5	39.4 ± 3.7	38.9 ± 4.3
Discharge weight (g) *	2539 ± 817	2692 ± 639	2564 ± 820
Length of NICU stay (d) ***	61(42-84) ^b	79 (53.75-110.25) ^a	63.5 (44.5-93)
Growth velocity from birth to discharge (g/kg/d) ***	12.7(11.3-14.1)	12.7 (11.7-13.5)	12.8 (11.0-14.0)
Below 10 th percentile at discharge **	87 (40%)	27 (44%)	86 (51%)
Postnatal growth restriction **	50 (23%)	19 (31%)	40 (24%)
TPN (d) ***	14 (9-22.25) ^b n 146	19 (13-33) ^{a,c} n 61	14 (11-20.5) ^b n 149
Late onset sepsis (unrelated to NEC) **	24 (11%)	15 (24%) ^c	15 (9%) ^b
Death **	8 (4%)	0 (0%)	1 (1%)

* Mean ± SD;

**
n (%);

Median (IQR);

IQR, interquartile range; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PMA, postmenstrual age; QI, Quality improvement; TPN, total parenteral nutrition.

^a p<0.05 compared to Baseline.

^b p<0.05 compared to QI phase 1.

^c p<0.05 compared to QI phase 2.