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# A Standardized Slow Enteral Feeding Protocol and the Incidence of Necrotizing Enterocolitis in Extremely Low Birth Weight Infants

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## Abstract

*Background:* Compared with early enteral feeds, the delayed introduction and slow advancement of enteral feedings to reduce the incidence of necrotizing enterocolitis (NEC) are not well studied in extremely low birth weight (ELBW) infants. *Objective*: To study the effects of a standardized slow enteral feeding (SSEF) protocol in ELBW infants. *Methods*: ELBW infants who followed an SSEF protocol (September 2009 to December 2012) were compared with a similar group of historical controls (January 2003 to July 2009). Short-term outcomes between the 2 groups were compared by propensity score (PS) analysis. *Results*: One hundred twenty-five infants in the SSEF group were compared with 294 historical controls. Compared with the controls, feeding initiation day, full enteral feeding day, parenteral nutrition (PN) days, and total central line days were longer in the SSEF group. There was no significant difference in overall NEC (5.6% vs 11.2%, respectively; $P = .10$) or surgical NEC (1.6% vs 4.8%, respectively; $P = .17$) between the SSEF group and controls. However, in infants with birth weight <750 g, NEC (2.1% vs 16.2%, respectively; $P < .01$) or combined NEC/death (12.8% vs 29.5%, respectively; $P = .03$) was significantly less in the SSEF group compared with controls. In infants who survived to discharge, there was no significant difference in the discharge weight or length of stay in PS-adjusted analysis. *Conclusions*: An SSEF protocol significantly reduces the incidence of NEC and combined NEC/death in infants with birth weight <750 g. Despite taking longer to achieve full enteral feeding on this protocol, surviving ELBW infants demonstrated comparable weight gain at discharge without prolonging their hospital stay. (*JPEN J Parenter Enteral Nutr*. XXXX;XX:xx-xx.)

## Keywords

necrotizing enterocolitis; preterm infants; extremely low birth weight infants; feeding protocol

## Clinical Relevancy Statement

Necrotizing enterocolitis (NEC) continues to be a significant cause of mortality and morbidity in extreme preterm infants. The increased use of human breast milk and implementation of standardized feeding protocols have helped to reduce the incidence of NEC. In units where preterm formula is used when breast milk is not available, this study has shown a way to sustain the reduction of NEC by slower standardized enteral feeding advancements, especially in babies with birth weight <750 g, which is the group with the highest risk of dying from NEC.

## Introduction

Necrotizing enterocolitis (NEC) continues to be a devastating neonatal illness, especially in extremely low birth weight (ELBW, birth weight [BW] ≤1000 g) preterm infants.[1-3] In very low birth weight (VLBW, BW <1500 g) infants, the mean incidence of NEC ranges from 7%–9%, with an estimated case fatality rate of 15%–30% and the greatest mortality in infants requiring surgery for NEC.[1,4-7] In the most recently published Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) research network outcome data, the incidence of NEC was 11% for preterm infants born at <28 weeks' gestation.[8] In addition to short-term complications such as feeding intolerance, intestinal obstruction, and

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**Table 1.** Enteral Feeding Practices for ELBW Infants During the Respective Study Period.

| | Control Group | | SSEF Group | |
|---|---|---|---|---|
| Characteristics | Birth Weight <750 g | Birth Weight = 750–1000 g | Birth Weight <750 g | Birth Weight = 750–1000 g |
| NPO days | Not defined | Not defined | 14 | 7 |
| Trophic feeding days | 3–7 | 3–7 | 7 | 7 |
| Trophic feeding volume | 10 mL/kg/d | 10 mL/kg/d | 0.5 mL every 2 h | 1 mL every 2 h |
| Feeding advancement | 15 mL/kg/d | 15–20 mL/kg/d | 0.5 mL/feed every other day | 0.5 mL/feed every day |
| Days to full feeds (150 mL/kg/d) | 18–22 | 16–20 | 44–52 | 32–36 |
| | Provide progressive feedings of human milk or 24-kcal/oz preterm formula every 2–3 h. Add HMF when enteral feeds reach 150 mL/kg/d. | | In both weight groups, change 2 hourly to 3 hourly feeds when infant weight is >1250 g and then advance feeds by 1 mL/feed/d until full feeds. Add HMF (1:50 mL) when enteral feeds reach 100 mL/kg/d and HMF (1:25 mL) at 150 mL/kg/d. | |

ELBW, extremely low birth weight; HMF, human milk fortifier; NPO, nil per os; SSEF, standardized slow enteral feeding.

short gut syndrome, surviving infants, particularly infants with surgical NEC, have poorer neurodevelopmental outcomes and represent a huge financial burden to the healthcare system.[9] The pathophysiology of NEC is poorly understood, but it is likely a multifactorial disease.[7,10] Immaturity of the intestinal tract, inappropriate responses to injuries, abnormal bacterial colonization, and genetic predisposition have all been implicated in the etiology of NEC.[7] Since little progress has been made in the management of NEC once it occurs, preventive strategies are more likely to have a greater impact in reducing the mortality and morbidity from NEC.[11]

Most preterm infants who develop NEC have received enteral feeds. However, it remains unclear which aspects of feeding regimens affect the risk of NEC. Significant variations in practice exist as to when feeds are initiated, how they are advanced, and how feeding intolerance is managed in preterm infants.[2] The modifiable risk factors related to enteral feeding for the development of NEC in preterm infants include the timing of introducing the feeds, the duration of trophic feeding and the rate of advancement of feeding, and the type of milk (human milk vs formula feeding).[12,13] Standardizing the feeding regimen itself has been shown to reduce the incidence of NEC.[13]

An immature enteric nervous system and intestinal dysmotility warrant gradual and cautious increments in enteral feedings. Observational studies have reported a higher incidence of NEC in centers where enteral feeding is introduced earlier and feeding volumes are advanced more quickly.[12-15] Pietz et al[15] reported a 0.4% incidence of NEC in 1158 VLBW infants (~60% were ELBW infants) who followed a late-onset, slow, continuous drip feeding protocol. In contrast, a recent meta-analysis of 5 randomized controlled trials (RCTs) comparing slow advancement (<15–20 mL/kg/d) vs faster advancement (30–35 mL/kg/d) did not detect any significant difference in NEC or all-cause mortality.[16] However, ELBW infants were only included in 2 of the studies, and both had broad exclusion criteria.[17,18] Due to the limited number of ELBW infants enrolled in these studies, caution must be used when generalizing these results to all ELBW infants, the group at highest risk for developing NEC.[16]

The precise effect of enteral feeding advancement on the occurrence of NEC has not yet been thoroughly investigated in ELBW infants. We hypothesized that exposure to a standardized slow enteral feeding (SSEF) protocol might reduce the incidence of NEC in ELBW infants without inducing significant adverse events. To investigate this hypothesis, we carried out a prospective study in a cohort of ELBW infants who followed the SSEF protocol and compared the short-term outcomes with a historical control group of ELBW infants admitted to the same neonatal intensive care unit (NICU) prior to implementation of the SSEF protocol.

## Methods

The study took place in the level III NICU at the MetroHealth Medical Center (MHMC). The NICU receives nearly 600 admissions per year, including approximately 50 ELBW infants, and serves a diverse, underserved inner city population in Cleveland, Ohio. The nonstandardized feeding guideline for ELBW infants admitted to the MHMC NICU was replaced by the SSEF protocol in August 2009 (see Table 1 for protocol description). We stratified ELBW infants into 2 weight groups (BW <750 g and BW 750–1000 g), and separate SSEF protocols were developed for each group. The SSEF protocols differed from previous feeding guidelines by delaying the start of enteral feeding, with more days to prime the intestine and more cautious increments in feeding. In addition, powdered human milk fortifier (HMF) was introduced earlier during the SSEF protocol when the enteral feed reached 100 mL/kg/d compared with 150 mL/kg/d with the previous guideline. At the attending physician's discretion, the initiation of feeds was allowed to be delayed, if indicated, but no infant was fed sooner than the

designated times specified by the protocol. Feeding intolerance was defined as gastric residuals >2 mL for infants with BW <750 g and 3 mL for infants between BW 750–1000 g or >50% of the prior feeding, bile- or blood-stained aspirates, abdominal distention/tenderness, or presence of blood in the stool. Feeding intolerance was quantified by the number of days that feeding was withheld ≥24 hours. Parenteral nutrition (PN) with a minimum 1 g/kg/d of protein was initiated on admission to the NICU during the whole study period. The protein content of starter PN was increased to 2.5 g/kg/d halfway through the SSEF study period. Intravenous fat emulsion was discontinued when enteral feedings reached 100 mL/kg/d, and PN was discontinued when enteral feedings reached 120 mL/kg/d. Human milk feeding was encouraged, and if not available, standard preterm formula (24 cal/oz) was used. Donor breast milk (DBM) or probiotic preparations were not used during the entire study period.

The incidence of NEC in ELBW infants of ≤30 weeks' birth gestation admitted to the MHMC NICU between September 2009 and December 2012, who followed the SSEF protocol (SSEF group, prospective cohort), was compared with ELBW infants of ≤30 weeks' gestation admitted to the MHMC NICU between January 2003 and July 2009, who followed a nonstandardized feeding guideline (historical controls). We excluded infants with major anomalies/known gastrointestinal anomalies, operative diagnosis of spontaneous intestinal perforation, as well as infants who developed NEC/died before the initiation of feeds or were transferred to another facility before reaching full enteral feeding.

The primary outcome of the study was the incidence of NEC in ELBW infants. We defined the occurrence of NEC as Bell stage 2 or greater as per the modified Bell classification[19] or when diagnosed at surgery . Secondary outcomes included the incidence of NEC or death combined, discharge weight, late-onset sepsis, cholestasis, and metabolic bone disease of prematurity. We reviewed all medical records for infants' demographics, including gestational age (GA), BW, small for GA (SGA), sex, race, mode of delivery, Apgar scores at 1 and 5 minutes, exposure to antenatal steroids and chorioamnionitis, and severity of illness measured by the Score for Neonatal Acute Physiology–Perinatal Extension (SNAP-PE). The SNAP-PE score is a 9-item neonatal illness severity and mortality risk score.[20] It is calculated from data collected on the day of admission to the NICU, with points given for physiological items, BW, low Apgar score, and SGA. Nutrition data collected include enteral feeding initiation day, trophic feeding days, trophic feeding volume, days to reach full enteral feeding (150 mL/kg/d), human milk use, PN days, and the duration of central line use (umbilical arterial line [UAC], umbilical venous line, peripherally inserted central catheter, Broviac lines, and total central line days [excluding UAC days]). We also reviewed the medical records for the number of days of mechanical ventilation, the incidence of chronic lung disease (CLD; oxygen requirement at 36 weeks of corrected gestation), intraventricular hemorrhaging (IVH), blood or cerebrospinal fluid (CSF) culture–positive sepsis/meningitis, cholestasis (direct bilirubin levels), metabolic bone disease (serum alkaline phosphatase [ALP] levels), patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), and use of medications (postnatal steroids, inotropes, antibiotics, ibuprofen/indomethacin). Late-onset sepsis/meningitis was defined as clinical signs and symptoms consistent with sepsis occurring >3 days after birth associated with the isolation of a causative organism from at least 1 blood or CSF culture. Patients' outcomes including mortality rate, length of hospital stay, and weight at discharge from the NICU (among survivors) were recorded. The study was approved by the institutional review board of the MHMC.

## *Statistical Analysis*

Based on the historical data, the incidence of NEC in ELBW infants was 11% at the study initiation (MHMC NICU statistics). We determined that a prospective group sample size of 125 ELBW infants compared with 300 controls would have 80% power to detect a decrease in the incidence of NEC to 3.3%, using a 2-tailed 95% confidence interval (CI). This low value for the incidence of NEC was chosen based on the incidence of NEC observed in prior studies using comparable late-onset slow enteral feeding.[15] We performed an appropriate bivariate analysis to identify the unadjusted differences between the SSEF group and historical controls. All quantitative data are expressed as the mean ± standard deviation or median (interquartile range). A $P$ value <.05 was considered to be statistically significant. We also performed a propensity score (PS) analysis to calculate the adjusted SSEF group effect compared with controls on various outcomes. The PS analysis represents an improvement over traditional modeling strategies. With PS methods, infants in the SSEF group are matched on a range of potentially confounding factors to infants in the control group. The 2 groups can then be considered equivalent to each other if no statistical difference exists between the groups on all the covariates included in the model. The 2 PS-matched groups are then compared with each other on various outcomes; thus, the PS analysis represents a quasirandomized controlled design using observational data. Using multiple logistic regression including baseline demographic and nutrition variables, we calculated a PS for entering the SSEF group for each infant. Analyses using 1:1 greedy PS matching stratified by BW group as well as PS weighting by the inverse PS to calculate the mean intervention effect were performed. Conditional logistic regression/paired $t$ test (PS matching) and survey design (PS weighting) were performed based on the PS-matched/weighted pairs as well as direct PS-adjusted comparisons of the SSEF group to the controls on NEC and other secondary outcomes. Statistical software R version R-2.14.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis of the data.

**Table 2.** Demographics of ELBW Infants in the Control and SSEF Groups.

| Characteristics | Control Group (n = 294) | SSEF Group (n = 125) | *P* Value |
|---|---|---|---|
| Birth weight, g | 754.1 ± 147.7 | 766.8 ± 155.5 | .44 |
| Birth weight percentile | 34.4 ± 25.1 | 38.6 ± 25.6 | .12 |
| Birth gestation, wk | 25.9 ± 1.8 | 25.7 ± 1.8 | .33 |
| Male sex, % | 48.9 | 60.8 | .03 |
| Black race, % | 60.5 | 57.6 | .59 |
| Small for gestational age, % | 20.7 | 25.6 | .30 |
| 1-minute Apgar score, median (IQR) | 4 (3–6) | 4 (2–6) | .05 |
| 5-minute Apgar score, median (IQR) | 7 (6–8) | 7 (6–8) | .10 |
| Cesarean delivery, % | 67.8 | 69.6 | .74 |
| Antenatal steroids, % | 75.8 | 75.2 | .99 |
| Chorioamnionitis, % | 17.3 | 14.4 | .56 |
| SNAP-PE | 44.3 ± 14.7 | 40.9 ± 16.4 | .05 |

Values are expressed as mean ± standard deviation unless otherwise indicated. ELBW, extremely low birth weight; IQR, interquartile range; SNAP-PE, Score for Neonatal Acute Physiology–Perinatal Extension; SSEF, standardized slow enteral feeding.

**Table 3.** Nutrition Characteristics of ELBW Infants in the Control and SSEF Groups.

| Characteristics | Control Group (n = 294) | SSEF Group (n = 125) | *P* Value |
|---|---|---|---|
| Enteral feeding initiation day | 11.1 ± 7.1 | 14.2 ± 7.3 | <.001 |
| Trophic feeding days | 5.3 ± 3.2 | 7.9 ± 1.6 | <.01 |
| NPO days (feed start to full feeds) | 6.0 ± 9.4 | 5.2 ± 6.6 | .368 |
| Enteral full feed day | 35.1 ± 19.3 | 63.6 ± 19.1 | <.001 |
| Any human milk use, % | 68.1 | 80.2 | .013 |
| Human milk to formula before full feeds, % | 36.8 | 53.6 | .001 |
| Human milk on full feeds, % | 38.3 | 28.5 | .073 |
| Regain birth weight day | 15.9 ± 6.3 | 17.1 ± 6.5 | .095 |
| Weight on full feed, g | 1046.5 ± 345.6 | 1665.9 ± 413.1 | <.001 |
| PN days | 36.3 ± 22.5 | 62.7 ± 22.9 | <.001 |

Values are expressed as mean ± standard deviation unless otherwise indicated. ELBW, extremely low birth weight; NPO, nil per os; PN, parenteral nutrition; SSEF, standardized slow enteral feeding.

## Results

During the control study period, 391 ELBW infants were admitted to the MHMC NICU. A total of 97 infants met the exclusion criteria (72 infants died and 3 developed NEC before the initiation of enteral feeds, 3 infants were diagnosed with spontaneous intestinal perforation, 13 infants were ≥31 weeks' birth gestation, 5 infants were transferred out before reaching full enteral feeds, and 1 infant had a major congenital anomaly). During the SSEF study period, 145 ELBW infants were admitted to the MHMC NICU, and 20 of them met the exclusion criteria (17 infants died before the initiation of enteral feeds, and 3 infants were ≥31 weeks' birth gestation). The final study sample consisted of 294 infants in the control group and 125 infants in the SSEF group.

The demographics of patients in the control and SSEF groups are shown in Table 2. Overall, there were no significant differences between the SSEF group and controls, except there were more male infants in the SSEF group (Table 2). Compared with controls, the SSEF group had significantly delayed initiation of enteral feeds, took more days to reach full enteral feeds, and required more PN days (Table 3). The rate of human milk initiation was greater in the SSEF group, but in both groups, the majority of infants were on formula when they reached full enteral feeds (Table 3).

The overall incidence of NEC (5.6% vs 11.2%, respectively) and surgical NEC (1.6% vs 4.8%, respectively) were not significantly different between the SSEF group and controls (Table 4). However, in infants with BW <750 g, there was a significant reduction in NEC (2.1% vs 16.2%, respectively; $P < .01$) in the SSEF group compared with controls (Table 4 and Figure 1). No infants with BW <750 g in the SSEF group developed surgical NEC compared with 7.8% in controls (Figure 1). The timing of NEC onset was significantly delayed in the SSEF group compared with controls (57.9 ± 23.7 days [range, 28–97 days] vs 31.2 ± 14.9 days [range, 9–66 days], respectively; $P = .02$] . The incidence of NEC before reaching full enteral feeds was similar between the SSEF group and controls (57.1% vs 54.5%, respectively; $P > .99$).

**Table 4.** Incidence of NEC in ELBW Infants in the Control and SSEF Groups.

| NEC Incidence | Control Group, n (%) | SSEF Group, n (%) | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| All ELBW infants | | | | |
| Overall NEC ≥ stage 2 | 33/294 (11.2) | 7/125 (5.6) | 0.47 (0.17–1.12) | .10 |
| Surgical NEC | 14/294 (4.8) | 2/125 (1.6) | 0.33 (0.04–1.45) | .17 |
| Birth weight <750 g | | | | |
| Overall NEC ≥ stage 2 | 21/129 (16.2) | 1/47 (2.1) | 0.11 (0.002–0.74) | <.01 |
| Surgical NEC | 10/129 (7.8) | 0/47 (0.0) | 0.00 (0.000–1.18) | .06 |
| Birth weight = 750–1000 g | | | | |
| Overall NEC ≥ stage 2 | 12/165 (7.3) | 6/78 (7.7) | 1.06 (0.31–3.20) | .99 |
| Surgical NEC | 4/165 (2.4) | 2/78 (2.6) | 1.06 (0.09–7.57) | .99 |

CI, confidence interval; ELBW, extremely low birth weight; NEC, necrotizing enterocolitis; SSEF, standardized slow enteral feeding.

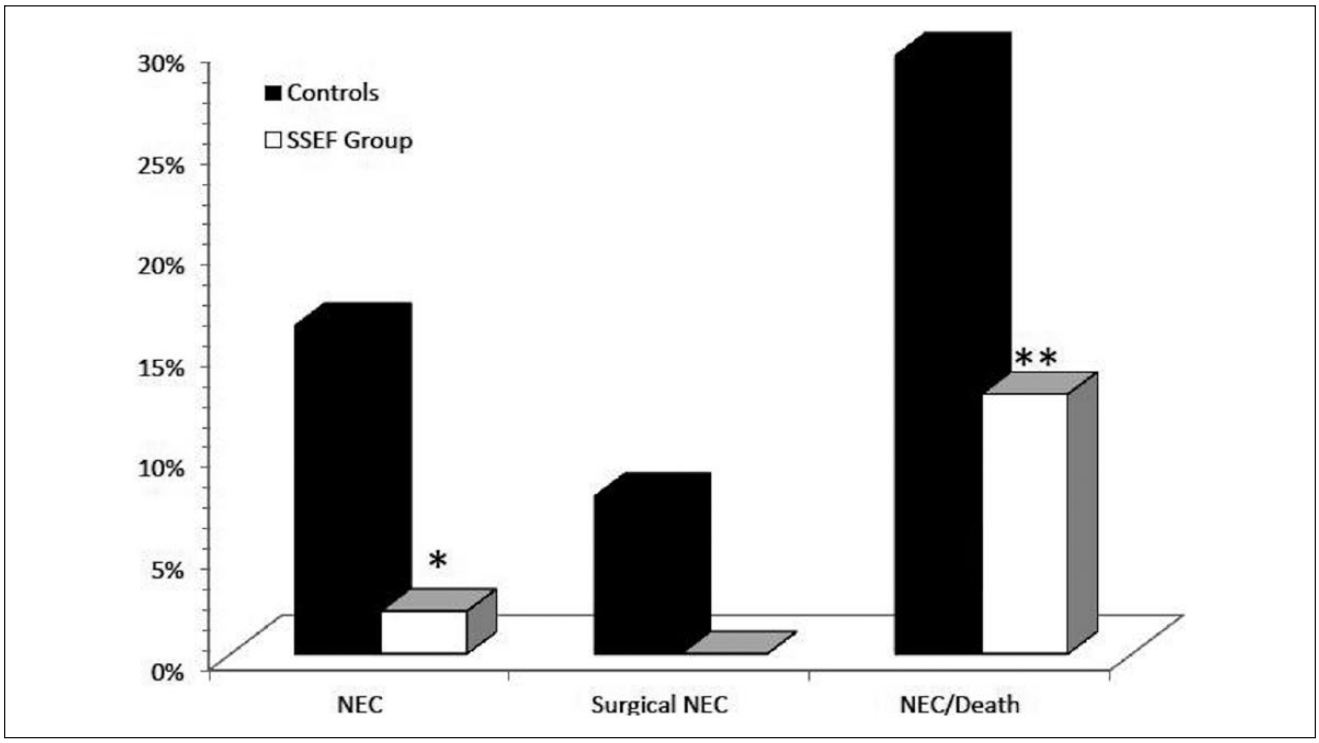


**Figure 1.** Incidence of necrotizing enterocolitis (NEC), surgical NEC, and NEC/death in infants with birth weight <750 g in the standardized slow enteral feeding (SSEF) group compared with the control group. **P* < .01. ***P* = .03.

The SSEF group required significantly more total central line days compared with controls (60.1 ± 29 days vs 34.4 ± 31 days, respectively; *P* < .001) during their NICU stay (Table 5). The incidence of culture-positive sepsis was not significantly different between the 2 groups, but infants in the SSEF group developed infections later in their NICU stay and were exposed to a longer duration of antibiotics (Table 5). None of the infants in the SSEF group with NEC had concomitant sepsis compared with 33% in controls (*P* = .16). The SSEF group had significantly higher peak ALP levels with no difference in the incidence of cholestasis compared with controls (Table 5). The SSEF group had less CLD, hypotension requiring inotropic medications, PDA ligation, and ROP laser surgery compared with the controls (Table 5).

In infants who survived to NICU discharge, the SSEF group had significantly greater body weight (2981 ± 912 g vs 2694 ± 842 g, respectively), with a similar length of NICU stay (110.2 ± 41 days vs 106.7 ± 43 days, respectively), compared with the controls (Table 6). Extrauterine growth restriction (<10th percentile of weight for corrected GA) was significantly less in the SSEF group compared with the controls, while the percentage of infants with a head circumference in <10th percentile at NICU

**Table 5.** Comorbidities Observed in ELBW Infants in the Control and SSEF Groups.

| Characteristics | Control Group | SSEF Group | *P* Value |
|---|---|---|---|
| Any sepsis, % | 44.2 | 42.4 | .75 |
| Late-onset sepsis, % | 42.9 | 40.8 | .75 |
| CONS sepsis, % | 34.0 | 31.2 | .65 |
| Sepsis day of life | 26.4 ± 27.8 | 38.2 ± 27.4 | .01 |
| Total antibiotic days | 21.3 ± 20.3 | 25.4 ± 16.3 | .03 |
| Highest direct bilirubin | 1.8 ± 2.6 | 2.1 ± 2.9 | .10 |
| Direct bilirubin ≥2 mg/dL, % | 22.1 | 28.8 | .13 |
| Peak ALP, IU/dL | 477.1 ± 211.6 | 545.9 ± 261.5 | .01 |
| UAC days | 7.7 ± 4.5 | 7.5 ± 4.8 | .70 |
| UVC days | 8.9 ± 4.5 | 6.6 ± 4.9 | <.001 |
| PICC line days | 16.2 ± 16.9 | 51.4 ± 27.8 | <.001 |
| Broviac line days | 9.8 ± 27.3 | 2.4 ± 9.9 | <.001 |
| Total central line days[a] | 34.4 ± 31.3 | 60.1 ± 29.5 | <.001 |
| Chronic lung disease, % | 67.2 | 51.6 | <.01 |
| Mechanical ventilation days | 39.3 ± 28.5 | 33.6 ± 31.1 | .08 |
| Postnatal steroid use, % | 20.4 | 16.8 | .42 |
| Hypotension (inotrope use), % | 46.6 | 27.2 | <.001 |
| Medical PDA, % | 31.3 | 44.0 | .01 |
| Surgical PDA (ligation), % | 42.5 | 27.2 | <.01 |
| Any IVH, % | 37.0 | 34.4 | .65 |
| Grade 3/4 IVH, % | 14.3 | 12.0 | .64 |
| Any ROP, % | 82.3 | 73.6 | .05 |
| ROP laser treatment, % | 28.9 | 18.4 | .03 |

Values are expressed as mean ± standard deviation unless otherwise indicated. ALP, alkaline phosphatase; CONS, coagulase negative staphylococcal; ELBW, extremely low birth weight; IVH, intraventricular hemorrhaging; PDA, patent ductus arteriosus; PICC, peripherally inserted central catheter; ROP, retinopathy of prematurity; SSEF, standardized slow enteral feeding; UAC, umbilical arterial line; UVC, umbilical venous line.
[a]Excluding UAC days.

**Table 6.** NICU Discharge Outcomes of ELBW Infants in the Control and SSEF Groups.

| Outcome | Control Group | SSEF Group | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Weight (median),[a] g | 2694.2 ± 842.5 (2484) | 2981.2 ± 912.0 (2885) | | <.01 |
| Weight percentile[a] | 8.6 ± 11.9 | 14.8 ± 15.1 | | <.001 |
| Weight <10th percentile,[a] % | 75.4 | 57.1 | | <.001 |
| Head circumference <10th percentile,[a] % | 48.4 | 38.1 | | .10 |
| Length of stay (median),[a] d | 106.7 ± 43.5 (99) | 110.2 ± 41.5 (104) | | .47 |
| Death, n (%) | 37/294 (12.6) | 6/125 (4.8) | 0.35 (0.11–0.87) | .02 |
| <750 g | 27/129 (20.9) | 5/47 (10.6) | 0.45 (0.16–1.25) | .13 |
| 750–1000 g | 10/165 (6.0) | 1/78 (1.2) | 0.20 (0.03–1.60) | .11 |
| Combined NEC/death, n (%) | 57 (19.4) | 13 (10.4) | 0.48 (0.23–0.94) | .03 |
| <750 g | 38/129 (29.5) | 6/47 (12.8) | 0.35 (0.14–0.89) | .03 |
| 750–1000 g | 19/165 (11.5) | 7/78 (9.0) | 0.76 (0.30–1.89) | .65 |

Values are expressed as mean ± standard deviation unless otherwise indicated. CI, confidence interval; ELBW, extremely low birth weight; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; SSEF, standardized slow enteral feeding.
[a]Only infants who survived to NICU discharge are included.

discharge was similar between the groups (Table 6). The SSEF group had significantly lower death (4.8% vs 12.6%, respectively; $P = .02$) and combined NEC/death (10.4% vs 19.4%, respectively; $P = .03$) rates compared with controls (Table 6). However, in the subgroup analysis, the significant reduction in combined NEC/death observed in the SSEF group was present only in infants with BW <750 g (12.8% vs 29.5%, respectively; $P = .03$), while it was similar in the group with BW of 750–1000 g (9.0% vs 11.5%, respectively; $P = .66$). All the infants in the SSEF group with NEC survived to NICU discharge, while

**Table 7.** PS-Adjusted Outcomes in the SSEF Group Compared With the Control Group.

| Outcome | Unadjusted | 1:1 PS Matching | PS Weighting | Direct PS Adjustment |
|---|---|---|---|---|
| NEC | 0.47 (0.17 to 1.12) | 0.44 (0.17 to 1.11) | 0.45 (0.19 to 1.10) | 0.41 (0.15 to 1.01) |
| Death | 0.35 (0.11 to 0.87) | 0.30 (0.11 to 0.78) | 0.27 (0.11 to 0.68) | 0.28 (0.10 to 0.66) |
| Combined NEC/death | 0.48 (0.23 to 0.94) | 0.42 (0.21 to 0.86) | 0.42 (0.22 to 0.83) | 0.40 (0.19 to 0.80) |
| Late-onset sepsis | 0.92 (0.60 to 1.41) | 0.85 (0.51 to 1.40) | 0.87 (0.55 to 1.36) | 0.84 (0.50 to 1.39) |
| Cholestasis[a] | 1.47 (0.92 to 2.38) | 1.12 (0.64 to 1.95) | 1.27 (0.76 to 2.13) | 1.08 (0.62 to 1.90) |
| Peak ALP, IU/dL | 68.8 (20.9 to 116.9) | 64.0 (3.6 to 124.3) | 68.1 (12.6 to 123.6) | 61.2 (0.62 to 121.8) |
| Discharge weight,[b] g | 287.1 (98.6 to 475.6) | 132.0 (–144.6 to 408.7) | 202.0 (–18.0 to 422.0) | 115.3 (–133.8 to 364.4) |
| Length of stay,[b] d | 3.50 (–5.9 to 12.8) | 6.12 (–4.1 to 16.4) | 0.89 (–9.0 to 10.7) | 5.7 (–4.8 to 16.1) |

Values are expressed as odds ratio (95% confidence interval) for proportions for NEC, death, combined NEC/death, late-onset sepsis, and cholestasis or estimated mean difference (95% confidence interval) for continuous variables for peak ALP, discharge weight, and length of stay . ALP, alkaline phosphatase; NEC, necrotizing enterocolitis; PS, propensity score; SSEF, standardized slow enteral feeding.
[a]Direct bilirubin ≥2 mg/dL.
[b]Only infants who survived to NICU discharge are included.

39.4% (13/33) (<750 g: 10/21 [47.6%]; 750–1000 g: 3/12 [25%]) of infants with NEC in the control group died ($P = .07$). NEC was an attributable cause of death in 35.1% (13/37) (<750 g: 10/27 [37.0%]; 750–1000 g: 3/10 [30%]) of the controls compared with 0% (0/6) in the SSEF group.

To calculate the PS, the following baseline (BW, birth gestation, sex, race, SGA, mode of delivery, antenatal steroid exposure, pre-eclampsia, maternal diabetes, maternal smoking, substance abuse, magnesium tocolysis, chorioamnionitis, SNAP-PE score, Apgar scores of 1 and 5 minutes, early sepsis, UAC days, IVH) and nutrition (human milk as initial milk) variables were included in the multiple logistic regression model. The SSEF group had a mean PS of 0.36 ± 0.12, whereas the control group had a mean PS of 0.27 ± 0.15 ($P < .001$). In both the PS-matched groups (1:1 match of all infants in the SSEF group to the nearest PS-matched controls without replacement) and the PS-weighted groups, all the covariates included in the model were well balanced (none with a $P$ value <.05). The important PS-adjusted outcomes using various PS methods are summarized in Table 7. The incidence of NEC was not significantly different between the SSEF group and controls in PS score–adjusted analysis. The PS-adjusted all-cause death and combined NEC/death rates were significantly lower in the SSEF group compared with controls. In the subgroup analysis of infants with BW <750 g, the SSEF group had a significantly lower incidence of NEC (odds ratio [OR], 0.14; 95% CI, 0.007–0.74) and combined NEC/death (OR, 0.32; 95% CI, 0.11–0.82) compared with controls , while both of these outcomes were similar in the 750–1000 g weight group. The PS-adjusted incidence of late-onset sepsis and cholestasis were similar between the groups; however, the peak ALP level was significantly higher in the SSEF group compared with the controls. In infants who survived to NICU discharge, the PS-adjusted discharge weight and length of stay were similar between the SSEF group and controls.

Since there were significant differences in comorbidities between the SSEF and control groups (Table 5) that may be potentially associated with death, an additional logistic regression was performed to determine the adjusted SSEF group effect on the combined NEC/death outcome using all the covariates potentially related to combined NEC/death with a $P$ value ≤.10 in the unadjusted analysis (total antibiotics days, cholestasis, peak ALP, total central line days, CLD, inotropic use, PDA ligation, ROP laser). When controlling for these factors, being in the SSEF group was independently associated with a significant reduction in combined NEC/death (OR, 0.30; 95% CI, 0.12–0.71; $P < .01$).

## Discussion

Our study demonstrates that an SSEF protocol with maternal human milk/preterm formula reduces the incidence of NEC and combined NEC/death in infants with BW <750 g. These results are comparable to those in studies that used an exclusive human milk diet for reducing NEC. However, due to the prolonged nature of the SSEF protocol, these infants were exposed to longer central line and PN days. Despite taking longer to achieve full enteral feeding with the SSEF protocol, these infants demonstrated comparable weight gain at NICU discharge without prolonging their hospital stay.

Epidemiological studies have found that compared with non-Hispanic white infants, non-Hispanic black infants have a higher incidence of NEC.[21] The incidence of NEC is also reported to be higher in male infants.[22] Holman et al[23] described the trends and risk factors for infant mortality in the United States and showed that death from NEC was highest in VLBW infants who were black and male. In addition, the SNAP-PE score in the range of 40–49 observed in our study population represents a high neonatal severity illness score, with a predicted mortality rate of 15.9%.[20] Thus, the demographic characteristics of ELBW infants in our study (higher proportion of black male infants) represent a group at particularly high risk for developing NEC.

Observational data suggest that delaying the introduction of enteral feeds until 5–10 days postnatally reduces the risk of

NEC in VLBW infants.[12,13,15] However, prolonged nil per os (NPO) status may cause atrophy of the intestinal mucosa, delayed development of absorptive function, decreased motility, and development of proinflammatory changes.[24] In various observational studies, infants who received early trophic feeds were reported to have better feeding tolerance, improved growth, reduced length of hospitalization, and decreased likelihood of sepsis compared with infants who received delayed enteral feeds.[25-27] However, these potential short-term benefits of early enteral feeding were not shown to demonstrate a difference in preventing NEC.[16] A meta-analysis of 9 RCTs did not find a significant difference in the NEC rate, time to regain BW, time to reach full enteral feeds, incidence of invasive infections, duration of hospital stay, or all-cause mortality between early trophic feeding and enteral fasting (defined as NPO for 5–7 days).[16] The largest RCT that included ELBW infants randomized appropriately grown infants of 26–30 weeks' gestation to enteral fasting or trophic feeding for the first 14 days of life.[28] There was no difference in the NEC rate (15.9% vs 11.2%, respectively) and days to reach full enteral feeds (35 days vs 32 days, respectively) between the trophic feeding and enteral fasting groups.[28] However, the primary outcome of the several included RCTs was not the incidence of NEC but rather feeding intolerance or time to reach full enteral feeds. Additionally, only a minority of the participants in the included trials were ELBW infants. In our study, the mean initial NPO period was only 3 days longer in the SSEF group compared with controls (13 days vs 10 days, respectively), and the time to reach full enteral feeds was significantly longer (63.6 ± 19.1 days vs 35.1 ± 19.3 days, respectively) (Table 3). This suggests that the slow feeding advancement is more likely associated with NEC reduction rather than the initial NPO period.

An immature enteric nervous system and intestinal dysmotility warrant gradual and cautious increments in enteral feedings. The advancement of aggressive enteral feeding is a risk factor associated with NEC.[29,30] However, a recent meta-analysis of 5 RCTs between slow advancement (<15–20 mL/kg/d) vs faster advancement (30–35 mL/kg/d) did not detect any significant difference in NEC or all-cause mortality.[16] Infants who had slower advancement took longer to regain BW (difference of 2–6 days) and to reach full enteral feeds (difference of 2–5 days).[16] However, ELBW infants were only included in 2 studies, and both had broad exclusion criteria.[17,18] One RCT that considered NEC as the primary outcome evaluated the effect of stable (20 mL/kg/d without advancement) vs advancing (20 mL/kg/d to goal of 140 mL/kg/d) feeding volumes for a 10-day period in non-SGA VLBW infants.[30] Enteral feeds were initiated at a mean age of 10 days, as feeds were initiated only after the removal of umbilical catheters and the discontinuation of inotropic medications. Only one third of the infants received human milk, and the remainder were fed 24-cal/oz preterm formula. This study was prematurely terminated because they found a significantly higher incidence of NEC in infants fed advancing volumes compared with those fed with a minimal enteral feeding volume (10.4% vs 1.4%, respectively; $P = .03$) .[30] Since it is difficult to blind the caregivers to the group assignment, measurement bias may have overestimated the NEC rate in the advancing feed group. However, the large difference in the NEC rate suggests that one should be cautious with the advancement of aggressive feeding in the early days of enteral feeding, especially when using formula.

In a recently reported multicenter RCT, the incidence of NEC and surgical NEC in preterm infants with BW <1250 g, exclusively fed human milk, were 5.8% and 1.4% compared with 15.9% and 10.1% in infants who were fed human milk supplemented with bovine milk–based products, respectively.[31] The infants included in this study were less at risk for NEC (21.6% black infants, 9.6% SGA infants; mean BW, 925 g) compared with our study participants (57.6% black infants, 25.6% SGA infants; mean BW, 766 g). The rates of feeding in the Sullivan et al[31] study (up to 5 days of trophic feeding [10–20 mL/kg/d], followed by 10–20 mL/kg/d of feed advancement) were also "slow" as per the definition set by Cochrane Reviews (feed advancement <24 mL/kg/d). The days to full enteral feeding and days of PN (22 and 21 days, respectively) were significantly less compared with our study results (63 and 62 days, respectively). Subgroup data (BW <1000 g) from this study were not available to compare other outcomes such as sepsis, cholestasis, central line days, and hospital length of stay. With our SSEF protocol, we have achieved a similar rate of NEC to infants fed on an exclusively human milk–based diet. In Sullivan et al's[31] study, even after following a standardized feeding regimen, the high rate of NEC (15.9%) in infants who received human milk supplemented with bovine milk–based products suggests that a much slower advancement of feeds such as in our SSEF protocol may be necessary to reduce NEC in infants receiving bovine milk–based formula or fortifiers.

Although no RCT has compared the effect of mother's own milk (MM) vs formula on NEC or death, there is widespread consensus about the short- and long-term benefits of MM in preterm infants including its protective effect on NEC.[32,33] A recently reported quality improvement project in California to increase human milk use in VLBW infants resulted in a reduction of NEC from 7% to 2.4%.[34] In another prospective cohort study of VLBW infants, infants who received ≥50% enteral feeds with human milk within the first 14 days of life had one sixth the odds of developing NEC compared with infants who received <50% enteral feeds with human milk (3.2% vs 10.6%, respectively; OR, 0.17; 95% CI, 0.04–0.68; $P = .01$).[35] The higher rate of human milk initiation in the SSEF group compared with controls could be a potential confounder in our study, but this difference was balanced by PS methods, and the outcomes were unchanged after PS analysis. If MM is not available, the American Academy of Pediatrics (AAP) policy on breast feeding advocates DBM as suitable alternative feeding.[33]

**Table 8.** Key Discharge Outcome Variables of ELBW Infants for the SSEF Group and the VON.

| Outcome | SSEF Group | VON,[a] 2010–2012 |
|---|---|---|
| Mean weight,[b] g | 2981.2 | 2816.1 |
| Weight <10th percentile, % | 57.1 | 55.0 |
| Head circumference <10th percentile, % | 38.1 | 39.0 |
| Mean length of stay (median),[c] d | 110.2 (104) | 102.2 (99.3) |

ELBW, extremely low birth weight; SSEF, standardized slow enteral feeding; VON, Vermont Oxford Network.
[a]United States centers only.
[b]Infants who survived to discharge "home."
[c]Total hospital stay by final disposition "alive."

A meta-analysis of studies comparing DBM and formula demonstrated that preterm infants fed with formula had more than twice the odds of NEC compared with infants fed with DBM.[36,37] However, these studies included only a minority of extremely preterm infants, and the effects of DBM combined with HMF were not evaluated.[31] An RCT that compared fortified, pasteurized DBM and preterm formula, both used as supplements when MM was not available, did not find a protective effect of DBM on the combined incidence of late-onset sepsis and NEC.[32] Similarly, in Sullivan et al's[31] study, a high incidence of NEC (15.6%) was observed in infants who received human milk (MM or DBM) supplemented with bovine milk–based HMF. The use of MM/DBM may help in the earlier initiation and attainment of full enteral feeding, but slowing the feeding advancement after supplementing with bovine milk–based HMF may help the immature intestine to adapt and reduce the risk for developing NEC. Diet-dependent modification to the standardized feeding regimen may be needed for the sustained prevention of NEC, for example, slower advancement of feeds in infants fed with bovine milk–based products alone or mixed with MM/DBM compared with an exclusive human milk diet.

In a population-based cohort study of ELBW infants, NEC occurred at a mean postnatal age of 32 days,[38] similar to our controls. The nearly doubled time to the onset of NEC in the SSEF group suggests that delaying the establishment of enteral feeds also delays the onset of NEC. This is also consistent with the observation that NEC commonly occurs when the feeding volume exceeds 100 mL/kg/d.[17,30,39] The need for surgical interventions is often used as a surrogate marker for the severity of NEC.[6,7,40] About 50% of infants <750 g who developed NEC in our control group progressed to surgical NEC compared with none in the SSEF group (Table 4). It is plausible that by using an SSEF protocol, these extremely premature infants are more physiologically mature and have better protective mechanisms to tolerate the delayed onset of NEC, leading to a lower risk of progressing to advanced NEC that requires a surgical intervention.

Since conservative feeding strategies are associated with the prolonged use of PN and central line days, they may alter other competing outcomes, especially the rate of nosocomial infections. There was no increase in the incidence of late-onset sepsis in the SSEF group compared with controls; however, the adoption of bundle strategies to prevent central line–associated bloodstream infections potentially helped us to control the infection rate during the prospective study period. The statistically significantly higher peak ALP level in the SSEF group vs the controls (545 IU/dL vs 477 IU/dL, respectively) reflects the potential nutrition-related harm associated with the SSEF protocol; however, the magnitude of difference may not be clinically meaningful. We believe that the potential benefits of the SSEF protocol outweigh the risks, as these infants had a significant reduction in NEC/death and demonstrated comparable weight gain and head growth at NICU discharge without prolonging the NICU stay.

In Sullivan et al's[31] study of infants ≤1250 g, the combined outcome of NEC/death was significantly less common in exclusively human milk–fed infants compared with human milk supplemented with a bovine milk–based product (7.3% vs 20%, respectively). With the SSEF protocol, we have demonstrated a similar reduction in NEC/death in ELBW infants (10.4% vs 19.4%, respectively). This is even more significant, as most of the reduction in NEC/death happened in infants with BW <750 g (12.8% vs 29.5%, respectively), which is the group with a reported NEC mortality rate of 40%–60% as per the largest NEC study cohort published.[6] Based on our study results, the number of infants with BW <750 g that would be needed to treat with the SSEF protocol to prevent 1 case of NEC is 7, and the number needed to treat to prevent 1 combined NEC/death is 6.

Key discharge outcome variables of the SSEF group compared with the corresponding period's Vermont Oxford Network (VON) data for ELBW infants (2010–2012 in the United States only) are given in Table 8.[41] The SSEF group has comparable growth outcomes at NICU discharge to the VON cohort. We believe that the modest increase in the length of NICU stay is due to the improved survival of infants with BW <750 g.

One of the strengths of our study is the use of NEC incidence as the primary outcome. Most of the previous single-center studies were underpowered to detect a difference in the NEC rate due to the relatively low incidence of NEC. However, our study is not without limitations. Only about one third of the infants remained on human milk at full enteral feeds in spite of the higher rate of human milk initiation (80.2%). Our results

are not isolated, as 1 study reported that only 30% of mothers were able to supply 100% of their extremely premature infants' needs.[32] This suggests that our outcomes are not generalizable to the population fed mainly with a human milk diet. Since our study spans more than a decade, it is possible that practice changes in the care of ELBW infants have affected the outcomes reported. For example, more medical treatments of PDA compared with primary PDA ligation and earlier extubation and aggressive noninvasive ventilation in the SSEF group reflect current neonatal practice. Also, we have reported only the short-term outcomes associated with the SSEF protocol, as the study was not designed to assess the long-term neurodevelopmental outcomes.

## Conclusion

NEC is a devastating disease with high morbidity and mortality. Enteral feeding practices and the type of milk used represent 2 major modifiable risk factors of NEC in ELBW infants. Our study demonstrates that when using human milk or preterm formula, following an SSEF protocol helps to reduce NEC and combined NEC/death in infants with BW <750 g. We believe that the benefits of reducing the combined NEC/death rate outweigh the potential nutrition-related harm associated with the delayed initiation and slower advancement of enteral feeds, especially when using formula as the initiation milk. However, because the etiology of NEC is multifactorial, only adequately powered, vigorously conducted randomized trials with sufficient follow-up can conclusively assess the effect of slow feeding advancement on NEC and other related short- and long-term outcomes in ELBW infants.

### References


1. Neu J, Walker WA. Necrotizing enterocolitis. *N Engl J Med*. 2011;364(3):255-264.
2. Athalye-Jape G, More K, Patole S. Progress in the field of necrotising enterocolitis: year 2012. *J Matern Fetal Neonatal Med*. 2013;26(7):625-632.
3. Holman RC, Stoll BJ, Curns AT, Yorita KL, Steiner CA, Schonberger LB. Necrotising enterocolitis hospitalisations among neonates in the United States. *Paediatr Perinat Epidemiol*. 2006;20(6):498-506.
4. Fitzgibbons SC, Ching Y, Yu D, et al. Mortality of necrotizing enterocolitis expressed by birth weight categories. *J Pediatr Surg*. 2009;44(6):1072-1075, discussion 1075-1076.
5. Clark RH, Gordon P, Walker WM, et al. Characteristics of patients who die of necrotizing enterocolitis. *J Perinatol*. 2012;32(3):199-204.8.
6. Hull MA, Fisher JG, Gutierrez IM, et al. Mortality and management of surgical necrotizing enterocolitis in very low birth weight neonates: a prospective cohort study. *J Am Coll Surg*. 2014;218(6):1148-1155.
7. Lin PW, Nasr TR, Stoll BJ. Necrotizing enterocolitis: recent scientific advances in pathophysiology and prevention. *Semin Perinatol*. 2008;32(2):70-82.
8. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126:443-456.
9. Bisquera JA, Cooper TR, Berseth CL. Impact of necrotizing enterocolitis on length of stay and hospital charges in very low birth weight infants. *Pediatrics*. 2002;109(3):423-428.
10. Henry MC, Moss RL. Necrotizing enterocolitis. *Annu Rev Med*. 2009;60:111-124.
11. Neu J, Mihatsch W. Recent developments in necrotizing enterocolitis. *JPEN J Parenter Enteral Nutr*. 2012;36(1 Suppl):30S-35S.
12. Henderson G, Craig S, Brocklehurst P, McGuire W. Enteral feeding regimens and necrotising enterocolitis in preterm infants: a multicentre case-control study. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(2):F120-F123.
13. Patole SK, de Klerk N. Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies. *Arch Dis Child Fetal Neonatal Ed*. 2005;90:F147-F151.
14. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birth weight infants. *Am J Obstet Gynecol*. 2007;196:147.e1-147.e8.
15. Pietz J, Achanti B, Lilien L, et al. Prevention of necrotizing enterocolitis in preterm infants: a 20-year experience. *Pediatrics*. 2007;119:e164-e170.
16. Morgan J, Young L, McGuire W. Slowly advancing milk feeds does not reduce the risk of necrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev*;28:CD001241.
17. Rayyis SF, Ambalavanan N, Wright L, Carlo WA. Randomized trial of "slow" versus "fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. *J Pediatr*. 1999;134(3):293-297.
18. Karagol BS, Zenciroglu A, Okumus N, Polin RA. Randomised controlled trial of slow versus rapid enteral feeding advancements on the clinical outcomes of preterm infants with 750-1250g. *JPEN J Parenter Enteral Nutr*. 2013;37(2):223-228.
19. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am*. 1986;33(1):179-201.
20. Richardson DK, Corcoran JD, Escobar GJ, Lee SK. SNAP-II and SNAPPE-II: simplified newborn illness severity and mortality risk scores. *J Pediatr*. 2001;138(1):92-100.
21. Llanos AR, Moss ME, Pinzon MC, Dye T, Sinkin RA, Kendig JW. Epidemiology of neonatal necrotizing enterocolitis: a population-based study. *Paediatr Perinat Epidemiol*. 2002;16:342-349.
22. Guner YS, Friedlich P, Wee CP, Dorey F, Camerini V, Upperman JS. State-based analysis of necrotizing enterocolitis outcomes. *J Surg Res*. 2009;157(1):21-29.
23. Holman RC, Stoll BJ, Clarke MJ, Glass RI. The epidemiology of necrotizing enterocolitis infant mortality in the United States. *Am J Public Health*. 1997;87:2026-2031.
24. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. *Am J Surg*. 2002;183:390-398.
25. De Silva A, Jones PW, Spencer SA. Does human milk reduce infection rates in preterm infants? A systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2004;89:F509-F513.
26. Flidel-Rimon O, Branski D, Shinwell ES. The fear of necrotizing enterocolitis versus achieving optimal growth in preterm infants: an opinion. *Acta Paediatr*. 2006;95(11):1341-1344.
27. McClure RJ. Trophic feeding of the preterm infant. *Acta Paediatr Suppl*. 2001;90(436):19-21.
28. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk vs. preterm formula. *Pediatrics*. 1999;103:1150-1157.
29. Anderson DM, Kliegman RM. The relationship of neonatal alimentation practices to the occurrence of endemic necrotizing enterocolitis. *Am J Perinatol*. 1991;8:62-67.
30. Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2003;111:529-534.
31. Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *J Pediatr*. 2010;156(4):562-567.

32. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics*. 2005;116(2):400-406.
33. Eidelman AI, Schanler RJ. Section on Breastfeeding Executive Committee. Breastfeeding and the use of human milk: policy statement. *Pediatrics*. 2012;129:e827-e841.
34. Lee HC, Kurtin PS, Wight NE, et al. A quality improvement project to increase breast milk use in very low birth weight infants. *Pediatrics*. 2012;130:e1679-e1687.
35. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feedings associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *J Perinatol*. 2007;27(7):428-433.
36. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2014;4:CD002971.
37. Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2007;92:F169-F175.
38. Yee WH, Soraisham AS, Shah VS, et al. Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. *Pediatrics*. 2012;129(2):e298-e304.
39. Owens L, Berseth CL. Is there a volume threshold for enteral feeding and necrotizing enterocolitis? *Pediatr Res*. 1995;37:315A.
40. Guthrie SO, Gordon PV, Thomas V, Thorp JA, Peabody J, Clark RH. Necrotizing enterocolitis among neonates in the United States. *J Perinatol*. 2003;23:278-285.
41. Vermont Oxford Network. Database of very low birth weight infants. 2010-2012. Nightingale Internet Reporting System. Available at: http://www.vtoxford.org/. Accessed July 2, 2014.