Pediatrics and Neonatology 63 (2022) 181—187

Available online at www.sciencedirect.com

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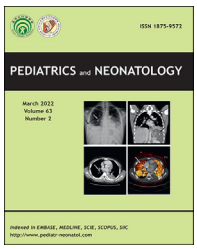

Original Article

The impact of a multifaceted quality improvement program on the incidence of necrotizing enterocolitis in very low birth weight infants

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Received Jun 7, 2021; received in revised form Sep 27, 2021; accepted Oct 7, 2021
Available online 5 December 2021

Key Words
Very low birth weight Infants;
necrotizing entero colitis;
structured feeding protocol;
enteral feeding osmolality;
gastric residual management

Background: Necrotizing enterocolitis (NEC) is a multifactorial gastrointestinal disease which mostly occurs in very low birth weight (VLBW) infants. In addition to decreasing gestational age (GA) or birth weight (BW), artificial formula, delayed initiation or rapidly advanced feeding, severe anemia and systemic infections were associated with NEC. Several studies demonstrated that breast milk, standardized feeding advancement regimens and treatment of anemia are associated with less incidence of NEC. It is not known if including all these interventions in one multifaceted program will lead to significant reduction in NEC.
Methods: The NICU team at The George Washington University Hospital created a multifaceted interdisciplinary quality improvement project to tackle several aspects of NEC prevention that addressed researched risk factors for NEC. The program was made of four quality improvement protocols: 1) Standardized Structured Feeding Program, 2) Feeding Intolerance Management Algorithm, 3) Enteral Osmolality Control Tool, and 4) Packed Red Blood Cell (RBC) Standardized Transfusion Protocol. This time-series, quasi experimental study design examined the differences in the incidence of NEC between infants with BW $<$ 1500 g who were admitted to the GW Hospital NICU before and after the program implementation.
Results: Data from 408 VLBW infants were included in the study. Although not statistically significant, there was a decreasing trend of NEC incidence in the post-implementation group (n $=$ 199) compared to the pre-implementation group (n $=$ 209), (3.5% vs. 5.3%, p $=$ 0.88).

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https://doi.org/10.1016/j.pedneo.2021.10.002

The trend in the incidence of NEC declined further after the introduction of RBC transfusion protocol which was introduced ten month after starting the other elements of the program.
Conclusion: Integration of the multifaceted quality improvement program may be associated with a decline in the occurrence of NEC. Further analysis with a larger sample size is required to determine if the changes seen are statistically significant.

1. Introduction

Necrotizing enterocolitis (NEC) is among the major morbidities experienced by very low birth weight infants (VLBW) in the neonatal intensive care unit (NICU).[1,2] Prevention and early detection are key factors in reducing NEC adverse effects that have a mortality rate of about 30%, with higher rates in the more severe and surgical cases.[3] Additionally, of those who survive NEC, there is an increased chance of long-term physiological and neurodevelopmental complications.[4] There continues to be no universal practice for NEC prevention. Changes to gastrointestinal microbiota were suggested as a contributing factor to NEC in preterm infants.[5–7] Multiple factors impact this change in bacterial colonization including feeding type and methods, medication use, and perfusion conditions.[8,9] While *in utero*, fetal swallowing of the amniotic fluid helps in developing the gastrointestinal (GI) tract, a process that starts as early as 11 weeks post conception and continues until birth.[10,11] Therefore, infants born prematurely are deprived of these natural effects and they are more susceptible to NEC.

Although it continues to be a topic of debate, standardized feeding protocols in preterm infants have been shown to decrease incidence of severe NEC among VLBW infants.[12] A meta-analysis with eligible studies (1978—2003) showed that implementation of standardized feeding led to an 87% reduction in NEC.[12] A more recent systematic review (2004—2016) reaffirmed that evidence-based standardized feeding regimens continue to be vital in the reduction of NEC.[13]

Increased gastric residuals (GR) have been shown to be one of the many clinical signs of NEC.[14] One of the reasons some NICUs perform GR monitoring is to evaluate whether prior feeding remained in the stomach, which can be attributed to feeding intolerance.[15] One study suggested that higher GR volumes in VLBW infants are more indicative of NEC compared to infants with lower GR volumes.[16] However, others evaluating gastric residuals state that there is lack of evidence of whether this practice should be continued.[17,18]

Preterm infants are given several enteral medications and supplements. This can increase osmolality, which has been linked to NEC.[19,20] One meta-analysis evaluated studies that had groups of two or more feeds with different osmolality but could not correlate higher osmolality with adverse outcomes as each study used different feeding volumes with different compositions.[21] The addition, medication to expressed breast milk (EBM) can increase osmolality.[20] Two review studies revealed that although there is no evidence of direct mucosal injury from hyperosmolar substances, it is recommended to dilute additives, to avoid multiple individual supplements at the same time, and to be aware of osmolality during additive administration.[19,21]

Several recent prospective and retrospective observational studies have concluded that RBC transfusions are not associated with an increased risk of NEC, and others have concluded that RBC transfusion is actually protective against the disease.[22–25] A review article summarized two studies evaluating the association between feeds and transfusion in preterm babies. The author concluded that while there was still a need for more evidence, there seemed to be a protective effect when feeds were withheld before and during transfusion.[26] Although Bell Staging criteria of NEC classification have been modified to improve diagnosis, early identification of NEC-portending signs are difficult to recognize since many NEC clinical presentations are shared with other morbidities.[27]

This study examined the impact of creating new protocols for several modifiable risk factors including standardized feeding, residuals management, osmolality control, and packed red blood cells (RBC) transfusion guidelines in reducing NEC in all level III NICUs.

2. Methods

2.1. Study design

The NICU team at The George Washington University Hospital, Washington, D.C., strategically executed a series of protocols that made up a multifaceted quality improvement program specifically for NEC reduction based on both scientific evidence and accumulated experience. Since the onset of NEC is multifactorial, these protocols were designed to target multiple factors at the same time including feeding advancement, residuals management, enteral osmolality, and treatment of anemia and RBC transfusion protocol. All guidelines in the program were followed simultaneously and periodically evaluated by the multidisciplinary team. Feedback and corrective measures were offered to the faculty and staff accordingly. This analysis used a time-series, quasi experimental design comparing the incidence of NEC before and after implementation of the NEC reduction quality improvement program.

2.2. Patient selection

Patients eligible for this study were defined as infant born at GWU Hospital with birth weight (BW) $<$ 1500 g.[28] The

three initial protocols of the NEC quality improvement Program (standardized feeding, residuals management and osmolality control) were implemented starting on 07/01/2016 and the transfusion protocol was introduced on 05/01/2017. In order to analyze whether the combination of protocols had an impact on NEC reduction, pre-program implementation dates were defined as admissions between 07/01/2012 and 06/30/2016 and post-implementation as between 07/01/2016 and 12/31/2019.

The main outcome of this data analysis was confirmed NEC as defined by the presence of a combination of abdominal signs (at least one of the following symptoms: excessive residuals or vomiting, excessive abdominal distention, abdominal tenderness or guarding or abdominal wall discoloration), presence of pneumatosis on x-ray, infants needing to be on nothing per oral for 72 h or more and to be on antibiotics for more than 72 h. Charts of infants who were labeled as having NEC during their hospital course were reexamined and abdominal x-rays were re-verified by an independent physician to confirm the diagnosis of NEC.

Demographic and clinical variables that were used as confounders in the analysis included both maternal characteristics (age, diabetes, hypertension, infection, and prenatal steroids) and infant characteristics (race, sex, singleton pregnancy, C-section delivery, Apgar scores at 1 and 5 min, GA, BW, small for gestational age (SGA) status, surfactant therapy, number of transfusions, postnatal steroid, and UAC and UVC duration). The retrospective analysis of collected data was approved by the George Washington University institutional review board.

2.3. Interventions

The driver diagram was developed to achieve the objective of decreasing incidence of NEC among VLBW preterm infants (Fig. 1). The NEC reduction quality improvement program encompassed four interventions: standardized feeding program, feeding intolerance management algorithm, enteral osmolality control tool, and packed red blood cell transfusion protocol. The multidisciplinary team included a neonatologist, a neonatal dietician and neonatal nursing staff. Monitoring and feedback education for staff and trainees were provided monthly, printed copies of the protocols were kept in the NICU for easy accessibility, and standardized audits were conducted bi-weekly to monitor compliance with interventions. A run chart, which looked at the trends of NEC over time, was constructed quarterly to monitor the effectiveness of the NEC Program.

2.3.1. Protocol 1: standardized feeding program (implementation started in 07/2016)

The first protocol focused on standardized feeding (Supplementary Figure 1). The trophic feed and nutritional advancement rates were determined by established risk factors. Infants were divided into high-risk, moderate-risk, and low-risk populations with regard to feeding initiation and advancement. The inclusion factors for the high-risk population included infants $<$1500 g BW who had a history of absent or reversed end-diastolic flow (EDF), who were small for gestational age (SGA), used umbilical lines for more than five days, with birth weight less than 750 g and/or gestational age $\leq$28 weeks. The moderate-risk population included infants with birth weight $<$1500 g who did not meet other high-risk population criteria. The low-risk population included neonates who were equal to or larger than 1500 g at birth (this group was not included in this data analysis). The advancing regimen of the trophic feeding and both bolus and continuous nutritional feeding were according to the infant's weight in 100 g increments.

Feeding started as early as the first day of life with trophic volumes that were not advanced until the infants established bowel movement pattern. Gradual volume advancement followed the trophic feeding phase until infants reached full target volume. Advancement scheme was set to allow a

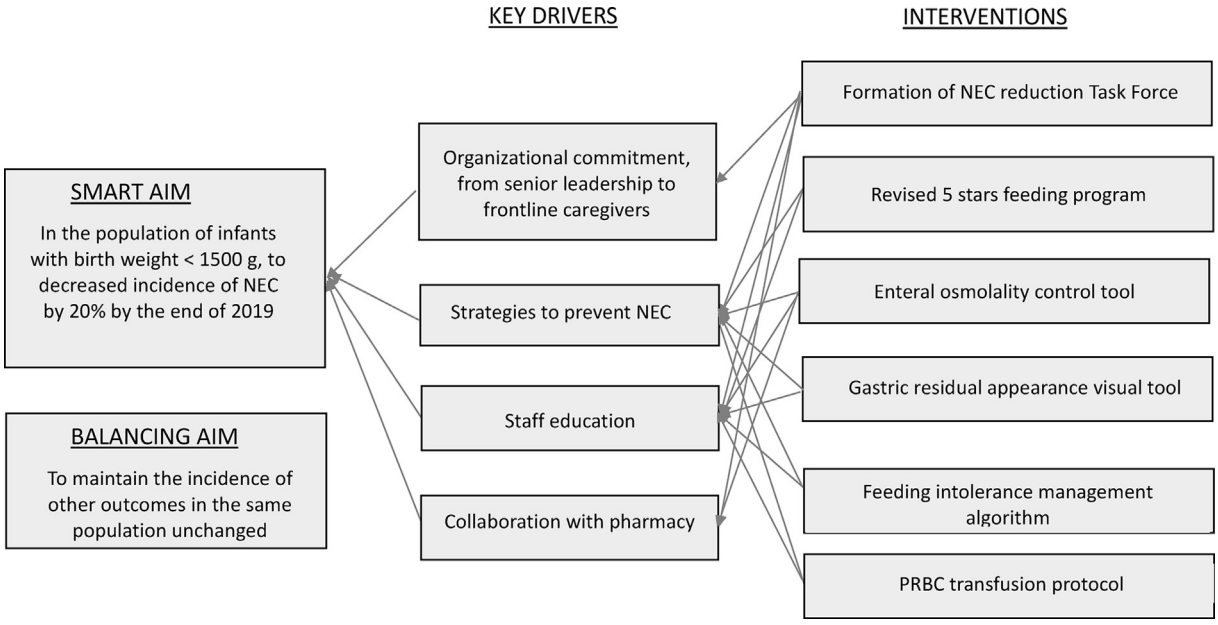

Figure 1 Driver diagram for decreasing NEC incidence among VLBW preterm infants.

range of minimum and maximum daily increase to respond to different clinical scenarios not counted for in the original protocol design and to accommodate variability among team members. Mother's breast milk or donor breast milk were used in all infants <1500 g. Use of artificial formula was restricted to those infants for whom families did not provide breast milk and declined to consent to donor's milk. Fortification of breast milk occurred in two increments after successfully achieving volume advancement milestones.

2.3.2. Protocol 2: feeding intolerance management algorithm (implementation started in 07/2016)

The second protocol used a feeding intolerance management algorithm (Supplementary Figure 2) to monitor gastric residuals. Preterm infants with GR were categorized into two groups, a) non-bilious and b) bilious or hemorrhagic GR. Neonates in the non-bilious GR group were further divided into mild (<25% of previous feeding volume), moderate (25–50%), and severe (>50%). Those in the 'mild' category were refed their GR and received planned volume of feeding. Infants in the 'moderate' category were first refed their GR, which was subtracted from the planned feeding volume. If they were still in the moderate category after 12 h, the GR was discarded, and the feed was held. If they were still in the moderate category after 24 h, these infants were placed on NPO for 12 h.

Infants in the 'severe' category were placed immediately on NPO for 12 h. During the NPO time, a complete blood count (CBC), C reactive protein (CRP) and blood culture were considered if infants were showing other signs of being sick. If the abdomen was not soft, abdominal x-ray was also considered. After the 12 h, neonates were checked for no or minimal GR, soft abdomen with no distention (<2 cm increase in girth from baseline) and positive bowel sounds or bowel movement in the last 24 h. If all these criteria were met, plain human milk or formula was restarted in gradual structured increments. Infants who were originally in the bilious or hemorrhagic GR were immediately placed on NPO for 24 h and an abdominal x-ray and blood culture was considered during this time. Neonates in this group were then checked for the same criteria as those placed on NPO for 12 h in the non-bilious group. If all criteria were met, plain human milk was restarted in gradual increments till reaching pre-incident level then fortification was added. If not, further evaluation would be conducted. Small residual volumes were not considered during the early initiation of feeding (trophic phase: <20 ml/kg/d). Only residuals that contained undigested or semi-digested milk or bloody content were considered as feeding residuals. Clear yellow or light green gastric secretions were not considered as feeding residuals.

2.3.3. Protocol 3: enteral osmolality control tool (implemented: 07/2016)

The third protocol focused on osmolality of enteral feedings (Supplementary Figure 3). Common enteral medications, including Vitamin D, sodium chloride (NaCl) supplement, caffeine citrate, ferrous sulfate, Vitamin E, aldactazide (mixture of spironolactone and hydrochlorothiazide), and multivitamins (Poly-Vi-Sol), were timed and given on a regular schedule coordinated with feeding times and were distributed over the 24 h based on osmolality load. Additionally, the protocol stated that infants who were NPO for RBC transfusion should not receive any enteral medications during the NPO time.

2.3.4. Protocol 4: packed Red Blood Cell transfusion protocol (implemented: 05/2017)

The fourth protocol provided guidelines for RBC transfusion in relation to feeding (Supplementary Figure 4). A set criteria for RBC transfusion was constructed based on infants' GA, postnatal age and hematocrit level (HCT). If infants met the transfusion criteria, they would go on NPO 2 h prior to transfusion, during transfusion, and 4 h post transfusion. After RBC transfusion was complete and NPO time was over, infants were to resume feeding in gradual increments and weaned off IVF gradually. Similar precautions would be exercised for starting and advancing feeding after NPO time. If any of the exceptions were met, reassessment would occur every 3 h until the exam and GR normalized. Further advancement in volume or fortification is deferred until 24 h after transfusion.

2.4. Statistical analysis

Data were analyzed using SAS software version 9.4 (Cary, NC). Descriptive statistics, including means and standard deviations for normally distributed (parametric) data, medians and interquartile ranges (IQR) for non-parametric data, were generated for all continuous variables. Frequency distributions and percentages were generated for categorical variables.

Comparison between pre- and post-implementation groups were done using Chi-squared and Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Bivariable analysis was performed to test the association between quality improvement project and NEC (pre-implementation vs. post-implementation). Multivariate analysis was performed to examine the association of the quality improvement project and NEC and while controlling for potential confounders as listed above and in Table 1. All predictor variables with a p-value <0.05 in both bivariable analyses were considered potential confounders and included in the multivariable model and adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated accordingly.

3. Results

The study included a total of 408 infants who met the eligibility criteria. Of these infants, 209 were admitted to the NICU between 07/01/2012 and 06/30/2016 (pre-implementation group) and 199 infants were admitted between 07/01/2016 and 12/31/2019 (post-implementation group). Compliance with quality improvement interventions from bi-weekly audits was equal to or above 90%. Table 1 compares the pre- and post-implementation groups. Infants in the post-implementation group had greater odds of being SGA (OR: 1.64; CI: 1.02–2.65, $p = 0.04$) and received more surfactant (OR: 2.76; CI: 1.65–4.61, $p = 0.01$) compared to infants in the pre-implementation group.

Unadjusted and adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association of the quality improvement projects (pre and post) with NEC are shown in

Table 1 Demographic and clinical characteristics of the study groups.

	Post-Implementation n = 199	Pre-Implementation n = 209	OR (CI)	*p* value
Maternal Characteristics				
Maternal Age, median (IQR)[b]	29.0 (25.0, 34.0)	31.0 (25.0, 35.0)	0.97 (0.95, 1.00)	0.08
Maternal Diabetes	15 (7.5)	22 (10.5)	0.69 (0.35, 1.38)	0.30
Maternal Hypertension	70 (35.2)	70 (33.5)	1.08 (0.72, 1.62)	0.72
Maternal Infection	51 (25.6)	47 (22.5)	1.19 (0.75, 1.87)	0.46
Maternal Steroids	113 (57.1)	112 (53.6)	1.15 (0.78, 1.70)	0.48
Cesarean Section	121 (60.8)	127 (60.8)	1.00 (0.67, 1.49)	0.99
Infants' characteristics				
Male sex	92 (46.2)	103 (49.3)	0.89 (0.60, 1.31)	0.54
African American race	140 (70.4)	149 (71.6)	0.94 (0.61, 1.44)	0.78
Gestational Age, mean (SD)[a]	28.8 (3.6)	28.4 (3.4)	1.03 (0.97, 1.09)	0.33
Birth weight, mean (SD)[a]	1022.3 (326.0)	1032.2 (341.3)	0.99 (0.94, 1.05)	0.76
Multiple Gestation	44 (22.1)	52 (24.9)	0.86 (0.54, 1.36)	0.51
Small for gestational age	52 (26.1)	37 (17.7)	1.64 (1.02, 2.65)	**0.04**
Apgar Score at 1 Minute, median (IQR)[b]	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	1.00 (0.93, 1.09)	0.92
Apgar Score at 5 Minutes, median (IQR)[b]	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)	0.96 (0.87, 1.06)	0.42
UAC Duration, median (IQR)[b]	0.0 (0.0, 1.0)	0.0 (0.0, 2.0)	0.97 (0.90, 1.05)	0.48
UVC Duration, median (IQR)[b]	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)	1.05 (0.98, 1.12)	0.16
RBC Transfusions, median (IQR)[b]	2.0 (0.0, 4.0)	1.0 (0.0, 3.0)	1.02 (0.96, 1.07)	0.59
Surfactant Administration	56 (28.1)	26 (12.4)	2.76 (1.65, 4.61)	**<0.01**
Postnatal Steroids	22 (11.1)	12 (5.7)	2.04 (0.98, 4.24)	0.06
Necrotizing enterocolitis	7 (3.5)	11 (5.3)	0.66 (0.25,1.73)	0.39

Abbreviations: RBC: packed red blood cells, UAC: umbilical arterial catheter, UVC: umbilical venous catheter, IQR: interquartile range, OR: odds ratio, CI: confidence intervals.

[a] Data is presented as frequencies and percentages except continuous data where it is presented as means and standard deviations.

[b] Data is presented as frequencies and percentages except continuous data where it is presented as medians with interquartile ranges.

Table 1. The aOR were calculated through multivariate logistic regression models adjusting for confounding variables including maternal and infants' characteristics described in Table 1. Although statistically non-significant, NEC incidence in the post-implementation group was lower than the pre-implementation group (3.5% vs. 5.3%), OR: 0.66 (0.25, 1.73), $p = 0.39$. After controlling for all confounders in the multi-logistic regression analysis, the association remained statistically insignificant, adjusted OR: 0.91 (CI: 0.28—3.00, $p = 0.88$).

In subgroups analysis, the incidence of NEC decreased from 11 cases in 209 infants (5.3%) in the pre-implementation group to 2 cases in 49 infants (4.1%) in the post-implementation period (07/01/2016—04/30/2017) when only the first three protocols were in effect (excluding the blood transfusion protocol). The NEC incidence further declined to 5 cases in 150 infants (3.3%) in the post-implementation time where all protocols were in effect (05/01/2017—12/31/2019). However, no statistical significance was noted comparing pre-implementation phase with either of the post-implementation periods.

4. Discussion

This study analyzed the impact of implementing a multifaceted quality improvement project (four simultaneous protocols) to reduce the incidence of NEC. Although not statistically significant, the results demonstrated a lower proportion of NEC in the post-implementation group. In addition, it demonstrated that standardized transfusion practice based on hematocrit value and NPO time with transfusion are more likely to affect NEC incidence compared to other interventions.

Some of the interventions implemented in this program are novel, such as the residual management protocol with structured periods of NPO time and the osmolality check and control tool with uniform distribution over the first 24 h. In addition, implementing existing ideas such as the standardized feeding and transfusion management were innovative. As an example, the standardized feeding protocol was designed to observe success of trophic feedings, gradual advancement prior to the start of fortification, and fortification over 2 steps after successfully achieving at least 2/3 of target enteral goal. Feeding advancement was managed with a reasonable range of lower and upper limits to accommodate infants' physiological variability and readiness for enteral feeding. Human milk fortifier was introduced on specific midpoints that were followed with no advancement to enhance infants' nutrition while exercising caution not to stress the gut with both fortification and feeding advancement on the same time. Similarly, RBC transfusion protocol followed clear threshold guidelines for transfusion and strict criteria for NPO time before, during, and after transfusion, with a subsequent gradual advancement to resume feeding.

There was no similar quality improvement projects that carried more than two different elements conducted in parallel to compare to our multifaceted quality improvement program with a combination of simultaneously implemented four protocols, as well as introducing novel interventions. The decrease in NEC was expected because the four protocols were chosen based on scientific evidence and prior literature review. This study adds to the pool of existing knowledge and further emphasizes the impact that combined protocols can have on reducing NEC. We anticipated a statistically significant reduction in rates of NEC. However, the lack of statistical significance could have been due to the small sample size.

The study itself was well structured with quality assurance checks, biweekly audits and monthly assessments. Monitoring and feedback training were provided monthly to ensure proper adherence to the protocols. Furthermore, data used in this study were taken directly from medical charts. This allowed for accurate data collection of the infants' date of birth, predictors, and the precise definition of NEC. Data extracted from the medical charts were verified at least twice by research assistants.

There were limitations to this study that might have impacted the results. The sample size was small with a total of only 408 infants. Despite visual depictions of a decrease in the outcome of NEC during monthly assessments, there was no statistical significance between the pre- and post-implementation groups after analyzing the data using multivariate regression analysis and controlling for significant confounders. Also, since NEC is a multifactorial gastrointestinal illness, there may be other factors that were not captured within the protocols, as well as other confounders that may not have been factored into the analysis. There were significant differences in the prevalence of SGA and surfactant administration between both groups. However, after including both in the logistic regression analysis, there was no difference in the significance of the incidence of NEC between the groups. Finally, this was a quasi experimental study design. The ideal study would have been a prospective randomized control trial to help reduce the concern for unmeasured confounders and any variation due to temporal trends. Only one case (in the intervention group) developed hemodynamically significant ductus who did not develop NEC.

Further analysis with a larger sample size would better examine the impact of the quality improvement program. Additional programs looking at a combination of NEC reduction protocols are necessary to determine if combined protocol programs have a more significant effect compared to single protocol implementation.

Funding source

No external funding for this manuscript.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

References

1. Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. *Pediatrics* 2012;**129**:1019—26.
2. Gregory KE, Deforge CE, Natale KM, Phillips M, Van Marter LJ. Necrotizing enterocolitis in the premature infant: neonatal nursing assessment, disease pathogenesis, and clinical presentation. *Adv Neonatal Care* 2011;**11**:155—64.
3. Fitzgibbons SC, Ching Y, Yu D, Carpenter J, Kenny M, Weldon C, et al. Mortality of necrotizing enterocolitis expressed by birth weight categories. *J Pediatr Surg* 2009;**44**:1072—5. discussion 1075—6.
4. Federici S, De Biagi L. Long term outcome of infants with NEC. *Curr Pediatr Rev* 2019;**15**:111—4.
5. Jin YT, Duan Y, Deng XK, Lin J. Prevention of necrotizing enterocolitis in premature infants - an updated review. *World J Clin Pediatr* 2019;**8**:23—32.
6. Gephart SM, McGrath JM, Effken JA, Halpern MD. Necrotizing enterocolitis risk: state of the science. *Adv Neonatal Care* 2012;**12**:77—87.
7. Samuels N, van de Graaf RA, de Jonge RCJ, Reiss IKM, Vermeulen MJ. Risk factors for necrotizing enterocolitis in neonates: a systematic review of prognostic studies. *BMC Pediatr* 2017;**17**:105.
8. Baranowski JR, Claud EC. Necrotizing enterocolitis and the preterm infant microbiome. *Adv Exp Med Biol* 2019;**1125**:25—36.
9. Niño DF, Sodhi CP, Hackam DJ. Necrotizing enterocolitis: new insights into pathogenesis and mechanisms. *Nat Rev Gastroenterol Hepatol* 2016;**13**:590—600.
10. Trahair JF, Harding R. Ultrastructural anomalies in the fetal small intestine indicate that fetal swallowing is important for normal development: an experimental study. *Virchows Arch A Pathol Anat Histopathol* 1992;**420**:305—12.
11. Herbst JJ. Development of suck and swallow. *J Pediatr Gastroenterol Nutr* 1983;**2**(Suppl 1):S131—5.
12. 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—51.
13. Jasani B, Patole S. Standardized feeding regimen for reducing necrotizing enterocolitis in preterm infants: an updated systematic review. *J Perinatol* 2017;**37**:827—33.
14. Gortner L, Limmer J, Pohlandt F, Bartmann P, Kelsch G. Necrotizing enterocolitis: a 12-year retrospective study. *Klin Padiatr* 1995;**207**:28—33 [Article in German].
15. Kenton AB, Fernandes CJ, Berseth CL. Gastric residuals in prediction of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2004;**113**:1848—9.
16. Cobb BA, Carlo WA, Ambalavanan N. Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2004;**113**:50—3.
17. Li YF, Lin HC, Torrazza RM, Parker L, Talaga E, Neu J. Gastric residual evaluation in preterm neonates: a useful monitoring technique or a hindrance? *Pediatr Neonatol* 2014;**55**:335—40.
18. Parker L, Torrazza RM, Li Y, Talaga E, Shuster J, Neu J. Aspiration and evaluation of gastric residuals in the neonatal intensive care unit: state of the science. *J Perinat Neonatal Nurs* 2015;**29**:51—9.
19. Srinivasan L, Bokiniec R, King C, Weaver G, Edwards AD. Increased osmolality of breast milk with therapeutic additives. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F514—7.
20. Pearson F, Johnson MJ, Leaf AA. Milk osmolality: does it matter? *Arch Dis Child Fetal Neonatal Ed* 2013;**98**:F166—9.

21. Ellis ZM, Tan HSG, Embleton ND, Sangild PT, van Elburg RM. Milk feed osmolality and adverse events in newborn infants and animals: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2019;**104**:F333—40.
22. Patel RM, Knezevic A, Shenvi N, Hinkes M, Keene S, Roback JD, et al. Association of red blood cell transfusion, anemia, and necrotizing enterocolitis in very low-birth-weight infants. *JAMA* 2016;**315**:889—97.
23. Wallenstein MB, Arain YH, Birnie KL, Andrews J, Palma JP, Benitz WE, et al. Red blood cell transfusion is not associated with necrotizing enterocolitis: a review of consecutive transfusions in a tertiary neonatal intensive care unit. *J Pediatr* 2014;**165**:678—82.
24. Sharma R, Kraemer DF, Torrazza RM, Mai V, Neu J, Shuster JJ, et al. Packed red blood cell transfusion is not associated with increased risk of necrotizing enterocolitis in premature infants. *J Perinatol* 2014;**34**:858—62.
25. Sood BG, Rambhatla A, Thomas R, Chen X. Decreased hazard of necrotizing enterocolitis in preterm neonates receiving red cell transfusions. *J Matern Fetal Neonatal Med* 2016;**29**:737—44.
26. Gephart SM. Transfusion-associated necrotizing enterocolitis: evidence and uncertainty. *Adv Neonatal Care* 2012;**12**:232—6.
27. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. *Curr Probl Pediatr* 1987;**17**:213—88.
28. Patel BK, Shah JS. Necrotizing enterocolitis in very low birth weight infants: a systemic review. *ISRN Gastroenterol* 2012; **2012**:562594.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2021.10.002.