Impact of a Care Bundle on the Incidence of Necrotizing Enterocolitis in the Neonatal Intensive Care Unit

Jerome P. Lee, MD, Winona K. Lee, MD, Chieko Kimata, PhD, MPH, MBA, Alyssa Honda, MD, Charles R. Macías Neal, MD, PhD

Abstract:

Objective: Evaluate the impact of a care bundle on the incidence of necrotizing enterocolitis (NEC) in the neonatal intensive care unit.

Study Design: Retrospective, single-center, population comparison of patients diagnosed with NEC before and after implementing a NEC care bundle utilizing standardized feeding protocol, donor milk program, transfusion protocol, early antibiotic protocol, and restricted indomethacin use.

Result: Incidence of NEC fell from 1.92 to 0.83% ($P < 0.0001$). Incidence of NEC in the 23-27 weeks gestation group decreased from 14.21 to 6.09% ($P = 0.0009$). In the 28-30 weeks gestation group, NEC incidence decreased from 5.56 to 2.10% ($P = 0.0096$). Significant reduction of recurrent NEC and transfusion-associated NEC was observed.

Conclusion: Implementation of a NEC care bundle reduced NEC incidence, with the greatest impact seen in the most vulnerable preterm and very preterm infants.

Introduction

Necrotizing enterocolitis (NEC) remains a devastating disease of the premature infant. When encountered in the neonatal intensive care unit (NICU), NEC carries a mortality rate of up to 44%, with significant long-term morbidity in survivors.⁽¹⁾ The incidence of NEC is highly variable and is dependent on gestational age and birth weight. Preterm and very preterm infants are at the highest risk for NEC. In a recent review by Battersby *et al.*, NEC occurred in 5-7% of infants born < 35 weeks gestation and in 5-22% of preterm infants with birth weight < 1000 grams.⁽²⁾ Incidence of recurrent NEC has been reported to be 6-10%.^(3,4)

NEC delays the establishment of full enteral nutrition, leads to poor growth, and increases the length of hospital stay with a concomitant increase in hospital costs. Providing optimal nutritional support to premature infants is vital to their survival, growth, and long-term neurodevelopmental outcomes.⁽⁵⁻⁷⁾ Optimizing nutrition while minimizing the occurrence of NEC continues to be a major challenge in the NICU.

Following decades of basic research into the mechanism of this disease, the pathophysiology of NEC remains poorly understood. No single etiology has been shown to cause NEC, and no single preventative measure has been shown to eliminate NEC. As a result, various prevention strategies have been reported in attempts to limit its occurrence.⁽⁸⁻¹⁷⁾ Of the prevention strategies studied, establishing a standardized feeding protocol and exclusive human milk feeds appears to have the greatest impact on decreasing the

incidence of NEC in the premature infant.

To enhance the care of the premature infant and improve outcomes, quality improvement initiatives in the NICU are now becoming standard practice worldwide. Quality initiatives dealing with complex disease processes, such as NEC, have demonstrated that care bundles when properly initiated, improve patient care and ultimately patient outcomes. As defined by the Institute for Healthcare Improvement, care bundles are a group or set of evidence-based practice protocols that, when followed consistently together, can improve patient care processes and patient outcomes more than the individual protocols alone.^(18,19) In the NICU setting, care bundles have been shown to decrease the incidence of ventilator-associated pneumonia, central line-associated bloodstream infections, and nosocomial infections.⁽²⁰⁻²³⁾ Recently, Talavera *et al.* reported a reduction in the incidence of NEC after the implementation of a quality improvement initiative that included early feedings with maternal breast milk (MBM), a feeding protocol, and limited use of ranitidine.⁽²⁴⁾

“A care bundle for NEC was developed and implemented for the level IIID NICU at Kapi‘olani Medical Center for Women and Children in an effort to decrease NEC and its associated morbidity and mortality, particularly in the most fragile ELBW population. The purpose of this study was to retrospectively analyze the incidence, severity, and mortality rate of NEC in our NICU population before and after implementation of the NEC care bundle.”

A care bundle for NEC was developed and implemented for the level IIID NICU at Kapi‘olani Medical Center for Women and Children in an effort to decrease NEC and its associated morbidity and mortality, particularly in the most fragile ELBW population. The purpose of this study was to retrospectively analyze the incidence, severity, and mortality rate of NEC in our NICU population before and after implementation of a NEC care bundle.

Methods

NEC care bundle

In November 2007, we implemented a NEC care bundle in the NICU, the elements of which included: 1) a standardized feeding protocol; 2) initiation of a donor milk program; 3) a transfusion protocol; 4) a protocol to limit early empiric antibiotics, and 5) restriction of the use of indomethacin.

Standardized feeding protocol

We developed a standardized feeding protocol that included all

Readers can also follow

NEONATOLOGY TODAY

via our Twitter Feed

@NEOTODAY

infants < 31 weeks gestation and any infant ≥ 31 weeks with any of the following risk factors: multiple gestation, congenital heart disease, perinatal asphyxia, intrauterine growth restriction, sepsis, and shock, gastroschisis, and polycythemia requiring partial exchange transfusion. The protocol included specific criteria for initiation and duration of trophic feedings, advancement of feedings, standard fortification practices, and use of parenteral nutrition.

We adopted a multidisciplinary approach with lactation consultants and nursing to establish early maternal breast milk feedings through maternal counseling and support. Education included information provided during the prenatal consult and an educational video on manual colostrum expression. An electric breast pump was provided to each mother. Lactation consultants were staffed to be available to the nursing mothers in the NICU 7 days a week.

Donor breast milk program

We also implemented a donor milk program that allowed infants to receive donated maternal breast milk (MBM) when the mother was unable to produce enough expressed MBM for her preterm infant. Donor breast milk (DBM) was obtained through a human milk bank licensed by the Human Milk Banking Association of North America. This assured supplementation of MBM feedings with a human milk alternative, reducing the use of preterm infant formula.

Packed red cell transfusion protocol

The packed red blood cell (PRBC) transfusion protocol included guidelines for PRBC transfusion based on infant age, need for respiratory support, and hemoglobin/hematocrit levels. Neonatologists agreed to not deviate from transfusion guidelines, limiting premature transfusion in VLBW infants while also not allowing hematocrits to become dangerously low. Transfusions were given in two 10 ml/kg aliquots, given 20-24 hours apart. Routine furosemide was not used. Feedings were decreased to trophic volumes during transfusion and advanced back to baseline volumes over 24-48 hours. Hemoglobin and hematocrit values were monitored weekly for infants up to 32 weeks post-conceptual age and every two weeks thereafter.

Antibiotic protocol

We modified our empiric antibiotic therapy practice by limiting

empiric treatment in non-septic appearing infants to 48 hours. A time-out note is documented for any use of antibiotics beyond 48 hours if the initial baby blood culture is negative. Previously, empiric antibiotic therapy was given for a minimum of 72 hours and up to a week for infants with a negative blood culture.

“We had inconsistent practice among our providers with the use of indomethacin for intraventricular hemorrhage (IVH) prophylaxis, patent ductus arteriosus (PDA) prophylaxis and PDA treatment. We stopped the practice of using indomethacin for IVH and PDA prophylaxis and transitioned to ibuprofen as first-line medical therapy for the symptomatic PDA.”

Indomethacin protocol

We had inconsistent practice among our providers with the use of indomethacin for intraventricular hemorrhage (IVH) prophylaxis, patent ductus arteriosus (PDA) prophylaxis and PDA treatment. We stopped the practice of using indomethacin for IVH and PDA prophylaxis and transitioned to ibuprofen as first-line medical therapy for the symptomatic PDA.

Study Design

After implementing our NEC care bundle, we conducted a 14 year retrospective population comparison study of two groups of patients diagnosed with NEC in the NICU at Kapi'olani Medical Center for Women and Children. The Pre-Bundle NEC group included infants born between 2004 and 2007 (4 year period). The Post-Bundle NEC group included infants born between 2008 and 2017 (10 year period). Infants were stratified into three categories,

Table 1 Incidence of NEC in Pre-Bundle and Post-Bundle Cohorts in the NICU

	Pre-Bundle		Post-Bundle		P-value
	Frequency	%	Frequency	%	
NEC Incidence					
Total	54	1.92%	70	0.83%	<0.0001
23 to 27 week gestation	26	14.21%	33	6.09%	0.0009
28 to 30 week gestation	14	5.56%	14	2.10%	0.0096
≥31 week gestation	14	0.59%	23	0.32%	0.084
Recurrent NEC	9	16.67%	1	1.43%	0.0024
Transfusion related NEC	13	24.07%	5	7.14%	0.010
Surgical NEC	27	50.00%	29	41.43%	NS
Death related to NEC	14	26.92%	21	30.00%	NS

Abbreviations: NEC, necrotizing enterocolitis, NS, non-significant

Table 2 Comparison of Pre-Bundle NEC and Post-Bundle NEC groups

Characteristics	Pre-Bundle NEC		Post-Bundle NEC		P-value
	N=54		N=70		
	Mean/Freq.	(SD/%)	Mean/Freq.	(SD/%)	
<u>Demographics</u>					
Gestation age at Birth (All)	28.61	(3.87)	29.16	(4.65)	NS
23 to 27 weeks	26	(48.15%)	33	(47.14%)	NS
28 to 30 weeks	14	(25.93%)	14	(20.00%)	
≥ 31 weeks	14	(25.93%)	23	(32.86%)	
Birth Weight (All)	1257.31	(686.61)	1391.14	(931.54)	NS
23 to 27 weeks	836.19	(214.24)	772.45	(168.64)	NS
28 to 30 weeks	1158.21	(261.81)	1044.71	(361.40)	NS
≥ 31 weeks	2138.50	(750.79)	2489.70	(831.18)	NS
Male Gender	32	59.26%	41	58.57%	NS
Days of life at NEC diagnosis	16.44	(11.61)	25.10	(26.76)	NS
<u>Prenatal factors</u>					
Cocaine/Methamphetamine use	3	5.56%	4	6.56%	NS
Tobacco use	9	16.98%	4	6.56%	NS
PIH/Preeclampsia/HTN	8	14.81%	14	22.95%	NS
Chorioamnionitis	6	11.11%	3	5.00%	NS
Indomethacin	4	7.41%	4	6.45%	NS
Betamethasone	36	66.67%	39	60.94%	NS
Fetal Distress	9	16.67%	11	18.33%	NS
Multiple gestation	16	29.63%	16	23.88%	NS
<u>Co-morbidities</u>					
Pneumothorax	4	7.41%	2	3.03%	NS
PDA	21	38.89%	34	50.75%	NS
PDA Ligation	10	18.52%	13	19.40%	NS
GI anomal	2	3.70%	12	17.91%	0.020
IVH	21	38.89%	21	31.82%	NS
IUGR/SGA	3	5.26%	11	16.92%	NS
CV Abnormalities	4	7.41%	4	6.25%	NS
<u>NEC Care Bundle interventions</u>					
Received trophic feeds	32	60.38%	48	72.73%	NS
Days of trophic feeds	3.38	(2.42)	4.59	(2.73)	NS
Types of trophic Feed					
MBM only	8	(25.00%)	39	(84.78%)	<0.0001
MBM/DBM	0	(0.00%)	5	(10.87%)	
MBM/Formula	11	(34.38%)	0	(0.00%)	
MBM/DBM/Formula	0	(0.00%)	1	(2.17%)	
Formula only	13	(40.63%)	1	(2.17%)	
Non-trophic Feeds	46	85.19%	54	83.08%	NS
Feeds Type					
MBM only	3	(6.52%)	27	(51.92%)	<0.0001
MBM/DBM	0	(0.00%)	3	(5.77%)	
MBM/Formula	31	(67.39%)	15	(28.85%)	
MBM/DBM/Formula	0	(0.00%)	2	(3.85%)	
Formula only	12	(26.09%)	5	(9.62%)	
PRBC	29	53.70%	36	51.43%	NS
Antibiotic use prior to NEC	38	70.37%	43	62.32%	NS
Days antibiotics, 1st week of life	3.20	(2.27)	3.23	(2.63)	NS
Indocin	22	40.74%	1	1.56%	<0.0001
<u>Other Interventions</u>					
Hydrocortisone	5	9.26%	7	11.29%	NS
Dexamethasone	2	3.70%	6	9.23%	NS
Epogen	14	25.93%	4	6.15%	0.0040
Ferrous sulfate	16	30.77%	16	24.24%	NS
Ranitidine	6	11.11%	4	6.45%	NS
Caffeine	23	42.59%	37	56.92%	NS
Dopamine	18	33.33%	18	27.69%	NS
Dobutamine	1	1.85%	3	4.76%	NS
Epinephrine	1	1.85%	4	6.35%	NS

Abbreviations: NEC, necrotizing enterocolitis, NS, non-significant, PIH, pregnancy induced hypertension, HTN, hypertension, PDA, patent ductus arteriosus, GI, gastrointestinal, IVH, intraventricular hemorrhage, IUGR, intrauterine growth restriction, SGA, small for gestation, CV, cardiovascular, MBM, maternal breast milk, DBM, donor breast milk, PRBC, packed red blood cells.

Total	Pre-Bundle NEC		Pre-Bundle Control		P-value (paired)
	N=54		N=105		
Characteristics	Mean/Freq. (SD/%)		Mean/Freq. (SD/%)		
<u>Demographics</u>					
Gestation age at Birth (All)	28.61	(3.87)	28.77	(4.03)	NS
23 to 27 weeks	26	(48.15%)	48	(45.71%)	
28 to 30 weeks	14	(25.93%)	28	(26.67%)	NS
≥ 31 weeks	14	(25.93%)	29	(27.62%)	
Male Gender	32	(59.26%)	63	(60.00%)	NS
<u>Prenatal factors</u>					
Cocaine/Methamphetamine use	3	(5.56%)	6	(5.71%)	NS
Tobacco use	9	(16.98%)	12	(11.43%)	NS
PIH/Preeclampsia/HTN	8	(14.81%)	14	(13.33%)	NS
Chorioamnionitis	6	(11.11%)	5	(4.76%)	NS
Indomethacin	4	(7.41%)	6	(5.71%)	NS
Betamethasone	36	(66.67%)	67	(63.81%)	NS
Fetal Distress	9	(16.67%)	23	(21.90%)	NS
Multiple gestation	16	(29.63%)	24	(22.86%)	NS
<u>Co-morbidities</u>					
Pneumothorax	4	(7.41%)	2	(1.90%)	NS
PDA	21	(38.89%)	39	(37.14%)	NS
PDA Ligation	10	(18.52%)	12	(11.43%)	NS
GI anomal	2	(3.70%)	3	(2.86%)	NS
IVH	21	(38.89%)	24	(22.86%)	0.034
IUGR/SGA	3	(5.56%)	4	(3.81%)	NS
CV Abnor	4	(7.41%)	2	(1.90%)	NS
<u>NEC Care Bundle interventions</u>					
Received trophic feeds	32	(60.38%)	58	(55.24%)	NS
Days of trophic feeds	3.38	(2.42)	3.66	(3.14)	NS
Types of trophic Feed					
MBM only	8	(25.00%)	25	(43.10%)	
MBM/DBM	0	(0.00%)	0	(0.00%)	
MBM/Formula	11	(34.38%)	18	(31.03%)	NS
MBM/DBM/Formula	0	(0.00%)	0	(0.00%)	
Formula only	13	(40.63%)	15	(25.86%)	
Non-trophic Feeds	46	(85.19%)	94	(89.52%)	NS
Feeds Type					
MBM only	3	(6.52%)	11	(11.70%)	
MBM/DBM	0	(0.00%)	0	(0.00%)	
MBM/Formula	31	(67.39%)	66	(70.21%)	NS
MBM/DBM/Formula	0	(0.00%)	0	(0.00%)	
Formula only	12	(26.09%)	17	(18.09%)	
PRBC	25	(46.30%)	50	(47.62%)	NS
Antibiotics	38	(70.37%)	72	(68.57%)	NS
Days antibiotics, 1st week of life	3.20	(2.27)	3.41	(3.06)	NS
Indocin	22	(40.74%)	34	(32.38%)	NS

Abbreviations: NEC, necrotizing enterocolitis, NS, non-significant, PIH, pregnancy induced hypertension, HTN, hypertension, PDA, patent ductus arteriosus, GI, gastrointestinal, IVH, intraventricular hemorrhage, IUGR, intrauterine growth restriction, SGA, small for gestation, CV, cardiovascular, MBM, maternal breast milk, DBM, donor breast milk, TPN, total parenteral nutrition, PRBC, packed red blood cells.

Table 4 Comparison of Post-Bundle NEC and Post-Bundle Control groups					
	Post-Bundle NEC		Post-Bundle Control		
Total	N=70		N=131		
					P-value
Characteristics	Mean/Freq.	(SD/%)	Mean/Freq.	(SD/%)	(paired)
<u>Demographics</u>					
Gestation age at Birth (All)	29.16	(4.65)	29.41	(4.70)	NS
23 to 27 weeks	33	(47.14%)	62	(47.33%)	
28 to 30 weeks	14	(20.00%)	24	(18.32%)	NS
≥ 31 weeks	23	(32.86%)	45	(34.35%)	
Male Gender	41	(58.57%)	76	(58.02%)	NS
<u>Prenatal factors</u>					
Cocaine/Methamphetamine use	4	(6.56%)	5	(4.59%)	NS
Tobacco use	4	(6.56%)	4	(3.74%)	NS
PIH/Preeclampsia/HTN	14	(22.95%)	32	(29.09%)	NS
Chorioamnionitis	3	(5.00%)	11	(10.09%)	NS
Indomethacin	4	(6.45%)	5	(4.63%)	NS
Betamethasone	39	(60.94%)	70	(63.06%)	NS
Fetal Distress	11	(18.33%)	23	(21.30%)	NS
Multiple gestation	16	(23.88%)	17	(15.32%)	NS
<u>Co-morbidities</u>					
Pneumothorax	2	(3.03%)	4	(3.48%)	NS
PDA	34	(50.75%)	37	(30.83%)	0.020
PDA Ligation	13	(19.40%)	12	(10.00%)	NS
GI anomal	12	(17.91%)	18	(15.65%)	NS
IVH	21	(31.82)	22	(18.64%)	NS
IUGR/SGA	11	(16.92%)	13	(11.50%)	NS
CV Abnor	4	(6.25%)	11	(9.82%)	NS
<u>NEC Care Bundle interventions</u>					
Received trophic feeds	48	(72.73%)	77	(66.96%)	NS
Days of trophic feeds	4.59	(2.73)	5.03	(2.61)	NS
Types of trophic Feed					
MBM only	39	(84.78%)	65	(89.04%)	
MBM/DBM	5	(10.87%)	6	(8.22%)	
MBM/Formula	0	(0.00%)	1	(1.37%)	NS
MBM/DBM/Formula	1	(2.17%)	0	(0.00%)	
Formula only	1	(2.17%)	1	(1.37%)	
Non-trophic Feeds	54	(83.08%)	107	(92.24%)	NS
Feeds Type					
MBM only	27	(51.92%)	37	(37.37%)	
MBM/DBM	3	(5.77%)	3	(3.03%)	
MBM/Formula	15	(28.85%)	29	(29.29%)	0.032
MBM/DBM/Formula	2	(3.85%)	24	(24.24%)	
Formula only	5	(9.62%)	6	(6.06%)	
PRBC	36	(51.43%)	50	(39.37%)	NS
Antibiotics	43	(62.32%)	70	(54.69%)	NS
Days antibiotics, 1st week of life	3.23	(2.63)	2.24	(2.62)	0.0033
Indocin	1	(1.56%)	7	(5.93%)	NS

Abbreviations: NEC, necrotizing enterocolitis, NS, non-significant, PIH, pregnancy induced hypertension, HTN, hypertension, PDA, patent ductus arteriosus, GI, gastrointestinal, IVH, intraventricular hemorrhage, IUGR, intrauterine growth restriction, SGA, small for gestation, CV, cardiovascular, MBM, maternal breast milk, DBM, donor breast milk, TPN, total parenteral nutrition, PRBC, packed red blood cells.

Table 5 Comparison of Pre-Bundle Control and Post-Bundle Control groups					
	Pre-Bundle Control		Post-Bundle Control		
	N=105		N=131		
Characteristics	Mean/Freq.	(SD/%)	Mean/Freq.	(SD/%)	P-value
<u>Demographics</u>					
Gestation age at Birth (All)	28.77	(4.03)	29.41	(4.70)	NS
23 to 27 weeks	48	(45.71%)	62	(47.33%)	
28 to 30 weeks	28	(26.67%)	24	(18.32%)	NS
≥ 31 weeks	29	(27.62%)	45	(34.35%)	
Birth Weight (All)	1346.81	(741.52)	1471.27	(926.75)	NS
23 to 27 weeks	808.49	(208.83)	833.48	(173.86)	NS
28 to 30 weeks	1264.79	(284.44)	1174.46	(242.40)	NS
≥ 31 weeks	2298.45	(664.76)	2508.29	(862.47)	NS
Male Gender	63	(60.00%)	76	(58.02%)	NS
<u>NEC Care Bundle interventions</u>					
Received trophic feeds	58	(55.24%)	38	(33.04%)	NS
Days of trophic feeds	3.66	(3.14)	5.03	(2.61)	0.0015
Types of trophic Feed					
MBM only	25	(43.10%)	65	(89.04%)	
MBM/DBM	0	(0.00%)	6	(8.22%)	
MBM/Formula	18	(31.03%)	1	(1.37%)	<0.0001
MBM/DBM/Formula	0	(0.00%)	0	(0.00%)	
Formula only	15	(25.86%)	1	(1.37%)	
Non-trophic Feeds	94	(89.52%)	107	(92.24%)	NS
Feeds Type					
MBM only	11	(11.70%)	37	(37.37%)	
MBM/DBM	0	(0.00%)	3	(3.03%)	
MBM/Formula	66	(70.21%)	29	(29.29%)	<0.0001
MBM/DBM/Formula	0	(0.00%)	24	(24.24%)	
Formula only	17	(18.09%)	6	(6.06%)	
PRBC	50	(47.62%)	50	(39.37%)	NS
Antibiotics	72	(68.57%)	70	(54.69%)	0.032
Days antibiotics, 1st week of life	3.41	(3.06)	2.24	(2.62)	0.0009
Indocin	34	(32.38%)	7	(5.93%)	<0.0001

Abbreviations: NEC, necrotizing enterocolitis, NS, non-significant, MBM, maternal breast milk, DBM, donor breast milk, PRBC, packed red blood cells.

23-27 weeks gestation, 28-30 weeks gestation, and ≥ 31 weeks gestation.

Infants were initially identified by a diagnosis of NEC in the problem list or discharge summary in the electronic medical record. From this initial search, we then limited the group to infants that completed at least 7 days NPO with antibiotic treatment. Infants diagnosed with spontaneous intestinal perforation were excluded. We also excluded patients that were transferred to our NICU with a preexisting diagnosis of NEC. Controls for each case were selected, matched with birth year, gestational age, and gender. The demographic and clinical data were summarized using descriptive statistics.

Institutional review board approval was obtained for access to the electronic medical records. Multiple clinical and demographic data were evaluated. Fischer's exact test, chi-square test, Kruskal-Wallis test, paired Wilcoxon signed-rank test, and exact conditional logistical regression were used for statistical analysis.

Results

During the study period, 124 patients met the criteria for NEC diagnosis, and their charts were reviewed. There were 54 patients in the Pre-Bundle cohort and 70 patients in the Post-Bundle cohort. In addition, 236 patient charts were reviewed as NEC controls, 105 in the Pre-Bundle group and 131 in the Post-Bundle group. Each cohort was further classified into three age groups as assigned at birth: 23-27 weeks gestation, 28-30 weeks gestation, and ≥ 31 weeks gestation.

Pre-Bundle NEC vs. Post-Bundle NEC

The incidence of NEC in the Pre-Bundle and Post-Bundle cohorts is displayed in Table 1. There was a 56.8% reduction in overall incidence of NEC in the Post-Bundle group compared to the Pre-Bundle group in our NICU. NEC incidence was 1.92% in the Pre-Bundle group and 0.83% in the Post-Bundle group (p -value < 0.0001). This reduction in NEC was primarily seen in the 23-27 weeks and 28-30 weeks gestation groups. In the 23-27 weeks gestation group, there was a 57.1% reduction in the incidence (14.21 to 6.09%). The 28-30 weeks gestation group had a 62.2% reduction (5.56 to 2.10%). In the ≥ 31 weeks gestation age group, there was a trend in NEC reduction that was not statistically significant. There was a significant reduction (16.67 to 1.43%) of recurrent NEC in the Post-Bundle NEC group. There was a significant reduction in transfusion-associated NEC in the Post-Bundle group from 24.07 to 7.14%. We define transfusion-associated NEC as NEC occurring within 72 hours after initiation of a PRBC transfusion. There was no significant difference in the incidence of surgical NEC or deaths associated with NEC between the two historical cohorts.

“There were no significant differences in the incidence of IVH, intrauterine growth restriction (IUGR), small for gestational age (SGA), or other congenital or cardiac anomalies. In the Post-Bundle NEC group, there was a significant reduction in the use of indomethacin and erythropoietin.”

Table 2 compares demographic, maternal, and infant characteristics between Pre-Bundle and Post-Bundle NEC groups. There were no significant differences in gestational age at birth, birth weight, gender, or maternal conditions. In the Post-Bundle group, there was increased use of MBM and DBM and reduced preterm infant formula for both trophic and non-trophic feedings. Interestingly, the Post-Bundle NEC group had a higher incidence of gastrointestinal anomalies (17.91 vs. 3.70%) compared to the Pre-Bundle NEC group. There were no significant differences in the incidence of IVH, intrauterine growth restriction (IUGR), small for gestational age (SGA), or other congenital or cardiac anomalies. In the Post-Bundle NEC group, there was a significant reduction in the use of indomethacin and erythropoietin.

NEC vs Control

Demographic, maternal, and infant characteristics comparing each NEC cohort with its respective control group are listed in Tables 3 and 4. There were no significant differences in gestational age at birth, gender, maternal conditions, or perinatal factors between the NEC and control groups in either the Pre-Bundle or Post-Bundle cohorts. There were no significant differences in the use of MBM, DBM, PRBC transfusions, or indomethacin use in either the Pre-Bundle or Post-Bundle cohorts.

There was a higher incidence of IVH ($P = 0.034$) in the Pre-Bundle NEC group compared to Pre-Bundle Control. There was a higher incidence of PDA ($P = 0.020$) in the Post-Bundle NEC group compared to Post-Bundle Control. There was also a significantly higher mean days of antibiotics during the first week of life in the Post-Bundle NEC group compared to the Post-Bundle Control ($P = 0.003$).

Pre-Bundle Control vs. Post-Bundle Control

The changes in practice before and after implementing the NEC care bundle are displayed in Table 5, which compares the Pre-Bundle and Post-Bundle control groups. There was no difference between the two groups with the implementation of trophic feeds. However, the duration of trophic feedings increased from mean of 3.66 to 5.03 days ($P = 0.0015$). There was also a significant change in practice for the type of feeding given to patients, with increased use of MBM and DBM and reduction in the use of preterm infant formula. In the Post-Bundle control group, there was a significant reduction in the use of antibiotics 68.57 to 54.69% ($P = 0.032$) as well as a reduction in the mean number of days of early empiric antibiotics in culture-negative infants, 3.06 to 2.24 days ($P = 0.0009$).

There was a significant decrease in indomethacin from 32.38 to 5.93% ($P < 0.0001$). We did not see a change in PRBC transfusions between the two control groups.

“After implementing an NEC care bundle, there was a significant reduction in the incidence of NEC from 14.21 to 6.09% in our 23-27 weeks gestation infants and a reduction from 5.56 to 2.10% in our 28-30 weeks gestation infants.”

Discussion

After implementing a NEC care bundle, there was a significant reduction in the incidence of NEC from 14.21 to 6.09% in our 23-27 weeks gestation infants and a reduction from 5.56 to 2.10% in

our 28-30 weeks gestation infants. In the ten-year Post-Bundle cohort, we had one patient with recurrent NEC, an incidence of 1.43%, compared to a recurrent NEC incidence of 16.67% in the Pre-Bundle group. We also saw a reduction in transfusion-associated NEC from 24.07% in the Pre-Bundle group to 7.14% in the Post-Bundle group.

When the NEC care bundle was implemented in our NICU, it was done in a stepwise approach over a 12 month period. Each intervention, when combined, had a cumulative effect that would not have been achieved were each component implemented alone. Although the use of protocols that decrease the incidence of NEC has been described previously, this is the first study, to our knowledge, that evaluates the impact of a NEC care bundle on both incidence and recurrence of NEC.

We suggest that several factors played a significant role in decreasing NEC incidence in our NICU. Implementation of a standardized feeding protocol eliminated variation in feeding practices within our group. In addition, using an exclusive human milk policy supported by the adoption of a donor human milk program virtually eliminated the use of preterm formula in our VLBW population. Implementation of a standardized transfusion protocol eliminated variation in transfusion practices, minimized unnecessary transfusions, and exposure to high-risk transfusions with severe anemia. Limiting empiric antibiotic therapy duration also impacted the unnecessary use of antibiotics in infants with low-risk factors and few clinical signs of sepsis at admission. Lastly, stopping the use of indomethacin in the NICU eliminated the associated risks for feeding and gastrointestinal complications without increasing PDA incidence of complications.

Previous studies support the importance of a standardized feeding protocol. Patole *et al.* concluded that the single most effective strategy to prevent NEC was implementing a standardized feeding regimen.(9) Standardized feeding regimens are beneficial since they decrease practice variations and increase awareness of potential feeding problems.(9) Our feeding protocol resulted in less variation in feeding advancements and fortification practices. Standardized feeding protocols have been found to be safe, resulting in the earlier achievement of full enteral feeds, reduced time on hyperalimentation therapy, better growth outcomes, and decreased length of stay.(25-27)

“Implementation of early empiric antibiotic treatment in preterm infants born for non-maternal reasons is a common practice because of this population’s immature immune system and risk for morbidity and mortality from early-onset sepsis. Duration of treatment is often based on individual practice and NICU policy as opposed to strong evidence-based practices.”

Our donor milk program was started to support infants whose mothers did not have enough MBM. It has been well documented that feeding preterm infants an exclusive human milk diet decreases NEC.(15,16,28-31) When there is insufficient MBM available, DBM is the preferred alternative for preventing NEC. A Cochrane meta-analysis review comparing formula milk versus donor milk

for feeding preterm infants showed a higher risk of developing NEC with formula-fed infants.(32)

Although controversial, several studies have described an association between PRBC transfusion and NEC.(2,33-35) The etiology of transfusion-associated NEC or gut injury remains unclear. The association may be related to the level of anemia,(2) inflammatory factors associated with transfusion, or a combination of both. It has been suggested that withholding feeds during the transfusion may be protective.(34) As an alternative to completely withholding enteral feedings during transfusions, we chose to provide trophic feedings during this time period. In large part, we adopted a transfusion protocol due to observations and experience with transfusion-associated NEC in our NICU. This decision was reinforced by the significant reduction in the number of transfusion-associated gastrointestinal and NEC events seen in our Post-Bundle NEC cohort.

Implementation of early empiric antibiotic treatment in preterm infants born for non-maternal reasons is a common practice because of this population’s immature immune system and risk for morbidity and mortality from early-onset sepsis. Duration of treatment is often based on individual practice and NICU policy as opposed to strong evidence-based practices. It is generally accepted that empiric antibiotics are safe, with perceived benefits outweighing potential risks. This is evident in the common practice of treating culture-negative sepsis.(36) However, emerging studies have reported that prolonged initial empiric antibiotic treatment (> 5 days) may be associated with adverse outcomes, including late-onset sepsis and death, and that each additional day of antibiotic use increases the risk of NEC.(37-39) Because of the increased morbidity associated with prolonged empiric antibiotic treatment, we reduced our use of early empiric treatment from 72 to 48 hours for infants with sterile culture results. To date, the use of any empiric antibiotics in our preterm population has decreased significantly as a result of these awareness practices.

In the NICU, indomethacin has been used both as prophylaxis for IVH and PDA and as a medical treatment for PDA closure. Studies report an increased risk of spontaneous perforation and NEC with prophylactic and therapeutic indomethacin use in preterm infants.(40,41) In a large retrospective study, O’Donovan *et al.* reported that indomethacin was not associated with an increased risk for NEC,(42) and although supported in a subsequent study, an increased risk for intestinal perforation with indomethacin was noted.(43) Prior to our NEC bundle, there was inconsistent practice using prophylactic indomethacin for IVH and PDA prophylaxis. With the NEC bundle implementation, routine use of prophylactic indomethacin was discontinued, and ibuprofen became the drug of choice for medical treatment of a symptomatic PDA. We did not see a significant change in PDA incidence or number of PDA ligations in the Pre-Bundle Control and Post-Bundle Control groups.

Our NEC care bundle was instrumental in decreasing the incidence and recurrence of NEC in a NICU with an already relatively low NEC rate. Balancing protocol-driven care for routine and common decisions with the autonomy for individualized care is important for physician buy-in and adherence to the care bundle. The strength of adherence to the NEC care bundle in our NICU is supported by the significant changes seen in the Pre-Bundle and Post-Bundle control group comparison results.

Limitations of our study should be noted. First and most importantly, we describe the implementation of a bundle specific to our NICU population. Generalization of this bundle to other NICU populations may not necessarily generate similar results. Secondly, our organization transitioned EMR systems between our Pre-Bundle and Post-Bundle study periods. As a result, there were missing or unavailable data for some analysis in the early Post-Bundle chart reviews. Finally, the protocols were introduced

stepwise to improve compliance, so the early Post-Bundle group did not reflect the full impact of all the protocols. We also did not measure the impact of each protocol individually. Future studies could evaluate the impact of each protocol separately.

“This decreased incidence of NEC was attained after implementing an NEC care bundle that centered on a standardized feeding protocol that relied primarily on a human milk-based diet, along with protocols for PRBC transfusions, the use of empiric antibiotics, and indomethacin.”

Conclusion

Implementation of a NEC care bundle decreased NEC incidence in our NICU population, with the greatest impact seen in the most vulnerable preterm and very preterm infants. Incidence of recurrent NEC and transfusion-associated NEC were significantly decreased. This decreased incidence of NEC was attained after implementing a NEC care bundle that centered on a standardized feeding protocol that relied primarily on a human milk-based diet, along with protocols for PRBC transfusions, the use of empiric antibiotics, and indomethacin.

References:

1. Singh R, Visintainer P, Frantz III I, Shah BL, Meyer KM, Favila SA et al. Association of necrotizing enterocolitis with anemia and packed red blood cell transfusions of preterm infants. *Journal of Perinatology* 2011; **31**(3): 176-182.
2. Battersby C, Santhalingam T, Costeloe K, Modi N. Incidence of neonatal necrotizing enterocolitis in high-income countries: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2018; **103**(2):F182-F189.
3. Stringer MD, Brereton RF, Drake DP, Kiely EM, Capps SN, Spitz L. Recurrent necrotizing enterocolitis. *Journal of Pediatric Surgery* 1993; **28**(8): 979-981.
4. Thyoka M, Eaton S, Hall NJ, Drake D, Kiely E, Curry J et al. Advanced necrotizing enterocolitis part 2: recurrence of necrotizing enterocolitis. *European Journal of Pediatric Surgery* 2012; **22**(1): 13-16.
5. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics* 2006; **117**: 1253-1261.
6. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. *BMJ* 1998; **317**: 1481-1487.
7. Chan SHT, Johnson MJ, Leaf AA, Vollmer B. Nutrition and neurodevelopmental outcomes in preterm infants: a systematic review. *Acta Paediatrica* 2016; **105**: 587-599.
8. Young L, Morgan J, McGuire W. Preventing necrotizing enterocolitis in very low birth weight infants: current evidence. *Paediatrics and Child Health* 2010; **21**(6): 258-264.
9. Patole SK, de Klerk N. Impact of standardized feeding regimens on incidence of neonatal necrotizing enterocolitis: a systematic review and meta-analysis of observational studies. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F147-F151.
10. Gephart SM, Hanson CK. Preventing necrotizing enterocolitis with standardized feeding protocols. *Advances in Neonatal Care* 2013; **13**(1): 48-54.
11. Kamitsuka MD, Horton MK, Williams MA. The incidence of necrotizing enterocolitis after introducing standardized feeding schedules for infants between 1250 and 2500 grams and less than 35 weeks of gestation. *Pediatrics* 2000; **105**: 379-384.
12. 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.
13. Colaizy TT, Bartick MC, Jegier BJ, Green BD, Reinhold AG, Schaefer AJ et al. Impact of optimized breastfeeding on the costs of necrotizing enterocolitis in extremely low birthweight infants. *The Journal of Pediatrics* 2016; **175**: 100-105.
14. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *Journal of Perinatology* 2007; **27**(7): 428-433.
15. Herrmann K, Carroll K. An exclusively human milk diet reduces necrotizing enterocolitis. *Breastfeeding medicine* 2014; **9**: 184-190.
16. Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U 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. *The Journal of Pediatrics* 2010; **156**(4):562-567.
17. McGuire A, Anthony MY. Donor human milk versus formula for preventing necrotizing enterocolitis in preterm infants: systematic review. *Arch Dis Child Fetal Neonatal Ed* 2003; **88**: 11-14.
18. Haraden C. What is a Bundle? IHI Web site Improvement Stories. <http://www.ihl.org/resources/Pages/Improvement-Stories/WhatIsaBundle.aspx>. Published April 26, 2011.
19. Resar R, Pronovost P, Haraden C. Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. *Jt Comm J Qual Patient Saf* 2005; **31**: 243-48.
20. Weber C. Applying adult ventilator-associated pneumonia bundle evidence to the ventilated neonate. *Advances in Neonatal Care* 2016; **16**(3): 178-190.
21. Pogorzelska-Maziarz M. The use and effectiveness of bundles for prevention of central line-associated bloodstream

NEONATOLOGY TODAY is interested in publishing manuscripts from Neonatologists, Fellows, NNPs and those involved in caring for neonates on case studies, research results, hospital news, meeting announcements, and other pertinent topics.

Please submit your manuscript to: LomaLindaPublishingCompany@gmail.com

- infections in neonates. *J Perinat Neonat Nurs* 2016; **30**(2): 148-159.
22. Steiner M, Langgartner M, Cardona F, Waldhör T, Schwindt J, Haiden J et al. Significant reduction of catheter-associated blood stream infections in preterm neonates after implementation of a care bundle focusing on simulation training of central line insertion. *The Pediatric Infectious Disease Journal* 2015; **34**(11): 1193-1196.
 23. Melish M, Carey-Goo P, Delaney H, Neal C, Tao K, Kimata C et al. Reducing nosocomial infections in the nicu. *American Journal of Infection Control* 2013; S5-S6 (oral abstract 006).
 24. Talavera MM, Bixler G, Cozzi C, Dail J, Miller RR, McClelland Jr R et al. Quality improvement initiative to reduce the necrotizing enterocolitis rate in premature infants. *Pediatrics* 2016; **137**(5): e1-e8.
 25. McCallie KR, Lee HC, Mayer O, Cohen RS, Hintz SR, Rhine WD. Improved outcomes with a standardized feeding protocol for very low birth weight infants. *Journal of Perinatology* 2011; **31**: S61-S67.
 26. Butler TJ, Szekely LJ, Grow JL. A standardized nutrition approach for very low birth weight neonates improves outcomes, reduces cost and is not associated with increased rates of necrotizing enterocolitis, sepsis or mortality. *Journal of Perinatology* 2013; **33**: 851-857.
 27. Kuzma-O'Reilly B, Duenas ML, Greecher C, Kimberlin L, Muijsce D, Miller D et al. Evaluation, development, and implementation of potentially better practices in neonatal intensive care nutrition. *Pediatrics* 2014; **111**(4): e461-e470.
 28. Lucas A, Cole TJ. Breast milk and neonatal necrotizing enterocolitis. *The Lancet* 1990; 336(8730): 1519-1523.
 29. Patel AL, Meier PP, Engstrom JL. The evidence for use of human milk in very low-birthweight preterm infants. *NeoReviews* 2007; **8**(11): e459-e466.
 30. Shulhan J, Dicken B, Hartling L, Larsen BMK. Current knowledge of necrotizing enterocolitis in preterm infants and the impact of different types of enteral nutrition products. *Advances in Nutrition* 2017; **8**(1): 80-91.
 31. Miller J, Tonkin E, Damarell RA, McPhee AJ, Suganuma M, Suganuma H, Middleton PF, Makrides M, Collins CT. A systematic review and meta-analysis of human milk feeding and morbidity in very low birth weight infants. *Nutrients* 2018; **10**(6), 707.
 32. Quigley M, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2014; **4**: Art. No.:CD002971. DOI:10.1002/14651858.CD002971.pub3.
 33. Mohamed A, Shah P. Transfusion associated necrotizing enterocolitis: a meta-analysis of observational data. *Pediatrics* 2012; **129**: 529-540.
 34. El-Dib M, Narang S, Lee E, Massaro AN, Aly H. Red blood cell transfusion, feeding and necrotizing enterocolitis in preterm infants. *Journal of Perinatology* 2011; **31**: 183-187.
 35. Paul DA, Mackley A, Novitsky A, Zhao Y, Brooks A, Locke RG. Increased odds of necrotizing enterocolitis after transfusion of red blood cells in premature infants. *Pediatrics* 2011; **127**(4): 635-641.
 36. Cantey JB, Baird SD. Ending the culture of culture-negative sepsis in the neonatal icu. *Pediatrics* 2017; **140**(4): 1-4.
 37. Cotton CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics* 2009; **123**: 58-66.
 38. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J Pediatr* 2011; **159**(5): 720-725.
 39. Alexander VN, Northrup V, Bizzarro J. Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. *The Journal of Pediatrics* 2011; **159**(3): 392-397.
 40. Grosfeld JL, Chaet M, Molinari F, Engle W, Engum SA, West KW et al. Increased risk of necrotizing enterocolitis in premature infants with patent ductus arteriosus treated with indomethacin. *Annals of Surgery* 1996; **224**(3): 350-357.
 41. Fujii AM, Brown E, Mirochnick M, O'Brien S, Kaufman G. Neonatal necrotizing enterocolitis with intestinal perforation in extremely premature infants receiving early indomethacin treatment for patent ductus arteriosus. *Journal of Perinatology* 2002; **22**: 535-540.
 42. O'Donovan DJ, Baetiong A, Adams K, Chen A, O'Brian Smith E, Adams JM et al. Necrotizing enterocolitis and gastrointestinal complications after indomethacin therapy and surgical ligation in premature infants with patent ductus arteriosus. *Journal of Perinatology* 2003; **23**: 286-290.
 43. McPherson C, Gal P, Smith M, Wilder W, Richter S, Ransom JL et al. Necrotizing enterocolitis in preterm infants with patent ductus arteriosus: does indomethacin increase risk? *Journal of Neonatal-Perinatal Medicine* 2008; **1**(4): 209-216.

Funding Sources: No funding has been provided to support this research.

Conflicts of Interest: The authors declare no conflicts of interest.

Author Contributions: All authors contributed to the writing and the review of this paper

NT

New subscribers are always welcome!

NEONATOLOGY TODAY

**To sign up for a free monthly subscription,
just click on this box to go directly to our
subscription page**

Corresponding Author

*Jerome P. Lee, MD
Neonatal Hospitalist,
Hawai'i Pacific Health
Neonatal Intensive Care Unit
1319 Punahou Street
Honolulu, HI 96826
Email: jeromel@hphmg.org
808-983-6392 (fax)*

*Alyssa Honda, MD
University of Hawai'i
John A. Burns School of Medicine
Mānoa 651 Ilalo Street
Honolulu, Hawai'i 96813*

*Winona K. Lee, MD
University of Hawai'i
John A. Burns School of Medicine
Mānoa 651 Ilalo Street
Honolulu, Hawai'i 96813*

*Charles R. Macías Neal, MD, PhD
University of Hawai'i
John A. Burns School of Medicine
Mānoa 651 Ilalo Street
Honolulu, Hawai'i 96813*

*Chieko Kimata, PhD, MPH, MBA
Hawai'i Pacific Health
Neonatal Intensive Care Unit
1319 Punahou Street
Honolulu, HI 96826*