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Prevention and early recognition of necrotizing enterocolitis, a tale of two tools: eNEC and GutCheck^{NEC}

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Abstract

Risk for neonatal necrotizing enterocolitis (NEC) is complex, reflecting its multi-factorial pathogenesis. To improve risk awareness and facilitate communication among neonatal caregivers especially nurses, two tools were developed. GutCheck^{NEC} was derived and validated as part of a formal research study over three phases including evidence synthesis, expert consensus building and statistical modeling. The Wetzel/Krisman tool, eNEC™ was developed and tested as part of a quality improvement (QI) initiative in a single clinical setting using evidence synthesis, review by internal expert clinicians and implementation and evaluation of its use by direct line neonatal staff. Refinement of both tools is underway to evaluate their effect on clinical decision making, early identification of NEC and surgical NEC. Clinicians can take an active role to reduce NEC in their units by focusing on modifiable risk factors such as adoption of standardized feeding protocols, preferential feeding of human milk, antibiotic and histamine blocker stewardship. Feeding during transfusion remains controversial but judicious use of transfusions, adoption of transfusion guidelines and withholding feeding during transfusion are feasible measures with potential benefit to prevent NEC and little risk.

Keywords

Early recognition; neonatal care; neonatal intensive care; necrotizing enterocolitis; very low birth weight infant; prevention; nursing; risk assessment; risk score; GutCheck^{NEC}; eNEC™

BACKGROUND OF NEC RISK AWARENESS

Necrotizing enterocolitis (NEC) is a disease affecting the gastrointestinal tract involving an exaggerated inflammatory response,[1] altered bacterial colonization, [2] and damage from immaturity and compromised mucosa[3] with most cases occurring in premature infants[4] yet nurses have few tools at their disposal to improve NEC risk awareness. NEC leads to death

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in 15–30% of cases.[4,5] Treated medically, NEC adds an additional $92,858 per patient (inflation adjusted from 2002 study), 3 weeks to the length of stay and about 22% mortality[6, 7] When surgery is necessary to treat NEC, additional costs are estimated at $234,603. Surgical NEC mortality ranges from 30–50% and average length of stay exceeds 60 days beyond expected stays for prematurity alone. Incidence rates vary among neonatal intensive care units (NICU)[8–10] and overall rates have been stable over at least a decade in the US.[11,12] Early recognition of NEC can be challenging when symptoms are non-specific, although recognizing NEC in its early stage is important to reduce the extent of intestinal damage and widespread sepsis. We define risk awareness for NEC as a state of heightened vigilance where a clinician understands an individual infant's risk for developing the disease and institutes measures to recognize it early so as to intervene before surgery becomes necessary.

NEC is a progressive disease and may first present with feeding intolerance and non-specific symptoms before gastrointestinal symptoms are evident.[13,14] If the disease is not diagnosed and treated in the early stages, the infant's bowel becomes severely necrotic, and if not removed the infant will die. In recent studies, diminished heart rate characteristic variability has been shown 6 hours preceding a diagnosis of medical NEC and up to 16 hours preceding the diagnosis of NEC requiring surgical intervention.[15] This ten hour difference in time to diagnosis may explain the challenge of early recognition and effect of delayed diagnosis on disease progression. More research is needed. Similarly, but not definitively, a recent cohort study found that infants who died from NEC were diagnosed on average at 3 days later (day of life) compared to those survived, but recognized that those infants who died were also smaller and of lower gestational age thus typically experiencing later disease onset.[16] Definitions for NEC are a topic of debate. The presence of pneumatosis (i.e. gas between the mucosal and submucosal layers of the bowel) is an important distinctive feature when accompanied by clinical signs (e.g. bilious gastric aspirate, emesis, abdominal distention, and/or occult blood in the stool). [17,18]

Neonatal nurses are the first line responders detecting signs of NEC development.[19] Nurses are witness to the devastation that NEC causes premature infants and their families.. NICU nurses and nurse researchers who have witnessed the pain and suffering secondary to NEC were inspired to search the science and apply the available evidence to create new bedside nursing tools in an effort to improve outcomes. Delays in the diagnosis of NEC when nursing and parent concerns mount are particularly concerning, and such delays are what inspired the writing of an article applying the morally distressing topic of failure to rescue (i.e. save a life through timely recognition of a complication) to the neonatal setting.[19] Of particular concern to us, is targeting the time of highest vigilance to coincide to the peak onset times when infants are most likely to develop NEC. Yet, we recognize that the time of onset varies and ongoing nursing vigilance is necessary.

NEC RISK AWARENESS AND THE PROBLEM OF TRANSITIONS

Information about NEC risk may be in multiple places in the neonatal medical record and is often poorly integrated. Using a risk score enables the clinician to assign meaning to pieces of information by thinking of them as a whole. To facilitate communicate and improve

timely treatment we separately developed NEC risk tools. As NEC develops later in life (2–3 weeks on average but as late as 45 days and beyond), it is possible that communication about NEC risk breaks down and is not consistently shared over multiple changes in staff. Standardizing communication of NEC risk across transitions in care using a risk score could improve early recognition and allow for better tailoring of care based on infant's risk. Gephart's risk index, GutCheck^{NEC} was derived and validated as part of a formal research study over three phases including evidence synthesis,[43] expert consensus building,[75] and statistical modeling.[76,78] Another tool, eNEC™, was developed by Wetzel & Krisman then tested in a clinical setting as part of a quality improvement initiative. Following evidence synthesis and review by internal expert clinicians, eNEC™ was implemented and evaluated by neonatal staff providing direct patient care. Although we approached the problem of early recognition and NEC risk awareness from two different paradigms (one research, one QI) we did so with similar goals. This goal was to improve the timely and early recognition of NEC, minimize disease severity and save lives. The purpose of this paper is to report the findings of both projects and to join voices to call neonatal nurses to action to prevent and improve early recognition for this devastating neonatal disease.

NEC RISK

Evidence about NEC risk is generated from cohort and case-controlled studies, often using many years of data for a single NICU or group of NICUs. Few studies include adjustment for NEC risk reducers, significantly human milk feeding and probiotics administration. Human milk feeding is the gold standard of NEC prevention springing from a study by Lucas and Cole over 2 decades ago.[20] Contemporary evidence supports feeding a proportion of human milk > 50% of the feeding and approximately 50 ml/kg/day in the first 28 days of life as a goal conferring maximal NEC protection.[21–23] Increased risk for mortality from both sepsis and NEC is strongly related to the volume and dose of human milk fed. Especially in the critical first weeks of life, when the gut is being colonized, feeding human milk confers protection that no other treatment offers. Two meta-analyses support the delivery of probiotics for NEC prevention, particularly when the preparation includes a bifidobacterium.[24,25] Although increasingly used abroad, widespread adoption of probiotics in US NICUs is stalled by the lack of a consistent formulation, a lack of consistency in the type of probiotics tested and used and the lack of Federal Drug Administration (FDA) approval.[26,27] Risk factors for NEC most often described in the literature included maternal cocaine use, [28–30] intrauterine growth restriction, [31] chorioamnionitis- especially if it is severe, [32–34] being formula-fed [20,35] having had multiple infections,[36] a patent ductus arteriosus (PDA),[37] receiving histamine-blocker therapy,[38] receiving an initial course of antibiotics > 4 days with negative blood culture,[39,40] receiving a packed red blood cell (PRBC) transfusion [41] and being cared for in a hospital with a high NEC rate.[8–10] Other risk factors less often described include African-American[8] or Hispanic race,[42] male gender,[8] and having received an exchange transfusion.[43] Risk for NEC varies by gestational age.[44,45] Older, bigger babies have been shown to acquire NEC after being fed large volumes of formula concurrent with history of chorioamnionitis,[34,46,47] intrauterine growth restriction,[31,48–50] maternal drug use[44] and/or presence of congenital heart disease.[51–54]

HISTORY OF NEC RISK SCORES

A NEC risk score (NRS) was developed in 1985, before the widespread use of surfactant for Respiratory Distress Syndrome (RDS) when NEC pathogenesis was still shrouded in mystery.[55] The NRS was derived retrospectively using data from a single center with an extraordinarily high NEC rate (20–30% of VLBW infants). Data from 29 infants (< 1500 grams) born within a three month time frame was used to develop a cumulative score that classified correctly 80% of infants (n=29) as either low or high risk. The 10-point score was assigned within the first 24 hours of life and included 9 items, each worth one point except for birth weight which contributed up to 2 points (< 1500 grams= 1 point, < 1000 grams=2 points). Other items included gestational age < 32 weeks, Apgar score at five minutes < 5, oxygen requirement, mechanical ventilation, low blood pressure for age and weight, presence of seizures or intraventricular hemorrhage, PDA, and presence of umbilical catheters. Scores above 6 were considered high risk. An alternative scoring procedure could be used to calculate the score each day for the first three days of life with a cumulative score > 21 considered high risk.

Several years later McKeown and colleagues (1994) tested the NRS to determine if it correctly classified infants at high risk for NEC, severe NEC requiring surgery and/or death. Using a case-control design in a single center, they compared NRSs and the interaction of the score with feeding variables. Scores on the NRS did not predict NEC. Conversely, infants who did not develop NEC had higher scores than those who did, mostly because their respiratory disease was more severe. In the post-surfactant era, the contribution of respiratory disease to NEC risk is not supported. Overall, testing of the NRS was incomplete, confounded by feeding issues that impact NEC risk, and underpowered to detect significant effects.[55,56] An updating of NEC risk assessment scoring is warranted.

TWO CONTEMPORARY NEC RISK TOOLS

Derivation of the tools

Both tools, eNEC™ and GutCheck^{NEC} were developed beginning with synthesis of evidence for the purpose of making risk assessment and NEC risk communication simple and standardized for the bedside NICU nurse. Risk factors identified in the literature were assembled (see table 1). Expecting the bedside clinician to efficiently and reliably assess NEC risk based on memory is unrealistic and beyond the cognitive limits of humans when balancing multiple tasks in the context of a high risk, fast-paced and interruptive environment.[57,58] So we separately set out to assimilate the risk factors into a tool for clinical use. Attention was focused in our parallel projects on usability of the tool to enable consistent scoring and minimize the work to complete it.

eNEC™—As part of a quality improvement project, the derivation of eNEC™ was initiated by a neonatal nursing team from Carle, led by Ms. Wetzel. This NICU provides care for infants ranging from 22 weeks gestation age at birth through term gestation and provides pediatric surgical services for infants who require surgery for the treatment of NEC. Two clinical questions were explored: 1) in the premature infant population what interventions prevent feeding intolerance and NEC, and 2) what comparative factors impact the

development of feeding intolerance and NEC? A literature search was then conducted using the terms feeding intolerance, necrotizing enterocolitis, premature infant, prevention and Prolacta.® Databases searched included Cochrane Library, Pubmed and EBSCOhost. A total of 45 research articles from peer reviewed journals and professional position papers were used in the development of the two tools, one to identify NEC risk (eNEC™) and one with targeted nursing assessments and interventions to implement for infants who score in the high to moderate risk categories. To avoid any appearance of a medical diagnostic tool, the tool was called "eNEC™" to infer evaluation for NEC which is within the nursing scope of practice.

Evidence included in the eNEC™ and nursing intervention practice guide spanned evidence about NEC risk, [59–68] importance of feeding an exclusive human milk diet, [35]beginning trophic feeding early to avoid a prolonged NPO course, [69] careful but consistent advance of feeding, [70] a shared understanding about managing feeding intolerance, [13,71,72] and a consistent nursing response to communicate symptoms and initiate actions when NEC was developing.[43]

Scoring of eNEC™ is done weekly for the first month of life. Weekly scoring captures those events or risk factors that may increase the infant's risk for developing NEC. Using eNEC™, the infant's risk is cumulative therefore can only increase. This design was guided with the premise that NEC's disease process is multilayered and the original risk factors cannot be erased, so the score cannot decrease. Medical records for the infants classified high-risk were tagged for follow-up. This visual cue serves as a reminder for each nurse to use preventative interventions and focused assessment tool because the infant is at high risk.

GutCheck^{NEC}—GutCheck^{NEC} was formally derived and validated over three phases of a formal research study. The University of Arizona Institutional Review Board (IRB) approved the study. The working hypothesis was that NEC risk increases when multiple risk factors occur.

In phase I, evidence about NEC risk was synthesized and published,[43] followed by evidence for NEC prevention.[73,74] In phase II, 35 neonatal experts from across the US and four other countries participated in an e-Delphi study to come to consensus about the relevance of NEC risk factors in GutCheck^{NEC}.[75] Experts agreed strongly that being born < 1000 grams, before 28 weeks, and formula fed increase risk while breast milk and use of standardized feeding protocols decrease risk. [75] At the end of the three rounds of iterative surveys, GutCheck^{NEC} was revised to include 33 distinct risk factors. Using qualitative content analysis of experts' comments, two themes about NEC risk were identified: that individual vulnerability and institutional (NICU care practice) variation both contribute.

In phase III, electronic health record (EHR) data was used to build a statistical model of the most predictive risk factors, first for the very low birth weight infant (< 1500 gram) and then for the low birth weight infant (1501–2499 grams). Mimicking a method to build other risk scores including the Score for Neonatal Acute Physiology (SNAP), we used data from 58, 820 babies cared for across 284 NICUs. De-identified patient data from the Pediatrix Clinical Data Warehouse (CDW) was used, representing about 20% of the NICU discharges

in the US from 2007–2011. We first determined what risk factors were most predictive, weighted the items and calculated a risk score using 60% of the cases (n= 35, 013), reserving the remaining 40% for validation and calibration. The statistical model with the best fit to the data included 9 risk factors and 2 risk reducers. Risk factors contained in the final GutCheck^{NEC} include: gestational age, PRBC transfusion, unit NEC rate, late onset sepsis, multiple infections (> 2 before a NEC diagnosis), hypotension treated with inotropic medications, Black or Hispanic race, birth in a different NICU (i.e. outborn status), and metabolic acidosis. Human milk feeding (on both day 7 and 14 of life) and probiotics reduced risk.[76] The highest contributing factor to the GutCheck^{NEC} score was the unit's NEC risk, and carried up to 3 times the weight of gestational age. This finding supports a supposition that NEC risk is modifiable at least in part. Compared to the NRS, the only risk factors retained in GutCheck^{NEC} were gestational age and hypotension when treated with inotropic medications.

Validation and clinical testing of the tools

eNEC™—A strength of eNEC™ is that it has been tested directly in the clinical setting. Initial eNEC™ testing took place in the Carle Hospital, 42 bed, Level III NICU. Bedside NICU nurses from both day and night shifts participated. Medical leadership and the NICU administrators endorsed the tool prior to the trial. Institutional review board approval was not sought as it was a QI project. During the QI project staff nurses scored eligible infants on the first day of life, then weekly and scores were compared to those of project leaders. Tool scores were validated for accuracy by comparing the staff score and the project leader score. A high percentage of the tools (94.68%) were found to be reliable with scoring by the PI project leaders in all but 10 tools with high agreement on assigning the correct risk category (low, medium, or high). Individual scores showed more variability. Based on the variances in scoring, categories were clarified and the tool revised.

A total of 72 infants had scores calculated during the QI project. Out of the 72 infants, 58 (81%) were scored high risk. One factor that placed so many infants in the high-risk category was that almost all babies were given points for antibiotic administration. After re-examining the evidence, only those who received antibiotics for > 5 days were given points for that category.[39,40,77] Based on changing the antibiotic criteria, 13 infants (18%) in the high-risk category were re-categorized as moderate risk. Avoiding a large number of infants categorized as high risk is important to maintain the value of a score to heighten vigilance. If many or most infants fall into high risk categories, the score will generate a large number of false positives who never develop NEC, and potentially reducing clinicians' trust in the score.

Scores for high risk infants were positively related to infants most likely to have abdominal imaging and/or feeding interruption. In the high risk category, 39.7% received some type of abdominal x-ray (KUB, decubitus, or babygram) that was not related to line or tube placement. In this unit, abdominal x-rays are ordered when an infant has had signs of feeding intolerance including abdominal distention, multiple emesis, repeated large residuals (over 50% of volume fed), bloody stools or emesis, or bilious emesis. Only 10% of the infants in the moderate risk category had an abdominal x-ray related to possible feeding

intolerance and none in the low risk category. In the high risk category 34.48% had some type of feeding interruption (NPO status) secondary to symptoms of feeding intolerance and/or medical evaluation for NEC. No infant in any other category had a documented feeding interruption.

GutCheck^{NEC}—GutCheck^{NEC} was validated by testing for the accuracy with which it discriminated those infants who developed NEC from those who did not using infant data from the Pediatric Clinical Data Warehouse. For validation, a case-control design was used in which 120 NEC cases were each matched by birth weight (within 100 grams), gestational age (within one week), and discharge year (within one year) to two controls. It was then calibrated using a separate validation set (N=23, 447) which did not match cases to controls. Identification of infants who developed NEC for both the validation and calibration steps was evaluated using receiver operator characteristic (ROC) curves. With this method, interpretation of the areas under the curve is akin to interpreting academic grades (e.g. AUC > 0.90 is excellent, 0.80–0.89 is very good, 0.70–0.79 is good, 0.60–0.69 is fair and < 0.60 is poor). GutCheck^{NEC} demonstrated very good (B-range) prediction for infants who developed surgical NEC and those who died. Prediction of medical NEC was good (C-range). Overall, prediction of GutCheckNEC was more favorable in the calibration set (N= 23, 447) than the case-control validation set (N=360). Prospective clinical testing is underway and until complete, GutCheck^{NEC} can be obtained by contacting the first author. Full results of the validation study are available elsewhere.[76,78]

IMPLICATIONS FOR RESEARCH

It is clear to us that testing the two tools for parallel validity and prediction is a logical next step in our research trajectory. GutCheck^{NEC} requires prospective clinical testing, currently in progress and both tools would need to undergo more complete evaluation in the clinical setting prior to widespread use. Broader validation and statistical analysis is needed for eNEC™ including validation of risk factor weighting and optimal scoring frequency. The impact of either tool on early recognition and reduction in disease progression leading to surgical NEC is a broader goal for us. Relationships of either tool's use by nurses to feeding interruptions, abdominal x-rays and feeding changes based on signs of intolerance needs to be explored prospectively. Finally, how standardizing risk assessment impacts clinician to clinician communication across transitions in caregivers is also another question worthy of exploration.

IMPLICATIONS FOR PRACTICE AND POLICY

At every stage in the process of prevention and early recognition of NEC, nurses play a critical role. Nurses are powerful patient advocates and can work with physician leaders to encourage the adoption of prevention and early recognition practices for NEC. An infant at risk for necrotizing enterocolitis (NEC) is often described as very low birth weight, born early and likely to have been severely ill yet research studies report occurrence of various risk factors.[43] What is less widely understood is how treatment differences account for NEC risk and how the widely varied NEC rates from NICU to NICU contribute. [9,10,12] An increasingly vocal cohort of NICU clinicians has been successful to reduce NEC rates within

their units by adopting evidence-based prevention practices.[6,62,79] Leaders in units with low NEC rates have prioritized ensuring all mothers with premature labor receive antenatal steroids,[80,81] feeding of human milk,[82,83] use of a feeding protocol,[84] judicious use of antibiotics,[39,40] and holding feeding during transfusion.[6,85] A recent quality improvement collaborative in California reported a reduction in NEC from 7% to < 3% of infants < 1500 grams when a change package of prevention practices was adopted in 11 NICUs. The change package included using colostrum for oral care,[86,87] preferential human milk feeding[88] and use of a standardized feeding protocol. [89] In another quality improvement initiative, dramatic reductions in surgical NEC rates were documented after changing practice to hold feedings during transfusions in Ohio. [85]Although NEC risk may be thought of as non-modifiable, it appears there is a modifiable component amenable to change. [6,89–92]

At the unit level of policy change, revisiting a standardized approach to encouraging the feeding of human milk and using a standardized feeding protocol is warranted.[74] Consistency in approach to feeding intolerance, feeding advancement and breastmilk promotion all impact NEC. Beyond that, using a NEC risk tool in practice may be a logical next step. We recommend a critical analysis of NEC rates within an individual NICU. If rates are well above 5%, they are likely reducible- but culture change is necessary. In the Carle NICU, policies have been revised to reflect current evidence for NEC prevention including: promotion of human milk feeding, using a feeding intolerance algorithm, using a feeding guideline, minimizing excessive antibiotic exposure, and holding feedings during transfusion. Rates are currently at 2% for VLBW infants in this unit and NEC vigilance continues.

Providing donor milk as a species specific alternative when mother's milk is not available is supported by research.[82,93] Yet, insurance reimbursement is not uniform for donor human milk. As Medicaid reimburses a large proportion of neonatal costs, the statewide financial impact of not covering donor milk is dwarfed substantially by the concomitant increase in costs from NEC. Based on an economic analysis from the last decade, a conservative estimate of state-based cost savings estimates that reimbursement and use of human donor milk could save a state Medicaid system about 32, 682, 000 annually on NICU-related costs (calculated in 2002 using costs saved from NEC and sepsis using an average decreased length of stay by 15 days). [94] We recommend broad policy initiatives to make donor milk a viable alternative when mother's milk is not available, particularly in infants < 33 weeks gestation.

Finally, at the national level implications for policy are an issue of debate. As long as NEC is thought of as inevitable in the most vulnerable infants, progress for change may be slow. However, in other arena, increased vigilance for "never events" has spread across the country for Medicare reimbursable conditions. We similarly conceive that we are on the verge of a tipping point for NEC reimbursement. At the very least, we recommend national surveillance and public reporting of NEC rates so that parents as consumers can understand the differences unit to unit. Until that change is realized, nurses at the bedside can consider the use of a tool to facilitate risk awareness for NEC using a tool, perhaps one of which is described here.

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Table 1

Risk Factors in NEC Early Recognition Tools

Risk Assessment Factors					
	eNEC™	**GutCheck^{NEC}**			
		Original	**After expert consensus building**	**After statistical modeling (< 1500 grams)**	**After statistical modeling (1501–2499 grams)**
Biodemographic					
Birth weight	x	x	x		x
Gestational age	x	x	x	x	
Intrauterine Growth Restriction	x	x	x		
Small for gestational age (SGA)	x	x	x		
Multiple birth		x			
Male		x			
Hispanic race		x		x	reduced risk
Black race		x		x	
Maternal					
Outborn				x	x
Placental abruption	x	x	x		
Prolapsed umbilical cord with evidence of perinatal asphyxia		x	x		
Perinatal asphyxia		x	x		
Chorioamnionitis*	x	x	x		
Absent or reversed end diastolic flow	x	x			
Cigarette use	x				
Incomplete or no antenatal steroid	x	x	x		
Illicit drug use, not cocaine	x	x			
Illicit drug use- cocaine	x	x	x		
Premature rupture of membranes	x				
Pregnancy induced hypertension		x	x		

Risk Assessment Factors					
	eNEC™	**GutCheck^{NEC}**			
		Original	**After expert consensus building**	**After statistical modeling (< 1500 grams)**	**After statistical modeling (1501–2499 grams)**
Chronic hypertensive disease		x			
Indomethacin prenatally to treat preterm labor		x			
HIV positive, treated with antiretroviral therapy		x			
Prolonged rupture of membranes	x	x			
Feeding					
Bovine-based formula	x	x	x		
Bovine human milk fortifier	x				
Human milk feeding reduces risk	x	x	x	x	
Fed both formula and breast milk		x	x		
Lack of unit-based adoption of standardized feeding protocol		x	x		
NPO longer than 5 days for any reason then fed		x			
Probiotics reduce risk		x		x	x
Prolonged trophic feeding for > 3 days		x			
Donor milk with prolacta	x				
Postnatal factors					
Hypoxic-ischemic events	x				
5 minute Apgar < 7; ≤ 6 in GutCheck^{NEC}	x	x	x		reduced risk
Prolonged resuscitation	x	x	x***		
Epinephrine at delivery		x	x		
Cold stress at delivery or any time during the clinical course			x		
Hypotension requiring inotropic medications	x	x	x	x	x
Acidosis; Persistent metabolic acidosis before a diagnosis of NEC (GutCheckNEC)	x	x	x	x	x
Respiratory distress	x	x			
Patent Ductus Arteriosus	x	x	x		x

Risk Assessment Factors					
	eNEC™	**GutCheck^{NEC}**			
		Original	**After expert consensus building**	**After statistical modeling (< 1500 grams)**	**After statistical modeling (1501–2499 grams)**
Congenital Heart Disease	x	x	x		x
Early onset sepsis		x	x		
Multiple infections (2 or more in the first 4 weeks of life but before NEC diagnosis)		x	x	x	reduced risk
Late onset sepsis before NEC diagnosis		x	x	x	x
Sepsis	x				
Bloody gastric residuals after the 3rd day of life		x			
Polycythemia	x				
Treatment Factors					
Packed Red Blood Cell (PRBC) transfusion	x			x	x
PRBC transfusion, not NPO		x	x		
Received ≥ 3 different antibiotics at once to treat infection		x			
Antibiotics given for ≥ 5 days	x	x			
NICU in which the infant is cared for has an impact on NEC risk		x	x	x	x
PDA treated with indomethacin and fed during treatment that progresses to a surgical PDA			x		
Histamine 2 (H2) blocker therapy		x	x		
Surfactant given for RDS		x			
IV immunogloblin		x			
Erythropoeitin		x			
Increased risk with each day on the ventilator		x			
Indomethacin***		x			
Exchange transfusion		x			
Umbilical arterial lines longer than 4 days		x			
Given both glucocorticoids and indomethacin		x	x		

* eNEC includes clinical chorioamnionitis and GutCheckNEC includes histological chorioamnionitis

** Prolonged resuscitation defined in GutCheckNEC as need for chest compressions at delivery and positive pressure ventilation > 2 minutes

*** Indomethacin was considered in the e-Delphi in multiple items including a) Indomethacin and NPO, b) Indomethacin and fed, c) Indomethacin and later surgery. None of the indomethacin items were retained in the e-Delphi, contrasting to findings from a meta-analysis.