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SPECIAL ARTICLE

Grading the evidence to identify strategies to modify risk for necrotizing enterocolitis

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Although risk for necrotizing enterocolitis (NEC) is often presented from the perspective of a premature infant's vulnerability to nonmodifiable risk factors, in this paper we describe the evidence and present recommendations to manage modifiable risks that are amenable to clinical actions. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, we present recommendations in the context of their supporting evidence in a way that balances risks (e.g. potential harm, cost) and benefits. Across the prenatal, intrapartum, early and late clinical course, strategies to limit NEC risk in premature infants are presented. Our goal is to summarize modifiable NEC risk factors, grade the evidence to offer quality improvement (QI) targets for healthcare teams and offer a patient-family advocate's perspective on how to engage parents to recognize and reduce NEC risk.

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INTRODUCTION

Clinical and epidemiologic investigations have identified a range of modifiable and nonmodifiable risk factors that influence the development of necrotizing enterocolitis (NEC) in fragile infants, especially those born premature.[1,2] Authors have recently used the terms "modifiable" and "nonmodifiable" in the context of NEC risk.[3–5] To refer to risk as modifiable aligns with approaches to risk awareness used in many other conditions, including heart disease, stroke, and cancer. If risk is modifiable, then clinicians may potentially recognize and intervene to reduce that risk. This is in contrast to nonmodifiable risk from biodemographic factors or untreatable conditions. Marked differences in NEC incidence between centers and the significant progress made by some institutions in decreasing NEC underscore the value of addressing modifiable risk factors to lower NEC burden through programmatic quality improvement efforts.[6–9] In June 2019, one of the presentations at the Necrotizing Enterocolitis Symposium in Ann Arbor, Michigan focused on risk for NEC from the multifaceted lens of clinical practice, research, and patient-family voice. Essential to the NEC Symposium was recognizing the value of co-creating research and NEC quality improvement programs that include the entire healthcare team, in which parents of fragile infants play an essential role. This manuscript provides a summative reflection on premature infants' NEC risk as discussed at the symposium and is not intended to be a state-of-the-art review. For those familiar with the evidence base, this paper organizes it along the continuum of care, providing a timeline to support quality improvement (QI) teams who are examining their care practices to reduce NEC in their units.

A 2017 systematic review of 14 prognostic studies revealed 43 significant NEC risk factors reported in the literature.[10] The following risk factors were shown to increase risk of NEC in more than one study: small for gestational age status, lower gestational age, assisted ventilation, low blood pressure, sepsis, prolonged rupture of membranes, Black or Hispanic race, and outborn status.[10,11–13] A qualitative analysis of experts' perspectives about NEC risk revealed two thematic sources of NEC risk: individual infant vulnerability and organizational patterns of caregiving.[14] Several studies have shown associations between unit NEC risk and an individual baby's risk.[12,13,15]

In this paper, our goal is to summarize modifiable NEC risk factors to represent quality improvement targets and offer a patient-family advocate's perspective on how to engage parents to reduce NEC risk. When possible, we have assessed the quality of evidence using the GRADE criteria for evidence-based medicine—a process that we undertook as a team where consensus was achieved after two teleconferences and multiple email exchanges.[16,17] In GRADE, recommendations are categorized by letter. A GRADE of A carries a strong recommendation where benefits are considered to outweigh the risks and the evidence is of high quality. A GRADE of B is given when the recommendation is moderate, it is likely that benefits outweigh risk, and the underlying evidence is of moderate quality. A GRADE of C represents a weak recommendation, evidence is considered to be low quality, risks may outweigh the benefits or the treatment may be costly. Along with a GRADE, the evidence quality is portrayed using both Roman numerals I–V (I = systematic review with meta-analysis, II = well-designed trials, III = cohort or quasi-experimental trials, IV = descriptive and V = expert opinion or consensus) and lower-case letters (a = good quality and b = lesser quality). For example, a meta-analysis of well-designed RCTs that show a precise effect with great benefit and low risks is described as Level Ia evidence that carries an A recommendation. GRADE requires the expert panel to weigh the risks and benefits of an intervention in the *context* of how it would be delivered (e.g. cost-impacts, complexity, and feasibility to implement). Although

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Table 1. Mapping NEC pathophysiology to modifiable actions and mechanisms modifiable risk to preventive interventions and mechanisms.

Contributing NEC pathophysiology	Modifying clinical action	Risk modifying mechanism
Immature innate and adaptive immunity	Prenatal steroids	Increase maturation
	Colostrum swabbing	Stimulate oropharyngeal immune system
	Human milk feeding	Provide IgA, IgM, lactoferrin and other bioactive molecules and cellular components
Intestinal dysbiosis	Human milk feeding	Prebiotic functions of human milk oligosaccharides and other milk glycans
	Probiotics	Increase commensal microbes and decrease pathogens
Variability in intestinal perfusion	Delayed umbilical cord clamping	Decrease hypotension, hypo-perfusion, and anemia
	Limit severe anemia	
Poorly controlled inflammatory response	Human milk feeding	Anti-inflammatory and anti-oxidant factors
	Probiotics	Suppress TLR4/NFκB-induced cytokines (IL1β, IL6, IL8, TNFα)
Increased intestinal permeability	Human milk feeding	Stimulate villous growth and enterocyte production (possible role for human milk stem cells?)
	Probiotics	Decrease apoptosis and strengthen tight junctions
Stress	Kangaroo care	Decrease heart rate variability, increase maternal milk production

others have described NEC risk and shown the effect of NEC QI to reduce rates, to our knowledge none have systematically applied a GRADE to the evidence, offered expert-consensus-derived recommendations to inform care, or reflected on how to engage parents in recognizing and reducing NEC risk. In this review, we independently reviewed the evidence and collectively agreed on the GRADE and strength of recommendations. Initial disagreements on GRADE or recommendation strength were resolved through discussion.

CLINICAL ACTIONS TO MODIFY RISK

In the following sections, interventions to modify NEC risk are presented along the continuum of care (prenatal, at birth, first 72 h of life, and subsequent NICU course). Based on clinical and experimental evidence, these interventions likely alter pathophysiologic processes that coalesce to put a premature baby at risk (Table 1). To accomplish these changes requires a comprehensive, multidisciplinary programmatic approach that engages parents.[18] The GRADE and level of evidence for recommendations that may modify NEC risk are presented in Table 2.

Modifiable prenatal risk factors and clinical actions

Corticosteroids (GRADE A; Level Ia). If birth between 23 and 34 weeks is anticipated, administration of antenatal corticosteroids reduces NEC likelihood (10 studies, 4702 participants, relative risk (RR) 0.50, 95% CI 0.32−0.78).[19]

Intrapartum antibiotics (No recommendation; Level IIIb). Multiple maternal infections[20] and prolonged rupture of membranes have been shown to increase NEC risk (nonmodifiable risks).[10] One might expect that maternal antibiotic administration would be protective against NEC; however, limited data suggest the opposite.[21] Obstetricians need to continue to weigh the risks and benefits of prenatal and intrapartum antibiotics considering current guidelines and the individual needs of the mother.

Promote early education about the value of human milk (GRADE B; Level IVb). Providing education to mothers who may deliver preterm about the critical importance of human milk is an important first step in the mother initiating pumping.[7,22–24] Framing a consistent prenatal message to promote human milk involves the obstetrician and the labor and delivery nursing staff with additional input during prenatal consultations from the neonatologist, the NICU nursing staff, the lactation support staff, and dietitians. Although evidence is not strong, mothers reporting early education enables them to prepare for the early pumping and long-term prospects of providing human milk for their infant.

Interventions at birth

Umbilical cord clamping management (No recommendation; Level Ia). Delayed clamping of the umbilical cord for 30–120 s has been associated with lower risk of NEC.[25] Although a recent meta-analysis showed no impact on NEC rates,[26] there is benefit to limit anemia and reduce mortality. A recent randomized trial showed no difference in NEC risk, although mortality was reduced.[27] Both ACOG and the AAP endorse delayed cord clamping.[28,29] When the infant needs immediate resuscitation, some have opted for cord milking instead of delayed clamping.[30,31] A meta-analysis of cord milking studies demonstrated a decrease in NEC (4 RCTs, 487 infants, RR 0.60, 95% CI 0.39–0.93).[32] Three small studies (total 375 infants) published since the meta-analysis have each shown no benefit of cord milking in NEC prevention, though all investigated primary outcomes other than NEC.[33–35] In a multisite, multinational RCT comparing delayed umbilical cord clamping to cord milking, the trial was terminated because of a higher incidence of severe IVH in the milking group compared to those who received delayed cord clamping ($P = 0.02$), primarily in infants born at 23–27 weeks gestation (22% with milking vs. 6% delayed clamping).[36] More research is needed and for now, it appears that delayed clamping is preferred to milking for the earliest infants.[37] Drawing admission labs from the umbilical cord is another strategy to reduce iatrogenic blood loss and anemia.[31]

Initiate lactation support with early hand expression and pumping (GRADE B; Level IVb). Promoting early access to human milk requires that mothers are engaged early to express their colostrum and are helped to initiate hand expression and use the breast pump.[23,38] The earlier mothers begin pumping, the more likely the success of long-term human milk feeding. A meta-analysis of methods of milk expression showed a high degree of variability in nutrient content and maternal satisfaction between methods suggesting the value of both hand expression and pumping.[39]

Interventions in the first 72 h of life

Limit excessive antibiotic use (GRADE B; Level IIIa). Several studies show an increased risk for NEC, sepsis, and death when initial

Table 2. GRADE recommendation and level of evidence for modifying NEC risk.

	GRADE	Level of evidence
Antenatal corticosteroids for infant born between 23 and 34 weeks	GRADE A	Ia
Antenatal antibiotics	No recommendation	IIIb
Delayed umbilical cord clamping	No recommendation	Ia
Cord milking at delivery	No recommendation	Ia
Early initiation of lactation support	Grade B	IVb
Limit excessive antibiotics (>48 h of empiric therapy without positive blood culture)	Grade B	IIIa
Colostrum swabbing to provide oral immune therapy	Grade C	IIIb
Standardized feeding approach (no specific protocol, see Table 3 for specific components)	Grade B	Ib
Limit use of histamine-2 antagonists	Grade B	IIIb
Limit profound anemia (Hemoglobin < 8 g/dl)	Grade B	IIIa
Limit treating PDA with indomethacin	Grade B	Ia
Designate sterile milk preparation areas, standardize ways to mix fortifiers and warm milk, consider changing feeding tubes weekly	Grade C	V
Consider the decision to provide or not provide probiotics as an opportunity for shared decision-making with parents.	No recommendation	Ia
Prophylactic enteral antibiotics	No recommendation	Ib
Parental involvement to include kangaroo (skin-to-skin) care	Grade A	Ib

empiric antibiotic therapy is prolonged.[40–42] Antibiotics should only be used when clinically indicated and stopped between 36 and 48 h unless bacterial cultures are positive or the infant has clear evidence of sepsis to modify NEC risk.

Colostrum swabbing to provide oral immune therapy (GRADE C; Level IIIb). Several small studies have explored the benefits of early swabbing of the oral mucosa with mother's own colostrum. Colostrum is rich in immune-stimulating nutrients, and exposing the infant oral mucosa to the multiple bioactive factors it contains boosts the infant's production of secretory immunoglobulin[43] and lactoferrin while reducing levels of salivary transforming growth factor-β-1 and interleukin-8.[44,45] Early use of colostrum for oral swabbing increases mother's interest in pumping and her ability to sustain it long term.[38,46] Oral colostrum swabbing to prevent NEC is not conclusive.[47] A small trial (117 infants) showed no reduction[48] and a larger trial is underway.[49] It is recommended here because of its role to boost immunity[50,51] and engage mothers early to promote early and consistent pumping which is essential to stimulate milk production.[46]

Initiate a standardized feeding approach (GRADE B; Level Ib). A systematic review of 15 observational studies ($N = 18{,}160$) showed standardized feeding regimens (SFRs) reduced NEC by nearly 80% (RR 0.22; 95% CI 0.13−0.36; $P < 0.00001$).[52] Another meta-analysis restricted to the VLBW and eliminating studies that included bundles estimated that NEC risk was reduced by 67% (RR 0.33, 95% CI 0.17, 0.65, $P = 0.001$).[5] Early introduction of feeding stimulates intestinal epithelial cells, promotes gut maturation, and fosters beneficial colonization. The details of effective SFRs vary widely. Most effective SFRs include: when to start minimal enteral (trophic) feeding, breast milk as the feeding of choice, when and how to advance, when to fortify, clear criteria to stop feeding, and goals for growth.[5,52] For consistency, we recommend that units integrate SFRs into standard order sets, use feeding schedules, communicate them to all clinical team members, conduct audits of compliance, and provide feedback to clinicians.[6,7] Graded recommendations and level of evidence for specific components of feeding regimens are presented in Table 3.

Interventions along the NICU course

Limit histamine-2 antagonists (GRADE B, Level IIIb). A meta-analysis combining results from ten studies showed increased odds of NEC with H-2 antagonists (pooled OR 2.81, 95% CI 1.19–6.64, $P = 0.02$).[53] H-2 blockers have been shown to alter the fecal microbiota with a significant increase in proteobacteria, perhaps due to changing the acidic environment that allows proteobacteria to proliferate.[54] Limiting H2 blockers was part of the NEC bundle in several effective QI programs.[6,8,55] In the American Academy of Pediatrics *Choosing Wisely* campaign, discontinuing H2 blockers is recommended because of their high risk and few benefits.

Limit profound anemia (GRADE B; Level IIIa). In a recent multicenter observational study including 598 VLBW infants, severe anemia (defined as hemoglobin (HgB) < 8 g/dl) in a given week was associated with increased risk of NEC (adjusted HR 5.99, 95% CI, 2.00–18.0); however, red blood cell transfusion in a given week was not.[56] Others have demonstrated associations between NEC and both anemia and transfusion.[57] The observation that anemia is often a result of NEC in addition to a potential risk factor adds to uncertainty as to cause and effect. It is likely that ongoing trials will shed further light on this modifiable risk factor; until additional data are available, it seems prudent to avoid severe anemia in VLBW infants.

Indomethacin treatment for patent ductus arteriosus (GRADE B; Level Ia). While there is a clear association between NEC and a hemodynamically significant patent ductus arteriosus (PDA), causality has not been determined. Early screening (before day 3 of life) for a significant PDA in infants born at <29 weeks did not decrease the risk of NEC.[58] It is thought that a hemodynamically significant PDA diverts blood flow from the mesenteric circulation and may increase the risk for NEC, yet studies are not definitive and no clear recommendation is justified. Fluid restriction has been associated with lower risk of PDA (typical RR 0.52, 95% CI 0.37–0.73) and NEC (typical RR 0.43, 95% CI 0.21–0.87).[59] Treating a PDA with ibuprofen instead of indomethacin lowered NEC risk (16 RCTs, $N = 948$, typical RR 0.64, 95% CI 0.45–0.93),[60] and continuing trophic feeding during drug therapy for PDA appears safe.[61]

Table 3. GRADE and rationale for feeding protocol components.

Components and GRADE	Evidence applied to generate GRADE
Prioritize human milk beginning with mother's own milk and using pasteurized donor human milk when mother's milk is unavailable (Level IIIa, GRADE B)	One RCT showed less NEC in each gestational age strata compared to formula feedings.[77] Human milk-fed preterm infants have a 60–80% decrease in the risk of NEC. The primary risk of unpasteurized human milk is CMV infection which is more frequent in extremely premature infants.[78] Mother's milk is more effective than donor human milk in protecting against NEC. Total volume of human milk correlates with NEC reduction in a dose-dependent manner.[79,80] Meta-analysis of RCTs comparing donor human milk to formula revealed a higher risk with formula ($N = 869$, seven studies, RR = 2.77, 95% CI 1.40, 5.46, $P = 0.003$).[81]
Dose and duration of trophic feeding (Level IIb, GRADE B)	Trophic feedings (10–20 ml/kg/day) for 2–5 days, started by 72 h of age.[52,82] Early advancement without trophic feeds led to more NEC compared to including a period of trophic feeding.[83] Effective bundles include trophic feedings.[8,65]
Speed of feeding advancement Level Ia, feeding advancement at a faster rate for stable infants with birth weight > 1 kg	Slow feeding advancements (up to 24 ml/kg/day increase) were compared to fast rates (30–40 ml/kg/day increase) in a meta-analysis of nine RCTs ($N =$ 949 infants, most between 1000 and 1500 g) with no difference in NEC (typical RR 1.02, 95% CI 0.64, 1.62). Slow advancement rates delayed meeting feeding goals and led to longer duration of parenteral nutrition with higher risk for infection (typical RR 1.46, 95% CI 1.03, 2.06).[84] We caution against applying these findings to extremely low birth weight, growth restricted or extremely preterm infants because they were often excluded from these studies and refer the reader to high-risk population feeding protocol examples.[65,85]
Fortification (Level IIb, GRADE B)	Multi-nutrient bovine-based fortifier does not significantly influence NEC risk (11 RCTs, $N = 882$, typical RR 1.57, 95% CI 0.76−3.23) but weak methodology, inconsistent blinding, presence of confounders and not accounting for exposure to human milk all weaken the quality of the evidence.[86] One small RCT compared fortification at 20 ml/kg/day to fortification at 100 ml/kg/day with no difference in feeding tolerance, NEC or death, but higher protein intake in each of the first 3 weeks of life with early fortification.[87] Pooling RCTs and cohort studies of donor human milk-derived fortifiers[88,89] showed a trend towards lower odds of NEC compared to bovine-based fortifiers and formula (four studies, $N = 1164$, OR 0.36, 95% CI 0.13, 1.00, $P = 0.05$).[5]
Feeding interruptions (Level IIIb, no recommendation)	Meta-analysis of seven cohort studies ($N = 7492$) found that holding feeding during transfusion reduced risk of transfusion-associated NEC (RR 0.47, 95% CI 0.28, 0.80, $P = 0.005$).[90] A single pilot RCT found no decrease in NEC with holding feedings during transfusion.[91] More RCTs are needed.

Supporting mothers to provide their own milk (GRADE B; Level IIIa). Evidence-based strategies to support mothers are programmatic and require consistent efforts over time. Examples of effective programs include Spatz's 10 Steps to promote human milk,[23] the University of California at San Diego's SPIN program,[62] and Meier's Rush Mother's Milk Club.[22] Effective lactation support includes: consistent messaging about the importance of human milk, support for initiating pumping, daily monitoring to reach goal volumes, use of colostrum for oral care, providing high-quality pumps and spaces for mothers to use them, promoting peer support, enabling access to lactation consultants, and monitoring for adequate milk volume. In diverse populations, peer breastfeeding counselors have been particularly effective.[63] Benefits of prioritized human milk and an exclusive human milk diet are addressed with recommendations related to feeding approaches in Table 3.

Storage and handling of feeding devices and substrates (GRADE C; Level V). To avoid contamination, we recommend the use of designated milk preparation areas where human milk can be labeled and mixed with fortifiers in a clean, separate environment from patient care. A prospective study of 50 infants showed that 71 of 125 feeding tubes met the criteria for "contamination" with three different types of bacteria on average and of seven NEC cases, all had contaminated tubes. Noncontaminated tubes were associated with fewer days of feeding intolerance.[64] Routine weekly changes of feeding tubes with extension tubing changed between feedings has been associated with a reduction in NEC rates.[65]

Probiotics (No recommendation; Level Ia). The administration of probiotics to prevent NEC has been studied, and several meta-analyses of RCTs are available.[66–70] Though the level of evidence is perhaps the most compelling among all the interventions reviewed, probiotic use in US NICUs remains uncommon. The degree of hesitation to adopt routine probiotic administration is reflected among the authors with some providing probiotics to all VLBWs beginning with the onset of feeding or colostrum swabbing and others awaiting more compelling evidence of safety and efficacy resulting in no recommendation regarding routine probiotic administration. There was agreement, however, that parents have the right to be fully informed early in the NICU stay regarding both the risks and benefits of probiotic administration and that a conversation about probiotics offers an important opportunity for shared decision-making in the NICU.

Prophylactic enteral antibiotics (No recommendation; Level Ib). A meta-analysis of five RCTs of prophylactic oral antibiotics, most commonly gentamicin or vancomycin ($N = 456$ low birth weight or preterm infants), showed reduction in NEC (RR 0.47 95% CI 0.28–0.78)[71]; however, experts have been hesitant to endorse this

A comprehensive list of modifiable risk factors, from pre- to post-natal, and the interventions that could impact NEC could engage parents and raise NEC awareness. It is imperative to tell parents that NEC exists so they are not caught off guard should it happen to their baby and to discuss strategies that could, potentially, reduce risk. Instituto PGG (Pequenos Grandes Guerreiros) is a Brazil-based non-profit NEC-focused advocacy organization. We surveyed forty families and found that none of them had heard of NEC before their baby got sick. Most were in such a state of mental distress that it was hard to assimilate information. Once parents understand their infant is at-risk, interventions to reduce risk can be fully explained, especially those that rely on engaging parents like providing human milk. Clinicians can offer no guarantees that NEC will not occur because NEC mechanisms are not fully understood. Mothers, especially, are often convinced their babies developed NEC as a direct result of something they did (e.g. because of their absence from the bedside, due to problems with their milk or because they had a turbulent pregnancy), so full disclosure that no intervention is infallible (including human milk) is needed. It is very important that health professionals are prepared to communicate in a comprehensive way the options available and their impact, as well as pointing out in a clear, but sensitive, way what defines a baby at risk. For instance, for the premature infant with sepsis, antibiotics are lifesaving but may increase NEC risk. Engaging parents empowers them in a NICU environment where they are unable to fully care for their baby, while also ensuring that families who know the baby best are working as partners with clinicians to modify risk.

Authored by Simone Rosito, Founder Instituto Pequenos Grandes Guerreiros

Fig. 1 Simone Rosito, MBA is the Founder of the NEC advocacy group called "Instituto Pequenos Grandes Guerreiros," based in Sao Paulo, Brazil. In Portuguese, "Pequenos grandes guerreiros" means "little warriors." Her interest in NEC advocacy was inspired by her nephew, Tom's, fight with the disease. Although Tom died from complications of NEC at 10 months old, his pure love and smiles inspire the mission to help other families touched by NEC.

Table 4. Summary of recommendations to modify NEC risk.

Strong evidence supports [Justifies a bold recommendation]	Antenatal corticosteroids before delivery
	Prioritizing mother's own milk
	Unit-based feeding protocol adoption
	Use of a programmatic approach to reducing NEC using QI methods
	Discussing risks and benefits of probiotic administration with parents
	Skin-to-skin care
Modest evidence supports [Consider as standard of care]	Donor human milk (compared to infant formula) as a substitute for mother's own milk
	Limit prolonged empiric antibiotic therapy
	Limit use of histamine-2 antagonists
Weak evidence supports [Weigh risks/benefits]	Oral colostrum swabbing
	Donor human milk-based fortifier instead of bovine-based fortifier (weigh cost/benefits and adoption of other lower cost interventions first)
	Optimal feeding regimen
	Optimal changing time for feeding tubes and extension tubing
	Sterile milk preparation areas
	Limit severe anemia

approach due to concerns about the emergence of resistant bacterial strains as was seen recently in an infant treated with prophylactic colistin.[72] Antibiotic stewardship is important to avoid antibiotic resistance and at this time, enteral antibiotics as a prophylactic intervention potentially offer risks that outweigh the benefits.

Parental involvement and kangaroo care (GRADE A; Level Ib). Skin-to-skin care of premature infants, also known as kangaroo care (KC), improves a variety of health and neurodevelopmental outcomes, decreasing morbidity and mortality and boosting bonding, milk production, transition to breastfeeding, and satisfaction for the parents.[73,74] An analysis of economic benefits of KC and breastfeeding in NICUs found a 4–14-fold return on investment in supporting parents in these activities with most of the cost savings coming from decreases in NEC.[75] Family-integrated care has been shown to impact neonatal outcomes, including NEC and enhances the parent experience and transition to home.[76] Engaging families early in conversations about NEC, its risk factors and warning signs is recommended by our team and by patient-family advocates who have experienced NEC. One patient-family advocate's perspective is presented in Fig. 1.

CONCLUSIONS

This paper presents expert-consensus-derived recommendations based on using the GRADE criteria to guide QI initiatives in NICUs (Table 4). We focused on the premature infant and not term infants or those born with congenital anomalies because the evidence has focused primarily on the premature infant. We cannot say with the same confidence that the strategies will impact NEC risk in other populations of fragile infants, although more research is needed. In light of all the work presented at the NEC symposium, we offer the essential need to engage the healthcare team to implement prevention strategies in ways that co-create QI initiatives with parents. As the research engine runs

hot after untangling the NEC enigma, the team can focus their energy to implement prevention strategies to modify NEC risk.

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ADDITIONAL INFORMATION

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