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A Critical Analysis of Risk Factors for NEC

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Abstract

Necrotizing enterocolitis (NEC) is the most common serious gastrointestinal morbidity in preterm infants. A number of risk factors for NEC have been reported in the literature. With the exception of decreasing gestational age, decreasing birth weight and formula feeding, there is disagreement on the importance of reported risk factors with uncertain causality. Causal risk factors may be observed at any time before the onset of NEC, including prior to an infant's birth. The purpose of this review is to examine the existing literature and summarize risk factors for NEC. This review may be helpful in understanding the epidemiology of NEC and inform the measurement and assessment of risks factors for NEC in research studies and improvement projects.

Keywords

Necrotizing enterocolitis; Risk factor; Prematurity; Epidemiology; Neonate

A. Introduction

Necrotizing enterocolitis (NEC) is a serious and deadly gastrointestinal disease with a multifactorial etiology that primarily occurs in preterm infants. Data from the US shows a decreasing incidence of NEC.^{1–3} Among high-income countries, there is a large variation in the incidence of NEC with differences ranging up to fivefold, from less than 2% to almost 9% for infants <1500 g.⁴ However, comparisons of studies are limited by different populations and different definitions of NEC; this variation, however, suggests that modifiable risk factors exist that could allow clinicians and researchers the opportunity to intervene to reduce the risk of NEC. This potential opportunity is reinforced by large scale, multifaceted quality improvement projects that have demonstrated decreases in NEC incidence associated with implementation of targeted interventions.³ However, clinicians and experts disagree about the importance of different risk factors. In a group of 35

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international NEC experts asked to review 64 identified risk factors, the only factors for which there was high agreement were gestational age, birth weight and feeding (formula vs. breastfeeding).⁵ The purpose of this review is to evaluate the evidence on risk factors for NEC and summarize the consistency and direction of association of commonly reported risk factors with NEC (Table 1).

B. Approach

To identify studies, we used the search term “necrotizing enterocolitis” or “necrotising enterocolitis” in PubMed with the search limited to systematic reviews. Additional randomized controlled trials (RCTs) and multicenter or regional/national observational studies specifically assessing risk factors for NEC were reviewed, including reference lists. Risk factors are presented as they occur in sequence during the fetal and neonatal life course: maternal and antenatal, perinatal and delivery, early neonatal, and postnatal (including enteral feeding). This review focuses on NEC as it develops in moderately or extremely preterm infants, and therefore does not discuss factors unique to more mature late-preterm and term infants. Given the distinction between factors associated with NEC and factors that *cause* NEC, we distinguished when data was from randomized trials in comparison to observational studies and when findings are consistent between the two study types.

C. Maternal and antenatal

Multiple studies have shown NEC rates vary by region, network and country;^{1,2,4} ethnic, racial and genetic factors specific to a given region are likely non-modifiable risk factors for certain infants. In US studies, black race has consistently been associated with NEC^{6–8} as well as death from NEC (risk of death from NEC for black infants compared to white infants in the US, RR 3.1, 95% CI 3.0–3.4).⁹ Other maternal demographic factors including age, weight, multiparity, smoking, education, and employment status have not been consistently associated with NEC.

There is conflicting data on the role of hypertensive disorders of pregnancy and NEC risk. A meta-analysis including observational studies between 2000–2016 showed no difference in NEC risk between all mothers with pregnancy induced hypertensive disorders and those without (OR 1.89, 95% CI 0.82–4.37, 4 studies, 28 724 infants).¹⁰ However, in the study’s subgroup analysis of mothers with preeclampsia, there was a 2.5 fold increased risk for NEC based on data from 3 studies (n=878). Analysis of three RCTs of interventional management (e.g. delivery), compared to expectant management for pre-eclampsia between 24–34 weeks, showed a non-significant trend toward increased NEC among infants in the intervention group, likely due to delivery at an earlier gestational age (RR 2.10, 95% CI 0.93–4.79, 3 studies, 395 infants).¹¹

Antenatal steroid (ANS) administration reduces neonatal mortality; a meta-analysis of 10 randomized control trials shows ANS decreases the relative risk of NEC by 50% (RR 0.50; 95% CI 0.32–0.78, 10 studies, 4702 infants).¹² However, a meta-analysis of observational studies shows no benefit of ANS on NEC at very low gestational ages (OR 1.01, 95% CI

0.84–1.22, 7 studies, 8737 infants < 25 weeks gestation), potentially due to effects on the competing cause of death (i.e. more survivors increase the number of infants at risk for NEC).¹³

Some therapies given to mothers have been shown to decrease the risk of NEC. Progesterone given to women at risk for preterm birth decreased the relative risk of NEC by 70% (RR 0.30; 95% CI 0.10–0.89; 3 studies, 1170 infants).¹⁴ A review of RCT data examining the use of calcium channel blockers for tocolysis compared to betamimetics showed a reduced risk of NEC (RR 0.21, 95% CI 0.05–0.96; 5 studies, 490 infants), which may be due to increases in gestational age at birth from pregnancy prolongation.¹⁵ However, meta-analysis of observational studies suggests the use of indomethacin for tocolysis may increase the risk of NEC (RR 1.36, 95% CI 1.08–1.71, 18 studies, 4273 infants).¹⁶

Magnesium sulfate has several indications for use in obstetrics including use in pre-eclampsia or eclampsia, fetal neuroprotection in threatened preterm delivery (< 32 weeks gestation), and short-term prolongation of pregnancy to allow for administration of ANS. Indirect evidence from RCTs of magnesium sulfate to reduce cerebral palsy in premature infants (24–31 weeks gestation) shows no significant increased risk of NEC for those receiving magnesium prior to delivery (RR 1.27, 95% CI 0.97–1.66, 2415 infants).¹⁷

Maternal chorioamnionitis, both clinically and histologically defined, has been examined with varying results on its association with NEC. A 2013 meta-analysis found histological chorioamnionitis with fetal involvement associated with a 3-fold increase risk for NEC (OR 3.29, 95% CI 1.87–5.78).¹⁸ Prolonged rupture of membranes, a common antecedent to chorioamnionitis, has been associated with NEC across several studies spanning several decades.^{19–21} While maternal infection may increase NEC risk for the infant, maternal antibiotic treatment does not appear to increase risk and may, in fact, decrease it. Data from a prospective, observational microbiome study found a reduced risk of NEC if maternal antibiotics were given (OR 0.28, 95% CI 0.14–0.56, 580 infants).²² However, meta-analysis of RCT data of maternal antibiotics in the setting of premature rupture of membranes showed no effect of antibiotic administration on NEC (RR 1.09, 95% CI 0.65–1.83, 11 studies, 6229 infants), except with the use of amoxicillin-clavulanate (RR 4.72, 95% CI 1.57–14.23, 2 studies, 1880 infants).²³ Differences between these studies may be due to residual confounding, differences in the populations, including presence or absence of premature rupture of membranes (PROM) and ascertainment of chorioamnionitis.

D. Perinatal and delivery characteristics

a. Fetal ischemia and growth

Compromised fetal blood flow before or at the time of delivery may result in fetal ischemia that could contribute to NEC. An Australian cohort of infants 24–31 weeks gestation had a 2-fold increased risk of NEC in the setting of placental abruption (aOR 2.09, 95% CI 1.30–3.35; 4649 infants).²⁴ An observational study found a similar association with vaginal bleeding after 12 weeks of gestation and NEC.⁶

Infants with intrauterine growth restriction (IUGR), with or without abnormal Doppler studies, and small for gestational age (SGA) infants are at increased risk for NEC.^{24–26} A 2005 meta-analysis of observational studies of infants with absent end diastolic flow (AEDF) versus controls showed increased odds of NEC in the AEDF group (OR 2.13, 95% CI 1.49–3.03, 14 studies 1837 infants).²⁷

b. Delivery

Approximately 60% of extremely preterm infants are delivered by cesarean section.¹ Studies have reported conflicting data regarding the relationship of cesarean delivery to risk of NEC with studies showing cesarean to be protective^{8,20}, not associated,²⁸ or associated with increased NEC risk.¹⁹ Secondary analysis of RCT data showed no association with cesarean delivery and NEC (OR 0.73, 95% CI 0.46–1.16, 2012 infants).²⁹ Emerging literature suggests the potential for the gut microbiome to develop before delivery.³⁰ Therefore, the effect of mode of delivery on NEC and related changes to the gut microbiome is likely complex and multifactorial.

The evidence for a reduced risk of NEC in premature infants who receive delayed cord clamping has recently changed. A meta-analysis that includes the Australian Placental Transfusion Study³¹ found no effect of delayed cord clamping on NEC in infants born < 37 weeks gestation or in a subgroup of those born ≥ 28 weeks (OR 0.88, 95% CI 0.65–1.18, 12 studies, 2397 infants; OR 0.87, 95% CI 0.61–1.24, 4 studies, 977 infants, respectively).³² This data contrasts a prior meta-analysis of 241 infants showing a 40% reduction in NEC for infants receiving delayed cord clamping.³³

E. Baseline or early neonatal

a. Baseline

Decreasing gestational age and birth weight are consistently reported in the literature as clear risk factors for NEC.¹ In a national study of infants in the United Kingdom, the incidence of NEC was 11% in those born at 24 weeks gestation and decreased to 0.5% for infants born at 31 weeks gestation.³⁴ This study also demonstrated an increased risk for NEC in the setting of decreasing birth weight z-score (aOR 1.29, 95% CI 1.17–1.43 for each unit decrease in birth weight z-score). A large national study in the US had similar findings and demonstrated an increased risk of death from NEC in the setting of decreasing gestational age and decreasing birth weight.⁷

There have not been consistent findings for the association between infant sex and NEC. A study of incidence of NEC in Sweden found male sex to be associated with NEC; however a case-control study during the same time period, did not associate male sex with an increased risk of NEC.^{19,35} Because of the established association of sex and mortality in extremely preterm infants, consideration of the association between sex and NEC would require an understanding of changes in the competing causes of death within a given cohort and also potential interaction with other factors such as race or birth weight.

Multiple measures of poor neonatal transition have been associated with NEC, including need for resuscitation in the delivery room, low Apgar score, hypotension, low umbilical

cord pH or base deficit, and early mechanical ventilation.^{8,36–38} These factors are primarily reported in observational studies and have not been consistently associated with NEC, raising questions regarding whether they are a cause of NEC or only associated with NEC. Regardless, the associations suggest the potential importance of early physiology stability that could contribute to the subsequent risk of NEC.

b. Early neonatal

While some large observational studies report on the positive association between surfactant and NEC^{8,24}, a meta-analysis of randomized trials of prophylactic and selective surfactant use found no association with NEC (RR 0.90, 95% CI 0.73–1.10, 8 studies, 4237 infants).³⁹ In addition, the administration of multiple doses of surfactant, compared to a single dose, resulted in a decreased risk of NEC (RR 0.20, 95% CI 0.08–0.51).⁴⁰ Animal derived surfactant, however, has been associated with an increased risk of NEC (RR 1.38, 95% CI 1.08 to 1.76, 8 studies 3462 infants).⁴¹ In addition, lower oxygen saturation targets increase the risk of NEC in extremely preterm infants; the Neonatal Oxygen Prospective Meta-analysis Collaborative showed that NEC risk increased for infants <28 weeks with a lower oxygen saturation goal of 85–89% compared to those in the 91–95% target group (RR 1.24, 95% CI 1.05–1.47, 5 studies, 4929 infants).⁴²

The presence of an indwelling umbilical arterial catheter has been an exclusion criteria for infants in feeding advancement studies suggesting concern that these catheters may put infants at risk for NEC.⁴³ However, there is inconsistent evidence of the risk associated with umbilical catheters^{8,36} and the location of umbilical artery catheters, with a meta-analysis of RCTs showing no effect of umbilical arterial catheters on the risk of NEC (RR 1.34, 95% CI 0.79–2.25, 5 studies, 1569 infants).⁴⁴

F. Postnatal factors

a. Common complications associated with prematurity

A patent ductus arteriosus (PDA) may be present in up to 65% of infants born < 29 weeks gestation⁴⁵ and treatment for a PDA may occur prior to the development of NEC. In observational studies, it can be difficult to determine if the presence of a PDA or the treatment of the PDA modifies an infant's risk of NEC. In a cohort of infants < 34 weeks in Israel, those with a PDA without indomethacin treatment and those with a PDA with indomethacin treatment had an increased risk for NEC compared to infants without a PDA (OR 1.85, 95% CI 1.24–2.69 and OR 1.53, 95% CI 1.15–2.02, respectively, 6044 infants).⁴⁶ In a recent network meta-analysis of randomized trials, there was no increased risk of NEC with no treatment (or placebo) for PDA compared to pharmacologic treatment; the analysis found some pharmacological regimens performed worse than placebo/no treatment, although the differences did not reach statistical significance.⁴⁷

Sepsis places an infant at risk for NEC.^{21,37,38} However, empiric antibiotics and the duration of antibiotic exposure has unclear effects on the risk of NEC. Several studies have found that the duration of empiric antibiotics in extremely low birth weight infants with sterile cultures is associated with an increased risk of NEC.⁴⁸ A recent meta-analysis of

observational studies found prolonged antibiotic exposure was associated with NEC in 5 studies (5003 infants), but among RCTs found no statistically significant effect on NEC when looking at whether or not an infant received prophylactic antibiotics (OR 1.25, 95% CI 0.12–12.50, 2 RCT, 288 infants) or broad versus narrow spectrum antibiotics (OR 0.30, 95% CI 0.04–2.31, 3 RCT, 586 infants);⁴⁹ however the trend was toward increased risk of NEC although estimates were imprecise. As all of the data regarding duration of antibiotics and risk of NEC is from observational studies, the estimates of association with NEC from these studies could be biased by residual confounding.

Anemia, with the potential for poor intestinal oxygen delivery, has been studied as a risk factor for NEC. A prospective observational study found anemia (< 8 g/dl) was associated with an increased risk for NEC (hazard ratio (HR) 5.99, 95% CI 2.00–18.0) but not red cell transfusion (HR 0.44, 95% CI 0.17–1.12).⁵⁰ Data from RCTs shows no difference in the risk of NEC for infants transfused using a lower versus higher hemoglobin threshold (RR 1.62, 95% CI 0.83–3.13, 3 studies, 590 infants).⁵¹ The risk of red cell transfusion is discussed below and additional data from the Transfusion of Prematures Trial (clinicaltrials.gov NCT01702805) may provide additional insight into the relationship between red cell transfusion, anemia and NEC.

b. Care interventions

Whether red cell transfusion is a causal risk factor for NEC is not currently known. A recent meta-analysis shows no increased risk of NEC following red cell transfusion (OR 1.13, 95% CI 0.99–1.29, 13 observational trials, 11,602 infants)⁵² and another suggests transfusion may be protective (OR 0.55, 95% CI 0.31–0.98, 10 observational trials, 24,623 infants).⁵³ Observational data suggests feeding during transfusion is a risk factor for NEC within 48 hours (RR NEC, NPO vs. feeding: 0.47, 95% CI 0.28–0.80, 7 studies, 7492 infants).⁵⁴

Erythropoietin may be protective for endothelial cell barriers and, thus, may mitigate the development of NEC. A meta-analysis of RCTs of early (< 8 days after birth) erythropoiesis-stimulating agents used to modify transfusion exposure in very low birth weight infants demonstrated a decrease in NEC risk in those infants receiving the intervention (RR 0.69, 95% CI 0.52–0.91, 15 studies, 2639 infants).⁵⁵

Total fluid goals for premature infants are influenced by multiple factors but a restricted approach may decrease NEC risk. In a meta-analysis of RCTs, restricted versus liberal fluid intake reduced the risk of NEC in infants < 2000 g (RR 0.43, 95% CI 0.21–0.87, 4 studies, 526 infants).⁵⁶ An multicenter observational study found that centers more likely to restrict fluids also had the lowest NEC incidence.²⁰

Caffeine and postnatal corticosteroids are common treatments for respiratory morbidity. A large randomized trial found caffeine is not a risk factor for NEC⁵⁷; current studies examining early versus later caffeine use also report no difference in NEC.⁵⁸ A meta-analysis of timing of postnatal corticosteroids, dosing regimens, and methods suggest postnatal steroid use is not a risk factor for NEC.⁵⁹

c. NEC-specific treatments

Several RCTs have reported on the effects of oral lactoferrin, a naturally occurring glycoprotein with antimicrobial and immunomodulatory properties. A meta-analysis of 4 RCTs found a protective effect of oral lactoferrin over placebo or no intervention (RR 0.40, 95% CI 0.18–0.86, 4 studies, 750 infants).⁶⁰ Similar results were seen when oral lactoferrin was combined with probiotics.⁶⁰

Specific amino acid supplementation has been proposed to alter NEC incidence. Nitric oxide is thought to play a role in gut perfusion and motility; arginine may alter nitric oxide metabolism. Meta-analysis of small trials demonstrate that oral or parenteral supplementation with arginine decreases the risk for any stage of NEC (RR 0.38, 95% CI 0.23–0.64, 3 studies, 285 infants) and death due to NEC (RR 0.18, 94% CI 0.03–1.00).⁶¹

Rectal administration of osmotic agents is frequently used to prevent or treat feeding intolerance, lack of stooling or abdominal distention. Their prophylactic use does not appear to impact NEC risk. In a meta-analysis of 6 studies using different forms of meconium evacuation strategies, there was no effect on NEC (RR 1.71, 95% CI 0.63–4.65, 6 studies, 442 infants) but there was a trend towards increasing risk with oral gastrographin administration (RR 2.61, 95% CI 0.88–7.74, 1 study, 96 infants).⁶² A review of only glycerin laxative enemas or suppositories showed no effect on NEC (RR 2.75, 95% CI 0.58–13.1, 2 studies 96 infants), although the point estimate suggested a greater probability of harm than benefit in the risk of NEC with use of glycerin.⁶³

G. Feeding

Breastfeeding has been consistently shown to decrease the risk of NEC.⁶⁴ When maternal breast milk is unavailable, preterm formula, compared to donor breast milk, increases the risk of NEC (RR 2.61, 95% CI 1.27–5.35, 5 studies, 802 infants),⁶⁵ but this meta-analysis only contains 1 trial (173 infants) using fortified donor milk. A recent RCT of supplemental fortified donor human milk versus preterm formula found a decreased risk of NEC (all stages and II) in the donor milk group (Risk difference: –7.1, 95% CI –12.5 to –1.8 and risk difference: –4.9, 95% CI –9.0 to –0.9, respectively, 361 infants).⁶⁶ Bovine product exposure among human milk fed infants may be associated with a small increased risk of NEC.³⁴ At this time, there is no data on oropharyngeal colostrum administration and the risk of NEC.

Clinical instability and concerns for immature gut motility often lead to a delay in enteral feeding. Meta-analysis has shown that delayed feeding in infants <1500 g or <32 weeks does not alter NEC risk (RR 0.93, 95% CI 0.64–1.34, 8 studies, 1092 infants), including among IUGR infants with abnormal umbilical Doppler flow velocities (RR 0.87, 95% CI 0.54–1.41).⁶⁷ The studies included in the meta-analysis had few extremely low birth weight or extremely preterm infants and planned subgroup analysis of this cohort was not performed. Therefore, the best feeding strategy for the most immature infants remains unclear. Studies have incompletely examined trophic feeding versus enteral fasting in the extremely low birth weight infant, but meta-analysis of infants <1500 g suggests there is no increased risk of NEC with trophic feeds (RR 1.07, 95% CI 0.67–1.70).⁶⁸ Once feeds are initiated, there is no

difference in NEC risk for infants advanced at a slow rate (10–20 ml/kg/day) versus a faster rate (30–40 ml/kg/day).⁴³ This finding is consistent in multiple subgroup analysis including groups of extremely low birth weight or extremely preterm infants, SGA or IUGR infants, infants with absent or reversed end diastolic flow, infants fed mostly formula, and infants fed partially human milk.⁴³

Standardized feeding regimens have been associated with a reduction in risk of NEC. A 2017 systematic review of observational studies found an 80% reduction in relative risk of NEC when comparing standardized feedings with non-standardized feedings (RR 0.22, 95% CI 0.13–0.36, 15 studies, 18,160 infants). This benefit persisted in analysis limited to recent years (RR 0.26, 95% CI 0.19–0.35, 9 studies, 9456 infants).⁶⁹ Feeding regimens have varied in approaches, although all recommend breastfeeding. Approaches to feeding during transfusions have been discussed previously.

There have been numerous studies of the role of probiotics in decreasing the risk of NEC. While questions remain about optimal strain, dose, duration, and product quality, meta-analyses have shown consistent results on the effect of probiotics in decreasing the risk of NEC.⁷⁰ Further knowledge and understanding of the premature infant's microbiome may help target probiotic-like therapies. A meta-analysis of stool microbiome profiles in premature infants revealed a relative increase in *Proteobacteria* and a relative decrease in *Firmicutes* and *Bacteroidetes* in NEC cases compared to controls.⁷¹

While the administration of probiotics decreases the risk of NEC, enteral administration of medications that promote acid suppression have the opposite effect. Pooled analysis from two observational trials, one case-control and one prospective, shows a significant increased risk of NEC with acid-suppression medications (OR 1.78, 95% CI 1.4–2.27, 2 studies, 11,346 infants).⁷²

H. Risk factor scoring tools

NEC risk factor scoring tools have been developed to identify at-risk infants. GutCheck^{NEC} was developed with evidence review, international expert consensus, and statistical modeling; it has been validated with existing multi-institutional data.^{5,38} Unit NEC rate is the most heavily weighted variable when determining risk status (accounting for 9 to 23 of 32 necessary points used to consider risk of NEC). eNEC uses similar inputs as GutCheck, was developed in a single institution setting, and was designed to be completed on admission and a weekly basis. It has been studied for feasibility but not yet for outcomes.⁷³

NeoNEEDS differs from both the previous tools as it determines a risk status based on the infant's current clinical condition in 5 domains (behavior, cardiovascular, respiratory, abdominal and feeding) combined with gestational age or birth weight and exposure to formula.⁷⁴ It has significantly fewer inputs than the other models and was designed as part of a quality improvement project to be completed daily during care team rounds. An at-risk score triggers the clinician to consider ordering an abdominal x-ray. NEC severity rates decreased during the study period at a single site using this tool.⁷⁴

Summary

There are a number of factors associated with the risk of NEC reported in the literature. The interaction between these factors, the role of center, and the effect of residual confounding limit the interpretation of causality and the role of these factors for any given infant's risk of NEC. Despite this, this review found many potentially modifiable risk factors that could be targets of research and quality improvement efforts. In addition, the summary of risk factors may be useful to ensure appropriate measurement and assessment of factors in clinical studies.

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Practice Points

- Factors that increase or decrease the risk of NEC may be present prior to birth through the postnatal course.
- Studies of NEC should consider measurement of important risk factors to ensure appropriate balance of covariates in randomized trials or assessment of confounding in observational studies.
- Additional studies are needed to determine the interaction between risk factors and the influence of center.
- The causal structure of a variable's relationship to NEC is important to consider when determining whether a specific risk factor causes NEC.

Table 1

Summary of Risk factors for NEC

Factor		Relationship to NEC	OBS	RCT
Maternal and Antenatal	Black Race	↑	X	
	Maternal hypertension	~	X	X
	Pre-eclampsia	↑	X	
	ANS	↓		X
	Maternal progesterone	↓		X
	Tocolytics	~	X	X
	Magnesium Sulfate	–		X
	Maternal infection	↑	X	
	PROM	↑	X	
	Maternal Antibiotics	↓/~	X	X
	Placental Abruption	↑	X	
	IUGR	↑	X	
Infant Baseline and Delivery	Cesarean Delivery	~	X	X
	Delayed Cord Clamping	–		X
	Younger Gestational Age	↑	X	
	Lower Birth Weight	↑	X	
	Small for Gestational Age	↑	X	
	Male sex	~	X	
Postnatal	Surfactant	↑/~	X	X
	Lower O2 target	↑		X
	Umbilical Catheters	~	X	X
	PDA	↑/~	X	X
	Sepsis	↑	X	

Factor		Relationship to NEC	OBS	RCT
	Empiric Antibiotics	↑/~	X	X
	Severity of anemia	↑/~	X	X
	RBC transfusion	~	X	X
	EPO	↓		X
	Fluid restriction	↓	X	X
	Oral lactoferrin	↓		X
	Arginine supplementation	↓		X
	Glycerin enemas/suppositories	~		X
Feeding	Breast Milk	↓	X	X
	Preterm Formula	↑	X	X
	Donor Milk	↓	X	X
	Delayed feeding	–		X
	Trophic feeding	–		X
	Slow feeding	–		X
	Feeding Protocol	↓	X	
	Probiotics	↓	X	X
	Acid suppression	↑	X	

Assessment of risk factors based on studies identified in search strategy. Please refer to text for additional details. ↑ indicates factor associated with increased risk of NEC; ↓ notes factor associated with decreased risk of NEC; – notes no evidence of effect on risk of NEC; ~ notes indeterminate effect on risk of NEC. If multiple symbols present, indicates conflicting data from OBS and RCT (OBS/RCT). Abbreviations: OBS, observational study; RCT, randomized controlled trial. ANS, antenatal steroids; PROM, prolonged rupture of membranes; IUGR, intrauterine growth restriction; PDA, patent ductus arteriosus; RBC, red blood cell; EPO, erythropoietin.