A.S.P.E.N. Clinical Guidelines : Nutrition Support of Neonatal Patients at Risk for Necrotizing Enterocolitis

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Abstract

Background: Necrotizing enterocolitis (NEC) is one of the most devastating diseases in the neonatal population, with extremely low birth weight and extremely preterm infants at greatest risk. *Method*: A systematic review of the best available evidence to answer a series of questions regarding nutrition support of neonates at risk of NEC was undertaken and evaluated using concepts adopted from the Grading of Recommendations, Assessment, Development and Evaluation working group. A consensus process was used to develop the clinical guideline recommendations prior to external and internal review and approval by the A.S.P.E.N. Board of Directors. *Results/Conclusions*: (1) When and how should feeds be started in infants at high risk for NEC? We suggest that minimal enteral nutrition be initiated within the first 2 days of life and advanced by 30 mL/kg/d in infants ≥1000g. (Weak) (2) Does the provision of mother's milk reduce the risk of developing NEC? We suggest the exclusive use of mother's milk rather than bovine-based products or formula in infants at risk for NEC. (Weak) (3) Do probiotics reduce the risk of developing NEC? There are insufficient data to recommend the use of probiotics in infants at risk for NEC. (Further research needed.) (4) Do nutrients either prevent or predispose to the development of NEC? We do not recommend glutamine supplementation for infants at risk for NEC (Strong). There is insufficient evidence to recommend arginine and/or long chain polyunsaturated fatty acid supplementation for infants at risk for NEC. (Further research needed.) (5) When should feeds be reintroduced to infants with NEC? There are insufficient data to make a recommendation regarding time to reintroduce feedings to infants after NEC. (Further research needed.) (*JPEN J Parenter Enteral Nutr*. 2012;36:506-523)

Keywords

neonates; outcomes research/quality; parenteral nutrition

Background

Necrotizing enterocolitis (NEC) is one of the most devastating diseases in the neonatal population, with extremely low birth weight (ELBW) and extremely preterm infants at greatest risk.[1-3] Data from large, multicenter, neonatal network databases from the United States and Canada report a mean prevalence of 7% in infants weighing <1500 g[1,4,5] and an estimated mortality of 15%–30%,[6-8] resulting in an estimated total cost up to $1 billion annually in the United States alone.[9] NEC is classified into clinical stages (I, II, and III) based on the severity of disease, as proposed by Bell et al in 1978,[10] which were then modified (IA, IB, IIA, IIB, IIIA, IIIB) to include systemic, intestinal, and radiologic signs by Walsh and Kliegman in 1986.[11] Although the etiology remains undefined, multiple risk factors imply a multifactorial etiology. As gastrointestinal integrity and function are compromised in NEC, it is without question that nutrition considerations are important in the prevention and management of this disease. These clinical guidelines will address enteral nutrition practices, probiotic administration, and nutrient supplementation in patients at risk for and/or diagnosed with NEC.

Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization comprising healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of nutrition support therapy and metabolism. A.S.P.E.N. works vigorously to support quality patient care, education, and research in the fields of nutrition and metabolic

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Table 1. Nutrition Support Guideline Recommendations for Neonatal Patients at Risk for Necrotizing Enterocolitis

Question	Recommendation	Grade
When and how should feeds be started in infants at high risk for NEC?	We suggest that minimal enteral nutrition should be initiated within the first 2 days of life and advanced by 30 mL/kg/d in infants ≥1000 g.	Weak
Does the provision of mother's milk reduce the risk of developing NEC relative to bovine-based products or formula?	We suggest the exclusive use of mother's milk rather than bovine-based products or formula in infants at risk for NEC.	Weak
Do probiotics reduce the risk of developing NEC?	There are insufficient data to recommend the use of probiotics in infants at risk for NEC.	Further research needed
Do certain nutrients either prevent or predispose to the development of NEC?	We do not recommend glutamine supplementation for infants at risk for NEC.	Strong
	There is insufficient evidence at this time to recommend arginine and/or long-chain polyunsaturated fatty acid supplementation for infants at risk for NEC.	Further research needed
When should feeds be reintroduced to infants with NEC?	There are insufficient data to make a recommendation regarding time to reintroduce feedings to infants after NEC.	Further research needed

Abbreviation: NEC, necrotizing enterocolitis.

support in all healthcare settings. These Clinical Guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing Clinical Guidelines since 1986.[12-23] The A.S.P.E.N. Clinical Guidelines editorial board evaluates in an ongoing process when individual Clinical Guidelines should be updated.

These A.S.P.E.N. Clinical Guidelines are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, the practitioner must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

A.S.P.E.N. has adopted concepts of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (http://www.gradeworkinggroup.org) for development of its clinical guidelines. The GRADE working group combined the efforts of evidence analysis methodologists and clinical guidelines developers from diverse backgrounds and health organizations to develop an evaluation system that would provide a transparent process for evaluating the best available evidence and integration of the evidence with clinical knowledge and consideration of patient priorities. These procedures provide added transparency by developing separate grades for the body of evidence and for the recommendation. The procedures listed below were adopted from the GRADE process for use with A.S.P.E.N. Clinical Guidelines with consideration of the levels of review (by internal and external content reviewers, by the A.S.P.E.N. Board of Directors).

A rigorous literature search is undertaken to locate clinical outcomes associated with practice decisions in the population of interest. Each pertinent paper is appraised for evidence quality according to research quality (randomization, blinding, attrition, sample size, and risk of bias for clinical trials[24] and prospective vs retrospective observation, sample size, and potential bias for observational studies) and placed into an evidence table. A second table is used to provide an overview of the strength of the available evidence according to the clinical outcomes, in order to support a consensus decision regarding the guideline recommendation. If the evidence quality is high, it is unlikely that further research will change our confidence in the estimate of effect. With moderate grade evidence, further research is likely to modify the confidence in the effect estimate and may change the estimate. With low grade evidence, further research is very likely to change the estimate, and with very low evidence quality, the estimate of the effect is very uncertain. A clinical recommendation is then developed by consensus of the Clinical Guidelines authors, based on the best available evidence. The risks and benefits to the patient are weighed in light of the available evidence. Conditional language is used for weak recommendations. For further details on the A.S.P.E.N. application of GRADE, see the "Clinical Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients: Applying the GRADE System to Development of A.S.P.E.N. Clinical Guidelines."[24]

For the current Clinical Guideline, the search term *necrotizing enterocolitis* was used in PubMed with inclusion criteria including infants (birth to 23 months); humans; clinical trial; randomized controlled trial; case reports; clinical trial: phase I, phase II, phase III, phase IV; comparative study; controlled clinical trial; guideline; journal article; multicenter study; English language; and published within the last 10 years. The search was conducted on April 21, 2011. The questions are summarized in Table 1. For questions 1 and 3, an additional limitation of randomized controlled trial was implemented due to the plethora of literature on these topics. For questions 2, 4, and 5, pertinent literature within the past 10 years, without restriction to evidence type, was included. A total of 1335 abstracts were reviewed, of which 24 papers met the inclusion criteria of the Clinical Guidelines and were included.

Practice Guidelines and Rationales

Question 1: When and how should feeds be started in infants at high risk for NEC (Tables 2 and 3)?

Recommendation: We suggest that minimal enteral nutrition be initiated within the first 2 days of life and advanced by 30 mL/kg/d in infants ≥1000 g.

Grade: Weak

Rationale: Several randomized controlled trials (RCTs) have been conducted to gain insight into the optimal time of initiation and rate of advancement of enteral nutrition in infants at risk for NEC. Of the studies reviewed, 2 of 10[25,26] evaluated NEC (Bell's stage ≥II) as the primary outcome, whereas the remaining studies predominantly evaluated feeding tolerance and/or time to achievement of full enteral nutrition with NEC as a secondary outcome measure. With regard to the timing of initiation of EN, one RCT[25] evaluated the effect of early (≤5 days; median 2 days) vs delayed (≥6 days; median 7 days) initiation of minimal enteral feeding (MEF) in infants with an age-adjusted birth weight (BW) ≤10th percentile and intrauterine growth restriction (IUGR). No difference in the incidence of NEC between groups was found, although it was concluded that a larger sample size would be needed to adequately evaluate for an effect. Two RCTs[27,28] evaluated the effect of MEF vs nil per os (NPO) status within the first week of life with feeds beginning at a median age of 2 days in <1000-g and <2000-g infants, respectively, and found no significant differences in the incidence of NEC. For these studies, the quantity associated with MEF was ≤12 mL/kg/d.

Three RCTs[29-31] evaluated the effect of slow (15–20 mL/kg/d) vs rapid (30 mL/kg/d) enteral nutrition advancement to a goal rate of between 150 and 180 mL/kg/d and found that rapid advancement was well tolerated by infants with an average BW 1000–2000 g without an increased incidence of NEC. In these studies, enteral nutrition was initiated at a median age of 6 hours[29] or 2 days.[30,31] However, these studies were not powered to detect statistically significant differences in the incidence of NEC. In addition, it is important to note that hemodynamic instability can impact feeding practices, and thus, discretion should be employed under these circumstances. Last, one RCT[26] evaluated the effect of stable (20 mL/kg/d) vs advancing (20 mL/kg/d to goal 140 mL/kg/d) feeding volumes for a 10-day period following the initiation of enteral nutrition and found a significantly higher incidence of NEC in infants fed advancing volumes. Due to the high incidence of NEC in the advancing group (10% vs 1.4%), the study was prematurely terminated. It is important to recognize that a major difference in this study compared with the previous RCTs[29-31] is that enteral nutrition was initiated later in life, the timing of which was at the discretion of the neonatologist. Specifically, the earliest age of feed initiation was 4 days with a median age of 9.5 days in infants who developed NEC and 11 days for infants in the advancing group who developed NEC. This is a potentially important confounding variable, making the interpretation of these study results complicated and to be taken with caution.

Although the majority of these aforementioned studies have recommended larger, multicentered prospective trials to further evaluate questions on enteral nutrition initiation and advancement, based on the available data, early MEF within the first 2 days of life and advancement at 30 mL/kg/d in infants ≥1000 g can be suggested.

Question 2: Does the provision of mother's milk reduce the risk of developing NEC relative to bovine-based products or formula (Tables 4 and 5)?

Recommendation: We suggest the exclusive use of mother's milk rather than bovine-based products or formula in infants at risk for NEC

Grade: Weak

Rationale: The type of enteral nutrition administered to an infant at risk for NEC is important. Several studies have focused on whether the administration of human milk results in a reduction in the incidence of NEC compared with formula feeding. These studies used mother's milk (MM) with the exception of one,[32] which fed infants pasteurized donor milk (DM) if MM was unavailable. Exclusive feeding with MM is associated with a decreased risk of NEC as compared with preterm formula (PF).[33] As a substitute for MM, pasteurized DM has not been found to have any protective effect over PF with regard to the incidence of NEC,[34] but feeding with MM and/or DM has been found to be associated with a decreased risk of NEC as compared with a combination of MM and/or DM and bovine milk (BOV)–based products.[32] It is important to note that the source of enteral nutrition was explicitly evaluated; supplementation with milk fortifier was not evaluated. With respect to the quantity of MM administered, one prospective cohort study[35] found enteral nutrition with ≥50% MM within the first 14 days was associated with a 6-fold decreased risk of NEC. An observational study[36] found the amount of daily MM (1 to ≥50 mL/kg/d) fed through week 4 of life had no effect on the incidence of NEC. Based on the available data, exclusively fed MM has been shown to be beneficial in the prevention of

NEC and is therefore recommended over formula feeding. It is unclear whether the amount and/or timing of MM administered have an effect on the incidence of NEC, and therefore no recommendation regarding the optimal dose of MM can be made.

Question 3: Do probiotics reduce the risk of developing NEC (Tables 6 and 7)?

Recommendation: There are insufficient data to recommend the use of probiotics in infants at risk for NEC.

Grade: Further research needed

Rationale: There has been much debate over the administration of oral probiotics in the prevention of NEC. Seven RCTs evaluating the use of prophylactic probiotics in preterm and very low birth weight (VLBW) infants met inclusion criteria for these guidelines. NEC, defined as Bell's stage ≥II, was the primary end point in 6 of 7 studies.[37-42] The type of bacteria, dosage, frequency, and duration of treatment varied widely across studies. One study evaluated the effect of a probiotic with MM vs MM alone,[40] whereas 2 studies evaluated the effect of a probiotic with human milk (HM; MM or DM) vs HM alone,[37,42] and 3 studies evaluated the effect of a probiotic with MM or formula vs MM or formula alone.[39,41,43] One study[38] specifically compared the effect of killed probiotic (KP) vs living probiotic (LP) *Lactobacillus acidophilus* on the incidence of NEC and found no difference in the incidence of NEC between groups; LP and KP were both found to be preventative against NEC in comparison to a placebo group, with KP retaining similar benefits to live bacteria with no adverse effect. All 7 RCTs demonstrated a lower incidence of NEC in the group of infants who received probiotics as compared with those who did not receive probiotics, although 1 of 7 studies[43] did not demonstrate statistical significance between groups. Although the implementation of a "probiotic" resulted in a lower incidence of NEC across studies, it is important to emphasize that these studies used different types of probiotics, with some administering a combination of probiotics.[37,39-42] It is additionally important to mention that there is no Food and Drug Administration (FDA) approval to date for routine use of these products. Further studies are necessary to determine the most effective type(s) of probiotic, dosage, and duration of treatment; thus, no recommendation on the use of probiotics in infants at risk for NEC can be made at this time.

Question 4: Do certain nutrients either prevent or predispose to the development of NEC (Tables 8 and 9)?

Recommendation: We do not recommend glutamine supplementation for infants at risk for NEC. There is insufficient evidence at this time to recommend arginine and/or long-chain polyunsaturated fatty acid supplementation for infants at risk for NEC.

Grade: Strong (glutamine); further research needed (arginine, long-chain polyunsaturated fatty acids)

Rationale: A review of the literature suggests that certain nutrients may reduce the incidence of NEC, whereas others may actually predispose infants to NEC. With respect to amino acids (AA), recent literature has focused on the effect of arginine and glutamine supplementation on the incidence of NEC. The plasma arginine and asymmetric dimethylarginine (ADMA, a metabolic by-product of protein modification processes) concentrations as well as the arginine:ADMA ratio have been found to be lower in premature infants with NEC, which have subsequently been shown to be associated with an increased mortality.[44] Although there is not an abundance of literature, one RCT[45] focuses on the effect of prophylactic L-arginine supplementation (1.5 mmol/kg/d), the results of which suggest that supplementation may be effective in reducing the overall incidence of NEC. Of note, the results of this study must be taken with caution as the sample size was small and results demonstrated no difference in the reduction of Bell's stage ≥II. Glutamine supplementation has additionally been evaluated in one large, well-conducted RCT, and no statistically significant difference in the incidence of NEC between supplemented and nonsupplemented groups was found.[46] Apart from individual amino acid supplementation, the administration of AA in parenteral nutrition (PN) has additionally been studied. In a comparative pre- and postintervention study,[47] early AA administration was associated with an increased incidence of surgical NEC in VLBW infants. Last, fatty acid supplementation was evaluated in one RCT[48]; this study demonstrated a slightly increased incidence of NEC (5.3% vs 2%) in long-chain polyunsaturated fatty acid (LCPUFA)–supplemented (fat mixture containing linoleic, α-linolenic, and γ-linolenic acids) compared with nonsupplemented infants, although the difference between groups was not statistically significant. Based on the aforementioned studies, there is limited research on AA/fatty acid administration and supplementation, and it remains an important area for future research. However, based on the available literature, arginine supplementation may be effective, although the evidence is underpowered, whereas glutamine supplementation does not appear to prevent NEC, and LCPUFA supplementation may predispose infants to NEC. Therefore, although glutamine supplementation is not recommended for infants at risk for NEC, there is insufficient evidence to recommend arginine and/or LCPUFA supplementation at this time.

Question 5: When should feeds be reintroduced to infants with NEC (Tables 10 and 11)?

Recommendation: There are insufficient data to make a recommendation regarding time to reintroduce feedings to infants after NEC.

Grade: Further research needed

Rationale: There is no standard recommendation as to when enteral nutrition should be reinitiated after a definitive diagnosis of NEC. Historically, it has been suggested that

a period of fasting from 10 days to 3 weeks should be observed prior to the reintroduction of enteral nutrition for an infant with NEC; however, these recommendations are not founded on scientific data. It is without question that practices vary greatly among institutions and physicians. It has been suggested that prolonged fasting may actually be detrimental due to the potential need for prolonged central venous access and PN, and has prompted some institutions to introduce early feeding regimens in infants with NEC. To date, the literature on the impact of early feeding regimens is limited. In fact, only 2 retrospective reviews met the inclusion criteria for these guidelines. Both of these studies suggest that, for infants with Bell's stage II NEC, early feeding regimens may actually have potential beneficial effects, including a reduced incidence of catheter-related sepsis and post-NEC intestinal stricture formation as well as shorter time to full enteral nutrition and shorter hospitalization. It is important to note that both studies have serious limitations given their retrospective nature, and both are underpowered to assess the impact of early enteral nutrition on NEC recurrence, a very important outcome variable. Although these studies suggest that prolonged fasting periods traditionally recommended for infants with NEC may not be necessary, further prospective and randomized controlled trials are necessary before recommendations can be made as to when feeds should be reintroduced in infants with NEC.

(Text continues on p. 522.)

Table 2. Evidence Table Question 1: When and how should feeds be started in infants at high risk for NEC?

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Krishnamurthy,[29] 2010	RCT Nonblinded to intervention (investigators) Rate of attrition: 10/100	Preterm infants <34 weeks GA with BW 1000–1499 g, born 2/2008 to 9/2008, and followed until they had regained BW or developed NEC Tertiary care hospital (India) N = 100 (n = 50/group)	To evaluate the effect of slow (20 mL/kg/d) vs rapid (30 mL/kg/d) enteral nutrition advancement by nasogastric bolus on the time to achievement of full enteral nutrition (180 mL/kg/d) *Primary outcome:* Time to attainment of full enteral nutrition *Secondary outcome:* Incidence of feeding intolerance, NEC (Bell's stage ≥IIA), mortality, apnea, duration of hospital stay/ intravenous fluids, weight gain, and nosocomial sepsis	*Incidence of NEC:* 2% (1/50) in the slow-feeding advancement group and 4% (2/50) in the rapid-feeding advancement group (P = 1.0)	Rapid enteral nutrition advancement of 30 mL/kg/d is well tolerated without an increased incidence of NEC in stable preterm neonates weighing 1000–1499 g. There was no statistically significant difference in mortality between groups. The study was not powered to detect clinical or statistical differences in the incidence of NEC as NEC was not the primary outcome.
Karagianni,[25] 2010	RCT Nonblinded Pilot study Rate of attrition: 3/84	Preterm infants 27–34 weeks GA with age-adjusted BW ≤10th percentile (IUGR), Apgar score >5, and arterial cord blood pH ≥7.0 with abnormal antenatal Doppler results, admitted between 5/2004 and 5/2008 Level III NICU (Greece) N = 84 (n = 42/group)	To examine the effect of early (≤5 days) vs delayed (≥6 days) initiation of MEF on the incidence of NEC and feeding intolerance *Primary outcomes:* Incidence of NEC (Bell's stage ≥II) and feeding intolerance *Secondary outcome:* Mortality	*Incidence of NEC:* 15% (6/40) in the early MEF group and 9.8% (4/41) in the delayed MEF group (RR = 1.54 early MEF; 95% CI 0.469–5.043)	Early MEF for preterm infants with IUGR and abnormal antenatal Doppler results does not significantly impact the incidence of NEC. Mortality was not significantly different between groups (P = .512).
Mosqueda,[27] 2008	RCT Nonblinded Pilot study Rate of attrition: 23/84	ELBW infants (BW ≤1000 g), admitted between 1/2001 and 8/2003. Infants were separated into MEF and NPO groups from DOL 2–7. On DOL 8, all infants received bolus feedings (20 mL/kg/d) and were followed until 1 week after achievement of full enteral nutrition (150 mL/kg/d). Single-center NICU (Illinois, USA) N = 84 (n = 41 MEF group, n = 43 NPO group)	To evaluate the efficacy of early MEF (12 mL/kg/d) on overall feeding tolerance in infants from DOL 2–7 *Primary outcome:* Feeding tolerance *Secondary outcomes:* Incidence of NEC, sepsis, mortality, intraventricular hemorrhage, length of hospital stay	*Incidence of NEC:* 9% (3/33) in the MEF group and 14% (4/28) in the NPO group (P = .53) Mortality was 17% in the MEF group and 26% in the NPO group (P = .34); infants who expired were excluded from the analysis.	There was no difference in the incidence of NEC between MEF and NPO groups. Based on the incidence of NEC and mortality in this study, a sample size of 191 infants per group would be needed for an appropriately powered study.

(continued)

Table 2. (continued)

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Caple,[30] 2004	RCT Nonblinded Rate of attrition: 5/160 Intention-to-treat analysis	Infants ≤35 week GA with BW 1000–2000 g, admitted between 1994 and 1995, and followed until hospital discharge or the development of NEC Single-center level II and III NICU at community-based county hospital (Texas, USA) N = 155 (n = 72 rapid group, n = 83 slow group)	To determine whether infants fed initially and advanced at 30 mL/kg/d achieve full enteral nutrition sooner than infants fed initially and advanced at 20 mL/kg/d (goal 150 mL/kg/d) *Primary outcome:* Time to achievement of full enteral nutrition *Secondary outcomes:* Incidence of NEC (Bell's stage ≥II) and feeding complications, length of hospital stay, duration of intravenous fluid, weight gain	*Incidence of NEC:* 4.2% (3/72) in the rapid-advancement group and 2.4% (2/83) in the slow-advancement group; *P* value not given 3.2% overall incidence of NEC (RR, 1.73; 95% CI, 0.30–10.06; *P* = .66) for infants enrolled in study; 4.1% in preterm infants (1000–2000 g) during the same period not enrolled in the study	Advancement of feeds at 30 mL/kg/d is as safe as 20 mL/kg/d with a comparable incidence of NEC between groups. No information on mortality reported Authors recommend a large, multicenter prospective trial to evaluate ways of optimizing enteral nutrition without increasing morbidity.
van Elburg,[28] 2004	RCT Nonblinded Rate of attrition: 14/56	Preterm infants <37 weeks GA with BW <2000 g and BW for GA <10th percentile (IUGR), admitted from 1/1998 to 11/2000, enrolled within 48 hours of birth and followed for 5 days Single-center NICU in tertiary care referral center (Netherlands) N = 56 (n = 28 MEF group, n = 28 NPO group)	To evaluate the effect of MEF (12 × 0.5 mL daily if BW <1000 g or 12 × 1 mL daily if BW >1000 g) on intestinal permeability and feeding tolerance *Primary outcome:* Functional integrity of the small bowel *Secondary outcomes:* Feeding tolerance, growth, and incidence of NEC (Bell's stage ≥II)	*Incidence of NEC:* 0% (0/20) in the MEF and 4.5% (1/22) in the NPO group (*P* = .76)	MEF of preterm infants with IUGR had no effect on the development of NEC. No significant difference in mortality between groups However, a larger sample size is needed to draw definitive conclusions on the effect of MEF on measures of clinical outcome.
Salhotra,[31] 2004	RCT Nonblinded Rate of attrition: 19/53	Infants with BW <1250 g subject to gastrointestinal priming (5 mL/kg/d) via intermittent nasogastric tube bolus, on DOL 1–2, then randomized at 48 hours of life Tertiary-level teaching hospital (India) N = 53 (n = 27 fast group, n = 26 slow group)	To evaluate the tolerance of rapid (30 mL/kg/d) vs slow (15 mL/kg/d) advancement of enteral nutrition to goal of 180 mL/kg/d *Primary outcome:* Time to achieve full enteral nutrition *Secondary outcomes:* Incidence of NEC (Bell's stage ≥II) and apnea	*Incidence of NEC:* 7.4% (2/27) in the rapid-advancement group and 0% (0/26) in the slow-advancement group; no *P* value given *NEC-related mortality:* There were 2 cases of NEC (DOL 6 and 8), both in the fast group, and those infants died with associated septicemia.	Stable VLBW infants appear to tolerate rapid advancements of enteral nutrition without an increased risk of NEC. There was no significant difference in mortality between groups. Of note, of infants randomized to the fast group, 74% completed the trial vs 53.8% in the slow group. The small sample size precludes any firm conclusion on the risk of NEC.

(continued)

Table 2. (continued)

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Berseth,[26] 2003	RCT Nonblinded Rate of attrition: 3/144	Infants <32 weeks appropriate for GA, with feeds begun at the discretion of the neonatologist, and admitted between 1/1996 and 1/2000 Single-center NICU (Texas, USA) N = 141 (n = 70 advancing group, n = 71 control group)	To compare the risks and benefits of enteral nutrition advancement (20 mL/kg/d to goal 140 mL/kg/d) compared with stable feeding volumes (20 mL/kg/d) over a 10-day period *Primary outcome:* Incidence of NEC (Bell's stage ≥II) *Secondary outcomes:* Maturation of intestinal motor patterns, time to reach full enteral nutrition, incidence of late sepsis	*Incidence of NEC:* 10% (7/70) in the advancing group and 1.4% (1/71) in the control group (P = .03) The study was closed early due to the high incidence of NEC in the advancing group.	Higher risk for NEC in preterm infants when fed advancing feeding volumes compared with low/stable feeding volumes over a 10-day period Mortality was similar in both groups (4.2% vs 4.3%, P = .97). Mean age of enteral nutrition initiation was 13 days for the 7 infants in the advancing group who developed NEC. The 1 infant in the control group who developed NEC was fed at age 4 days. The age at feed initiation was only given for infants who developed NEC. Authors conclude that minimal feeding volumes should be evaluated until future trials further assess the safety of advancing feeding volumes.

BW, birth weight; CI, confidence interval; DOL, day of life; ELBW, extremely low birth weight; GA, gestational age; IUGR, intrauterine growth restriction; MEF, minimal enteral feeding; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NPO, nil per os; RCT, randomized controlled trial; RR, relative risk; VLBW, very low birth weight.

Table 3. GRADE Table Question 1: When and how should feeds be started in infants at high risk for NEC?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome	Overall Recommendation GRADE
Rapid vs slow enteral nutrition advancement[29-31]	Incidence of NEC	3 RCTs	No difference	Low	Weak
Early vs delayed minimal enteral feeding[25]	Incidence of NEC	1 RCT	No difference	Low	Weak
Minimal enteral feeding vs nil per os[27,28]	Incidence of NEC	2 RCTs	No difference	Low	Weak
Advancing vs low/stable feeding volume[26]	Incidence of NEC	1 RCT	Higher	Low	Weak

NEC, necrotizing enterocolitis; RCT, randomized controlled trial.

Table 4. Evidence Table Question 2: Does the provision of mother's milk reduce the risk of developing NEC relative to bovine-based products or formula?

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Sullivan,[32] 2010	RCT Nonblinded Rate of attrition: 31/207	Premature infants with BW 500–1250 g, fed HM (MM and/or DM) within the first 21 days after birth, followed until 91 days old, hospital discharge, or the achievement of 50% oral feeds (goal 160 mL/kg/d) Multicenter—12 NICUs (11 USA; 1 Austria) Total N = 207 (n = 71, 40 mL/kg/d, HM40 group; (HM40 mL/kg/d); n = 67, 100 mL/kg/d, HM100 group; (HM100 mL/kg/d); n = 69, bovine milk, BOV group)	To evaluate the health benefits of an exclusively HM-based diet (MM and/or DM) compared with a diet of both human and BOV-based products *Primary outcome:* PN duration *Secondary outcomes:* Incidence of NEC (Bell's stage ≥II), late-onset sepsis, growth, morbidity	*Incidence of NEC:* 7% (5/71) in the HM40 group, 4.5% (3/67) in the HM100 group, and 16% (11/69) in the BOV group ($P = .05$ between 3 groups) Fewer cases of NEC in the HM40 and HM100 groups, with $P = .09$ between HM40 and BOV groups, $P = 0.04$ between HM100 and BOV, and $P = .02$ between HM (40+100) and BOV groups For NEC cases requiring surgical intervention, $P = .03$ between the HM40 and HM100 groups independently compared with the BOV group and $P = .007$ for HM (100+40) compared with the BOV group Exclusive HM diet (OR 0.23, 95% CI 0.08-0.66, P=0.007)	The rates of NEC and NEC requiring surgery were markedly lower in the groups fed exclusively HM (MM and/or DM) compared with BOV-based products. 50% reduction in the incidence of NEC and almost 90% reduction in the incidence of surgical NEC in infants fed exclusive HM (MM and/or DM) vs BOV-based products Using exclusively HM-based diet, NNT to prevent 1 case of NEC is 10 and to prevent 1 case of surgical NEC or death is 8.
Schanler,[34] 2005	RCT Blinded to group assignment (caregivers) Rate of attrition: 8/243	Premature infants <30 weeks GA, stratified by GA and receipt of prenatal steroids, admitted between 8/1997 and 7/2001, and followed from birth to 90 days of age or hospital discharge Nurseries at Texas Children's Hospital (Texas) N = 243 (n = 70 MM only, n = 81 DM, n = 92 PF)	To determine the incidence of NEC in infants receiving pasteurized DM vs PF as a substitute for MM to achieve goal 160 mL/kg/d *Primary outcomes:* Incidence of NEC (Bell's stage ≥II) and late-onset sepsis *Secondary outcomes:* Duration of hospitalization, growth, mortality	*Incidence of NEC:* 6% (4/70) in the MM group, 6% (5/78) in the DM group, and 11% (10/88) in the PF group ($P = .39$ between MM and DM+PF and $P = .27$ between DM and PF)	As a substitute for MM, pasteurized DM offered no observed short-term advantage over PF for feeding premature infants. There was no significant difference in mortality between the groups.
Sisk,[35] 2007	OBS Prospective cohort study Rate of attrition: 3/202 Analysis of covariance and logistic regression analysis	Infants with BW 700–1500 g, born from 5/2001 to 8/2003, and followed during DOL 1–14. Infants were started on PN 1–2 days after birth if GA <30 weeks. Goal feeds were 100–120 mL/kg/d.	To determine if a high proportion of MM (HMM, ≥50% of enteral nutrition) protects against the development of NEC as compared with a low proportion of MM (LMM, <50% of enteral nutrition) within the first 14 days of life	*Incidence of NEC:* 3.2% (5/156) in the HMM group and 10.6% (5/46) in the LMM group (OR, 0.17; 95% CI, 0.04–0.68; $P = .01$ after adjustment for GA) The overall incidence of NEC negatively correlated with the proportion of MM fed in the first 14 days of life (OR, 0.62; CI, 0.51–0.77; $P = .02$) after adjustment for GA.	Enteral nutrition containing ≥50% MM within the first 14 days after birth is associated with a significant (6-fold) decreased risk of NEC. No difference in the incidence of surgical NEC or mortality between groups

(continued)

Table 4. (continued)

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	Study supported by International Lactation Consultant Association, University of North Carolina (Greensboro), and Wake Forest University School of Medicine	Level III obstetric referral center for women (North Carolina, USA) N = 202 (n = 156 HMM, n = 46 LMM)	*Primary outcome:* Incidence of NEC (Bell's stage ≥II) *Secondary outcomes:* Feeding tolerance, late-onset sepsis, chronic lung disease, retinopathy of prematurity	For every 25% increase in MM proportion, the odds of NEC decreased by 38%.	
Furman,[36] 2003	OBS Prospective Rate of attrition: not specified Regression analysis Supported by NIH grant M0100080 and University Hospitals of Cleveland Ohio	Infants <33 weeks GA with BW 600–1499 g, admitted between 1/1997 and 2/1999, followed through week 4 of life Urban tertiary care NICU (Ohio, USA) N = 119 (n = 40 group I: PF only; n = 29 group II: MM 1–24 mL/kg/d; n = 18 Group III: MM 25–49 mL/kg; n = 32 group IV: MM ≥50 mL/kg/d)	To evaluate the dose effect of MM compared with PF on neonatal morbidity *Primary outcome:* Neonatal morbidity *Secondary outcomes:* Incidence of NEC (Bell's stage ≥II), sepsis, length of hospital stay and ventilator dependence, retinopathy of prematurity, chronic lung disease	*Incidence of NEC:* 8% (3/40) group I (used as basis of comparison against groups II–IV), 7% (2/29) group II (OR, 1.15; 95% CI, 0.8–12.13), 11% (2/18) group III (OR, 1.99; CI, 0.14–21.03), 0% (0/32) group IV 0/32 (OR, 0; CI, 0–3.56)	The amount of MM administered does not affect the incidence of NEC in VLBW infants.
Lambert,[33] 2007	OBS Retrospective Rate of attrition: 12/30 Descriptive statistics	Infants >36 weeks GA, born from 2/2001 to 6/2006 Intermountain Healthcare NICUs (Utah, USA) N = 5877 (n = 30 with NEC)	To determine possible explanations for why patients develop NEC by comparison to age-matched patients without NEC *Primary outcome:* Incidence of NEC (Bell's stage ≥II) *Secondary outcomes:* Morbidity, feeding tolerance, length of hospital stay	*Incidence of NEC:* Overall incidence of 0.51% (30/5877) Patients with NEC more likely exclusively fed with PF (53%, 16/30) or PF+MM (43%, 13/30) vs exclusive MM (3%, 1/30); no *P* value *NEC-related mortality:* 13% mortality in infants with NEC	Formula feeding compared with exclusive MM feeding is one factor that may predispose infants to the development of NEC.

BOV, bovine milk; BW, birth weight; CI, confidence interval; DM, donor milk; DOL, day of life; GA, gestational age; HMM, high mother's milk; HM, human milk; LMM, low mother's milk; MM, mother's milk; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NIH, National Institutes of Health; NNT, number needed to treat; OBS, observational study; OR, odds ratio; PF, preterm formula; PN, parenteral nutrition; RCT, randomized controlled trial; VLBW, very low birth weight.

Table 5. GRADE Table Question 2: Does the provision of mother's milk reduce the risk of developing NEC relative to bovine-based products or formula?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome	Overall Recommendation GRADE
Human milk (mother's or donor) vs human milk (mother's or donor) + bovine-based products[32]	Incidence of NEC	1 RCT	Lower	Low	Weak
Donor milk vs preterm formula[34]	Incidence of NEC	1 RCT	No difference	Moderate	Weak
Mother's milk vs preterm formula[33]	Incidence of NEC	1 OBS	Lower	Low	Weak
Mother's milk ≥50% vs <50% from days of life 1–14[35]	Incidence of NEC	1 OBS	Lower	Low	Weak
Mother's milk high vs low dose (mL/kg/d)[36]	Incidence of NEC	1 OBS	No difference	Low	Weak

NEC, necrotizing enterocolitis; OBS, observational study; RCT, randomized controlled trial.

Table 6. Evidence Table Question 3: Do probiotics reduce the risk of developing NEC?

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Braga,[37] 2011	RCT Double blind Rate of attrition: 62/243	Preterm infants with BW 750–1499 g, with no congenital infections, fed MM or DM, and admitted 5/2007 to 4/2008 Randomized and started treatment on DOL 2, duration of treatment until DOL 30, NEC diagnosis, hospital discharge, or death Single-center NICU (Brazil) N = 231 (n = 119, probiotic group; n = 112, control group)	To assess whether oral supplementation of *Lactobacillus casei* and *Bifidobacterium breve* prevents the occurrence of NEC *Primary outcome:* NEC (Bell's stage ≥II)	*Incidence of NEC:* 0% (0/119) in the probiotic group and 3.6% (4/112) in the control group (*P* = .05)	Probiotic use decreased the incidence of NEC. No difference in mortality between groups Infants in the probiotic group reached full enteral nutrition faster than the control group (*P* = .02), suggesting that probiotics may play a role in intestinal motility. The study was interrupted by an external committee after 1 year, due to the significant differences found between groups.
Awad,[38] 2010	RCT Placebo control Double blind Rate of attrition: 25/150	Neonates 28–41 weeks GA with BW 1100–4300 g, with normal C-reactive protein and negative blood cultures, admitted from 1/2006 to 5/2007 on DOL 1 and followed until hospital discharge Single-center NICU (Egypt) N = 150 (n = 60 LP, n = 60 KP, n = 30 placebo)	To evaluate the use of the probiotic *Lactobacillus acidophilus* in the prevention of neonatal sepsis and NEC and to further investigate differences between LP and KP in comparison to placebo *Primary outcomes:* NEC (Bell's stage ≥II), sepsis	*Incidence of NEC:* 1.7% (1/60) in the LP group, 1.7% (1/60) in the KP group, and 16.7% (5/30) in the placebo group; P value not provided LP group (OR 0.53, 95% CI 0.16-1.74), KP group (OR 0.085; 95% CI 0.009-0.76), and placebo group (OR 3.4, 95% CI 2.44-4.72)	Decreased incidence of NEC in infants who received probiotics vs placebo. However, there was no difference in the incidence of NEC between LP and KP groups. LP and KP were preventative against NEC, whereas placebo was a risk factor for the development of NEC.

(continued)

Table 6. (continued)

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Mihatsch,[43] 2010	RCT Double-blinded Placebo controlled Rate of attrition: 20/183 Intention-to-treat analysis	VLBW infants <30 weeks GA with BW <1500 g, fed PF or MM, admitted 5/2000 to 8/2003 Single-center NICU, Children's Hospital (Germany) N = 180 (n = 91 probiotic group, n = 89 control group)	To investigate whether supplementation with the probiotic *Bifidobacterium lactis* for a duration of 6 weeks reduces the incidence of nosocomial infection *Primary outcome:* Nosocomial infection *Secondary outcome:* NEC (Bell's stage ≥II)	*Incidence of NEC:* 2.2% (2/91) in the probiotic group and 4.5% (4/89) in the control group (*P* = NS *NEC-related mortality:* 1.1% (1/91) in the probiotic group and 0% (0/89) in the control group, *P* = NS	No significant effect of *B lactis* on the incidence of NEC These study results emphasize the importance of an adequately powered trial to evaluate NEC as the primary outcome.
Samanta,[40] 2009	RCT Double-blinded Rate of attrition: 18/186	VLBW infants <32 weeks GA with BW <1500 g, having survived beyond DOL 2, fed exclusively MM, and admitted between 10/2007 and 3/2008 Single-center NICU (India) N = 186 (n = 91 probiotic group, n = 95 control group)	To evaluate the effect of probiotics (mixture of *Bifidobacteria bifidum, Bifidobacteria infantis, Bifidobacteria longum*, and *Lactobacillus acidophilus*) on feeding tolerance, the incidence/severity of NEC (Bell's stage ≥II), and mortality related to NEC or sepsis *Primary outcomes:* Feeding tolerance, length of hospitalization, morbidities (NEC, sepsis, and/or death due to NEC or sepsis)	*NEC incidence:* 5.5% (5/91) in the probiotic group and 15.8% (15/95) in the control group (*P* = .042) The severity of NEC was similar in both groups (*P* = .62). Mortality due to NEC or sepsis was lower in the probiotics group compared with the control group (4.4% vs 14.7%, respectively; *P* = .032).	Probiotics given to VLBW infants reduce the incidence of NEC.
Lin,[39] 2008	RCT Investigators at each center and the breast milk team not blinded but were not involved in the care of the study infants Multicenter Rate of attrition: 20/443	Infants <34 weeks GA with BW <1500 g, fed MM or PF, admitted between 4/2005 and 5/2007 Seven level III NICUs (Taiwan) N = 434 (n = 217 probiotic group, n = 217 control group)	To investigate the efficacy of oral probiotics, *Bifidobacterium bifidum* and *Lactobacillus acidophilus* (Infloran); 125 mg/kg/dose twice daily for 6 weeks in the prevention of NEC *Primary outcomes:* NEC (Bell's stage ≥II) and death *Secondary outcomes:* Culture-proven sepsis without NEC, chronic lung disease, periventricular leukomalacia, intraventricular hemorrhage, feeding amount and weight gain per week, days to full enteral nutrition	*Incidence of NEC:* 1.8% (4/217) in the probiotic group and 6.5% (14/217) in the control group (*P* = .02) *NEC-related mortality:* 0.9% (2/217) in the probiotic group and 1.4% (3/217) in the control group (*P* = .98)	The administration of probiotics to preterm VLBW infants reduced the incidence of NEC but did not affect NEC-related mortality. Based on study results, NNT to prevent 1 case of NEC was 20 patients.

(continued)

Table 6. (continued)

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Bin-Nun,[41] 2005	RCT Double-blind Placebo-controlled Rate of attrition: 11/145 Intention-to-treat analysis	Preterm neonates weighing ≤1500 g, recruited and enrolled when enteral nutrition (MM or PF) began, admitted from 9/2001 to 9/2004 and followed until 36 weeks post-conceptual age Single-center NICU (Israel) N = 145 (n = 72 probiotic group, n = 73 control group)	To investigate whether the daily provision of prophylactic probiotics (mixture of *Bifidobacteria infantis, Streptococcus thermophilus*, and *Bifidobacteria bifidus*) decreases the incidence and severity of NEC *Primary outcome:* NEC (Bell's stage ≥II) *Secondary outcomes:* Feeding tolerance, mortality, mortality related to NEC	*Incidence of NEC (all stages):* 4% (3/72) in the probiotic group and 16.4% (12/73) in the control group (RR, 0.25; 95% CI, 0.075–0.86) *Incidence of NEC (Bell's stage ≥II):* 1% (1/72) in the probiotic group and 14% (10/73) in control group (P = .013) *NEC-related mortality:* 0% (0/3) in the probiotic group and 25% (3/12) in the control group (P = .87)	Probiotic supplementation reduces the incidence and severity of NEC in preterm VLBW infants.
Lin,[42] 2005	RCT Investigators and breast milk team not blinded but were not involved in the care of the study infants Rate of attrition: 27/367 Logistic regression analysis	Infants <34 weeks GA and BW <1500 g, survived past DOL 7, fed MM or DM, admitted from 7/1999 to 12/2003, and followed until hospital discharge Single-center, level III NICU (Taiwan) N = 367 (n = 180 probiotic group, n = 187 control group)	To evaluate the effect of the probiotics *Lactobacillus acidophilus* and *Bifidobacterium infantis* (Infloran); 125 mg/kg/dose twice daily on the incidence and severity of NEC *Primary outcomes:* NEC (Bell's stage ≥II) and death *Secondary outcome:* Sepsis	*Incidence of NEC:* 1.1% (2/180) in the probiotic group and 5.3% (10/187) in the control group (P = .04) *Incidence of NEC (Bell's stage III):* 0% (0/2) in the probiotic group and 60% (6/10) in the control group (P = .03)	The administration of probiotics to preterm VLBW infants reduces the incidence and severity of NEC. Significant difference in mortality between the probiotic and control groups (3.9% vs 10.7%; P = .009) NNT to prevent 1 case of NEC is 27.

BW, birth weight; CI, confidence interval; DM, donor milk; DOL, day of life; GA, gestational age; KP, killed probiotic; LP, live probiotic; MM, mother's milk; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NNT, number needed to treat; NS, not significant; OR, odds ratio; PF, preterm formula; RCT, randomized controlled trial; RR, relative risk; VLBW, very low birth weight.

Table 7. GRADE Table Question 3: Do probiotics reduce the risk of developing NEC?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome	Overall Recommendation GRADE
Probiotic + human milk vs human milk[37,42]	Incidence of NEC	2 RCTs	Lower	High	Strong
Probiotic + mother's milk vs mother's milk[40]	Incidence of NEC	1 RCT	Lower	High	Strong
Probiotic + mother's milk or formula vs mother's milk or formula[39,41,43]	Incidence of NEC	2 RCTs 1 RCT	Lower No difference	Moderate	Strong
Probiotic vs placebo[38]	Incidence of NEC	1 RCT	Lower	Moderate	Strong

NEC, necrotizing enterocolitis; RCT, randomized controlled trial.

Table 8. Evidence Table Question 4: Do certain nutrients either prevent or predispose to the development of NEC?

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Poindexter,[46] 2004	RCT Double-blind Rate of attrition: 251/1432	ELBW infants 401–1000 g, stratified by BW (401–750 g and 751–1000 g), admitted between 10/1999 and 8/2001, followed until age 120 days, death, or hospital discharge Multicenter: 15 centers of the NICHD Neonatal Research Network (USA) N = 1433 (n = 721 glutamine supplementation group, n = 712 control group)	To evaluate whether supplementation of PN with 20% glutamine decreases mortality or late-onset sepsis compared with administration of a standard neonatal amino acid injection (TrophAmine) *Primary outcomes:* Death, late-onset sepsis *Secondary outcomes:* NEC, number of episodes of late-onset sepsis, ventilator days, enteral nutrition tolerance, PN duration, growth	*Incidence of NEC:* 10% (69/721) in the glutamine group and 10% (68/712) in the control group (RR, 0.99; 95% CI, 0.71–1.40; $P = .99$) When stratified by BW (401–750 g and 751–1000 g), there was no significant difference in NEC incidence ($P = .20$ and .24, respectively). *Incidence of surgical NEC:* 57% (39/69) in the glutamine group and 49% (33/68) in the control group (RR, 1.14; 95% CI, 0.90–1.44; $P = .19$)	Although parenteral glutamine supplementation seems to be well tolerated in ELBW infants, its routine use cannot be recommended given the lack of clinical efficacy.
Fewtrell,[48] 2002	RCT Double-blind Rate of attrition: 43/283	Preterm infants <37 weeks GA with BW <1750 g, tolerating enteral nutrition by 10 days of age, followed for an average of 32 days 3 NICUs (United Kingdom) N = 283 (n = 100 PF without LCPUFA, n = 95 PF+LCPUFA, n = 88 MM)	To evaluate the effect of LCPUFA supplementation in PF compared with nonsupplemented PF and MM on subsequent neurodevelopmental outcome *Primary outcomes:* Bayley MDI and PDI at age 18 months *Secondary outcomes:* Neurodevelopment (9 months), neurologic impairment and anthropometry measurements (9 and 18 months), enteral tolerance, infection, NEC, death	*Incidence of NEC:* 3.6% (7/195) in the PF group overall and 0% (0/88) in the MM group ($P = .10$) 2% (2/100) in PF without LCPUFA and 5.3% (5/95) in PF+LCPUFA ($P = .11$) These numbers include 2 infants who received <20 mL LCPUFA-supplemented formula and 1 infant who had no consumption of the control formula prior to the NEC. *Incidence of surgical NEC:* 0% (0/100) in PF without LCPUFA, 2.1% (2/95) in PF+LCPUFA, and 0% (0/81) in the MM group (no P value given)	Increased incidence of NEC in infants who received PF+LCPUFA supplementation, although the difference between groups was not statistically significant These findings emphasize the need for additional investigation to evaluate the efficacy and safety of LCPUFA supplementation of formula for preterm infants.
Amin,[45] 2002	RCT Double-blinded Placebo-controlled Rate of attrition: 5/152	Premature infants ≤32 weeks GA with BW ≤1250 g, admitted from 3/1997 to 7/1999, treatment duration days 1–28 of life, maintained on oral feeds or PN Single-center NICU (Canada) N = 152 (n = 75 L-arginine group, n = 77 placebo group)	To determine whether supplementation with L-arginine (1.5 mmol/kg/d) reduces the incidence of NEC *Primary outcome:* NEC, all stages *Secondary outcomes*: Mortality, feeding tolerance, nutrient intake, plasma ammonia, arginine, glutamine, amino acid concentrations	*Incidence of NEC (overall):* 6.7% (5/75) in the L-arginine group and 27.3% (21/77) in the placebo group ($P < .001$) *Incidence of NEC (Bell's stage II):* 6.7% (5/75) infants in the L-arginine group compared with 16.9% (13/77) of infants in the control group ($P = .077$) None of the infants developed Bell's stage III NEC requiring operative intervention.	Prophylactic administration of arginine appears to be effective in reducing the overall incidence of NEC in preterm infants, although there was no statistically significant difference in the incidence of Bell's stage II NEC.

BW, birth weight; CI, confidence interval; ELBW, extremely low birth weight; GA, gestational age; IV, intravenous; LCPUFA, long-chain polyunsaturated fatty acid; MDI, mental developmental index; MM, mother's milk; NEC, necrotizing enterocolitis; NICHD, National Institute of Child Health & Human Development; NICU, neonatal intensive care unit; PDI, psychomotor developmental index; PF, preterm formula; PN, parenteral nutrition; RCT, randomized controlled trial; RR, relative risk.

Table 9. GRADE Table Question 4: Do certain nutrients either prevent or predispose to the development of NEC?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome	Overall Recommendation GRADE
L-arginine supplementation vs no supplementation[45]	Incidence of NEC	1 RCT	Lower	Moderate	Further research needed
Glutamine vs no glutamine supplementation[46]	Incidence of NEC	1 RCT	No difference	Moderate	Strong
Long-chain polyunsaturated fatty acid supplementation vs no supplementation[48]	Incidence of NEC	1 RCT	No difference	Low	Further research needed

NEC, necrotizing enterocolitis; RCT, randomized controlled trial.

Table 10. Evidence Table Question 5: When should feeds be reintroduced to infants with NEC?

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Brotschi,[49] 2009	OBS Retrospective No attrition No financial disclosures	All term and preterm infants with NEC (Bell's stage II) admitted between 1/2000 and 12/2006 Multicenter study at 5 NICUs in tertiary care centers (Switzerland) N = 47 (n = 30 in ≤5-day group, n = 17 in >5-day group)	To compare the effect of fasting period duration (≤5 days vs >5 days) on the complication rates in infants with NEC managed conservatively *Primary end points:* Bowel stricture, NEC relapse, catheter-related sepsis	64% (30/47) of infants fasted for ≤5 days (range, 1–5) and 36% (17/47) fasted for >5 days (range, 6–16). *NEC relapse:* 3.3% (1/30) in the ≤5-day group and 11.8% (2/17) in the >5-day group (P = .27) Lower incidence of early post-NEC stricture (1/30 vs 4/17, P = .05) and catheter-related sepsis (0/30 vs 5/17, P = .004) in the ≤5-day group	Findings suggest that early enteral nutrition after conservatively managed NEC may lower morbidity after the acute phase of the disease. Infants who fasted for a shorter duration had a significantly lower incidence of catheter-related sepsis. Underpowered study for detecting potential differences in the incidence of NEC relapse

(continued)

Table 10. (continued)

Author, Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Bohnhorst,[50] 2003	OBS Retrospective Comparison to historical control group of infants with NEC admitted from 1993–1997 No financial disclosures	Infants <36 weeks GA admitted with NEC (Bell's stage ≥II) between 1998 and 2001 Single-institution NICU (Germany) N = 959 (n = 523 infants in secondary 4-year observation period, n = 436 infants in historical control group)	To report on an institutional experience with early initiation of enteral nutrition after NEC diagnosis Group 1: Feeds initiated after 3 consecutive days without evidence of portal venous gas on ultrasound; day 1: 20 mL/kg/d distilled water, day 2: PF or MM, advanced 20 mL/kg/d until achievement of goal at 150 mL/kg/d. Group 2 (control): Feeds initiated at discretion of neonatologist (typically 14 days after onset of NEC). *Primary end point:* Recurrence of NEC *Secondary end points:* Time to full enteral nutrition, duration of central access, incidence of catheter-related septicemia, duration of hospital stay	*Incidence of NEC:* 5% (26/523) in the early feeding group and 4% (18/436) in the historical control group Early feeding associated with: 1. Shorter time to reach goal feeds: 10 days (range, 8–22) vs 19 days (range, 9–76); $P < .001$ 2. Reduced duration of central venous access: 13.5 days (range, 8–24) vs 26 days (range, 8–39); $P < .01$ 3. Less catheter-related septicemia: 18% vs 29%; $P < .01$ 4. Shorter duration of hospital stay: 63 days (range, 28–133) vs 69 days (range, 36–150); $P < .05$	Early enteral nutrition after NEC is associated with significant benefits and no apparent adverse events. The study is underpowered to exclude a higher NEC recurrence risk as a result of early institution of enteral nutrition after NEC.

GA, gestational age; MM, mother's milk; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; OBS, observational study; PF, preterm formula.

Table 11. GRADE Table Question 5: When should feeds be reintroduced to infants with NEC?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome	Overall Recommendation GRADE
Early vs late introduction of enteral nutrition after NEC (Bell's stage II)[49,50]	NEC relapse	2 OBS	No difference	Low	Further research needed
	Central access duration		Lower	Low	Further research needed
	Catheter-related sepsis		Lower	Low	Further research needed
	Post-NEC stricture		Lower	Low	Further research needed
	Duration hospital stay		Lower	Low	Further research needed

NEC, necrotizing enterocolitis; OBS, observational study.

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