Published in final edited form as:
Clin Perinatol. 2013 March ; 40(1): 1–10. doi:10.1016/j.clp.2012.12.001.

Feeding Practices and NEC

Manimaran Ramani, MD [Assistant Professor] and
Department of Pediatrics, University of Alabama at Birmingham, Mailing Address: 176F Suite 9380, Women and Infants Center, 619 South 19th Street, Birmingham, AL 35249-7335, Tel Office (205) 934 4680 Fax Office (205) 934-3100

Namasivayam Ambalavanan, MD [Professor]
Departments of Pediatrics, Molecular and Cellular Pathology, and Cell, Developmental, and Integrative Biology, University of Alabama at Birmingham, Mailing Address: 176F Suite 9380, Women and Infants Center, 619 South 19th Street, Birmingham, AL 35249-7335, Tel Office (205) 934 4680 Fax Office (205) 934-3100

Manimaran Ramani: mramani@peds.uab.edu; Namasivayam Ambalavanan: ambal@uab.edu

Synopsis

Necrotizing enterocolitis (NEC) is a multifactorial disorder that primarily affects premature infants. Human milk as compared to formula reduces the incidence of NEC. Feeding practices such as minimal enteral nutrition (versus complete fasting) before progressive advancement of feeds, early introduction of feeds (before day 4 of life as compared to later), and a more rapid advancement of feeds (30–35 ml/kg/day as compared to 15–20 ml/kg/day) do not increase the incidence of NEC in preterm infants. There is no evidence supporting continuous over intermittent tube feedings in preterm infants. In a feed-intolerant preterm infant without any other clinical and radiological evidence of NEC, minimal enteral nutrition rather than complete suspension of enteral feeding may be an alternative. Human milk-based fortifier as compared to bovine-based fortifier may reduce the incidence of NEC but additional studies are required.

Keywords

Necrotizing enterocolitis; Feeding Methods; Enteral Nutrition; Premature Infant

Introduction

Necrotizing enterocolitis (NEC) is an acute ischemic necrotizing disease of the gastrointestinal (GI) tract that primarily affects premature infants. The incidence of NEC varies between 6 to 10% on average in Very Low Birth Weight (VLBW; birth weight <1500g) preterm infants admitted to Neonatal Intensive Care Units (NICUs) in the United States.[1–3] Despite remarkable advances in the care of extremely premature infants, the morbidity and mortality (10–30%) caused by NEC has not declined significantly, [2,3] and the total cost of care is estimated to be as much as 1 billion dollars annually in US alone.[3] NEC

Correspondence to: Namasivayam Ambalavanan, ambal@uab.edu.

Financial disclosure: Funding sources: NIH funding for Dr. Ambalavanan; Dixon Fellowship and IKARIA funding for Dr. Ramani. There are no conflicts of interest

is a multifactorial disease in which the integrity and function of the immature GI tract are compromised as a result of prematurity, inflammation, ischemia, or abnormal gut microbiota as described in other chapters of this issue. Various feeding practices such as the nature of feeds (human milk vs. formula feeding), time of initiation of enteral feeds, and the rate at which at feeds are advanced may also affect the immature GI tract and lead to the development of NEC.

Currently there is no consensus among healthcare professionals on feeding practices in preterm infants and there are wide variations in such practices across NICUs in the US. A recent survey of NICU directors, fellowship directors, neonatologists, NNPs, and dieticians across NICUs in the US indicated that most of responders would start parenteral nutrition on day 1 and the first enteral feed as soon as possible after birth (day 1: non- ventilated; day 3: ventilated), either as human milk (56%) or commercially available formula.[4] Responders indicated they would consider indomethacin use (83%), history of PDA (72%), and dopamine administration (63%) as contraindications for enteral feeding but not the placement of UAC (75%) or UVC (93%) or concurrent administration of hydrocortisone (70%).[4] Some of these feeding practices are not evidence-based but based on personal experience or unit culture. The objective of this article is to review the current data on various feeding practices and their impact on risk of NEC, mortality, and other morbidities in preterm infant. This article identifies and examines several feeding practices that are proven to be safe or unsafe or remain unproven in the prevention of NEC. We review recent randomized control trials, case control studies, observational studies, and expert opinions on feeding practices and NEC in preterm infants. For each subsection, we have indicated the quality of evidence (based on the U.S. Preventive Services Task Force “hierarchy of research design” available at: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual4.htm) and a recommendation (based on the U.S. Preventive Services Task Force Definitions available at: http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm).

Effect of Human Milk vs. Formula Feeding on NEC

Preterm formulas that are available today have been designed to match the composition of human milk with respect to calories and nutrients that are needed for the growth and development of preterm infants. However, these synthesized formulas do not provide the non-nutrient components of human milk such as secretory IgA, lysozyme, oligosaccharides, polyunsaturated fatty acids, and platelet-activating factor (PAF)-acetylhydrolase. These non-nutrient components of human milk contribute to GI mucosal integrity, function, and boost immunity against various GI infections. The AAP policy statement in 2012 on breast feeding and the use of human milk recommends human milk for term, preterm and other high risk infants either by direct breastfeeding and or by expressed breast milk.[5] The AAP statement also indicated that donor human milk might be a suitable alternative for infants whose mothers are unable or unwilling to provide their own milk.[5]

There is much data to suggest that human milk provides long-term benefits in term infants by lowering the incidence of sudden infant death syndrome, childhood infectious diseases (respiratory tract infections, otitis media, GI infection), allergic diseases, celiac disease, inflammatory bowel disease, obesity, etc.[5] In addition to these long-term benefits, preterm infants may also benefit in the short-term from the non-nutritive components of human milk by reduced susceptibility to sepsis or to NEC. However, there are currently no randomized controlled studies comparing the effect of mother’s own milk (not donor milk) with formula on the incidence of NEC and mortality.[6]

Several randomized controlled trials have been done to study the effect of donor human milk versus formula on the incidence of NEC and mortality in preterm infants. Meta-analysis of five of those randomized controlled trials comparing donor milk versus formula feeds in preterm infants showed that preterm infants fed with formula had more than twice the incidence of NEC (relative risk of 2.5 [95 % CI:1.2 to 5.1], number needed to harm was 33 [95% CI:17 to 100]) compared to the preterm infants fed with human milk.[7] The results of this meta-analysis underscore the importance of human milk intake in preterm infants.

Even though human milk intake reduces the risk of NEC, such reductions can only be achieved if preterm infants receive a certain minimal volume or proportion of their enteral feed as human milk. This dose-related benefit of human milk intake was evaluated in a secondary analysis of 1272 extremely low birth weight (ELBW) infants enrolled in the NICHD Glutamine Trial.[8] In this study population, approximately 13 percent of ELBW infants died or developed NEC 14 days after birth. For each 10% increase in the proportion of total intake as human milk, there was a reduction in NEC or death after 14 days by a factor of 0.83 [95 % CI: 0.72 to 0.96].[8]

Similar results were also shown in a prospective cohort study by Sisk et al, in which 10 percent of VLBW infants who received less than 50 percent of their total enteral intake as human milk developed NEC whereas only 3 percent of infants who received more than 50 percent as human milk developed NEC.[9] The odds of NEC decreased by 38% for every 25% increase in proportion of human milk in the first 14 days[9]. Overall, after adjustment for gestational age, higher human milk intake was associated with a lower risk of NEC (OR 0.17 [95% CI: 0.04 to 0.68], P<0.01).[9]

Quality of Evidence (I)

Recommendation Grade (*A):*

The evidence is very strong in favor of human milk (donor) compared to artificial formula in reducing the incidence of NEC in preterm infants. Even though such benefit is yet to be proven for mother's own milk by randomized controlled trials, we can strongly recommend based on existing evidence from donor human milk that the mother should be encouraged and persuaded to feed her preterm infant with preferably her own milk, or with donor human milk if she is unable or unwilling to feed with her own milk.

Effect of Minimal Enteral Nutrition on NEC

In utero, a fetus constantly swallows amniotic fluid, which contributes to the formation of meconium. In addition to the formation of meconium, amniotic fluid may also play an important role in growth and development of GI tract.[10] Postnatally, enteral feedings also stimulate the motility of the GI tract and various hormonal secretions. [11–13]

Fasting or delayed introduction of feeding may possibly impair these GI functions. To minimize feeding intolerance and the risk of developing NEC in preterm infants, the practice of "minimal enteral nutrition" is considered as an alternative to complete fasting in many units.

Minimal enteral nutrition, otherwise called as "trophic feeds" or "gut priming" is usually started within 1–3 days after birth with 15–20 ml/kg/day of enteral milk, given every 2–3 hours and continued for 5–7 days after birth without any advancement. A recent Cochrane systematic review evaluated the effect of minimal enteral nutrition on feeding intolerance, growth, incidence of NEC, and mortality in 754 VLBW infants.[14] "Early trophic feeding" was defined as enteral feeding with milk volume of up to 24 ml/kg/day began within 96 hrs

after birth and continued for at least one week while "enteral fasting" was defined as nothing per mouth for at least one week after birth. It was observed that there were no differences in the risk of developing NEC (RR 1.07 [95% CI: 0.67 to 1.7]; RD 0.01 [95% CI: 0.03 to 0.05]), time to achieve full feeds (weighted mean difference −0.97 [95% CI: −2.47 to −0.53]), mortality (RR 0.77 [95% CI: 0.46 to 1.30], RD −0.03 [95% CI: 0.09 to 0.03]) and duration of hospital stay (weighted mean difference −3.8 days [95% CI: −12.2 to 4.5]) between VLBW infants who received minimal enteral feeding within 1–4 days after birth as compared to complete enteral fasting for seven days after birth.[14] Despite biologic plausibility that minimal enteral nutrition may prime the gut and improve feeding intolerance and may thereby reduce the incidence of NEC, the data from available trials do not confirm that minimal enteral nutrition in preterm infants improves feeding tolerance and reduces NEC.

Quality of Evidence: (I)

Recommendation: (B)

The clinical importance of minimal enteral nutrition is still uncertain, although it is commonly practiced. Based on the existing evidence that minimal enteral nutrition (trophic feeds) do not increase the risk of NEC or feeding intolerance, minimal enteral nutrition may be considered as a safe alternative to complete fasting before the initiation of progressive feeding increments.

Effect of Rate of Increment in Feedings on NEC

NEC in preterm infants usually occurs a few weeks after birth.[2,3,15] At that time of diagnosis of NEC, most preterm infants have received enteral feeding, either with human milk or formula. Due to initial concerns that NEC may be associated with rapid advancement of enteral feeding,[16] many clinicians in the past have delayed initiating and slowed the rate of advancement of enteral feeding.

A Cochrane systematic review analyzed five randomized controlled trials involving 600 VLBW infants for the effect of delayed versus early progressive feeding on the incidence of NEC, mortality and morbidities of the preterm infant (growth, neurodevelopmental outcome, feeding intolerance, time to achieve full feeds and length of hospital study).[17] "Delayed introduction of progressive feeds" was defined as intention to advance feed volumes in excess of trophic feeds (up to 24 ml/kg/day) later than 5–7 days after birth, as compared to advancing feeds at less than 4 days after birth. Two of the five randomized controlled trials (n=488) recruited only growth-restricted infants with abnormal fetal circulatory distribution or flow in middle cerebral artery, umbilical arteries or uterine arteries. It was noted that delayed advancement of enteral feedings in preterm infants did not have a significant effect on the risk of NEC (RR 0.89 [95% CI: 0.58 to 1.37) or all-cause mortality (RR 0.93 [95% CI: 0.53 to 1.63]).[17] In addition, preterm infants who received delayed advancement of feeds took longer to achieve full feeds (mean difference of 3 days) compared to those who have received feeds from earlier than four days after birth. [17] Data from these trials do not provide evidence that delayed introduction of progressive enteral feeds reduces the risk of NEC in VLBW infants and moreover results in several days delay in establishing full feeds. Rather than the exact rate of feed advancement, it is possible that the use of a standardized feeding regimen is more important. A systematic review of six observational studies by Patole et al.[18] showed a reduction in the incidence of NEC by 87 % (RR 0.13[CI: 0.03 to 0.05]) with the use of a standardized feeding protocol.

Quality of Evidence: (I)

Recommendation: (B)

Based on the existing evidence, early advancements of feeding is safe and may be considered as an alternative to minimal enteral nutrition soon after birth in a clinically stable VLBW infant.

Feeding Advancement and NEC

Enteral feeding is often advanced after 3–7 days of tolerance to minimal enteral nutrition. The volume and the rate used to advance from minimal enteral nutrition to full feeds vary between units and it usually depends on the birth weight and the extent of cardiorespiratory support. A daily increment between 15–30 ml/kg/day of feeds is used in most units. A meta-analysis of four randomized controlled trials (n=496; less than 1500g or less than 32 w GA) evaluated the effect of “slow” (15–20 ml/kg/day) versus “fast” (30–35 ml/kg/day) rates of enteral feed advancements on the incidence of NEC, mortality and other morbidities in preterm infants.[19] No significant difference in the risk of NEC (RR 0.91[95% CI: 0.47 to 1.75], RD −0.01[95% CI: −0.05 to 0.04) and mortality (RR 1.43[95% CI: 0.78 to 2.61], RD 0.04 [95% CI: −0.02 to 0.09]) were noted between the slow and fast advancement groups.[19] Infants who were fed slowly took longer to regain birth weight (mean difference 2–6 days) and establish full feeds (2–5 days) compared to those who received more aggressive advancement of feeds. Data from this analysis do not provide evidence that slow advancement of feeds reduces NEC. In addition, slower advancement of feeds slows weight gain and establishment of full feeds. There may therefore be indirect effects on neonatal morbidity due to slow weight gain, delay in establishment of full feeds, prolongation of TPN and risk of central line infection. However, these studies did not include many severely growth restricted infants or those with birth weight <750g, and many clinicians increase feeds very cautiously in this subgroup of infants.

Quality of Evidence: (I)

Recommendation: (B)

Evidence indicates that both slow (15–20 ml/kg/day) and fast (30–35 ml/kg/day) advancement practices are safe and can be used in the preterm infants (especially larger VLBW infants) while advancing minimal enteral nutrition to full feeds. Randomized controlled trials are needed to determine the effect of slow versus fast feeding advancement on longer-term clinical outcomes of preterm infants and on the incidence of NEC and mortality in the subset of smaller ELBW infants (<750g).

Continuous versus Intermittent Bolus Feeding on NEC

Coordination of sucking and swallowing matures around 32–34 weeks of gestation. Hence, tube feeding is usually necessary in VLBW infants to ensure adequate milk intake for growth and development. Tube feeding may be either intermittent (bolus) or continuous, with a set volume per hour. Intermittent enteral feeding may be more physiological as it facilitates the normal cyclic surges of the gastrointestinal hormones.[20,21] Continuous enteral feeding may however reduce the energy required for digestion and absorption and decrease feeding intolerance. The Cochrane Systematic Review which included seven trials that enrolled 511 VLBW infants did not show any difference in the incidence of NEC (RR 1.5 [95% CI: 0.4 to 5.9]), time to achieve full enteral feeds (weighted mean difference 2 days [95% CI: −0.3 to 3.9]), and somatic growth between infants who were fed continuously and by intermittent tube feeding.[22] Available data do not provide evidence to determine best tube feeding practice in VLBW infants.

Quality of Evidence: (I)

Recommendation: (B)

Even though intermittent feeding may have some physiological advantages compared to continuous feeding, there is not enough evidence to recommend intermittent feeding over continuous feeding for reducing the risk of NEC, mortality or morbidity in preterm infants.

Relationship of Feeding Intolerance and NEC

Feeding intolerance is very common among preterm infants who are on enteral feeds, and may either be a benign sign of reduced GI tract motility or may be an initial manifestation of NEC. Feeding intolerance is the one of most common reasons to delay advancement of enteral feeds or for suspension of feeds in preterm infants. However, there is no consensus on the definition and management of feeding intolerance. Usually, an increased amount or abnormal nature (e.g. bilious, bloody) of gastric residuals or abdominal distension regardless of gastric residuals is considered feeding intolerance. A case control study by Cobb et al.[23] evaluating 51 infants with proven NEC versus 102 control infants without suspected or proven NEC indicated that a gastric residual volume of < 1.5 mL or <25% of a feed (the 25th centile for the NEC group) was probably within the range of normal but a gastric residual volume > 3.5 mL or >33% of a feed (the 75th centile for control subjects) was associated with a higher risk for NEC. There is no evidence that color (green versus milky) and or nature (mucus versus clear) of gastric residuals are early signs of NEC. Abdominal distension or visible loops may be a normal finding in preterm infant on CPAP and cannot be used as sole indicator in the diagnosis of NEC. Delayed advancement or suspension of enteral feeds based on gastric residuals or abdominal distension in the absence of other signs of NEC has not been shown to reduce the subsequent incidence of NEC. A retrospective chart analysis by Terrin G et al.[24] to determine the safety and efficacy of minimal enteral nutrition (MEN) in feed-intolerant VLBW infants suggested that stopping or holding enteral feeds on the basis of feeding intolerance would increase the risk for sepsis (33.3 % in NPO group and 15.7 % in MEN group P<0.038), days to achieve the full feeds (Mean days = 11 in NPO group and 8 in MEN group, P<0.001) and days to regain birth weight (Mean days =12 in NPO group and 8 MEM group, P<0.001).[24]

Quality of Evidence: (II-2)

Recommendation: (I)

Currently there is no evidence-based definition of feeding intolerance. A sudden increase in gastric residuals may be an early sign of NEC, [23] but abdominal distension and abnormal color or nature of gastric residuals are usually non-specific. If clinically stable infants develop feeding intolerance in the absence of any other clinical or radiological evidence of NEC, one may provide minimal enteral nutrition (trophic feeds) while continuing to re-evaluate the infant at frequent intervals, rather than suspending enteral feeding altogether.

Effect of Fortifiers on NEC

Preterm infants have higher protein turnover compared to term infants. Protein requirements for enterally fed preterm infants are inversely proportional to the body weight (i.e., the lower the body weight, the higher the protein requirement). [26] Even at full feeds (200 ml/kg/day), the protein, calcium and phosphorous content of human milk are not adequate to promote and sustain the tissue growth and bone mineralization in preterm infants. [27,28] Addition of fortifier increases levels of protein, calcium and phosphorous of human milk. It has been shown that the multicomponent fortification of human milk is associated with short-term

improvements in weight gain and linear and head growth.[29] However, there is a non-significant trend towards increased feeding intolerance in treated infants (RR 2.85 [95% CI: 0.62 to13.1]). There was no statistically significant increase in NEC in infants receiving fortified human milk (RR 1.33 [95%CI 0.7 to 2.5]). [29]

Human milk can be fortified with either a human milk-based fortifier or a bovine milk based fortifier. To study the effect of exclusive human milk-based diet on the risk of NEC, Sullivan et al.[30] performed a randomized controlled trial involving 207 VLBW infants fed with either "exclusive human milk based diet" or "bovine based diet". Exclusive human milk-based diet infants were fed only with either mother's own milk or human donor milk fortified only with donor human milk based-fortifier. Another group of infants were fed with mother's own milk or human donor milk fortified with bovine based-human milk fortifier. A third group (control) received mother's own milk fortified with bovine based-human milk fortifier and received preterm formula when mother's own milk was not available. The group receiving exclusive human milk diet had lower rates of NEC ($p = 0.02$) and NEC requiring surgical intervention ($p = 0.007$) compared to the group receiving human milk fortified with bovine based fortifier.[30] However, a limitation of this study was the relatively small sample size, and the higher incidence of NEC in the control group (18%).[2,3]

Quality of Evidence: (I)

Recommendation: (B)

Currently, limited evidence suggests that fortification of human milk improves short-term growth moderately without a significant increase in NEC or improved long-term outcomes. There is also some evidence that human milk-based fortifier reduces the incidence of NEC. The high cost and unknown biological product risks associated with human milk based fortifier currently limits its routine use in fortifying human milk.

Effect of Osmolality of Feeds on NEC

Osmolality is the concentration of a solution in terms of osmoles of solute per *kilogram* of solvent, whereas osmolarity is the concentration of a solution in terms of osmoles of solute per *liter* of solution. Current recommendations mostly based on historical consensus rather than experimental evidence are that the osmolality of enteral feeds should not exceed 450 mOsm/kg (~400 mOsm/L).[31,32] The recommendations seem to have been mostly based on small studies in the 1970s by Santulli et al.[33], Book et al. [34], and Willis et al.[35]. Human breast milk has an osmolality of around 300 mOsm/kg, while that of full fortified human milk is around 400 mOsm/kg, and all milk feeds that are currently used have an osmolality below 450 mOsm/kg.[31] However, the addition of supplements (e.g. sodium supplements, folate) may markedly increase osmolality, with the exact magnitude depending upon the amount of supplement and the volume of milk to which it is added.[36] The consequences of increased feed osmolality in human infants are not clear. Studies in neonatal dogs indicate that the actual osmolality of the feed itself was not a major determinant of the osmolality of the contents of the stomach or intestine, although hyperosmolar feeds led to delayed gastric emptying.[37] Even if hyperosmolar feeds led to increased hyperosmolarity in the intestinal lumen, it is not clear that this would result in mucosal damage.[31]

Quality of Evidence (II-3)

Recommendation (B):

Studies that showed the association of increased incidence of NEC with hyperosmolar formula feedings were done at a time when osmolality of the feeds were very high and

above the current recommended maximum (450 mOsm/kg). The increase in osmolality of enteral feedings by the addition of supplements and other therapeutic additives may possibly result in delayed gastric emptying, with an undetermined effect on NEC.

Summary

The evidence is convincing that human milk feeding, as compared to formula feeding, reduces the incidence of NEC in preterm infants. Minimal enteral nutrition is a safe alternative to complete fasting before initiation of progressive feedings and does not increase the incidence of NEC in extremely preterm infants. In clinically stable VLBW infants, early introduction of progressive feeds and advancement of feeds at a faster rate (30–35ml/kg/day) is safe and does not increase the incidence of NEC. There is no evidence supporting continuous over intermittent tube feedings in preterm infants. In a feed-intolerant preterm infant without any other clinical and radiological evidence of NEC, minimal enteral nutrition rather than complete suspension of enteral feeding may be an alternative. Human milk-based fortifier as compared to bovine-based fortifier may reduce the incidence of NEC but additional studies are required.

References

1. Guillet R, Stoll BJ, Cotten CM, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics. Feb; 2006 117(2):e137–142. [PubMed: 16390920]
2. Lin PW, Stoll BJ. Necrotising enterocolitis. Lancet. Oct 7; 2006 368(9543):1271–1283. [PubMed: 17027734]
3. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med. Jan 20; 2011 364(3):255–264. [PubMed: 21247316]
4. Hans DM, Pylipow M, Long JD, Thureen PJ, Georgieff MK. Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey. Pediatrics. Jan; 2009 123(1):51–57. [PubMed: 19117860]
5. Section on B. Breastfeeding and the use of human milk. Pediatrics. Mar; 2012 129(3):e827–841. [PubMed: 22371471]
6. Henderson G, Anthony MY, McGuire W. Formula milk versus maternal breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev. 2007; (4):CD002972. [PubMed: 17943777]
7. Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev. 2007; (4):CD002971. [PubMed: 17943776]
8. Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. J Perinatol. Jan; 2009 29(1):57–62. [PubMed: 18716628]
9. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol. Jul; 2007 27(7):428–433. [PubMed: 17443195]
10. Trahair JF, Harding R. Ultrastructural anomalies in the fetal small intestine indicate that fetal swallowing is important for normal development: an experimental study. Virchows Archiv A, Pathological anatomy and histopathology. 1992; 420(4):305–312.
11. Johnson LR. The trophic action of gastrointestinal hormones. Gastroenterology. Feb; 1976 70(2): 278–288. [PubMed: 765181]
12. Lucas A, Bloom SR, Aynsley-Green A. Gut hormones and 'minimal enteral feeding'. Acta paediatrica Scandinavica. Sep; 1986 75(5):719–723. [PubMed: 3105234]
13. Berseth CL. Neonatal small intestinal motility: motor responses to feeding in term and preterm infants. J Pediatr. Nov; 1990 117(5):777–782. [PubMed: 2121949]

14. Bombell S, McGuire W. Early trophic feeding for very low birth weight infants. Cochrane Database Syst Rev. 2009; (3):CD000504. [PubMed: 19588318]
15. Uauy RD, Fanaroff AA, Korones SB, Phillips EA, Phillips JB, Wright LL. Necrotizing enterocolitis in very low birth weight infants: biodemographic and clinical correlates. National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr. Oct; 1991 119(4):630–638. [PubMed: 1919897]
16. Anderson DM, Kliegman RM. The relationship of neonatal alimentation practices to the occurrence of endemic necrotizing enterocolitis. Am J Perinatol. Jan; 1991 8(1):62–67. [PubMed: 1899016]
17. Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2011; (3):CD001970. [PubMed: 21412877]
18. Patole SK, de Klerk N. Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies. Arch Dis Child Fetal Neonatal Ed. Mar; 2005 90(2):F147–151. [PubMed: 15724039]
19. Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2011; (3):CD001241. [PubMed: 21412870]
20. Strader AD, Woods SC. Gastrointestinal hormones and food intake. Gastroenterology. Jan; 2005 128(1):175–191. [PubMed: 15633135]
21. Aynsley-Green A, Adrian TE, Bloom SR. Feeding and the development of enteroinsular hormone secretion in the preterm infant: effects of continuous gastric infusions of human milk compared with intermittent boluses. Acta paediatrica Scandinavica. May; 1982 71(3):379–383. [PubMed: 6814175]
22. Premji SS, Chessell L. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. Cochrane Database Syst Rev. 2011; (11):CD001819. [PubMed: 22071802]
23. Cobb BA, Carlo WA, Ambalavanan N. Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants. Pediatrics. Jan; 2004 113(1 Pt 1):50–53. [PubMed: 14702446]
24. Terrin G, Passariello A, Canani RB, Manguso F, Paludetto R, Cascioli C. Minimal enteral feeding reduces the risk of sepsis in feed-intolerant very low birth weight newborns. Acta Paediatr. Jan; 2009 98(1):31–35. [PubMed: 18727685]
25. Thomas N, Cherian A, Santhanam S, Jana AK. A randomized control trial comparing two enteral feeding volumes in very low birth weight babies. Journal of tropical pediatrics. Feb; 2012 58(1): 55–58. [PubMed: 21320855]
26. Ziegler EE. Protein requirements of very low birth weight infants. Journal of pediatric gastroenterology and nutrition. Dec; 2007 45 (Suppl 3):S170–174. [PubMed: 18185086]
27. Cohen RS, McCallie KR. Feeding premature infants: why, when, and what to add to human milk. JPEN Journal of parenteral and enteral nutrition. Jan; 2012 36(1 Suppl):20S–24S. [PubMed: 22237872]
28. Schanler RJ. Evaluation of the evidence to support current recommendations to meet the needs of premature infants: the role of human milk. The American journal of clinical nutrition. Feb; 2007 85(2):625S–628S. [PubMed: 17284767]
29. Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. Cochrane Database Syst Rev. 2004; (1):CD000343. [PubMed: 14973953]
30. Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr. Apr; 2010 156(4):562–567. e561. [PubMed: 20036378]
31. Pearson F, Johnson MJ, Leaf AA. Milk osmolality: does it matter? Arch Dis Child Fetal Neonatal Ed. Sep 19.2011
32. Commentary on breast-feeding and infant formulas, including proposed standards for formulas. Pediatrics. Feb; 1976 57(2):278–285. [PubMed: 1250665]

33. Santulli TV, Schullinger JN, Heird WC, et al. Acute necrotizing enterocolitis in infancy: a review of 64 cases. Pediatrics. Mar; 1975 55(3):376–387. [PubMed: 1143976]

34. Book LS, Herbst JJ, Atherton SO, Jung AL. Necrotizing enterocolitis in low-birth-weight infants fed an elemental formula. J Pediatr. Oct; 1975 87(4):602–605. [PubMed: 1174138]

35. Willis DM, Chabot J, Radde IC, Chance GW. Unsuspected hyperosmolality of oral solutions contributing to necrotizing enterocolitis in very-low-birth-weight infants. Pediatrics. Oct; 1977 60(4):535–538. [PubMed: 905019]

36. Srinivasan L, Bokiniec R, King C, Weaver G, Edwards AD. Increased osmolality of breast milk with therapeutic additives. Arch Dis Child Fetal Neonatal Ed. Nov; 2004 89(6):F514–517. [PubMed: 15499144]

37. Goldblum OM, Holzman IR, Fisher SE. Intragastric feeding in the neonatal dog. Its effect on intestinal osmolality. Am J Dis Child. Jul; 1981 135(7):631–633. [PubMed: 6787914]

Key Points

- The evidence is convincing that human milk feeding, as compared to formula feeding, reduces the incidence of NEC in preterm infants.
- Minimal enteral nutrition is a safe alternative to complete fasting before initiation of progressive feedings and does not increase the incidence of NEC in extremely preterm infants. In clinically stable VLBW infants, early introduction of progressive feeds and advancement of feeds at a faster rate (30–35ml/kg/day) is safe and does not increase the incidence of NEC.
- There is no evidence supporting continuous over intermittent tube feedings in preterm infants.
- In a feed-intolerant preterm infant without any other clinical and radiological evidence of NEC, minimal enteral nutrition rather than complete suspension of enteral feeding may be an alternative.
- Human milk-based fortifier as compared to bovine-based fortifier may reduce the incidence of NEC but additional studies are required.