

Necrotizing Enterocolitis (NEC): The Process of Putting Evidence-Based Medicine into Practice

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NEC. Three letters that can evoke a visceral reaction of fear and dread in the hearts of neonatal clinicians. A beautiful little baby that you admitted on Monday is doing quite well by Friday; you come back on Sunday to find the baby on the ventilator with an ostomy, fighting for her life! Is there anything that could have been done to prevent this? What is the evidence and what is the folklore of NEC?

Cincinnati Children's Hospital Division of Neonatology chose necrotizing enterocolitis (NEC) as the topic for their first evidence-based medicine (EBM) guideline. To start the process they assembled a team of interested staff RNs, a neonatal nurse practitioner, a neonatal nutritionist, a pharmacist, pediatric surgeons, neonatologists, pediatric gastroenterologists, and EBM specialists. We recruited a group of parents to give input to the guideline as well. Many of the group attended a workshop on Evidence-Based Medicine to become better equipped with the tools of EBM.

Question sheets were posted in the NICU, e-mails were sent to elicit questions for the team. The collected questions were brought to the team and rephrased into PICO format¹:

in this:

Population: Infants <1500 grams; does the Intervention of X

Compared to Y have a/an (greater incidence of the)

Outcome of NEC.

After rephrasing the questions, searching the literature was the next skill set. Two independent searches were done; 608 articles were found and screened and 445 were reviewed.

These Medline searches, even though done by very experienced people, still missed articles, so it is important to search through the bibliographies to make sure something isn't missed.

What were the results of our literature review? There are many articles about NEC, but there are not many prospective, randomized, double-blind, controlled trials (PRDBCT) (the "gold standard" of research evidence) with NEC as an outcome. Meta-analyses have been done related to topics concerning NEC, but some of their results are obscured by the wide spectrum of articles combined for the meta-analyses. That is, statistically, these meta-analyses are significant, but the results are not as clear to clinicians trying to extrapolate the findings into care practices for the neonate with NEC.

NEC is almost exclusively a disease of the newborn, with increasing risk with decreasing gestational age. The cause(s) have not been identified and a multifactorial etiology is likely. The incidence has not changed significantly since 1977-78,² probably due to the survival of smaller and more immature babies. Our hospital's guideline was written to provide evidence-based recommendations for the evaluation and management of NEC in low-birth-weight infants. The goal of the guideline is to improve diagnostic accuracy, treatment options, and parent satisfaction, and eventually prevent NEC. The guideline was written originally in 2005 and is updated every 6 months. This article presents highlights of the guideline which can be viewed in its entire format at <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/nec-vlbw.htm> or www.guideline.gov.

In this article, the author's editorial comments appear in italics.

Prevention

The guideline recommends that mothers of infants at risk for NEC be encouraged to supply breast milk as the optimal enteral nutrition and to decrease their infant's risk of developing NEC. Studies show that providing human milk to 20 preterm infants will prevent one case of NEC.³ When mother's milk is unavailable, the guideline also recommends that donor milk be considered as an alternative (if available).⁴

Feeding Strategies

Minimal Enteral Feeding: The study group found insufficient evidence regarding the role of minimal enteral feeding (MEM) in the prevention of NEC. A meta-analysis of six studies showed the use of MEM had no effect on the risk of NEC.⁵ The addition of two more recent studies did not change the statistical effect.^{6,7} *However, in the meta-analysis, the definition of MEM used was <35 kcal/kg/day or 37 ml/kg/day, which is not equivalent to many clinicians' definition of MEM, which is 10 ml/kg/day.*

Timing of Initiation of Feeds: The study group found insufficient evidence to support either early or delayed initiation of feeding relative to the risk for NEC.⁸⁻¹¹

Rate of Advancement of Feeds:

There was insufficient evidence found to recommend a specific rate of feeding volume advancement in relation to NEC risk. No difference in NEC risk was observed in studies with ad-

vancement as low as 10 ml/kg/day and as high as 35 ml/kg/day.^{12,13} One large study by Berseth et al¹⁴ showed a decreased rate of NEC in infants maintained at 20 ml/kg/day compared to infants whose feedings were advanced. Inclusion of this study did not alter the results of the meta-analysis. *However, the meta-analysis results may have been influenced by the fact that “slow” feeds were 10-20 ml/kg/day and “fast” feeds were 20-35 ml/kg/day— so there was overlap.*

Transpyloric vs. gastric feedings: Insufficient evidence was found to support either transpyloric or gastric feeding methods relative to the risk of NEC.¹⁵

Bolus vs. continuous feeding: There was insufficient evidence to support either bolus or continuous tube feeding as a method to reduce the risk of NEC.¹⁶

Umbilical Artery Catheters: There was insufficient evidence to recommend a specific placement for the tip of the catheter (i.e., high vs. low) because catheter placement has not been found to influence the incidence of NEC.¹⁷ There is insufficient evidence to evaluate the risk of NEC associated with enteral feeding while the catheter is in place. One small randomized trial found no difference in the incidence of NEC between infants fed with an umbilical artery catheter (UAC) in place versus those in whom feedings were delayed until 24 hours after the UAC was removed.¹⁸

Use of Probiotics: There was insufficient evidence to recommend either use of or avoidance of probiotics. Clinical trials of the effects of probiotics relative to the risk of NEC have not consistently shown benefit. One large observational study using the probiotics *Lactobacillus* and *Bifidobacterium* showed a significant decrease in NEC when compared to historical controls.¹⁹ A large randomized controlled trial using *Lactoba-*

cillus GG found no significant effect on the incidence of NEC in very low-birth-weight infants.²⁰ Another somewhat large trial using *Lactobacillus* and *Bifidobacterium* found a significant reduction in NEC among the treated infants.²¹ Issues (i.e., the potential for sepsis) regarding the safety of using probiotics in premature infants with relative immunodeficiency have been raised. None of the clinical trials reviewed reported any harmful side effects; however, they were not powered to evaluate safety.²² *Different probiotics were used in the studies so the question for a larger study would be what probiotic to use and at what dose.*

Additional Prevention Strategies

Enteral glutamine²³, IV glutamine,²⁴ and enteral arginine²⁵ have been studied with no statistically significant effects on NEC risk.

Information on the topic of *acidification*, although present, was sparse. This topic is presented here for purposes of awareness. Recommendations were made that histamine-2 (H₂) receptor blocker therapy for gastric acidity be used with caution. One small randomized controlled trial showed that acidification of feeds was associated with a decreased risk of NEC.²⁶ Another large retrospective case-control study showed a significant association between H₂ blocker therapy and higher rates of NEC.²⁷

Medical Management

Evaluation: Clinical assessment and diagnosis: Bell's NEC staging system is commonly used to assess NEC severity.²⁸ In this guideline, Bell Stage II was commonly used as diagnostic criterion for definite NEC.

Diagnostics: No specific pathogen has been shown to have a consistent causal relationship with NEC, although specific pathogens have been isolated from stool and abdominal fluid during NEC outbreaks.²⁹⁻³⁷ There

is insufficient evidence to support the use of patterns of stooling, presence of occult blood, or presence of specific pathogens as diagnostic of NEC.^{30,38,39} There was also not enough evidence for the use of gastric residuals as a predictor of NEC. Gastric residuals from infants who developed NEC tended to be larger, but there was significant overlap in the amount of residual so that it was not useful as a marker for NEC.⁴⁰ *Despite a great deal of interest in this subject, there was little literature; this is an area which could benefit from nursing research.*

Intervention

There is insufficient evidence on the benefit or risk regarding timing of re-initiating feeding once the diagnosis of NEC has been made. Of note, one retrospective study evaluating early initiation of feeding (<10 days from diagnosis) suggested a positive finding. Early feeding was associated with shorter time to full feedings, less catheter-related sepsis, and a shorter hospital stay. The study was not powered sufficiently to evaluate recurrent risk of NEC.⁴¹

Conclusion

There is insufficient evidence to state a proven benefit to many topics. That does not necessarily mean that there is no value in them, just that there has not been sufficient evidence to make a statement. This, however, creates a research agenda of many topics that should be studied in the future. There are 41 references for this article that are available on the web site at www.abbottnutritionlearningcenter.com.

About the Author

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