Health Policy & Clinical Effectiveness Program

Evidence-Based Care Guideline

Necrotizing Enterocolitis (NEC)

among very low birth weight infants [a]

Changes to the guideline made in February, 2007 based on a literature review conducted in 2006; see Development Process section for method, results and discussion of changes

Original Publication Date: July 14, 2005

Target Population

Inclusion: Intended for use in

- preterm infants less than 1500 grams birth weight

Exclusion: not intended for use in

- term and near term infants
- infants with major congenital anomalies (e.g. congenital heart disease, Trisomy 21)

Target Users

Includes but is not limited to (in alphabetical order):

- Community physicians and practitioners
- Family
- Fellows / Residents
- Patient Care staff
- Physicians and surgeons caring for inpatients

Introduction

References in parentheses ( ), Evidence strengths in [ ] (See last page for definitions)

These guideline recommendations were formulated by an interdisciplinary team (see Methods, page 7).

For these recommendations NEC, is defined by Bell's clinical staging (Table 1) *(Bell 1978 [C])*.

This guideline is designed to provide a practical, evidence-based approach to:

- prevention and diagnosis of NEC
- treatment of infants with Bell stage II or greater NEC.

Using population-derived data, it is estimated that there are between 2000 to 5000 new cases of neonatal necrotizing enterocolitis (NEC) in the United States each year *(Rayyis 1999 [A], Wilson 1981 [D], Uauy 1991 [S], Kliegman 1984 [S])*. The incidence of NEC has apparently not changed since the last population-based estimates were made in 1977 to 1978. Despite advances in neonatal care, improved survival of smaller and more immature infants may account for the unchanged overall incidence.

NEC-associated mortality is estimated at 25 to 30% *(Wilson 1981 [D], Stoll 1994 [S], Uauy 1991 [S])*. Short bowel syndrome and other NEC-associated morbidities contribute significantly to poor growth and development and large health-care costs *(Vohr 2000 [C], Bisquera 2002 [D], Goulet 2004 [S])*. NEC and its associated comorbidities in extremely low birth weight infants are significant predictors for adverse neurodevelopmental outcomes regardless of current treatment strategies *(Salhab 2004 [D])*.

Table 1: Bell's Staging for Necrotizing Enterocolitis (NEC)

Stage I Suspect	Stage II Definite	Stage III Advanced
Any one or more historical factors producing perinatal stress	Any one or more historical factors	Any one or more historical factors
Systemic manifestations – temperature instability, lethargy, apnea, bradycardia	Signs and symptoms as in **Stage I plus** persistent occult or gross gastrointestinal bleeding; marked abdominal distention	Signs and symptoms plus as in **Stage II plus** deterioration of vital signs, evidence of septic shock or marked gastrointestinal hemorrhage
Gastrointestinal manifestations – poor feeding, increasing pre-gavage residuals, emesis (may be bilious or test positive for occult blood), mild abdominal distention, occult blood may be present in stool (no fissure)	Abdominal radiographs show significant intestinal distension with ileus; small bowel separation (edema in bowel wall or peritoneal fluid), unchanging or persistent "rigid" bowel loops, pneumatosis intestinalis, portal vein gas	Abdominal radiographs may show pneumoperitoneum in addition to signs listed for Stage II
Exclude other disorders via bacterial cultures, electrolyte analysis, maternal drug history, coagulation studies, and contrast studies		

[a] Please cite as: **Necrotizing Enterocolitis (NEC) Guideline Team, Cincinnati Children's Hospital Medical Center:** Evidence-based care guideline for medical management of very low birth weight infants at risk for NEC. http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/nec_vlbw.htm Guideline 28, pages 1-12, Feb., 2007.

This guideline provides evidence-based recommendations for the evaluation and management of Necrotizing Enterocolitis (NEC) among very low birth weight infants. The guideline objectives are to improve diagnostic accuracy, treatment outcomes, and patient/parent satisfaction.

Etiology

NEC is primarily a disease of the newborn with increasing risk as gestational age at birth decreases. Although specific clinical and demographic associations have been observed, the cause or causes of NEC have not been determined. Many have suggested that the etiology may be multifactorial; however, statistically significant effects of interactions among risk factors have not been observed *(Guthrie 2003 [D])*,

Guideline Recommendations

Prevention

Type of milk

1. It is recommended that mothers of infants at risk for NEC be encouraged to supply breast milk as the optimal enteral nutrition to decrease risk. Infants who received human milk were 4 times less likely to have confirmed NEC compared to infants who received formula (RR 0.25, 95% CI [b] 0.06 to 0.98) *(McGuire 2003b [M], Schanler 1999 [A], Lucas 1990 [A], Gross 1983 [B], Tyson 1983 [B], Svenningsen 1982 [B])*.
   Note 1: Studies show that providing human milk to twenty preterm infants will prevent one case of NEC *(McGuire 2003a [M])*.
   Note 2: Although the benefits of human milk to decrease NEC risk have been demonstrated primarily with donor milk, it is reasonable to encourage use of mother's own milk *(Schanler 2005 [A], Local Expert Consensus [E])*.
   Note 3: Conditions that would contraindicate the use of breast milk are detailed in the Pediatric Nutrition Handbook 5th Ed. American Academy of Pediatrics *(Kleinman 2004 [O])*.

[b] 95%CI: 95% Confidence Interval expresses the uncertainty (precision) of a measured value; it is the range of values within which we can be 95% sure that the true value lies. A study with a larger sample size will generate more precise measurements, resulting in a narrower confidence interval.

2. It is recommended that donor milk be considered, if available and affordable, as an alternative, when mother's own milk is unavailable *(Schanler 2005 [A], Local Expert Consensus [E])*.
   Note 1: Current cost of donor milk is 4 to 5 times higher than formula designed for premature infants.
   Note 2: When recommending the use of donor milk, reimbursement issues may need to be considered and discussed with the family. Donor milk may not be covered by insurance. For more information see www.hmbana.org .

Feeding strategies

Available studies were reviewed for use of minimal enteral feeds, timing of initiation of feeds, and rates for advancing feeds (see Table 2).

Table 2: Definitions used in studies of feeding issues

Minimal Enteral Feeding	Dilute or full strength formula feedings providing < 25kcal/kg/day (37cc/kg/day) for > 5 days *(Tyson 2003 [M])* 0.5 to 1ml/hr to extubation *(McClure 2000 [A])* 20ml/kg/day, day 4 to 14 *(Schanler 1999 [A])* In all studies, controls were not fed by mouth
Timing of Initiation of Feeds	Definitions of early versus late initiation varied among studies reviewed. Early – day 1 to 5 Late – day 5 to 14 *(Kennedy 2003b [M])*
Rate of Advancement of Feeds	Rates of advancement varied with overlapping categories from study to study 10 to 20cc/kg/day slow 20 to 35cc/kg/day fast *(Kennedy 2003a [M])* 20ml/kg/day X 10 day versus increase by 20ml/kg/day to 140ml/kg/day *(Berseth 2003 [A])*

Minimal Enteral Feeding:

3. There is insufficient evidence regarding the role of minimal enteral feedings in preventing NEC.
   Note 1: A meta-analysis reviewing 6 studies showed use of minimal feeds had no effect on risk of NEC *(Tyson 2003 [M])*.
   Note 2: Inclusion of two additional randomized controlled trials (RCTs) did not alter results of the meta-analysis *(McClure 2000 [A], Schanler 1999 [A])*.

Timing of Initiation of Feeds

4. There is insufficient evidence to support either early or delayed initiation of feeding relative to risk for NEC *(Kennedy 2003b [M], Wilson 1997 [A], LaGamma 1985 [C], McKeown 1992 [D])*.

Rate of Advancement of Feeds

5. There is insufficient evidence to recommend a specific rate of feeding volume advancement in relation to NEC risk.

   Note 1: No difference in NEC risk was observed in studies advancement as low as 10cc/kg/day and as high as 35cc/kg/day *(Kennedy 2003a [M], Kamitsuka 2000 [D])*.

   Note 2: One large study showed a decreased rate of NEC in infants maintained at 20cc compared to those children advanced. Inclusion of this study did not alter results of the meta-analysis *(Berseth 2003 [A])*.

Transpyloric versus gastric feeding

6. There is insufficient evidence to support either transpyloric or gastric feeding methods relative to the risk of NEC *(McGuire 2003b [M])*.

Bolus versus continuous feeding

7. There is insufficient evidence to support either bolus or continuous tube feeding as a method to reduce the risk of NEC *(Premji 2003 [M])*.

Umbilical Artery Catheters (UAC)

8. There is insufficient evidence to recommend a specific placement location for the tip of the umbilical artery catheter. Umbilical artery catheter position (high versus low) has not been found to effect the incidence of NEC *(Barrington 2003 [M])*.

9. There is insufficient evidence to evaluate the risk of NEC associated with enteral feeding while an umbilical artery catheter is in place.

   Note: One small randomized trial found no difference in the incidence of NEC between infants fed early, with a UAC in place, and those in which feeds were delayed until 24 hours after UAC removal *(Davey 1994 [B])*.

Probiotics

10. There is insufficient evidence to recommend either use or avoidance of probiotics. Clinical trials of the effects of probiotics on the risk of NEC have not consistently shown benefit.

    Note 1: One large observational study showed a significant decrease in NEC compared to historical controls when infants were treated with lactobacillus and bifidobacterium *(Hoyos 1999 [D])*.

    Note 2: One large RCT of lactobacillus GG found no significant effect on the incidence of NEC in very low birth weight (VLBW) infants *(Dani 2002 [A])*.

    Note 3: A second large RCT of lactobacillus and bifidobacterium in VLBW infants found a significant reduction in NEC incidence among treated infants *(Lin 2005 [A])*.

    Note 4: Issues regarding the safety of probiotic use in immunodeficient hosts such as preterm infants have been raised, particularly the potential for sepsis. None of the clinical trials reported harmful side effects although they were not powered to evaluate safety *(Land 2005 [O])*.

Additional Prevention Strategies

11. The following prevention strategies have been evaluated in large sample size, randomized, controlled trials or meta-analyses with no statistically significant effects on NEC risk.

    Amino acid supplementation

    - enteral glutamine *(Vaughn 2003 [A])*
    - IV glutamine *(Poindexter 2004 [A])*
    - enteral arginine *(Amin 2002 [A])*

    Immunoglobulins

    - oral IgG or IgA/IgG combination *(Foster 2004 [M], Rubaltelli 1991 [A], Eibl 1988 [A])*
      Note: There is no RCT of IgA alone for the prevention of NEC.
    - IV IgG *(Fanaroff 1994 [A])*

    Antibiotics

    - Results from a meta-analysis of 5 studies suggest that oral aminoglycosides decrease the incidence of NEC. However, lack of information on other outcomes including mortality and development of resistant bacteria precludes any recommendation *(Bury 2003 [M])*.
    - oral or intravenous erythromycin *(Ng 2003 [M])*

    Where evidence is present but sparse, information is shared below for purposes of awareness even if conclusions can not be made.

Acidification

12. It is recommended that histamine-2 receptor (H2) blocker therapy for gastric acidity be used with caution. Two studies suggest that gastric pH alters risk for NEC.

    Note 1: One small RCT showed that acidification of feeds was associated with decreased risk of NEC *(Carrion 1990 [B])*.

    Note 2: One large retrospective case-control study showed a significant association between H2-blocker therapy and higher rates of NEC *(Guillet 2006 [D])*.

Supplemental Vitamin E

13. In those at greatest risk for NEC, studies suggest that supplemental vitamin E may increase the risk of NEC with no effect on other outcomes with the exception of risk of severe retinopathy of prematurity which may be less *(Brion 2003 [M], Johnson 1985 [A], Finer 1984 [D])*.

Prenatal Indomethacin

14. There is insufficient evidence to recommend either use or avoidance of prenatal indomethacin related to risk of NEC *(Parilla 2000 [D], Vermillion 1999 [D], Major 1994 [D], Norton 1993 [D])*.

Postnatal Indomethacin

15. Evidence does not support an altered risk of NEC with use of indomethacin for prevention of intraventricular hemorrhage *(Fowlie 2003 [M])* or treatment of patent ductus arteriosus (PDA) *(Malviya 2003 [M], Gersony 1983 [A], Cooke 2000 [S])*.

    Note 1: Although the number of infants < 1000gm birth weight was small, a collaborative trial showed no difference on NEC risk using surgical versus indomethacin treatment for PDA *(Gersony 1983 [A])*.

    Note 2: No difference in NEC risk has been noted between ibuprofen and indomethacin used for PDA treatment or prevention *(Shah 2003 [M])*.

Medical Management

Evaluation

Clinical Assessment and Diagnosis

16. Bell's NEC staging system is commonly used to assess NEC severity *(Bell 1978 [C])*. Studies to firmly establish assessment and diagnosis criteria are not available (see Table 1).

Diagnostics

Laboratory Studies

17. While specific pathogens have been isolated from stools and abdominal fluid during outbreaks of NEC, no specific pathogen has been found to have a consistent causal relationship with NEC *(de la Cochetiere 2004 [C], Peter 1999 [C], Millar 1996 [C], Rotbart 1988 [C], Blakey 1985 [C], Thomas 1984 [C], Gupta 1994 [D], Keller 1991 [D], Sherertz 1982 [D])*.

18. There is insufficient evidence to support the use of stool patterns, presence of occult blood or presence of specific pathogens as clinical indicators of NEC risk *(Peter 1999 [C], Abramo 1988 [C], Andrews 1997 [D])*.

19. There is insufficient evidence for use of gastric residuals as a predictor of NEC. Gastric residuals in infants who developed NEC tended to be larger, but significant overlap in the amount of residual precludes its use as a marker for NEC *(Cobb 2004 [D])*.

Radiologic Studies

20. It is recommended that an abdominal radiograph be performed in infants with clinical suspicion of NEC *(Bell 1978 [C])*. The influences on infant outcome and diagnostic validity of the number of abdominal X-rays, the type of view(s) or the frequency or timing of abdominal radiographs have not been systematically studied.

    Note 1: Inter-observer reliability of radiographic signs of NEC is low *(Napoli 2004 [D])*.

    Note 2: While positive radiographic findings have good predictive value, negative studies must be interpreted with caution *(Tam 2002 [D], Kosloske 1994 [D])*.

Intervention

Medications

21. There is insufficient evidence on benefit or risk regarding choice of antibiotic regimens or duration of antibiotic treatment of NEC *(Faix 1988 [B], Scheifele 1987 [C])*.

    Note: Decisions regarding antibiotic choice and duration might best be guided by:
    - culture results
    - antibiotic resistance patterns present within nurseries

    (Local Expert Consensus [E]).

22. There is insufficient evidence on benefit or risk of routine clindamycin use for treatment of NEC *(Faix 1988 [B])*.

    Note: One small randomized controlled trial using clindamycin showed an increase in bowel strictures *(Faix 1988 [B])*.

23. There is insufficient evidence on benefit or risk of oral aminoglycoside use for the treatment of NEC *(Hansen 1980 [B])*.

Nutrition

24. There is insufficient evidence on benefit or risk regarding the timing of reinitiating feeding once the diagnosis of NEC has been made.

    Note: One retrospective study evaluating the impact of early initiation of feeding (< 10 days from diagnosis) suggests a positive impact. Early feeding was associated with a shorter time to full feeds, less catheter related sepsis, and a shorter hospital stay. The study was underpowered to evaluate recurrence risk of NEC *(Bohnhorst 2003 [C])*.

Paracentesis

25. Abdominal paracentesis may be helpful to confirm the presence of intestinal gangrene in infants with NEC *(Ricketts 1986 [D], Kosloske 1982 [D])*. Indications for paracentesis are absence of pneumoperitoneum and one of the following:
    - portal venous gas
    - erythema of abdominal wall
    - fixed, tender abdominal mass
    - persistently dilated intestinal segment
    - clinical deterioration (see Table 3)

    Note: Positive results reliably predict the presence of intestinal gangrene (accuracy 90% to 97.5%). A "positive" result is considered an aspiration of 0.5ml of peritoneal fluid and one of the following:
    - yellow-brown or brown staining fluid
    - Gram stain positive for bacteria

    However, a negative result does not reliably exclude the presence of intestinal gangrene (40% false negative rate) *(Kosloske 1994 [D], Ricketts 1986 [D])*.

Surgical Management

Site of Care

26. It is recommended that neonates with suspected NEC be transferred to a facility that can meet their possible surgical needs if surgical services are not available within the admitting institution. A safe transfer is best achieved when the child is hemodynamically stable. Indications for transfer might include.
    - pneumoperitoneum
    - radiographic evidence of portal venous gas *(Buras 1986 [D])*

    (Local Expert Consensus [E]).

    Note: Evidence suggests that portal gas or diffuse pneumatosis is associated with more severe disease (see Evaluation and Intervention Recommendation #28 below).

Evaluation and Intervention

27. It is recommended that neonates with clinical/radiographic evidence of pneumoperitoneum be evaluated by a surgeon in a center in which operative intervention can be performed if indicated. Pneumoperitoneum represents an **absolute** indication for surgical intervention *(Tam 2002 [D], Kosloske 1994 [D], Kosloske 1980 [D])*.

28. It is recommended that neonates with clinical/radiographic evidence of intrahepatic venous gas (portal venous gas) be evaluated by a surgeon in a center in which operative intervention can be performed if indicated *(Molik 2001 [C], Tam 2002 [D], Kosloske 1994 [D], Rowe 1994 [D], Kennedy 1987 [D], Buras 1986 [D])*.

29. The following conditions may be considered as **relative** indications for surgical consultation in a center in which operative intervention can be performed if indicated:
    - abdominal wall cellulitis
    - fixed dilated intestinal segment by X-ray
    - tender abdominal mass
    - clinical deterioration refractory to medical management (see Table 3)

    (Local Expert Consensus [E]).

Table 3: Relative indications for surgical consultation

- persistent metabolic acidosis
- persistent thrombocytopenia
- increasing respiratory support
- increased third-space fluid losses, hypovolemia, oliguria
- leukopenia, leukocytosis

(Ververidis 2001 [D], Gupta 1994 [D], Buras 1986 [D], Local Expert Consensus [E])

30. Radiographic signs of NEC have high specificity but low sensitivity, with poor negative predictive values. It is recommended that the decisions regarding surgical intervention be based on both the clinical and radiological presentation. It is recommended that decisions regarding the need for surgical intervention not be made solely on the basis of absent radiographic signs *(Tam 2002 [D], Kosloske 1994 [D])*.

31. One retrospective study compared the use of the neonatal intensive care unit for surgery versus transport to an operating room setting for neonates weighing less than 1500g with severe NEC. Transport of neonates less than 1500g from an intensive care unit to an operating room is associated with deterioration in physiologic parameters *(Frawley 1999 [D])*.

32. The role of percutaneous drainage versus exploratory laparotomy is controversial *(Moss 2001 [M], Ahmed 1998 [D], Azarow 1997 [D], Morgan 1994 [D], Cheu 1988 [D])*. A multicenter, prospective, randomized trial of percutaneous drainage compared to laparotomy, in 117 very low birth weight newborns with NEC and intestinal perforation, demonstrated no difference in short term outcomes *(Moss 2006 [A])*. No recommendation can be made on surgical approach at the time of publication of this guideline.

Future Research Agenda

In VLBW infants at risk for NEC:

- What is the best way to ensure that human milk is available, used and safe when needed?
- What is the impact of donor human milk compared to mothers own milk on NEC?
- Does delaying the initiation of enteral feeding, when breast milk is not immediately available, compared to early feeding with formula decrease the risk of NEC?
- Does early compared to late initiation of feeding decrease the risk of NEC? And, does nutrition related harm associated with delayed initiation of feeding outweigh the benefits of possibly reduced NEC risk?
- Does the rate of advancement of the volume of feeds impact the risk of NEC?
- Are the benefits of human milk to reduce the risk of NEC related to the type of milk (own versus donor, fresh versus frozen, early [colostrum] versus late, formula supplemented versus not)?
- What is the impact of use of human milk fortifiers on the risk of NEC?
- Does initiation of fortification of human milk earlier compared to later impact the risk of NEC? And, does nutrition related harm associated with use of fortifiers outweigh the benefits of possibly reduced NEC risk?
- Does supplementation with probiotics reduce the risk of NEC?

In the VLBW infant with suspected NEC

- Which abdominal X-ray views have the best diagnostic accuracy for NEC?
- Which X-ray views are the best predictors of need for surgical intervention?
- How often should abdominal X-rays be obtained to identify infants in need of surgical intervention?
- Does nutrition-related harm associated with discontinuing feedings outweigh the benefits on not feeding infants with active NEC?
- What are the best predictors of need for surgical intervention?

In the VLBW infant with definite NEC

- How long should gastric suction be continued for infants treated medically for NEC?
- How long should infants being treated medically for NEC remain NPO?
- How long should antibiotics be continued in infants with blood culture negative NEC?
- What are the indications for immediate surgical intervention in infants with NEC?
- Should surgery for NEC be performed in the NICU or in the OR?
- Is there a role for primary anastomosis after NEC resection?

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Development Process & Methods

The process by which this guideline was developed is documented in the CCHMC Guideline Development Process Manual http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/resources.htm .

Meeting minutes are maintained. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using the grading scale that follows. The working group also examined current local clinical practices.

CCHMC Grading Scale			
M	Meta-analysis or Systematic Review	S	Review Article
A	Randomized controlled trial: large sample	E	Expert opinion or consensus
B	Randomized controlled trial: small sample	F	Basic Laboratory Research
C	Prospective trial or large case series	L	Legal requirement
D	Retrospective analysis	Q	Decision analysis
O	Other evidence	X	No evidence

Cincinnati clinicians responsible for the care of patients with NEC were asked to submit clinical questions using the PICO format *(Moyer 2004 [S])*. Using these questions as guides, two independent computerized, OVID, literature searches of Medline and the Cochrane databases were performed (BH and ED). Searches employed a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by eliminating duplicates, most review articles, non-English articles and articles on NEC in adults. The resulting abstracts were reviewed by a methodologist to eliminate low quality citations.

The following search strategies were used: Necrotizing enterocolitis as a phrase in the title or as a subject heading was combined with established filters for clinical articles in the diagnosis, therapy, etiology or prognosis domains. The search was limited to human, English, infants as an age group, and 1980 through May 2003. During the course of the guideline development, additional clinical questions were generated and subjected to the search process.

Titles and abstracts of the identified citations (619) were initially categorized independently by two guideline team leaders as definitely included in guideline development (all RCTs, all meta-analyses, all systematic reviews and all observational studies with comparison groups and sample sizes greater than 50), definitely not included (case reports, letters, observational studies without control groups and/or sample size less than 30) and those possibly included. Studies in the included and possibly included categories were re-reviewed by the methodologist and other guideline team members to assure that studies to be appraised in detail were relevant to the clinical questions that were used to develop search terms. Complete copies of the remaining articles were organized by question and distributed to the team according to each member's expressed interest and area of expertise. All selected studies were appraised by the methodologist and at least two team members using a standardized form for evaluating design, sample size, methods and findings.

A search using the above criteria was conducted for dates of May, 2003 through July, 2006. Four of these citations have been added to the document, and one of these references was determined to require a change to the 2005 version of the guideline (recommendation #12). Thirty-four additional relevant articles were selected as potential future citations for the guideline.

Appropriate companion documents have been or will be developed to assist in the effective dissemination and implementation of the guideline.

The literature search will be rerun every 6 months. The guideline team will reconvene to explore identified, relevant studies of high quality.

During formulation of these guidelines, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

The guidelines have been reviewed and approved by clinical experts not involved in the development process, and other individuals as appropriate to their intended purposes.

The guideline was developed without external funding. All Team Members and Clinical Effectiveness support staff listed have declared whether they have any conflict of interest.

Building upon this guideline, a multi-organizational improvement team that includes representatives of Cincinnati's three Level 3 Neonatal Intensive Care Units (NICUs) was chartered in spring, 2005 to work as a team to decrease NEC incidence through increased human milk (HM) consumption.

The NEC Improvement team is applying a quality improvement (QI) approach to the implementation of recommendations in the guideline. We are using the Model for Improvement developed by the Institute for Healthcare Improvement, which guides us through developing aims for improvement in NEC rates, HM consumption, and other process measures; testing good ideas on a small scale to see if they lead to improvement; and using simple data collection and analysis strategies to understand the impact of the tests of change. With the support of the National Institute of Child Health and Human Development (NICHD) Neonatal Network, we will be tracking data related to both NEC incidence and human milk consumption in nearly 100% of VLBW babies admitted to the three NICUs. HM data will help us not only understand whether our QI work is leading to improvement in HM consumption, but will also further our knowledge regarding the potential relationship between HM, other factors, and NEC.

NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This guideline does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this guideline is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about these guidelines, their supporting evidences and the guideline development process, contact the Health Policy & Clinical Effectiveness office at: 513-636-2501 or ***HPCEInfo@cchmc.org*** .

References

Note: When using the electronic version of this document, _____☜ refers to journal articles that have a clickable link to the abstract.

1. **Abramo, T. J.; Evans, J. S.; Kokomoor, F. W.; and Kantak, A. D.:** Occult blood in stools and necrotizing enterocolitis. Is there a relationship? *American Journal of Diseases of Children*, 142(4): 451-2, 1988, *[C]* _____☜.
2. **Ahmed, T.; Ein, S.; and Moore, A.:** The role of peritoneal drains in treatment of perforated necrotizing enterocolitis: recommendations from recent experience. *Journal of Pediatric Surgery*, 33(10): 1468-70, 1998, *[D]* _____☜.
3. **Amin, H. J.; Zamora, S. A.; McMillan, D. D.; Fick, G. H.; Butzner, J. D.; Parsons, H. G.; and Scott, R. B.:** Arginine supplementation prevents necrotizing enterocolitis in the premature infant.[comment]. *Journal of Pediatrics*, 140(4): 425-31, 2002, *[A]* _____☜.
4. **Andrews, J. D., and Krowchuk, H. V.:** Stool patterns of infants diagnosed with necrotizing enterocolitis. *Neonatal Network - Journal of Neonatal Nursing*, 16(6): 51-7, 1997, *[D]* _____☜.
5. **Azarow, K. S.; Ein, S. H.; Shandling, B.; Wesson, D.; Superina, R.; and Filler, R. M.:** Laparotomy or drain for perforated necrotizing enterocolitis: who gets what and why? *Pediatric Surgery International*, 12(2-3): 137-9, 1997, *[D]* _____☜.
6. **Barrington, K. J.:** Umbilical artery catheters in the newborn. *Cochrane Database of Systematic Reviews*, (1), 2003, *[M]* _____☜.
7. **Bell, M. J.; Ternberg, J. L.; Feigin, R. D.; Keating, J. P.; Marshall, R.; Barton, L.; and Brotherton, T.:** Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*, 187(1): 1-7, 1978, *[C]* _____☜.
8. **Berseth, C. L.; Bisquera, J. A.; and Paje, V. U.:** Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*, 111(3): 529-34, 2003, *[A]* _____☜.
9. **Bisquera, J. A.; Cooper, T. R.; and Berseth, C. L.:** Impact of necrotizing enterocolitis on length of stay and hospital charges in very low birth weight infants. *Pediatrics*, 109(3): 423-8, 2002, *[D]* _____☜.
10. **Blakey, J. L.; Lubitz, L.; Campbell, N. T.; Gillam, G. L.; Bishop, R. F.; and Barnes, G. L.:** Enteric colonization in sporadic neonatal necrotizing enterocolitis. *Journal of Pediatric Gastroenterology & Nutrition*, 4(4): 591-5, 1985, *[C]* _____☜.
11. **Bohnhorst, B.; Muller, S.; Dordelmann, M.; Peter, C. S.; Petersen, C.; and Poets, C. F.:** Early feeding after necrotizing enterocolitis in preterm infants. *J Pediatr*, 143(4): 484-7, 2003, *[C]* _____☜.
12. **Brion, L.; Bell, E.; and Raghuveer, T.:** Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. *SO - Cochrane Database of Systematic Reviews 2003;(1)*, 2003, *[M]* _____☜.
13. **Buras, R.; Guzzetta, P.; Avery, G.; and Naulty, C.:** Acidosis and hepatic portal venous gas: indications for surgery in necrotizing enterocolitis. *Pediatrics*, 78(2): 273-7, 1986, *[D]* _____☜.
14. **Bury, R. G., and Tudehope, D.:** Enteral antibiotics for preventing necrotizing enterocolitis in low birthweight or preterm infants [Systematic Review]. *Cochrane Database of Systematic Reviews*, 1: 1, 2003, *[M]* _____☜.
15. **Carrion, V., and Egan, E. A.:** Prevention of neonatal necrotizing enterocolitis. *Journal of Pediatric Gastroenterology & Nutrition*, 11(3): 317-23, 1990, *[B]* _____☜.
16. **Cheu, H. W.; Sukarochana, K.; and Lloyd, D. A.:** Peritoneal drainage for necrotizing enterocolitis. *Journal of Pediatric Surgery*, 23(6): 557-61, 1988, *[D]* _____☜.
17. **Cobb, B. A.; Carlo, W. A.; and Ambalavanan, N.:** Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants. *Pediatrics*, 113(1 Pt 1): 50-3, 2004, *[D]* _____☜.
18. **Cooke, R. J., and Embleton, N. D.:** Feeding issues in preterm infants. *Arch Dis Child Fetal Neonatal Ed*, 83(3): F215-8, 2000, *[S]* _____☜.
19. **Dani, C.; Biadaioli, R.; Bertini, G.; Martelli, E.; and Rubaltelli, F. F.:** Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. A prospective double-blind study. *Biology of the Neonate*, 82(2): 103-8, 2002, *[A]* _____☜.
20. **Davey, A. M.; Wagner, C. L.; Cox, C.; and Kendig, J. W.:** Feeding premature infants while low umbilical artery catheters are in place: a prospective, randomized trial. *Journal of Pediatrics*, 124(5 Pt 1): 795-9, 1994, *[B]* _____☜.
21. **de la Cochetiere, M. F.; Piloquet, H.; des Robert, C.; Darmaun, D.; Galmiche, J. P.; and Roze, J. C.:** Early intestinal bacterial colonization and necrotizing enterocolitis in premature infants: the putative role of Clostridium. *Pediatr Res*, 56(3): 366-70, 2004, *[C]* _____☜.
22. **Eibl, M. M.; Wolf, H. M.; Furnkranz, H.; and Rosenkranz, A.:** Prevention of necrotizing enterocolitis in low-birth-weight infants by IgA-IgG feeding. *New England Journal of Medicine*, 319(1): 1-7, 1988, *[A]* _____☜.
23. **Faix, R. G.; Polley, T. Z.; and Grasela, T. H.:** A randomized, controlled trial of parenteral clindamycin in neonatal necrotizing enterocolitis. *Journal of Pediatrics*, 112(2): 271-7, 1988, *[B]* _____☜.

24. **Fanaroff, A. A. et al.:** A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. *New England Journal of Medicine*, 330(16): 1107-1113, 1994, *[A]* ☜.

25. **Finer, N. N.; Peters, K. L.; Hayek, Z.; and Merkel, C. L.:** Vitamin E and necrotizing enterocolitis. *Pediatrics*, 73(3): 387-93, 1984, *[D]* ☜.

26. **Foster, J., and Cole, M.:** Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates [Systematic Review]. *Cochrane Database of Systematic Reviews*, 1: 1, 2004, *[M]* ☜.

27. **Fowlie, P. W., and Davis, P. G.:** Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database of Systematic Reviews*, (1), 2003, *[M]* ☜.

28. **Frawley, G.; Bayley, G.; and Chondros, P.:** Laparotomy for necrotizing enterocolitis: intensive care nursery compared with operating theatre. *J Paediatr Child Health*, 35(3): 291-5, 1999, *[D]* ☜.

29. **Gersony, W. M.; Peckham, G. J.; Ellison, R. C.; Miettinen, O. S.; and Nadas, A. S.:** Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr*, 102(6): 895-906, 1983, *[A]* ☜.

30. **Goulet, O.; Ruemmele, F.; Lacaille, F.; and Colomb, V.:** Irreversible intestinal failure. *J Pediatr Gastroenterol Nutr*, 38(3): 250-69, 2004, *[S]* ☜.

31. **Gross, S. J.:** Growth and biochemical response of preterm infants fed human milk or modified infant formula. *N Engl J Med*, 308(5): 237-41, 1983, *[B]* ☜.

32. **Guillet, R.; Stoll, B. J.; Cotten, C. M.; Gantz, M.; McDonald, S.; Poole, W. K.; Phelps, D. L.; and National Institute of Child Health and Human Development Neonatal Research, N.:** Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants.[see comment]. *Pediatrics*, 117(2): e137-42, 2006, *[D]* ☜.

33. **Gupta, S. K.; Burke, G.; and Herson, V. C.:** Necrotizing enterocolitis: laboratory indicators of surgical disease. *Journal of Pediatric Surgery*, 29(11): 1472-5, 1994, *[D]* ☜.

34. **Guthrie, S. O.; Gordon, P. V.; Thomas, V.; Thorp, J. A.; Peabody, J.; and Clark, R. H.:** Necrotizing enterocolitis among neonates in the United States. *J Perinatol*, 23(4): 278-85, 2003, *[D]* ☜.

35. **Hansen, T. N.; Ritter, D. A.; Speer, M. E.; Kenny, J. D.; and Rudolph, A. J.:** A randomized, controlled study of oral gentamicin in the treatment of neonatal necrotizing enterocolitis. *Journal of Pediatrics*, 97(5): 836-9, 1980, *[B]* ☜.

36. **Hoyos, A. B.:** Reduced incidence of necrotizing enterocolitis associated with enteral administration of Lactobacillus acidophilus and Bifidobacterium infantis to neonates in an intensive care unit. *International Journal of Infectious Diseases*, 3(4): 197-202, 1999, *[D]* ☜.

37. **Johnson, L. et al.:** Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birth weight 1,500 grams or less. *Pediatrics*, 75(4): 619-38, 1985, *[A]* ☜.

38. **Kamitsuka, M. D.; Horton, M. K.; and Williams, M. A.:** The incidence of necrotizing enterocolitis after introducing standardized feeding schedules for infants between 1250 and 2500 grams and less than 35 weeks of gestation. *Pediatrics*, 105(2): 379-84, 2000, *[D]* ☜.

39. **Keller, K. M.; Schmidt, H.; Wirth, S.; Queisser-Luft, A.; and Schumacher, R.:** Differences in the clinical and radiologic patterns of rotavirus and non-rotavirus necrotizing enterocolitis. *Pediatric Infectious Disease Journal*, 10(10): 734-8, 1991, *[D]* ☜.

40. **Kennedy, J.; Holt, C. L.; and Ricketts, R. R.:** The significance of portal vein gas in necrotizing enterocolitis. *Am Surg*, 53(4): 231-4, 1987, *[D]* ☜.

41. **Kennedy, K. A.; Tyson, J. E.; and Chamnanvanakij, S.:** Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infants. *Cochrane Database of Systematic Reviews*, 1(1), 2003a, *[M]* ☜.

42. **Kennedy, K. A.; Tyson, J. E.; and Chamnanvanikij, S.:** Early versus delayed initiation of progressive enteral feedings for parenterally fed low birth weight or preterm infants. *Cochrane Database of Systematic Reviews*, (1), 2003b, *[M]* ☜.

43. **Kleinman, R.:** *Pediatric Nutrition Handbook.* American Academy of Pediatrics: Chicago, IL, 2004, *[O]*.

44. **Kliegman, R. M., and Fanaroff, A. A.:** Necrotizing enterocolitis. *N Engl J Med*, 310(17): 1093-103, 1984, *[S]* ☜.

45. **Kosloske, A. M.:** Indications for operation in necrotizing enterocolitis revisited. *Journal of Pediatric Surgery*, 29(5): 663-6, 1994, *[D]* ☜.

46. **Kosloske, A. M., and Goldthorn, J. F.:** Paracentesis as an aid to the diagnosis of intestinal gangrene: experience in 50 infants and children. *Arch Surg*, 117(5): 571-5, 1982, *[D]* ☜.

47. **Kosloske, A. M.; Papile, L. A.; and Burstein, J.:** Indications for operation in acute necrotizing enterocolitis of the neonate. *Surgery*, 87(5): 502-8, 1980, *[D]* ☜.

48. **LaGamma, E. F.; Ostertag, S. G.; and Birenbaum, H.:** Failure of delayed oral feedings to prevent necrotizing enterocolitis. Results of study in very-low-birth-weight neonates. *American Journal of Diseases of Children*, 139(4): 385-9, 1985, *[C]* ☜.

49. **Land, M. H.; Rouster-Stevens, K.; Woods, C. R.; Cannon, M. L.; Cnota, J.; and Shetty, A. K.:** Lactobacillus sepsis associated with probiotic therapy. *Pediatrics*, 115(1): 178-81, 2005, *[O]* _____.

50. **Lin, H. C.; Su, B. H.; Chen, A. C.; Lin, T. W.; Tsai, C. H.; Yeh, T. F.; and Oh, W.:** Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*, 115(1): 1-4, 2005, *[A]* _____.

51. **Local Expert Consensus:** During Guideline Development Timeframe, *[E]*.

52. **Lucas, A., and Cole, T. J.:** Breast milk and neonatal necrotising enterocolitis. *Lancet*, 336(8730): 1519-23, 1990, *[A]* _____.

53. **Major, C. A.; Lewis, D. F.; Harding, J. A.; Porto, M. A.; and Garite, T. J.:** Tocolysis with indomethacin increases the incidence of necrotizing enterocolitis in the low-birth-weight neonate. *American Journal of Obstetrics & Gynecology*, 170(1 Pt 1): 102-6, 1994, *[D]* _____.

54. **Malviya, M.; Ohlsson, A.; and Shah, S.:** Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. *Cochrane Database of Systematic Reviews*, (1), 2003, *[M]* _____.

55. **McClure, R. J., and Newell, S. J.:** Randomised controlled study of clinical outcome following trophic feeding. *Arch Dis Child Fetal Neonatal Ed*, 82(1): F29-33, 2000, *[A]* _____.

56. **McGuire, W., and Anthony, M. Y.:** Formula milk versus preterm human milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews*, (1), 2003a, *[M]* _____.

57. **McGuire, W., and Anthony, M. Y.:** Formula milk versus term human milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews*, (1), 2003b, *[M]* _____.

58. **McKeown, R. E.; Marsh, T. D.; Amarnath, U.; Garrison, C. Z.; Addy, C. L.; Thompson, S. J.; and Austin, J. L.:** Role of delayed feeding and of feeding increments in necrotizing enterocolitis. *Journal of Pediatrics*, 121(5 Pt 1): 764-70, 1992, *[D]* _____.

59. **Millar, M. R.; Linton, C. J.; Cade, A.; Glancy, D.; Hall, M.; and Jalal, H.:** Application of 16S rRNA gene PCR to study bowel flora of preterm infants with and without necrotizing enterocolitis. *J Clin Microbiol*, 34(10): 2506-10, 1996, *[C]* _____.

60. **Molik, K. A.; West, K. W.; Rescorla, F. J.; Scherer, L. R.; Engum, S. A.; and Grosfeld, J. L.:** Portal venous air: the poor prognosis persists. *J Pediatr Surg*, 36(8): 1143-5, 2001, *[C]* _____.

61. **Morgan, L. J.; Shochat, S. J.; and Hartman, G. E.:** Peritoneal drainage as primary management of perforated NEC in the very low birth weight infant. *J Pediatr Surg*, 29(2): 310-4; discussion 314-5, 1994, *[D]* _____.

62. **Moss, R. L. et al.:** Laparotomy versus peritoneal drainage for necrotizing enterocolitis and perforation. *N Engl J Med*, 354(21): 2225-34, 2006, *[A]* _____.

63. **Moss, R. L.; Dimmitt, R. A.; Henry, M. C.; Geraghty, N.; and Efron, B.:** A meta-analysis of peritoneal drainage versus laparotomy for perforated necrotizing enterocolitis. *Journal of Pediatric Surgery*, 36(8): 1210-3, 2001, *[M]* _____.

64. **Moyer, V. A., and Elliott, E. J.:** *Evidence based pediatrics and child health.* BMJ Books: London, 2004, *[S]*.

65. **Napoli, A. D.; Di Lallo, D.; Perucci, C. A.; Schifano, P.; Orzalesi, M.; Franco, F.; and De Carolis, M. P.:** Inter-observer reliability of radiological signs of necrotising enterocolitis in a population of high-risk newborns. *Paediatric and Perinatal Epidemiology*, 18: 80-87, 2004, *[D]* _____.

66. **Ng, E., and Shah, V.:** Erythromycin for feeding intolerance in preterm infants. *Cochrane Database of Systematic Reviews*, (1), 2003, *[M]* _____.

67. **Norton, M. E.; Merrill, J.; Cooper, B. A.; Kuller, J. A.; and Clyman, R. I.:** Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med*, 329(22): 1602-7, 1993, *[D]* _____.

68. **Parilla, B. V.; Grobman, W. A.; Holtzman, R. B.; Thomas, H. A.; and Dooley, S. L.:** Indomethacin tocolysis and risk of necrotizing enterocolitis. *Obstetrics & Gynecology*, 96(1): 120-3, 2000, *[D]* _____.

69. **Peter, C. S.; Feuerhahn, M.; Bohnhorst, B.; Schlaud, M.; Ziesing, S.; von der Hardt, H.; and Poets, C. F.:** Necrotising enterocolitis: is there a relationship to specific pathogens? *Eur J Pediatr*, 158(1): 67-70, 1999, *[C]* _____.

70. **Poindexter, B. B. et al.:** Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants. *Pediatrics*, 113(5): 1209-15, 2004, *[A]* _____.

71. **Premji, S., and Chessell, L.:** Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. *Cochrane Database Syst Rev*, (1): CD001819, 2003, *[M]* _____.

72. **Rayyis, S. F.; Ambalavanan, N.; Wright, L.; and Carlo, W. A.:** Randomized trial of "slow" versus "fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. *Journal of Pediatrics*, 134(3): 293-7, 1999, *[A]* _____.

73. **Ricketts, R. R.:** The role of paracentesis in the management of infants with necrotizing enterocolitis. *American Surgeon*, 52(2): 61-5, 1986, *[D]* _____.

74. **Rotbart, H. A.; Nelson, W. L.; Glode, M. P.; Triffon, T. C.; Kogut, S. J.; Yolken, R. H.; Hernandez, J. A.; and Levin, M. J.:** Neonatal rotavirus-associated necrotizing enterocolitis: case control study and prospective surveillance during an outbreak. *Journal of Pediatrics*, 112(1): 87-93, 1988, *[C]* _____.

75. **Rowe, M. I.; Reblock, K. K.; Kurkchubasche, A. G.; and Healey, P. J.:** Necrotizing enterocolitis in the extremely low birth weight infant. *J Pediatr Surg*, 29(8): 987-90; discussion 990-1, 1994, *[D]* _____.

76. **Rubaltelli, F. F.; Benini, F.; and Sala, M.:** Prevention of necrotizing enterocolitis in neonates at risk by oral administration of monomeric IgG. *Developmental Pharmacology & Therapeutics*, 17(3-4): 138-43, 1991, *[A]* _____.

77. **Salhab, W. A.; Perlman, J. M.; Silver, L.; and Sue Broyles, R.:** Necrotizing enterocolitis and neurodevelopmental outcome in extremely low birth weight infants <1000 g. *J Perinatol*, 24(9): 534-40, 2004, *[D]* _____.

78. **Schanler, R. J.; Lau, C.; Hurst, N. M.; and Smith, E. O.:** Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants.[see comment]. *Pediatrics*, 116(2): 400-6, 2005, *[A]* _____.

79. **Schanler, R. J.; Shulman, R. J.; Lau, C.; Smith, E. O.; and Heitkemper, M. M.:** Feeding strategies for premature infants: randomized trial of gastrointestinal priming and tube-feeding method. *Pediatrics*, 103(2): 434-9, 1999, *[A]* _____.

80. **Scheifele, D. W.; Ginter, G. L.; Olsen, E.; Fussell, S.; and Pendray, M.:** Comparison of two antibiotic regimens for neonatal necrotizing enterocolitis. *Journal of Antimicrobial Chemotherapy*, 20(3): 421-9, 1987, *[C]* _____.

81. **Shah, S. S., and Ohlsson, A.:** Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews*, (1), 2003, *[M]* _____.

82. **Sherertz, R. J., and Sarubbi, F. A.:** The prevalence of Clostridium difficile and toxin in a nursery population: a comparison between patients with necrotizing enterocolitis and an asymptomatic group. *Journal of Pediatrics*, 100(3): 435-9, 1982, *[D]* _____.

83. **Stoll, B. J.:** Epidemiology of necrotizing enterocolitis. *Clin Perinatol*, 21(2): 205-18, 1994, *[S]* _____.

84. **Svenningsen, N. W.; Lindroth, M.; and Lindquist, B.:** A comparative study of varying protein intake in low birthweight infant feeding. *Acta Paediatr Scand Suppl*, 296: 28-31, 1982, *[B]* _____.

85. **Tam, A. L.; Camberos, A.; and Applebaum, H.:** Surgical decision making in necrotizing enterocolitis and focal intestinal perforation: predictive value of radiologic findings. *Journal of Pediatric Surgery*, 37(12): 1688-91, 2002, *[D]* _____.

86. **Thomas, D. F.; Fernie, D. S.; Bayston, R.; and Spitz, L.:** Clostridial toxins in neonatal necrotising enterocolitis. *Arch Dis Child*, 59(3): 270-2, 1984, *[C]* _____.

87. **Tyson, J. E., and Kennedy, K. A.:** Minimal enteral nutrition for promoting feeding tolerance and preventing morbidity in parenterally fed infants. *Cochrane Database of Systematic Reviews*, (1), 2003, *[M]* _____.

88. **Tyson, J. E.; Lasky, R. E.; Mize, C. E.; Richards, C. J.; Blair-Smith, N.; Whyte, R.; and Beer, A. E.:** Growth, metabolic response, and development in very-low-birth-weight infants fed banked human milk or enriched formula. I. Neonatal findings. *J Pediatr*, 103(1): 95-104, 1983, *[B]* _____.

89. **Uauy, R. D.; Fanaroff, A. A.; Korones, S. B.; Phillips, E. A.; Phillips, J. B.; and Wright, L. L.:** Necrotizing enterocolitis in very low birth weight infants: biodemographic and clinical correlates. National Institute of Child Health and Human Development Neonatal Research Network. *Journal of Pediatrics*, 119(4): 630-8, 1991, *[S]* _____.

90. **Vaughn, P.; Thomas, P.; Clark, R.; and Neu, J.:** Enteral glutamine supplementation and morbidity in low birth weight infants. *J Pediatr*, 142(6): 662-8, 2003, *[A]* _____.

91. **Vermillion, S. T., and Newman, R. B.:** Recent indomethacin tocolysis is not associated with neonatal complications in preterm infants. *Am J Obstet Gynecol*, 181(5 Pt 1): 1083-6, 1999, *[D]* _____.

92. **Ververidis, M.; Kiely, E. M.; Spitz, L.; Drake, D. P.; Eaton, S.; and Pierro, A.:** The clinical significance of thrombocytopenia in neonates with necrotizing enterocolitis. *Journal of Pediatric Surgery*, 36(5): 799-803, 2001, *[D]* _____.

93. **Vohr, B. R. et al.:** Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics*, 105(6): 1216-26, 2000, *[C]* _____.

94. **Wilson, D. C.; Cairns, P.; Halliday, H. L.; Reid, M.; McClure, G.; and Dodge, J. A.:** Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed*, 77(1): F4-11, 1997, *[A]* _____.

95. **Wilson, R.; Kanto, W. P., Jr.; McCarthy, B. J.; Burton, T.; Lewin, P.; Terry, J.; and Feldman, R. A.:** Epidemiologic characteristics of necrotizing enterocolitis: a population-based study. *American Journal of Epidemiology*, 114(6): 880-7, 1981, *[D]* _____.

