



Anderson Center for Health Systems
Excellence

Evidence-Based Care Guideline

Necrotizing Enterocolitis (NEC) among very low birth weight infants^a

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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)

For this guideline, NEC is classified according to Bell's clinical staging (see Appendix) (Bell 1978 [4b]).

Population-based estimates of NEC range from 0.72 to 2.4 cases per 1,000 live births (Holman 2006 [4a], Llanos 2002 [4a]). In-hospital case fatality rates are approximately 16% to 20% (Holman 2006 [4a]). Case fatality rates are higher in very low birth weight (VLBW) infants, infants with more severe disease, and infants requiring surgery (Holman 2006 [4a], Lin 2008 [5a]). NEC-associated morbidities, including short bowel syndrome, contribute significantly to poor growth and neurodevelopmental outcomes and to increased health-

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care costs (Schulzke 2007 [1b], Vohr 2000 [2b], Salhab 2004 [4a], Bisquera 2002 [4a], Goulet 2004 [5b]).

This guideline provides evidence-based recommendations for management of NEC. The objectives of this guideline are:

- To provide strategies for the prevention of NEC in VLBW infants
- To improve diagnostic accuracy
- To improve functional and quality of life outcomes for infants with Bell stage II or greater NEC
- To improve patient/parent and family satisfaction

Etiology

NEC is primarily a disease of premature infants. Low birth weight is the most important risk factor (Guthrie 2003 [4a]). The pathophysiology of NEC is poorly understood, but is likely multifactorial (Lin 2008 [5a], Henry 2009 [5b]). Immaturity of the intestinal tract which predisposes to intestinal injury and inappropriate responses to injury have been implicated in the etiology. Abnormal bacterial colonization and genetic predisposition are increasingly recognized as important contributing factors (Lin 2008 [5a]). In a cohort study of 4039 ELBW infants, longer durations of initial empirical antibiotic use (≥ 5 days) were associated with NEC or death (NNH [number needed to harm] = 22) (Cotten 2009 [3a]). The role, if any, of specific feeding strategies on NEC risk, such as the method of feeding (bolus versus continuous, gastric versus transpyloric) or the timing of introduction of feeding is also unclear (Premji 2009 [1b], Bombell 2008 [1b]). It has been suggested that certain pharmacological agents (e.g., supplemental Vitamin E (Brion 2003 [1a]), antenatal indomethacin (Amin 2007 [1b]), and histamine-2 receptor (H2) blocker therapy (Guillet 2006 [4b])) may contribute to NEC risk in VLBW infants.

Because the etiology of NEC remains uncertain, effective prevention and treatment strategies are a challenge. The most effective way to decrease morbidity and mortality from NEC would be to decrease the number of preterm births (Lin 2008 [5a]).

Potential prevention strategies with research ongoing include arginine supplementation, IgA supplementation, epidermal growth factor and erythropoietin (Shah 2007 [1a], Lin 2008 [5a]). Studies of glutamine supplementation have not shown benefit for the prevention of NEC (Tubman 2009 [1a]). Administration of oral or intravenous immunoglobulins has failed to demonstrate significant effects on NEC (Foster 2004 [1a], Ohlsson 2004 [1a]). 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 2009 [1a]*). There may be a role for probiotics in the prevention of NEC (*Deshpande 2010 [1a]*, *AlFaleh 2009 [1a]*, *Morowitz 2010 [5b]*, *Tarnow-Mordi 2010 [5b]*). In a meta-analysis of 11 trials (N=2176), the number needed to treat with probiotics to prevent 1 case of NEC was 25 (95% CI: 17, 34) (*Deshpande 2010 [1a]*).

The identification of markers for NEC is needed to improve prevention, early diagnosis and treatment. Gastric residuals are a factor in feeding intolerance that can be easily measured and compared. However, the relationship between gastric residuals and subsequent NEC remains unknown. Although gastric residuals in VLBW infants tend to be larger immediately before the diagnosis of NEC, a significant overlap in the volume of residuals among infants with and without a subsequent diagnosis of NEC precludes its use as a marker for the disease (*Cobb 2004 [4b]*).

Guideline Recommendations

Prevention

Feeding strategies

- It is recommended that infants be fed with mother's own milk to decrease risk of NEC (*Schanler 2005 [2a]*, *Sullivan 2010 [2b]*, *Meinzen-Derr 2009 [4a]*, *Local Consensus [5]*).

Note 1: The number of infants needed to treat with an exclusively human milk-based diet to prevent 1 case of NEC is 10 [NNT for NEC = 10]. The number needed to prevent 1 case of surgical NEC or death is 8 [NNT for surgical NEC or death = 8] (*Sullivan 2010 [2b]*)

Note 2: Conditions that would contraindicate the use of breast milk are detailed in the American Academy of Pediatrics Position Statement (*Gartner 2005 [5b]*).
- It is recommended that donor milk be considered, if accessible, as an alternative to formula when mother's own milk is unavailable (*Quigley 2009 [1a]*, *McGuire 2003 [1a]*, *Boyd 2007 [1b]*, *Sullivan 2010 [2b]*, *Local Consensus [5]*).

Note: 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

- It is recommended that enteral fasting^b **not** be used as a strategy to decrease NEC risk (*Bombell 2009 [1a]*).

Note: A meta-analysis of nine trials (n=754) did not detect a significant effect of early trophic feeding^c versus enteral fasting on incidence of NEC: typical relative risk 1.07 (95% CI 0.67, 1.70); typical risk difference 0.01 (95% CI -0.04, 0.05) (*Bombell 2009 [1a]*).
- It is recommended, when the infant is judged ready to tolerate feeding advancement, that feeding volume be advanced by 15 to 35ml/kg/day (*McGuire 2008 [1a]*, *Local Consensus [5]*).

Note 1: No difference in NEC risk was observed in three trials (396 total infants) of feeding volume advancement as low as 15ml/kg/day and as high as 35ml/kg/day (*McGuire 2008 [1a]*).

Note 2: Slow advancement of feeding volume may lengthen the need for parenteral nutrition and its associated complications.

Pharmacotherapy

- It is recommended that a single course of antenatal corticosteroid be given prior to preterm delivery (*Roberts 2009 [1a]*, *Smith 2000 [4b]*).

Note: Use of antenatal steroids is associated with a decreased risk of NEC (NNT = 32) (*Roberts 2009 [1a]*).
- It is recommended that ibuprofen rather than indomethacin be used for closure of patent ductus arteriosus (PDA) (*Ohlsson 2010 [1a]*).

Note 1: In a meta-analysis examining ibuprofen versus indomethacin for closure of PDA, 15 trials (n=865) reported on an outcome of NEC (any stage). The risk of developing NEC was reduced for ibuprofen (typical RR 0.68 (95% CI 0.47, 0.99); typical RD -0.04 (95% CI -0.08, -0.00); (p = 0.04) (*Ohlsson 2010 [1a]*).

Note 2: Although ibuprofen is associated with lower serum creatinine levels and a lower incidence of oliguria, both ibuprofen and indomethacin are associated with potentially

^b Enteral fasting is defined as delaying the introduction of enteral feeds until after five to seven postnatal days (*Bombell 2009 [1a]*).

^c Studies included in the meta-analysis used early trophic feeding of enteral milk volumes up to 24ml/kg/day (1mg/kg/hour) beginning within four days after birth and continuing until at least one week after birth (*Bombell 2009 [1a]*).

serious adverse effects (*Ohlsson 2008 [1a]*). See Table 1.

Table 1: Complications of ibuprofen compared to indomethacin for the treatment of PDA (*Ohlsson 2008 [1a]*)

Ibuprofen	Indomethacin
<ul style="list-style-type: none"> Decreased bilirubin albumin binding capacity Pulmonary hypertension Chronic lung disease 	<ul style="list-style-type: none"> Transient or permanent derangement of renal function NEC Gastrointestinal hemorrhage or perforation Altered platelet function Impairment of cerebral blood flow/ cerebral blood flow velocity

Assessment and Diagnosis

Radiologic Studies

7. It is recommended that an abdominal radiograph be performed in infants with clinical suspicion of NEC (*Tam 2002 [4a], Di Napoli 2004 [4b], Bell 1978 [4b]*).

Note 1: Inter-observer reliability of radiographic signs of NEC is low (*Di Napoli 2004 [4b]*).

Note 2: Radiographic signs of NEC have high specificity but low sensitivity, with poor negative predictive values (*Tam 2002 [4a]*).

Note 3: 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.

Consults and Referrals

8. It is recommended that infants
- with suspected NEC be cared for in a level III neonatal intensive care unit (NICU) (*Local Consensus [5]*)
 - with suspected NEC and one or more indications for surgical consultation (see Table 2) be considered for transfer to a level III facility with surgical services available (*Local Consensus [5]*)
 - with evidence of pneumoperitoneum or portal venous gas be evaluated by a surgeon in a facility in which operative intervention can be performed if indicated (*Molik 2001 [3b], Tam 2002 [4a], Kosloske 1994 [4b], Rowe 1994 [4b]*)

Table 2: Indications for surgical consultation (*Gupta 1994 [3b], Ververidis 2001 [4b], Buras 1986 [4b], Local Consensus [5]*)

<ul style="list-style-type: none"> Abdominal wall cellulitis
<ul style="list-style-type: none"> Fixed dilated intestinal segment by X-ray
<ul style="list-style-type: none"> Tender abdominal mass
<ul style="list-style-type: none"> Clinical deterioration refractory to medical management: <ul style="list-style-type: none"> metabolic acidosis thrombocytopenia increasing respiratory support increased third-space fluid losses, hypovolemia, oliguria leukopenia, leukocytosis hyperkalemia

Education

9. It is recommended that mothers at risk for preterm delivery be given information on the protective effects of human milk and be encouraged to express their milk (*Local Consensus [5], Gartner 2005 [5b]*).

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?
- How long should the use of donor milk be continued after it is initiated?
- 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 lack of fortifiers outweigh the benefits of possibly reduced NEC risk?

- Does supplementation with probiotics or prebiotics reduce the risk of NEC?
- Do the risks of prophylactic enteral antibiotics for prevention of NEC outweigh the benefits?
- Does longer duration of initial empirical antibiotic treatment increase the risk for NEC?
- Does the postnatal prophylactic use of indomethacin increase NEC risk?
- Does the placement of umbilical artery catheters effect 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?
- Does percutaneous drainage versus exploratory laparotomy improve outcomes for VLBW infants with NEC?
- What are the risks for progression to surgical NEC for infants with 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?
- Among infants with NEC receiving GI resection, what is the relationship between amount of intestine lost and long term outcome? What is the relationship between site of intestine lost and long term outcome?

Appendix

Bell's Staging for Necrotizing Enterocolitis (*Bell 1978 [4b]*)

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		

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Development Process

The process by which this guideline was developed is documented in the [Guideline Development Process Manual](#). The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic search and critical appraisal of the literature, using the Table of Evidence Levels described following the references, and examined current local clinical practices.

To select evidence for critical appraisal by the group for this guideline, the Medline, CINAHL and the Cochrane databases were searched for dates of 1996 through August 2010 to generate an unrefined, “combined evidence” database using a search strategy focused on answering clinical questions relevant to

necrotizing enterocolitis and employing 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, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. Some relevant review articles were identified. All citations from the original version of this guideline were reviewed for appropriateness to this revision.

Once the guideline has been in place for three years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed.

The guideline was externally appraised by three reviewers using the AGREE instrument and the results by domain are:

- Scope and Purpose 78%
- Stakeholder Involvement 50%
- Rigor of Development 87%
- Clarity and Presentation 75%
- Applicability 59%
- Editorial Independence 94%

Recommendations have been formulated by a consensus process directed by best evidence and clinical expertise. During formulation of these recommendations, 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.

The guideline has been reviewed and approved by clinical experts not involved in the development process, distributed to senior management, and other parties 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 and none were identified.

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.

Copies of this Evidence-based Care Guideline (EBCG) and its any available implementation tools are available online and may be

distributed by any organization for the global purpose of improving child health outcomes. Website address: <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/evidence-based/default.htm> Examples of approved uses of the EBCG include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care guidelines;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the EBCG may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any EBCG, or its companion documents, adopted, adapted, implemented or hyperlinked by the organization is appreciated.

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 Anderson Center for Health Systems Excellence (evidence group) at: 513-636-2501 or HPCEInfo@cchmc.org .

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Note: When using the electronic version of this document,  indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the CCHMC network.

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Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (*direct benefit*)
4. Burden to patient of adherence to recommendation (*cost, hassle, discomfort, pain, motivation, ability to adhere, time*)
5. Cost-effectiveness to healthcare system (*balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis*)
6. Directness (*the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]*)
7. Impact on morbidity/mortality or quality of life