

European Reference Network for Inherited and Congenital Anomalies Evidence-Based Guideline on Surgical Aspects of Necrotizing Enterocolitis in Premature Neonates.

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Spain v Department of Pediatric Surgery, Azienda Ospedaliera di Padova, Padua , Italy w Department of Developmental Biology and Cancer, UCL GOS Institute of Child Health, London , UK x Department of Pediatric Surgery, Karolinska University Hospital, Solna , Sweden Correspondence to: Jan Hulscher, j.b.f.hulscher@umcg.nl 19 11 2024 6 2025 122 3 489739 376 384 19 7 2024 29 10 2024 2025 19 11 2024 03 06 2025 05 06 2025 © 2024 The Author(s). Published by S. Karger AG, Basel 2024 <https://creativecommons.org/licenses/by-nc/4.0/> This article is licensed under the Creative Commons Attribution 4.0 International License (CC BY) (<http://www.karger.com/Services/OpenAccessLicense>). Usage, derivative works and distribution are permitted provided that proper credit is given to the author and the original publisher. Abstract Necrotizing enterocolitis (NEC) is a severe intestinal condition primarily affecting preterm neonates. It has a high mortality rate, particularly in infants with a birthweight of below 1,500 g or for those requiring surgical intervention. The European Reference Network for Inherited and Congenital Anomalies (ERNICA) has developed a clinical practice guideline to aid clinical decision-making pertaining to the surgical treatment and management of NEC in preterm neonates. This guideline was developed in accordance with the Guidelines 2.0 checklist and GRADE methodology. A multidisciplinary group of Europe's top experts collaborated with patient representatives to develop this guideline. After selecting critical points in care for which recommendations are required, a systematic review of the literature and critical appraisal of the evidence was performed. The Evidence to Decision framework was used as a guide to structure the consensus meetings and draft the recommendations. The panel developed seven recommendations and three good practice statements on the following topics: indications for surgery, peritoneal drainage, surgical technique, management of extensive NEC, enteral feeding, and neurodevelopmental outcomes in premature neonates with NEC. The certainty of evidence was graded as (very) low for most recommendations. However, the panel weighed up the benefits and harms in light of all relevant arguments and expert opinion. This guideline provides recommendations on caring for premature neonates with NEC. These recommendations can assist clinicians in their care decisions and can inform families on treatment options and relevant considerations. This guideline will be revised every 5 years to ensure it remains up to date.

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The European Reference Network for Inherited and Congenital Anomalies (ERNICA) is the ERN for rare inherited and congenital digestive disorders, including NEC. To the best of our knowledge, there are no systematically developed guidelines to assist clinical decision-making for NEC. We therefore aimed to develop such a guideline for the treatment of (surgical) NEC, specifically for preterm neonates with a confirmed diagnosis (based on clinical symptoms and/or pneumatosis intestinalis on imaging, Modified Bell's classification stage IIa and higher [2]) This guideline aims to answer important questions concerning the surgical treatment, management, and prognosis of preterm neonates with a NEC diagnosis. In doing so, it aims to support healthcare providers and parents to make informed decisions about the care for these babies while simultaneously highlighting evidence gaps and promoting a research agenda. We aim to set a standard for treatment and care pathways, to benefit preterm neonates with NEC requiring surgery, both in the short and long term. NEC in neonates born at term is not considered part of this guideline, nor is NEC prevention or diagnosis.

This guideline was developed in accordance with the Guidelines 2.0 checklist [3] and GRADE methodology [4 , 5]. The supplementary materials include a full description of the methods (online suppl. S1; for all online suppl. material, see <https://doi.org/10.1159/000542540>) that were applied to develop this guideline, as well as all Evidence to Decision (EtD) tables (online suppl. S2). The guideline development group (GDG) met on several occasions to (1) prioritize and select questions and critical outcomes, (2) discuss results of the literature review and (3) discuss recommendations according to the EtD framework. Using a shortened Delphi procedure the GDG selected 8 key questions and outcomes of interest to be addressed in this guideline, shown in Table 1 . The EtD framework was used as a guide to structure a 2 day consensus meeting, with most members of the GDG present. During this meeting, considerations, recommendations, and research needs emerging from the literature analysis were discussed. To prepare for this meeting, a summary of findings from all modules was distributed among GDG members. This was accompanied by an electronic survey seeking input on all aspects of the EtD framework (Panel Voice). The GDG selected a recommendation strength between Strong or Conditional and indicated whether they supported (for) or opposed (against) an intervention (shown in Table 2). In accordance with the GRADE methodology, a low “certainty” of evidence did not preclude a strong recommendation, and a weak recommendation was also possible with a high certainty of evidence. The strength of the recommendation was always determined by weighing up all relevant arguments.

Key questions addressed in this guideline

Types of recommendations and their wording

All recommendations are shown in Table 3 . Full EtD tables can be found in the online supplementary materials (S2). Revisions of this guideline will be scheduled every 5 years following the ERNICA protocol for revising guidelines. All recommendations can be considered valid until revised.

Recommendation The panel suggests not to interpret the presence of a fixed bowel loop (as a single parameter) as an absolute indication for surgery, but instead consider the presence of a fixed bowel loop in combination with other factors.

Evidence summary: One retrospective study on the prevalence of fixed bowel loop in 38 NEC patients, and its relationship with the type of treatment (surgical versus conservative) and death was retrieved [6]. No significant differences between patients with or without a fixed bowel loop were found and the certainty of evidence was rated ‘very low’. No articles were found eligible to analyze clinical deterioration while receiving intensive medical care or the presence of portal air as an indication for surgery.

Considerations and Justification: Despite the absence of RCTs, the available evidence suggests that both the intervention and the comparison yield similar outcomes. However, given that surgery is more invasive and carries a higher risk of side effects, the panel concluded that the balance of effects likely favors the comparison. Based on the current evidence, it appears that the presence of a fixed bowel loop alone may not be a definitive indication for surgery. Issuing a firm recommendation for the intervention is likely not feasible due to varying expert experiences and the lack of clear evidence favoring one approach over the other.

Recommendations The panel suggests to choose either initial laparotomy or initial drainage to treat patients with suspected or confirmed perforation due to NEC, based on preferences and experiences of the treatment center.

The panel suggests peritoneal drainage as a bridge treatment in cases where early operation is not possible or available.

The panel recommends that families of the patients should always be adequately informed that if drainage is chosen as the primary option, many patients will not improve or will deteriorate and subsequently require a laparotomy.

As many patients will require subsequent laparotomy if primary drainage is chosen, a pediatric surgeon should be consulted and the patient should always be transferred to an expert center.

Evidence summary: Two RCTs comparing initial drainage to initial laparotomy with a total of 212 patients were included [7 , 8]. Laparotomy seemed to result in fewer deaths compared to primary drainage, but results were not statistically significant. No significant differences were found in complications or neurodevelopment. Despite the inclusion of two RCTs, the certainty of evidence for mortality was rated as low as there were strong concerns regarding selection bias and imprecision. The certainty of evidence for the other outcomes was rated as moderate.

Considerations and Justification: Starting the treatment strategy with a peritoneal drainage seems to be as effective as the laparotomy when it comes to survival of the patient. A third trial which was initially excluded because of the population included (NEC as well as spontaneous intestinal perforation patients) was considered but also did not show a significant difference [9]. The panel recognized both as viable options for patients with NEC. However, it was recognized that many of the patients who received primary drainage had a subsequent laparotomy and a secondary laparotomy was significantly more frequent in the primary drainage group compared to the primary laparotomy group [7]. However, drainage is less invasive, may have the advantage of immediate decompression, and may prevent exposure to general anesthesia in at least some of the patients. No studies that explored drainage as a bridging treatment could be included. The aim of these studies was to compare drainage and laparotomy as primary interventions. However, since the mortality rates do not seem to differ, even after secondary laparotomy, these conclusions could support the idea of peritoneal drain placement as bridge treatment. The panel emphasized that the downsides of a drain (high possibility of needing a second intervention due to further deterioration of the patient or a lack of improvement) should always be considered and discussed with the family. As the analyzed studies only included patients based on pneumoperitoneum or pneumatosis intestinalis, we did not gain any insight into the role of drainage versus laparotomy in patients with a surgical indication due to deteriorating clinical or biochemical status.

Recommendation The panel suggests considering a primary anastomosis if the baby is stable and the remaining bowel is either unaffected or perfused well enough to attempt primary anastomosis, especially in the case of a threatening short bowel.

Evidence summary : Four studies with a total of 239 patients have been evaluated to explore the effect of bowel resection and enterostomy versus resection and primary anastomosis on mortality, NEC-related complications, NEC recurrence, and neurodevelopmental outcomes [10 – 13]. There were no significant differences in mortality or NEC recurrence, but intelligence at the age of 6–13 years was lower in children that were treated with enterostomy. The panel could not draw a conclusion on the effect of surgical techniques on the number of complications as only two small retrospective studies could be included, and their results were conflicting. The certainty of evidence for all conclusions is very low, mainly due to the retrospective design of the studies included.

Considerations and Justification: Compared to primary anastomosis, enterostomy creation warrants a second procedure for stoma closure. Undergoing only one as opposed to two surgical procedures is beneficial in order to avoid possible (serious) adverse events, risks related to anesthesia or prolonged hospital stay. The choice of surgical method should occur during laparotomy and depends on the stability of the baby, bowel viability, degree of contamination, and the extent of the resection. In addition, the personal experience of the operating surgeon may influence this decision. Primary anastomosis may not be feasible for some patients, but the panel concluded that if only one operation can achieve similar or better long-term outcomes, this probably has an advantage over two operations. Panel members further discussed situations or factors that could mean certain “subgroups” of patients benefit more from the recommendation than others. Even though we found

no evidence to support this, experts on the panel agreed that in the case of threatening short bowel, considering primary anastomosis is highly valuable (if feasible).

Good practice statement The decision to continue surgical treatment or to offer comfort care is up to the treating team to decide, but should not be based on the length of the bowel alone. All important factors need to be taken into account, as well as the uncertainty concerning the long-term outcomes for these patients.

Evidence summary: No evidence could be included for analysis.

Considerations and Justification : The panel found it difficult to define a grade of bowel affection severity indicating a withdrawal of care. Ethical considerations arise for disease progressions ranging from NEC-totalis or near-totalis to <30 cm of remaining bowel [14 – 16]. It remains undetermined if there is also an association between the length of the necrotic bowel and (neurodevelopmental) outcome if the patient survives surgery. Evidence that even <30 cm of the remaining small intestine may allow for parenteral nutrition weaning is increasing, and some authors suggest post-NEC patients have a greater weaning potential than those with short bowel syndrome arising from other causes [17]. Therefore, the panel agrees that the bowel length cannot solely be used to make a decision on whether to continue treatment.

Recommendation The panel suggests to start enteral feeding within 7 days after surgery for NEC in patients without active signs of ongoing disease or obstruction, with or without a stoma.

Evidence summary: Two studies with a total of 187 patients with surgical NEC were analyzed [18 , 19]. There are no differences in regard to mortality, NEC recurrence, or strictures between groups that had an early reintroduction and later reintroduction of enteral feeding. Despite a very low certainty of evidence, we found indications that patients with surgical NEC that have an early reintroduction of feeding are less likely to need parenteral nutrition at 28 days and have shorter hospital stays.

Considerations and Justification: The possible benefits of early reintroduction of feeding after medical surgery for NEC may be large, despite low evidence quality. Panel members agree that adequate nutrition supports normal brain development. Additionally, they also recognize that earlier enteral feeding is possibly beneficial for the development of the bowel (even if via nasogastric tube) and may prevent oral aversion. No undesirable effects of early feeding were detected in the evaluation of evidence; however, long-term effects were not considered in these studies. The decrease length of hospital stay for the early feeding groups could lead to large cost savings for hospitals. If earlier feeding does not lead to any disadvantage, a recommendation in favor of early feeding for medical NEC could make it accessible for more patients, thereby increasing equity.

Recommendations Extreme low birthweight and/or the (need for) surgical intervention seem to be factors that further increase the risk for neurodevelopmental disability and impaired quality of life. This should be considered when providing information on neurodevelopmental prognosis.

The panel recommends to include information on the neurodevelopmental prognosis alongside other factors relevant to the patient when counseling on care decisions such as surgery for NEC in preterm infants.

The panel recommends to closely follow-up these patients with regard to their neurodevelopment.

Evidence summary: The panel analyzed six studies reporting on neurodevelopment after surgery for NEC [20 – 24] and performed a subgroup analysis for neonates with a birthweight ≤ 750 g [25 , 26]. Where possible, surgical NEC patients were compared to peers with medical NEC and premature neonates without NEC. Compared to peers without NEC, surgical NEC patients seem to have lower scores on mental development and psychomotor development tests at 18–24 months of

age and at cognitive tests at school age. It is unclear if patients with surgical NEC have impaired mental and psychomotor development compared to peers with medical NEC as the results of studies in the analysis were conflicting. It is likely that neonates with a birthweight of ≤ 750 g who survived surgery for NEC are at higher risk for any severe or moderate neurodevelopmental disability, severe mental developmental delay, and severe psychomotor delay at 18–24 months old compared to peers with medical NEC and peers without a history of NEC.

Considerations and Justification: For the analysis without weight as a cut-off, the overall certainty of evidence is low. Evidence levels were rated as low because of the inconsistency and lack of correction for important confounders, such as intra-ventricular hemorrhages during NICU stay. The body of evidence for the subgroup of neonates with a birthweight of ≤ 750 g was low due to concerns regarding the correction for confounders; many but not all important confounders were included in the corrected analysis. Despite the limitations in regard to the quality of this evidence, panel members believe that this information on neurodevelopmental prognosis should be part of providing complete information to families and should not be left out. The importance families and physicians attach to neurodevelopmental outcomes will likely be different for different people in different countries. This may be strongly influenced by personal, cultural, social, and religious factors. Therefore, the panel does not provide a recommendation on care decisions based on this prognostic factor but wants to emphasize the importance of taking this prognostic factor into consideration during counseling.

This guideline aimed to provide answers to seven prominent clinical questions and form recommendations to optimize the care for neonates with NEC. Seven recommendations and three good practice statements were developed. These recommendations can assist clinicians in their care decisions and can inform families on the treatment options and relevant considerations.

As in other rare diseases, the available evidence on NEC is scarce and of poor quality. Almost all of the included studies have major methodological limitations. Some of these may be induced by the context of the disease, others by poor methodological design. As a consequence, the average certainty of evidence of the included studies is “low” to “very low.” This leaves the panel with very little certainty over the conclusion and with minimal evidence-based input for recommendations. In five of our six modules, the evidence quality was considered too low for the panel to be confident enough to make strong recommendations. This is recognized as a limitation for the applicability of evidence-based guideline development methods in rare diseases.

Besides the aforementioned limitations, there are also considerable strengths of this guideline, particularly falling within the AGREE II domains “rigor of development” and “stakeholder involvement.” Despite little available and low-quality evidence for most questions, the EtD framework was applied and offered structure to the discussion. The combination of digital surveys and live discussion facilitated a critical assessment of the available evidence and its possible implications for clinical practice. As the digital surveys prior to the consensus meeting enabled all panel members to comment on the different aspects of the EtD, even those who could not be present at the meeting. A large group of Europe’s top experts was closely involved in all steps of the process and was composed of pediatric surgeons, neonatologists, gastroenterologists, and patient/family representatives. A draft version of this guideline was circulated within ERNICA for peer review and key experts beyond Europe were invited to participate in this review as well. Altogether, this led to a set of balanced recommendations which were validated by a large, varied group of experts.

Despite a full systematic review of the literature and a rigorous methodological approach to development, several questions remain unanswered. To allow for continuous quality improvement in the care of premature neonates with NEC, the panel identified research priorities. Among other things, these research priorities include reaching a formal consensus on the definition of clinical deterioration (despite maximum conservative treatment) and the establishment of a European feeding protocol for NEC patients. Supplement 3 contains an overview of all identified knowledge gaps and research priorities. To allow for continuous quality improvement of NEC care, ERNICA

will add NEC to the European Pediatric Surgery Audit (EPSA).

This guideline provides recommendations on indications for surgery, peritoneal drainage, surgical techniques, extensive NEC, enteral feeding and neurodevelopment in premature neonates with NEC. These recommendations can assist clinicians in their care decisions and can inform families on treatment options and relevant considerations. This guideline will be revised every 5 years to ensure it remains up to date.

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