Review Article

An update on the management of necrotizing enterocolitis: Surgical perspective

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Abstract

Necrotizing enterocolitis (NEC) is the most common of neonatal surgical emergency. The initial signs are nonspecific and often indistinguishable from other neonatal problems. Abdominal radiography (AR) is the first modality imaging for diagnosis NEC and remains as the standard modality since the Bell staging system was developed. Ultrasonography (US) playing an increasing role in NEC. There is the potential for US to bridge the lack of sensitivity of AR for NEC. Understanding the influence of the pathophysiological dynamic of NEC and its variation with gestational age on AR or US findings is important to distinguish NEC from NEC-like conditions. Surgical NEC consisting of laparotomy and/or defunctionalize bowel and peritoneal drainage in unstable patients. The options are determined by hemodynamics, comorbidities and extend of the disease. There is wide variation in practice patterns across surgeons and institutions. Future guidelines should focus on evidence-based support for individualized decisions rather than uniform protocols to fit all.

Key word: Necrotizing enterocolitis, NEC

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Introduction

Key points

• Necrotizing enterocolitis is the most common type of neonatal surgical emergency.[1]

• Surgical NEC is in 30% to 50% of NEC cases, and carries a 30% to 50% mortality risk, with up to 70% morbidity.[2 - 5]

• The question of peritoneal drainage versus laparotomy as both primary and definitive forms of therapy are remains controversial.[2, 6]

Necrotizing enterocolitis (NEC) occurs in approximately 1 in 1,000 live births, 14% in extremely low birth weight infant, increasing as neonatal care is required for premature infants.[4] The pathogenesis of NEC is multifactorial. Some of the causes include: an immature gut barrier, altered bacterial colonization, and intestinal ischemia. These insults trigger the inflammatory process, resulting in intestinal barrier failure and as a result NEC.[4, 5, 7, 8] The factors associated with an increase in NEC incidence is shown in Table 1. The differential diagnosis varies according to experts. (Table 2) The aspects which influences the differential diagnosis include: the clinical picture, radiographic findings, degree of prematurity, and age of onset.[9] Although the initial signs are nonspecific and often indistinguishable from other GI emergencies and neonatal sepsis, the combination of radiological evidence and biomarker data can be substantial to the diagnosis.[4]

Table 1 Factors linked to increased NEC incidence[5, 8, 10 - 13]

Factors related to the infant
• Prematurity
• Very low birth weight (<1,500 g)
• Low Apgar score at 5 min
• Formula feeding
• Mechanical ventilation
• Intestinal dysbiosis
• Acute hypoxia
• Poor intestinal perfusion
• Blood transfusions
• Anaemia
• infection
• Congenital defects
o Congenital heart disease
o Patent ductus arteriosus
o Gastroschisis
• Pharmacological interventions
o Indomethacin
o Indomethacin tocolysis
o Histamine H2 receptor antagonists
o Prolonged empirical antibiotic use (≥5 days)
o Concomitant use of indomethacin and glucocorticoids

Table 1 Factors linked to increased NEC incidence[5, 8, 10 - 13]

Factors related to the mother
• HIV-positive status
• Illicit drug abuse (including opiates, cannabinoids and cocaine)
• Chorioamnionitis
• Mode of delivery
• In-utero growth restriction
• Increased body mass index
• Intrahepatic cholestasis during pregnancy
• Lack of prenatal steroids
• Placental abruption
• Preeclampsia
• Smoking

Table 2 Differential diagnosis[5, 6, 14]

Differential diagnosis
Paralytic ileus in sepsis
Spontaneous intestinal perforation
Feeding intolerance of the premature
Gastrointestinal malformation
Ileus from meconium or other obstruction
Hirschsprung's disease
Viral enteritis/gastroenteritis
Cow milk protein allergy
Food protein intolerance
Others:
Tympanism due to CPAP
Hypoperfusion/circulatory insufficiency, e.g. due to congenital heart disease, polycytemia
Immature gastrointestinal motility
Paralytic ileus due to other causes than sepsis (metabolic, hypokalemia, hypothyroidism, narcotics)
Incarcerated hernia
Obstipation
Eosinophilic proctocolitis

The role of imaging and investigations for monitoring and decision on surgery.

Abdominal radiography (AR) is the first modality imaging for diagnosis and management NEC. It remains as the standard modality since the Bell staging system was developed.[4, 6, 7, 9 - 14] (Table 3) AR with a vertical beam is commonly used, but for the horizontal beam, there is no uniform routine and no clear-cut preference for the supine or left decubitus position.[10] During clinical suspicion for bowel perforation, a horizontal beam cross-table lateral film with the infant placed in the left lateral decubitus position. This is preferable to the typical anterior-posterior abdominal film.

Table 3 Modified Bell's Staging Criteria for NEC [4, 13]

Stage	Systemic signs	Intestinal signs	Radiologic signs	Treatment
IA-suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Elevated pre gavage residuals, mild abdominal distension, emesis, guaiac-positive stool	Normal or intestinal dilation, mild ileus	NPO, antibacterials for 3 days
IB-suspected NEC	Same as IA	Same as above plus bright red blood in stool	Same as IA	Same as above
IIA-definite NEC (mildly ill)	Same as IA	IA and IB signs plus absent bowel sounds. Patient also may have abdominal tenderness.	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibacterials for 7 - 10 days
IIB-definite NEC (moderately ill)	Same as IA plus mild metabolic acidosis and mild thrombocytopenia	IA, IB, and IIA signs. Patient also may have abdominal cellulitis or right lower quadrant mass.	Same as IIA plus portal vein gas. Patient also may have ascites.	NPO, antibacterials for 10 - 14 days
IIIA-advanced NEC (severely ill-bowel intact)	Same as IIB plus hypotension, bradycardia, respiratory acidosis, metabolic acidosis, disseminated intravascular coagulation, and neutropenia	IA, IB, IIA, IIB signs plus peritonitis, marked abdominal tenderness and distension	Same as IIB plus definite ascites	NPO, antibacterials for 10 - 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis
IIIB-advanced NEC (severely ill-bowel perforation)	Same as IIIA	Same as IIIA	Same as IIB plus pneumoperitoneum	Same as IIA plus surgery

Although ultrasonography (US) is not typically used in the initial diagnostic evaluation of NEC, it may be used as first choice in combination with AR, or inconclusive AR.[4, 10, 11, 13] US has more sensitivity and specificity compared to AR.[13, 14] In the early stages of NEC, AR may show nonspecific dilated bowel loops. However, US can identify bowel wall thickening and decreased perfusion, portal venous gas, and pneumatosis intestinalis that may not be noticeable on AR.[6, 13, 14] (Table 4) There is the potential for US to bridge the lack of sensitivity of AR for intestinal perforation and bowel necrosis.[10, 12] Dynamic features of US also allows for real-time visualization of peristalsis when performed with Doppler.[9, 13 - 15] Suggested applications can evaluate fluid in the abdominal cavity and detect intraperitoneal gas in concealed perforation.[6,9,10,13] However, US is more variable in perceptions, depending on the experience.[10, 14] Saving pictures, especially cine loops, together with a systematic approach enables re-evaluation of ultrasonographic examinations and may reduce operator dependency.[4, 10] Despite the absence of radiation and high sensitivity of some ultrasonographic signs for the need of surgery the value and reliability in NEC remains controversial.[10, 13, 14]

Table 4 Comparison of abdominal radiography and ultrasonography signs [4, 6, 9, 14, 17 - 20]

Stage	Abdominal radiography signs	ultrasonography signs
I	- Normal or aspecific intestinal dilation	- Wall thickening: wall thickness greater than 2.6 mm - Abnormal bowel wall echoic pattern: the reduction of normal wall layering - Wall and mesenteric perfusion: increase in vascularity - Initial signs of intestinal pneumatosis: hyperechoic spots
II	- Intestinal dilation - Pneumatosis intestinalis - Portal vein gas - P ersistent loop on sequential radiograph - Separation of intestinal loops - Gasless abdomen	- Extensive pneumatosis intestinalis: multiple hyperechoic spots limited to some continuous wall portions or with a circumferential pattern and affects one or more loops - Portal vein gas: hyperechoic spots, irregularly distributed in the liver parenchyma - Extraintestinal gas/Free air (initial sign of intestinal perforation): hyperechoic spots, expression of small air bubbles between the front surface of the liver and the abdominal wall or between the intestinal loops - Simple ascites
III	-Same as II plus Pneumoperitoneum	- Free air - Bowel wall ischemia: wall thinning, reduction of the wall vascularization - Free fluid between the loops (complex ascites, focal fluid collection): inhomogeneous echostructure with internal echoes and septa - Absent peritalsis

Another modality is near-infrared spectroscopy (NIRS), which is noninvasive, and measures local tissue hemoglobin oxygen saturation by the difference between oxyhemoglobin and deoxyhemoglobin. The abdominal NIRS can detect splanchnic ischemia, reflecting diminishing bowel oxygenation and perfusion. This may allow for an early diagnosis of NEC. By combining NIRS with biomarkers, they could provide a screening tool for NEC.[9, 16]

Understanding the influence of the pathophysiological dynamic of NEC and its variation with gestational age on radiographic or ultrasonographic findings is important to distinguish surgical NEC from less serious NEC and NEC-like conditions.

Numerous approaches have been investigated included biomarkers, in order to detect NEC and to optimize the timing of surgery.[10] Biomarkers, such as platelet count, C-reactive protein, and leukocyte count are used to aid in decision-making.[7, 11, 17] Several other biomarkers are under investigation and none are routinely used in clinical practice. Some of these include: interleukin-8, claudin-3, inter-α inhibitor protein, fecal calprotectin, and urinary intestinal fatty acid binding protein.[7, 9, 17]

Management modality

Modified Bell's Staging Criteria is used to grade the severity of the disease. Based on clinical examination, laboratory results, and radiographic findings, these criteria also outline medical and surgical treatment goals. (Table 3)[4, 5, 10] An important aspect in the effective management of NEC is the need for early diagnosis, before progressing bowel necrosis and perforation. Predicting the need of surgery in Table 5 is regarded more important than formal staging.[10] The only absolute indication for surgery is an intra-abdominal perforation.[1, 6, 10] (Figure 1) There are however relative indications for surgery based on clinical, biochemical and radiological parameters.[1, 10] (Figure 2, 3) Notably, pneumoperitoneum is only present in approximately half of infants with perforation.

Table 5 Indication for surgery [1, 4, 6, 10, 12, 14, 19, 20, 24, 26]

Absolute indication
Pneumoperitoneum, Free intraperitoneal gas / free intraperitoneal fluid
Clinical deterioration despite maximal medical therapy[18]
Positive paracentesis
Relative indication
Clinical
Abdominal wall erythema/ echymosis
Abdominal tenderness
Palpable abdominal mass
Greenish discoloration of the inguinal regions
Metabolic
Metabolic acidosis
Precipitious thrombocytopenia
Hyponatremia
Elevated C-reactive protein (CRP)
Radiological
Extensive pneumatosis
Fixed and dilated bowel loop
Gasless abdomen
Portal venous gas

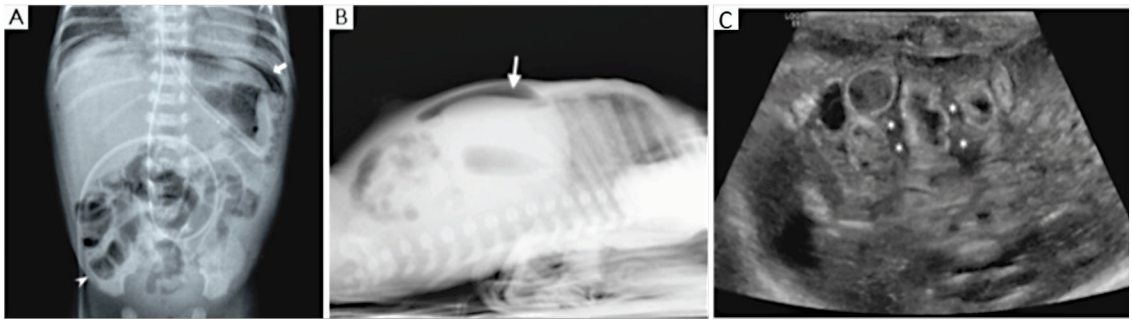

Figure 1 [13] Absolute indication for surgery. A. Supine abdominal film: Free air (arrow) and intestinal pneumatosis (arrow head), B. Lateral decubitus abdominal film: Free air (arrow), C. Ultrasonography: Intraperitoneal free fluid: inhomogeneous free fluid between bowel loops with internal echoes and septa (*). In some intestinal loops hyperechoic spots within the wall are present.

Figure 2 Clinical signs of abdominal and perineum ecchymosis. Notably, a coffee ground in a gastric tube.

Figure 3 [4, 13] A. Supine abdominal film: intestinal pneumatosis (Red circle), B. Ultrasonography: intestinal wall pneumatosis: multiple hyperechoic spots within bowel wall. Gas bubbles interest a limited portion of the wall (arrows).

The tenets of medical therapy are bowel rest, decompression, intravenous fluids and nutrition, antibiotics, serial physical examinations and radiographs.[10] Medical management focuses on preventing disease progression, treating intra-abdominal infection and septicemia, and maintaining hemodynamic stability. However, there is wide variation in antibiotic choice and duration, even within individual centers.[11]

Biological agents may have a role in preventing or treating NEC. In animal models, researchers found lactoferrin, oligosaccharides, Toll-like receptor 4 inhibitors, and probiotics in human breast milk.[4, 5, 8, 9, 11, 19] It has been reported during stem cell experiments that amniotic fluid stem cells, mesenchymal stem cells, and enteric neural system stem cells, could treat NEC.[9, 19]

Surgical NEC carries on 30% to 50% of NEC cases.[2, 3] That is, a 30% to 50% mortality rate and a 40% to 70% morbidity rate, consisting of laparotomy and/or enterostomy and primary peritoneal drainage (PD) in unstable patients.[2 - 4, 20, 21] There are multiple options for surgical therapy depending on hemodynamics, comorbidities, weight, intraoperative finding, surgeon preference and available resources. Regardless of operative strategy, adequate resuscitation efforts to improve perfusion, correct acidosis, and reverse coagulopathy are integral to the treatment of NEC patients.

PD can used as either an adjunctive or definitive therapy.[2 - 4, 11, 16, 20, 22] A bedside drainage catheter placed on the right lower quadrant providing abdominal decompression and removing toxic effluents may promote spontaneous healing. On the contrary, choosing not to excise necrotic bowel is considered to be deleterious due to the ongoing cytokine and inflammatory response it can generate.

Exploratory laparotomy will be performed in a stable patient. The aim of laparotomy is to remove the necrotic bowel and perform primary anastomosis when possible.[1 ,2] The traditional surgical management comprises of removing the necrotic bowel and diverting proximal enterostomy, an option in patients with comorbidity or hemodynamic instability.[1, 2, 6, 20] This method could decompress, divert feces, and get rid of ongoing necrotic bowel, allowing for spontaneous healing of affected segments. Moreover, creating enterostomy could preserve bowel length and get rid of short bowel syndrome by allowing spontaneous healing of disease segments. However, enterostomy also carries risks of fluid and electrolyte imbalances, skin breakdown, stoma complications. These are some strong arguments for considering a primary anastomosis.[1, 2] The primary anastomosis is selected for the more stable patient with limited disease.[1, 20]

Other options in questionably viable bowel, multisegmental NEC, or hemodynamically unstable patient, to preserve bowel length is damage control procedure by proximal diverting jejunostomy or placing a silo or patch or proceeding the clip and drop back technique. Then a follow-up operation within 24 - 48 hours can be used to determine the extension of the necrotic bowel.[1, 11, 20, 23, 24] However, the tendency is to attempt an abdominal closure when it is possible.[11]

Laparoscopy could be an option to evaluate the bowel and the need to further surgery.[11] Regarding the use of carbondioxide insufflation to create an effective laparoscopic it may have a negative impact on the acid-base stability of patients.[1]

Post-NEC complication is mostly stricture formation, which is a consequence of bowel ischemia or necrosis. (Table 6) Post-NEC strictures will present symptoms after initiation of enteral feeding and radiographic signs of obstruction. Unless strictures are symptomatic, they do not require surgical therapy. Thus, contrast studies should be performed in a patient with a history of NEC that developed obstructive symptoms.[2, 6, 20, 25] Currently, practice favors close clinical monitoring over routine contrast studies.[6]

Table 6 Surgical NEC morbidity [2, 4 - 6, 10, 12, 14, 15, 20]

	Incidence (percent)
TPN* dependence	10 - 40[5, 6]
Stricture	10 - 35[4, 5, 25]
Dehiscence	4 - 15[25]
Abscess	5 - 11[25]
Enterocutaneus fistula	5
NEC recurrence	
Short gut syndrome	8 - 35[5, 25]
Malabsorption	
Dysmotility	
Liver hemorrage	
Hernia	
Eenterostomy complications	43 - 50[1, 26, 27]
NDI**	30 - 50[1, 5, 6]

*Total parenteral nutrition, **Neurodevelopmental impairment

Conclusion

Many aspects of NEC management are controversial. There is wide variation in practice patterns across surgeons and institutions.[10, 11] Careful patient selection by the surgeon, based on metabolic derangement and other factors, maybe the key to optimal decision-making when considering laparotomy or PD for particular patient.[2, 22] Numerous questions concerning the optimal management of surgical NEC remains unanswered.

Best practices

What is the role of imaging in NEC management ? [6, 10]

- Used in diagnosis and management
- Identification of late complication
- Non-invasive, easy to perform and repeatable
- Should be bedside
- The first imaging option is abdominal radiography
- Ultrasonography playing an increasing role in NEC

What is the current practice ? [1, 2, 6]

Surgical NEC

Principles of surgical management

- Early intervention to reduce contamination and sepsis
- Resect or defunctionalize gangrenous bowel
- Avoid or reduce multi organ dysfunction
- Preserve bowel length to avoid short gut syndrome

Specific approach determined by three factors

- Size of the infant
- Extent of the disease
- Degree of metabolic derangement

What changes in current practice are likely to improve outcomes? [2]

- Differentiation between spontaneous intestinal perforation and NEC.
- Standardized preoperative management pathways.
- Increased consideration of primary anastomosis when feasible.

- Careful patient selection for PD and laparotomy, with attention to metabolic derangement and other clinical factors.
- Detecting post-NEC strictures by close clinical monitoring over routine contrast studies.

Summary: Resolving the controversies and moving forward

Future guidelines

- Should focus on evidence-based support for individualized decisions rather than uniform protocols to fit all.[10]
- Timing of ostomy takedown
- Strategies to improve neurodevelopmental outcomes in patients after surgery for NEC

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บทคัดย่อ

การรักษาโรคลำไส้อักเสบในทารกทันยุค

ตะวัน อิ่มวิเศษ
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ลำไส้อักเสบเป็นโรคที่พบบ่อยทางกุมารศัลยศาสตร์ อาการแสดงแยกได้ยากจากโรคหรือความผิดปรกติอื่นของทารก การวินิจฉัยได้จากภาพทางรังสีประกอบกับผลตรวจทางห้องปฏิบัติการ พบว่าอัลตราซาวนด์มีความไวในการวินิจฉัยและเป็นการตรวจที่ไม่มีรังสี แต่จากข้อจำกัดในความชำนาญของผู้ตรวจและความแพร่หลายของการใช้อัลตราซาวนด์ในโรงพยาบาลต่างๆ จึงทำให้ยังไม่ใช่การตรวจมาตรฐานของโรคลำไส้อักเสบ ความสำคัญของการวินิจฉัยและจำแนกโรค อ้างอิงตามการจำแนกของเบล และผ่าตัดเมื่อมีข้อบ่งชี้ ปัจจัยที่มีผลต่อการเลือกวิธีผ่าตัด คือ สัญญาณชีพ อายุครรภ์ ความผิดร่วมและความยาวของลำไส้ที่อักเสบ แนวทางรักษาแตกต่างกันแต่ละโรงพยาบาลรวมถึงแพทย์ผู้ผ่าตัด แผนการรักษาในอนาคตพิจารณาจากผลการวิจัยเพื่อให้ผลการรักษาที่มีประสิทธิภาพ

คำสำคัญ: ลำไส้อักเสบในทารก, NEC