Turkish Archives of Pediatrics

GUIDELINES
DOI: 10.5152/TurkArchPediatr.2021.21164

Turkish Neonatal Society Necrotizing Enterocolitis Diagnosis, Treatment and Prevention Guidelines

Ebru Ergenekon[1], Cüneyt Tayman[2], Hilal Özkan[3]

[1]Department of Neonatology, Gazi University, Ankara, Turkey
[2]Department of Neonatology, Health Sciences University, SUAM, Ankara City Hospital, Ankara, Turkey
[3]Department of Neonatology, Uludag University, Bursa, Turkey

ABSTRACT

Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies in the newborn infant, and the incidence varies between 3% and 15% in neonatal intensive care units (NICU). It has a high risk of mortality and both short- and long-term morbidity which severely impacts the quality of life in the survivors. Lack of specific clinical and laboratory findings makes early diagnosis difficult for the clinician and sometimes results in overtreatment for feeding intolerance which is quite frequent in preterms and can easily be confused with NEC. The fact that there are many definitions and presentations of NEC even complicates the management. This review aims to summarize the guideline of the Turkish Neonatal Society for diagnosis, treatment, and prevention of NEC for the clinician taking care of preterms. Etiopathogenesis and various clinical pictures of NEC, as well as diagnostic methods, are defined. Treatment and prognosis are discussed in detail with reference to current literature and preventive strategies are summarized based on evidence. Finally, the approach to baby presenting with suspected NEC is summarized in an algorithm.

Keywords: Necrotizing, enterocolitis, newborn

INTRODUCTION

Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies in the newborn infant. NEC is a disorder characterized by ischemic necrosis of the intestinal mucosa, which is associated with severe inflammation. Although first described in 1965, the etiology and pathogenesis still remain uncertain.[1]

The incidence of NEC is estimated to be approximately 3-15% in neonatal intensive care units (NICU). More than 90% of cases occur in very low-birth-weight (VLBW) infants born at < 32 weeks gestation, and the incidence decreases with increasing gestational age (GA) and birth weight.[1] A recent study conducted by the Turkish Neonatal Society in 2019 revealed that the incidence of NEC in VLBW premature babies was found to be 9.1%.[2]

Although early recognition and aggressive treatment of this disorder have improved clinical outcomes, the mortality of NEC ranges between 20% and 30%, with the highest mortality among those requiring surgery.[1] NEC accounts for substantial long-term morbidity in survivors of NICU, particularly in VLBW infants.

DEFINITIONS

Necrotizing Enterocolitis

NEC is a gastrointestinal pathology characterized by inflammation-related ischemic necrosis of the intestinal mucosa.[1] There are different definitions in the literature other than

Corresponding author:
Ebru Ergenekon
✉ebruergenekon@gmail.com
Received: May 21, 2021
Accepted: May 29, 2021

Cite this article as: Ergenekon E, Tayman C, Özkan H. Turkish neonatal society necrotizing enterocolitis diagnosis, treatment, and prevention guidelines. *Turk Arch Pediatr.* 2021; 56(5): 513-524.

classical NEC such as hypoxic-ischemic enterocolitis and early NEC (ENEC), transfusion-associated NEC (TANEC).

Hypoxic-Ischemic Enterocolitis, ENEC

Prenatal intestinal hypoxia-ischemia is the primary pathological factor leading to ENEC in the first week of life in preterm infants with intrauterine growth retardation and fetal hemodynamic disturbances such as absent or reversed end-diastolic blood flow in the umbilical artery. Unlike classical NEC, it is known to occur earlier, and there are studies showing that it progresses with severe inflammation.[3]

Transfusion-Associated NEC

TANEC has been described as NEC that arises within 48-72 h of a blood transfusion. Although the relationship between NEC and transfusion has been shown in various studies, it has been reported that this relationship is not clear in randomized controlled studies.[4]

Spontaneous Intestinal Perforation (SIP)

Spontaneous intestinal perforation (SIP) of the newborn, also referred to as isolated perforation, is a single intestinal perforation that is typically found at the terminal ileum. SIP mainly affects extremely low-birth-weight (ELBW) infants at an early postnatal age. SIP is differentiated from NEC and characterized as an isolated perforation without inflammation. Several studies have shown that postnatal corticosteroids and/or non-steroidal anti-inflammatory agents are associated with SIP.[5]

NEC in Term Infants

Although the majority of infants with NEC are preterm, approximately 10-15% of cases occur in term infants. Term infants who develop NEC typically have a preexisting illness and develop NEC without being fed. Associated conditions may affect intestinal perfusion and include congenital heart disease, primary gastrointestinal disorders, and perinatal hypoxia. Clinical findings occur earlier. In a retrospective study, it was shown that the severity of the disease, the need for inotropic, mechanical ventilation, and surgical intervention were less in term infants compared to preterm.[6]

Etiology and Pathogenesis

The main pathological findings in NEC are severe inflammation, bleeding, and transmural necrosis in the intestinal mucosa. Other findings are secondary bacterial infiltration and vascular thrombus. Terminal ileum and colon are most frequently involved, but in severe cases, all intestines may be affected.[1]

Although the pathogenesis of NEC is not known, various mechanisms have been suggested. The basic etiology is based on intestinal immaturity since 90% of cases are preterm, but it is known that multiple factors are effective. These factors include microbial dysbiosis, enteral feeding, hypoxia-ischemia, and inflammation together with some potential triggers and risk factors (Tables 1and 2).[7,8]

Pathogenesis of NEC is summarized in Figure 1.

Table 1. Potential Trigger Factors.

Trigger Factors	Mechanism
Formula feeding	Immune stimulation Microbial dysbiosis
Primary infection	Bacterial colonization
Anemia and transfusion	Reperfusion injury
Circulatory failure	Hypoxia-ischemia
H2 blockers	Microbial dysbiosis Bacterial colonization
Antibiotic therapy	Microbial dysbiosis
Hyperosmolar agents	Mucosal injury

Table 2. Risk Factors for Necrotizing Enterocolitis (NEC) by Infant Category.

All Gestational Ages	Premature Infants (<32 weeks)	Late Preterm and Term Infants
Formula feeding	Very low birthweight	Congenital heart disease
Hypoxia	Small gestational age	Chromosomal abnormalities
Inotropic support	Anemia and transfusion	Gastroschisis
Birth asphyxia	Patent ductus arteriosus	Sepsis
Intrauterine growth restriction		Postnatal respiratory distress
Polycythemia		Hypoxic-ischemic encephalopathy
Chorioamnionitis		Milk protein allergy
Exchange transfusion		Hypothyroidism
Umbilical lines		Protracted diarrhea
Premature rupture of membranes		Maternal history of preeclampsia
Severe anemia		Gestational diabetes
Maternal cocaine use		

Clinical Presentation and Diagnosis

Clinical, laboratory, and radiological findings are important in the diagnosis of NEC. The timing of the onset of symptoms varies and appears to be inversely related to GA. The median age at onset of NEC in infants with a GA < 26 weeks is 23 days, and for those with a GA > 31 weeks is 11 days. The onset time of the disease in term babies is 7-12 days on average.[9]

The most frequent but misleading sign of NEC is feeding intolerance whose symptoms include the presence of gastric residuals, vomiting, and abdominal distension.[9] These may be signs of NEC, but most often it is seen in patients without NEC. While gastric residuals are often seen in ENEC, checking for gastric residuals is increasingly abandoned for the value of it is not well supported by current evidence.[10] However, in babies whose residual control has been performed, residuals of more than 5 mL/kg or more than 30-50% of the volume and normal clinical, laboratory, and radiological findings other than abdominal distension suggest feeding intolerance.

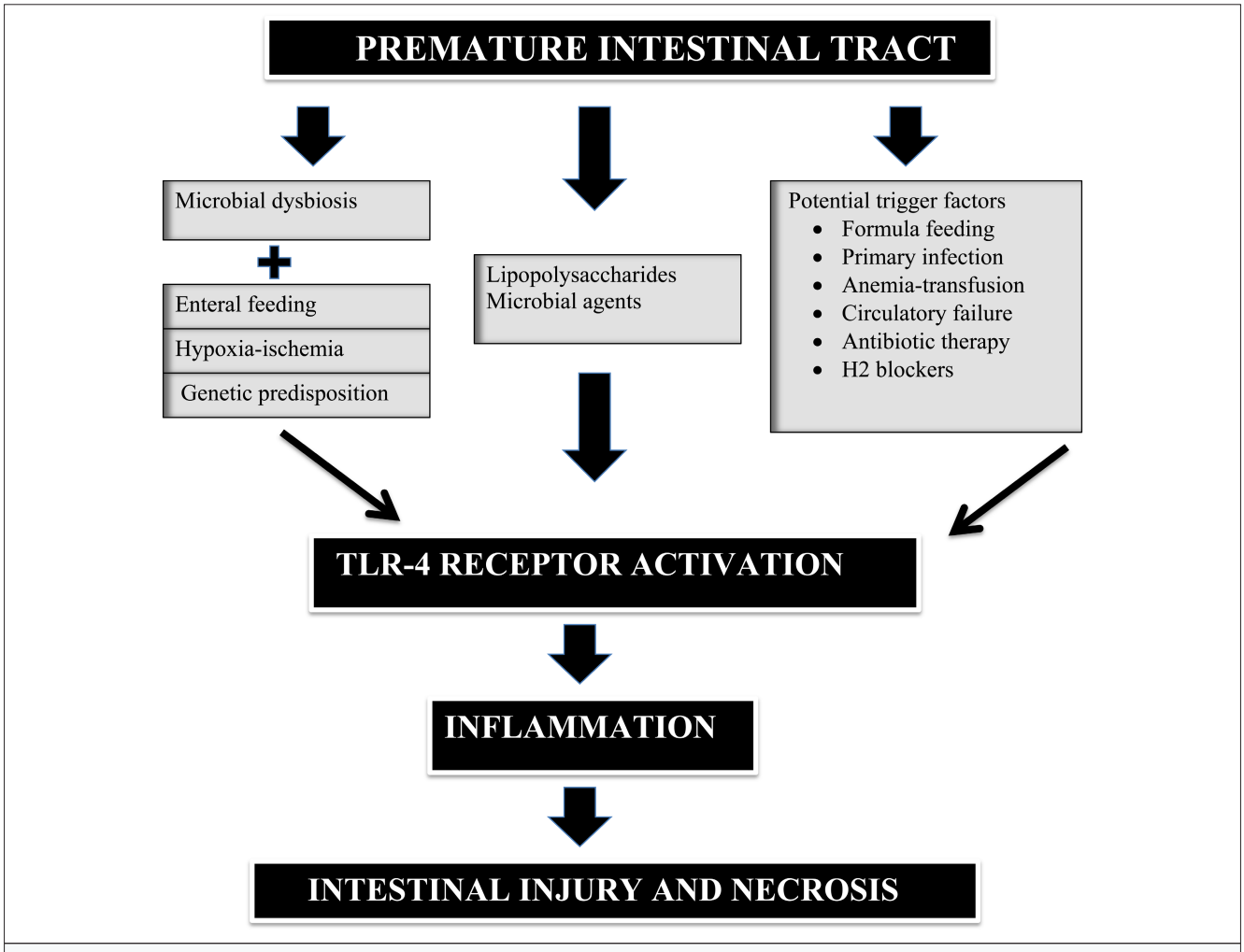

Figure 1. Necrotizing enterocolitis pathogenesis.

Findings supportive of NEC are listed below.

CLINICAL FINDINGS

Specific Findings

- Abdominal distention,
- Gastric residuals,
- Tenderness,
- Vomiting (usually bilious),
- Diarrhea,
- Rectal bleeding,
- Abdominal wall erythema, crepitus, and induration.

Nonspecific Systemic Findings

- Apnea,
- Respiratory failure,
- Lethargy or temperature instability,
- Hypotension resulting from septic shock,
- Bacteremia (20-30% of infants with NEC have associated).

Laboratory Findings

There is no definitive diagnostic laboratory test. Laboratory tests are used to determine the severity of the disease and follow-up. Thrombocytopenia and leukopenia are common.

Complete blood count, serum chemistries (serum electrolytes, blood urea nitrogen, creatinine), coagulation studies, and blood gas analysis are performed when NEC is suspected.

Sepsis evaluation is performed because sepsis is a common concomitant finding or one of the main differential diagnoses. Stool tests, generally not useful. Peritoneal culture is not routinely recommended.[11]

Radiological Findings

The main radiological findings are nonspecific such as gas distension, dilated bowel loops, and edema in the intestinal wall in the early period. Diagnostic radiological finding for NEC is pneumatosis intestinalis characterized by gas in the intestinal wall produced by bacteria (Figure 2). Portal venous gas, acid, and pneumoperitoneum are other radiological findings (Figure 3). Left lateral decubitus radiography may be helpful when pneumoperitoneum is suspected (Figure 4).[6]

Abdominal radiographs are usually used to confirm the diagnosis of NEC and follow the progression of the disease. However, they often lack sensitivity and specificity. Abdominal ultrasonography is being increasingly used for assessing pneumatosis intestinalis, pneumoperitoneum, ascites, bowel wall

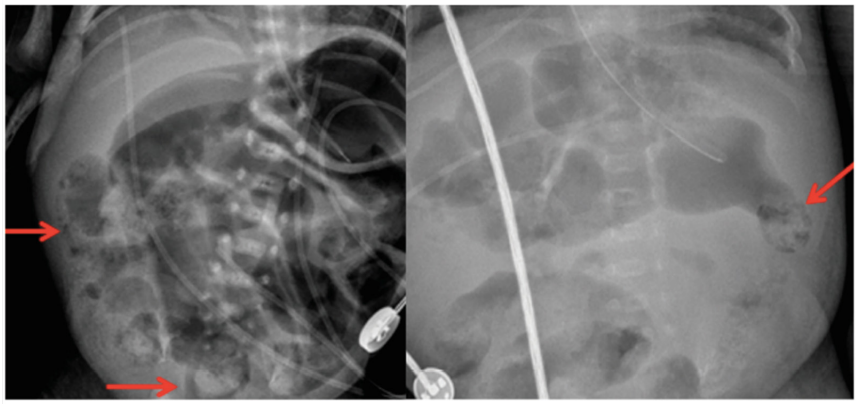

Figure 2. Arrows pointing pneumatosis intestinalis.

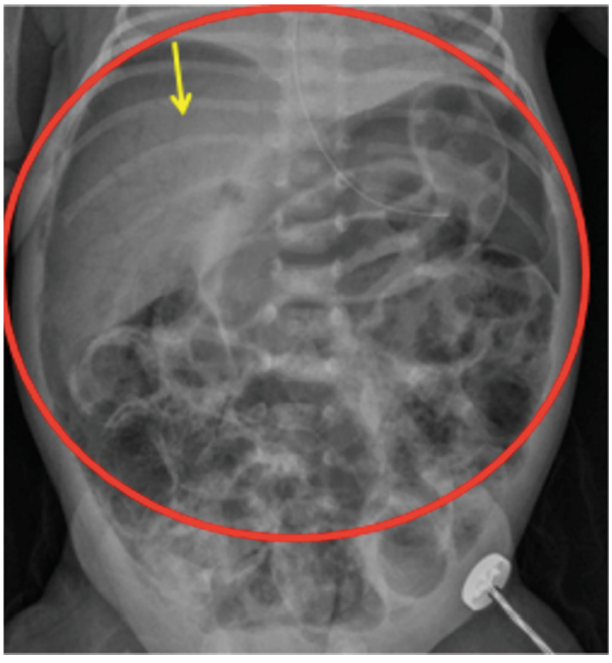

Figure 3. Yellow arrow: portal venous gas, red ring: pneumoperitoneum

Figure 4. Left lateral decubitis radiography and free air above liver.

thickness bowel dilatation, and presence or absence of peristalsis with high sensitivity and specificity.[12] However, expertise in abdominal sonography may not be widely available.

Classification

NEC was classified by Walsh and Kliegman.[13] They modified the Bell criteria based on clinical, radiological, and laboratory findings.[13] The modified Bell staging criteria provide a uniform clinical definition of NEC based upon the severity of systemic, intestinal, radiographic, and laboratory findings and are the most commonly used diagnostic and staging tool in practice (Table 3).

Risk Scores

Various scoring systems have been developed in order to predict the development of NEC and to provide early diagnosis and treatment. Although there are many risk scores that are in the research until today, none is routinely recommended. "eNEC" risk score, which includes GA, birth weight, and prenatal and postnatal characteristics, seems to be practical and usable.[14]

Treatment

Treatment of NEC includes medical management for all patients and surgical intervention for certain cases. However, there is no evidence-based consensus as to which patients require surgical intervention, except for those with evidence of bowel perforation. Therefore, modified Bell staging criteria continue to be used to make decisions regarding the severity of the disease.[15-17]

Medical Management

Medical management should be started immediately as soon as NEC is suspected. Supportive care, empirical antibiotic

Table 3. Modified Bell Staging in Necrotizing Enterocolitis (NEC).

Stage	Clinical	Abdominal	Radiographic
Suspected NEC			
IA	Apnea and bradycardia, instability temperature	Gastric residuals, occult blood in stool, abdominal distention	Normal gas pattern or mild ileus
IB	Stage IA signs	Grossly bloody stools	Stage IA signs
Definite NEC			
IIA	Stage IA signs	Prominent abdominal distention, absent bowel sounds	Ileus gas pattern with ≥ 1 dilated loops and focal pneumatosis
IIB	Thrombocytopenia and mild metabolic acidosis	Abdominal wall edema with palpable loops and tenderness	Widespread pneumatosis, ascites, portal venous gas
Advanced NEC			
IIIA	Mixed acidosis, oliguria, hypotension, coagulopathy shock	Worsening wall edema, erythema, and induration	Prominent bowel loops, worsening ascites, no free air
IIIB	Stage IIIA signs	Perforated bowel	Pneumoperitoneum

NEC, Necrotizing enterocolitis.

therapy, serial physical examination, close laboratory, and radiological follow-up should be provided. Supportive care and antibiotic therapy should be used in all patients, including those who subsequently undergo surgery, in order to limit the progression of the disease.[16-19] Medical management and follow-up of babies with NEC is summarized in Table 4.

Supportive Care

Components of supportive care include cessation of enteral feeding, gastric decompression, total parenteral nutrition (TPN), fluid and electrolyte support, cardiovascular and respiratory support, other supportive treatments for multi-organ failure.

- Cessation of enteral feeding: Enteral feeding should be stopped immediately, and the intestines should be rested. The duration to start enteral feeding depends on the severity and extent of the disease. The duration of bowel rest is 7 days for stage II NEC and about 14 days for advanced (stage III) NEC and is administered in parallel with 10-14 days of antibiotic treatment.[20] As the patient's clinical condition improves, enteral nutrition can be restarted and gradually increased.[8,16,17,20]
- Gastric decompression: Since ileus develops in patients due to intestinal inflammation and intestinal wall thickening, intermittent orogastric aspiration and gastric decompression are continued until the ileus is resolved and pneumatosis intestinalis disappeared on the abdominal radiography. The amount of gastric fluid obtained after decompression should be replaced with 0.9% sodium chloride added with potassium chloride or Lactated Ringer's solution. An increase in the abdominal circumference may indicate the onset of pneumoperitoneum and should be excluded by imaging studies.[8,17,20,21]
- TPN: During the period when enteral feeding cannot be performed, a central venous catheter of appropriate size should be placed, and sufficient calorie, lipid, protein, and electrolyte support should be provided with TPN until enteral nutrition is initiated.[8,21]
- Fluid and electrolyte support: Hydration status should be closely monitored and necessary fluid management should be provided meticulously. Transmural intestinal inflammation and capillary leak can lead to intravascular fluid loss.[17,20,21] Patients with multiple organ failure may develop renal failure and electrolyte imbalances such as hyponatremia, hyperkalemia, and lactic acidosis.[21]

Table 4. Management and Follow-Up.

Supportive Care	Antibiotic Treatment	Monitoring Response to Treatment and Surgical Treatment
• Cessation of enteral feeding – 48-72 h for stage I NEC – 7 days for stage 2 NEC – 10-14 days for stage 3 NEC • Gastric decompression: Until enteral feeding begins • Total parenteral nutrition • Fluid and electrolyte support • Cardiovascular and respiratory support • Other supportive treatments	• Broad-spectrum antibiotics, including gram (–) and anaerobic bacteria: ampicillin, gentamicin (or amikacin), and metronidazole • Vancomycin can be used instead of ampicillin for CNS and MRSA or ampicillin-resistant enterococci (+). • If cultures from blood or other sterile sites are (+), treatment can be narrowed or extended if necessary to treat isolated organisms. • For NEC stage I, early discontinuation of antibiotics at the end of 48-72 h and resumption of enteral feeding can be chosen depending on the course of the disease. • For NEC stage ≥ 2, a 10-14 day course of antibiotics is recommended, even if the culture results are (–).	• Serial physical examination and follow-up • Laboratory follow-up • Imaging of the abdomen (radiography and ultrasonography) Surgical intervention: (Laparotomy, PPD) • Pneumoperitoneum • Inadequate response to maximum medical treatment

CNS, coagulase negative staphylococcus; MRSA, methicillin resistance sataphylococcus aureus; PPD, primary peritoneal drainage; NEC, necrotizing enterocolitis.

- Cardiovascular and respiratory support: Multi-organ failure often develops in severe disease. These patients need both cardiovascular and respiratory support.[8,21]

Antibiotic Treatment

After obtaining appropriate samples for culture, broad-spectrum antibiotics, with gram-negative and anaerobic bacteria (often intestinal bacterial flora) coverage, should be initiated.[8,16,22] Since 20-30% of patients have accompanying bacteremia, empirical antimicrobial regimens are used to include pathogens that cause late-onset bacteremia.[17,20] Antibiotic selection should be made by considering the susceptibility patterns of the organisms in the NICU. Antifungal drugs should be considered in severely ill patients or patients who do not respond to antibiotic treatment.[8,23] The results of cultures of blood, peritoneal fluid, or surgical specimens will help to narrow the antimicrobial coverage and guide the duration of treatment.[8,24] Unless complicated by abdominal abscess formation, a treatment regimen of 10-14 days is usually sufficient. For NEC stage $\geq$ 2, treatment is continued for a total of 10-14 days, even if the culture results are negative. Depending on the course of the disease in stage I NEC cases, early discontinuation of antibiotics at the end of 48-72 h and resumption of feeding can be chosen.[20]

MONITORING RESPONSE TO TREATMENT

Serial physical examination, laboratory, and radiological studies are used to help monitor the course of the disease and to determine whether there is clinical improvement or deterioration. Surgical intervention may be considered for the disease which progresses or does not respond to medical management. Since the course of the disease can change rapidly, it helps to make early surgical evaluation.[25]

SURGICAL TREATMENT

Despite all interventions, approximately 30-50% of patients require surgical intervention.[16,18] Since it is desired to preserve the maximum bowel length as possible in advanced NEC, the necessity and timing of surgical intervention should be decided carefully. The ipurpose of surgical treatment involves: (1) resection of the necrotic intestine to reduce the risk of systemic sepsis and subsequent multiple organ failure, (2) early intervention to reduce the degree of contamination and sepsis, (3) prevention of short bowel syndrome.[17-19]

INDICATIONS FOR SURGICAL TREATMENT

The absolute indication and timing for surgical intervention is the presence of pneumoperitoneum showing intestinal perforation detected by abdominal imaging.[8,19,26] However, surgical intervention may be required in the absence of pneumoperitoneum in patients whose clinical deterioration persists despite maximum medical support, with worsening laboratory and imaging findings.[17-19] In addition, positive paracentesis (presence of brown fluid or positive bacteria in gram staining) has a positive predictive value of 100% for surgical intervention.[19]

TECHNIQUES FOR SURGICAL TREATMENT

In surgical treatment, laparotomy or primary peritoneal drainage (PPD) is performed. Although laparotomy is the standard approach used in infants with perforation, PPD can be used as a salvage procedure or as a definitive method in some cases. Currently, it is unclear which of these 2 procedures is the most effective.[18,19] Enterostomy formation with resection of the affected bowel regions with laparotomy and intestinal primary anastomosis can be applied in limited NEC. Stricture formation may occur as a result of the healing of intestinal damage by scarring in patients with uncomplicated NEC or after surgical treatment and may require additional surgical intervention.[8]

POST-SURGICAL TREATMENT

Intensive cardiovascular, hemodynamic, and respiratory support is required in the early period after surgical treatment. After orogastric decompression or dissolution of the ileus, large gastrointestinal fluid loss with high stoma output can be experienced. Fluid-electrolyte resuscitation, bowel rest, broad-spectrum antibiotics, and TPN support should be continued. In addition, possible postoperative complications such as sepsis, intestinal stenosis, wound infection, adhesive bowel obstructions, delayed anastomotic strictures, anastomotic ulcers, and short bowel syndrome should be recognized early and necessary treatments should be implemented.[17]

Restarting Enteral Feeding

The time to initiate enteral feeding after surgery depends on the clinical stability of the newborn, other comorbidities, stool/ostomy outputs, and bowel anatomy. Short bowel syndrome is the most common cause of bowel failure in infants with severe NEC. Enteral nutrition is aimed to start as soon as possible after bowel resection and after NEC cases that are not complicated by surgery.[21]

In the presence of hemodynamic stability without the need for vasoactive agents, reassuring abdominal examination findings, absence of serious respiratory support or presence of stable respiratory system with appropriate support, absence of electrolyte disturbance, discontinuation of antibiotics can be considered, and enteral nutrition can be increased gradually.[8] Breast milk is the most suitable nutritional option preferred in patients with NEC during the healing process. The enteral nutrition recommendations of the American Society for Parenteral and Enteral Nutrition (ASPEN) are summarized in Table 5.[21]

Prognosis

The prognosis of patients with stage II or above NEC according to modified Bell staging varies based on whether surgery is required or not. Both short- and long-term complications and mortality are more frequent if surgery is required. Surgery is performed in 30-50% of cases. Overall mortality is reported between 20% and 30%.[27] The factors determining mortality, especially in patients who require surgical treatment, are smaller GA, being small for GA, inotropic treatment requirement, and congenital anomalies.[27] In nonsurgical patients, the presence of hemodynamic instability and DIC are noted to impact mortality.

Patients with NEC, especially if they require surgery with enterostomy, have a 40-70% risk of developing short- and long-term morbidity, including leakage from anastomosis site, peritonitis,

Table 5. Nutritional Recommendations during the Treatment for Necrotizing Enterocolitis (NEC).

Fluid and Electrolyte Management during NEC	Enteral Nutrition > Stage 2 NEC	Enteral Nutrition after Bowel Resection
• Central venous catheter placement • Adequate nutritional support with TPN • Considering that capillary leaks and secondary fluid need will increase • Close monitoring of serum sodium and potassium, appropriate correction of hyponatremia and hyperkalemia • Proper treatment of metabolic acidosis	• Trophic feeding (<20 mL/kg/day) can be initiated with an orogastric/gastrostomy tube after at least 7 days of bowel rest. • Enteral nutrition may increase based on clinical indicators. • Breast milk is the preferred enteral food. • If breast milk is not available, a preterm formula containing a high proportion of medium and long chain triglycerides can be used. • Term babies can be fed with the standard term formula. • If cow's milk protein allergy is suspected, IHF may be considered (in patients with recurrent NEC or in the absence of typical risk factors for NEC). • Bolus feeds can be started at 20 mL/kg/day orally or with an orogastric/gastrostomy tube. • The volume of feeds should be increased gradually at a rate of 10-20 mL/kg/day.	• Trophic nutrition is started after 10-14 days of bowel rest. The indications for progression are the same as for uncomplicated NEC. • Breast milk is the preferred food. • If they are intolerant to standard preterm/term formulas, IHF can be considered with a semi-elemental or amino acid-based formulation. • Continuous feeds can be started with a 20 mL/kg/day orogastric/gastrostomy tube. • The feed volume should be increased gradually to 10-20 mL/kg/day.

TPN, total parenteral nutrition; NEC, necrotizing enterocolitis; IHF, intensive hydrolyzed formula.

sepsis, strictures, adhesions, short bowel syndrome, long-term TPN dependency, failure to thrive, liver failure, intraventricular hemorrhage, white matter injury, and neurodevelopmental problems.[28-30] Therefore, babies who suffer from NEC should be followed with a multidisciplinary approach for possible problems. Gastrointestinal problems should be paid attention to. Potential neurodevelopmental impairment should be kept in mind, and early intervention should be started to improve the prognosis.

PREVENTION

Despite technological advances and increased survival in neonatology, NEC incidence has not decreased significantly over the years. Moreover, the mortality and morbidity of the disease remain high underlining the importance of protective measures rather than focusing on potential treatment modalities. With this in mind, protective methods starting from the antenatal period have been studied in small- and large-scale clinical trials. Here, evidence-based methods for the prevention of stage II or above NEC according to Bell classification have been summarized.

Antenatal Methods

Prevention of prematurity is the most important intervention to avoid many complications of prematurity, including NEC, however, this topic is beyond the scope of this review.

Antenatal Corticosteroids

Antenatal corticosteroid administration has been shown to be effective in NEC prevention.[31]

Delivery Room Management

Standard neonatal resuscitation program (NRP) guidelines should be applied to all babies. There is not one specific intervention in DR shown to prevent NEC.

Delayed Cord Clamping/Cord Milking

A low grade of evidence has shown decreased incidence of NEC in preterms who have been exposed to delayed cord clamping or cord milking, however, these interventions should be based according to the NRP guidelines.[32,33]

Postnatal Methods

Ventilation and Oxygen Management

Ventilation techniques have not been shown to impact the occurence of NEC so far. However, oxygenation seems to have some effect. Clinical trials investigating the role of oxygen saturation targets in preterm newborns with regards to mortality and morbidity have revealed that the group with the target oxygen saturation between 91% and 95% had decreased NEC incidence compared to the group with the target saturation between 85% and 89%.[34]

PDA Management

PDA management and feeding practices during PDA have been studied with regards to impact on NEC, however, the results have not revealed concrete findings. In some studies, minimal feeding is suggested during PDA whereas, in others, feeding during PDA is reported to have no impact on the development of NEC.[35] Until we have better evidence, it seems reasonable to consider feeding on a case-by-case basis to prevent NEC in patients with PDA. On the other hand, therapeutic agents used for the treatment of PDA have also been studied, and Cochrane metanalysis has concluded that patients who received oral/IV ibuprofen have less NEC compared to patients who received oral/IV indomethacin.[36] Another metaanalysis comparing oral/IV paracetamol and ibuprofen has reported no difference in NEC incidence.[37]

Limited Antibiotic Use

It is known that disrupted intestinal microbiota is associated with increased NEC. Therefore, antibiotics may have a negative impact by changing intestinal flora. A limited number of studies have investigated the role of prolonged empirical antibiotic use in the postnatal period and have reported increased risk of NEC if antibiotics are used for more than 5 days. One of the studies has reported a 7% increase in NEC for each extra day of antibiotics.[38] Therefore, it might be

reasonable to limit empirical antibiotic use to < 5 days as a preventive strategy.

Limited H2 Blocker Use

H2 blocking agents increase gastric PH and change intestinal flora both causing an increased risk of NEC as shown in retrospective case-control or small prospective studies.[39] Therefore, it might be suggested to limit H2 blocker use, especially in newborns at a higher risk of developing NEC.

Enteral Nutrition

- Breast milk: Breast milk feeding is the most effective protective intervention for NEC prevention due to its content rich in many protective factors.[40] It is ethically unacceptable to perform RCT comparing breast milk with any other nutrient. However, in studies where mother's milk was not available, it has been shown that the protective effect of breast milk is dose-dependent. In the first 2 weeks of life, providing more than 50% of enteral nutrition with breast milk decreases NEC incidence significantly, and each 10% increase results in a further decrease.[41] Therefore, promoting breast milk supply for the preterm by maternal education and support is very important.
- Donor milk: Feeding with donor milk has been shown to result in a lower incidence of NEC when compared to feeding with a preterm formula when a mother's own milk is not available.[42]
- Breast milk fortifiers (BMF): BMF, both cow's milk-based and human milk-based, have not been associated with increased incidence of NEC.[43,44] The timing of adding BMF to enteral nutrition is a matter of discussion. Although adding BMFs when enteral nutrition volume has reached 20, 40, or 100 mL/kg has not resulted in any difference in NEC occurrence, especially in the ELBW preterms, it is advisable to start when enteral nutrition volume has reached 100 mL/kg.[45]
- Starting and advancing enteral nutrition: Initial feeding can be started as minimal enteral nutrition (MEN) or as standard nutrition.
  MEN: MEN is defined as starting with 10-20 mL/kg/day volume within the first 48-72 h of life and continuing it for 4-10 days without increase.
  Standard nutrition: Standard nutrition is defined as starting enteral feeding within 24-72 hours of life with 15-20 mL/kg/day volume and advancing it by 15-20 or 30-35 mL/kg/day.

The amount of daily increase and its association with NEC has been studied revealing no difference between 15 and 20 mL/kg versus 30-35 mL/kg advancement.[46] However, ELBW preterms may still be a subset requiring additional precautions while deciding daily feeding volume increase.

A recent well-accepted suggestion regarding enteral nutrition is that each unit should develop a standard nutrition protocol based on literature, patient population, and the conditions of the individual NICU. Timing of starting nutrition, MEN or standard regimen, the rate of advancement, timing of BMF addition, feeding intolerance definition, and the interventions for that can be decided by the NICU staff, and the feeding protocol for that NICU can be formed. This approach has been shown to reduce NEC incidence and should be considered within NEC preventive measures.[47]

Feeding during Erythrocyte Transfusion

NEC has been defined in preterms within 48-72 h of erythrocyte transfusion in retrospective or case-control studies and has been attributed to either free radicals increasing with transfusion or the anemia prior to transfusion and reperfusion injury following thereafter.[4] Based on the systematic review of observational or case-control studies, stopping feeds during erythrocyte transfusion can be considered although the level of evidence is low.[48]

Supplements

Probiotics

Since dysbiosis is considered an important factor for the development of NEC, probiotics aiming to form a healthy intestinal flora have been studied in more than 40 000 preterms in randomized clinical trials. Most of these studies have revealed a reduced incidence of NEC in groups who were given probiotics, however, great heterogeneity exists for the answers to the questions regarding the most effective combination, the most effective dose, when to start, and when to stop probiotics. Besides, there are still doubts regarding their efficacy in the most vulnerable population, namely preterms < 1000 g birth weight.[49] Probiotics are live microorganisms that make clinicians nervous about causing sepsis, and also lack of long-term data cause hesitation about their routine use. The fact that they are not drugs makes probiotics escape from the regular control mechanisms and results in a lack of standardization for content and storage conditions.[50]

Despite meta-analyses and systematic reviews finding a decreased incidence of NEC with probiotic use, ESPHGAN has cautioned clinicians about probiotic use and has particularly warned against the use of Lactobacillus *reuteri*, Bifidobacterium *breve*, and Saccharomyces *boulardii*.[51] The main problem that still remains is their efficacy in ELBW preterms and the risk of sepsis in this vulnerable population.

Lactoferrin

Lactoferrin is present in large amounts in breast milk and is effective in the maturation of the intestine and immunomodulation. Oral lactoferrin started from the first day of life has been found effective in reducing the incidence of NEC in a systematic review of small-scale studies.[52]

Preventive strategies are summarized in Table 6 according to the strength of recommendation.

CONCLUSION AND RECOMMENDATIONS

NEC, which is associated with a high risk of mortality and morbidity, continues to be one of the most important problems of preterm babies. To increase awareness of NEC, groups like NEC Society (necsociety.org) have been established, and May 17 has been declared as World NEC Awareness Day.

Lack of adequate laboratory tests for accurate and timely diagnosis either leads to delay in treatment or results in overdiagnosis with unnecessary use of antibiotics and pause in enteral nutrition. There is an urgent need for cheap, reliable, and easily applicable laboratory methods, which are specific for NEC.

Table 6. Strategies for NEC Prevention according to Strength of Recommendation.
Strong recommendation
Antenatal corticosteroids
Nutrition with mother's own milk or donor milk where it is not available
Maintaining oxygen saturation between 91 and 95 %
Patent ductus arteriosus treatment with ibuprophen (paracetamol)
Recommendation
Using standard enteral nutrition protocols
Stopping enteral nutrition during erythrocyte transfusion
Option
Limited ampirical antibiotic treatment to < 5 days (culture –)
Limited H2 blocker use
Probiotics (listed under low level of recommendation due to insufficient data regarding efficacy in preterms < 1000 g and lack of certainty about the most beneficial combination)
Lactoferrin

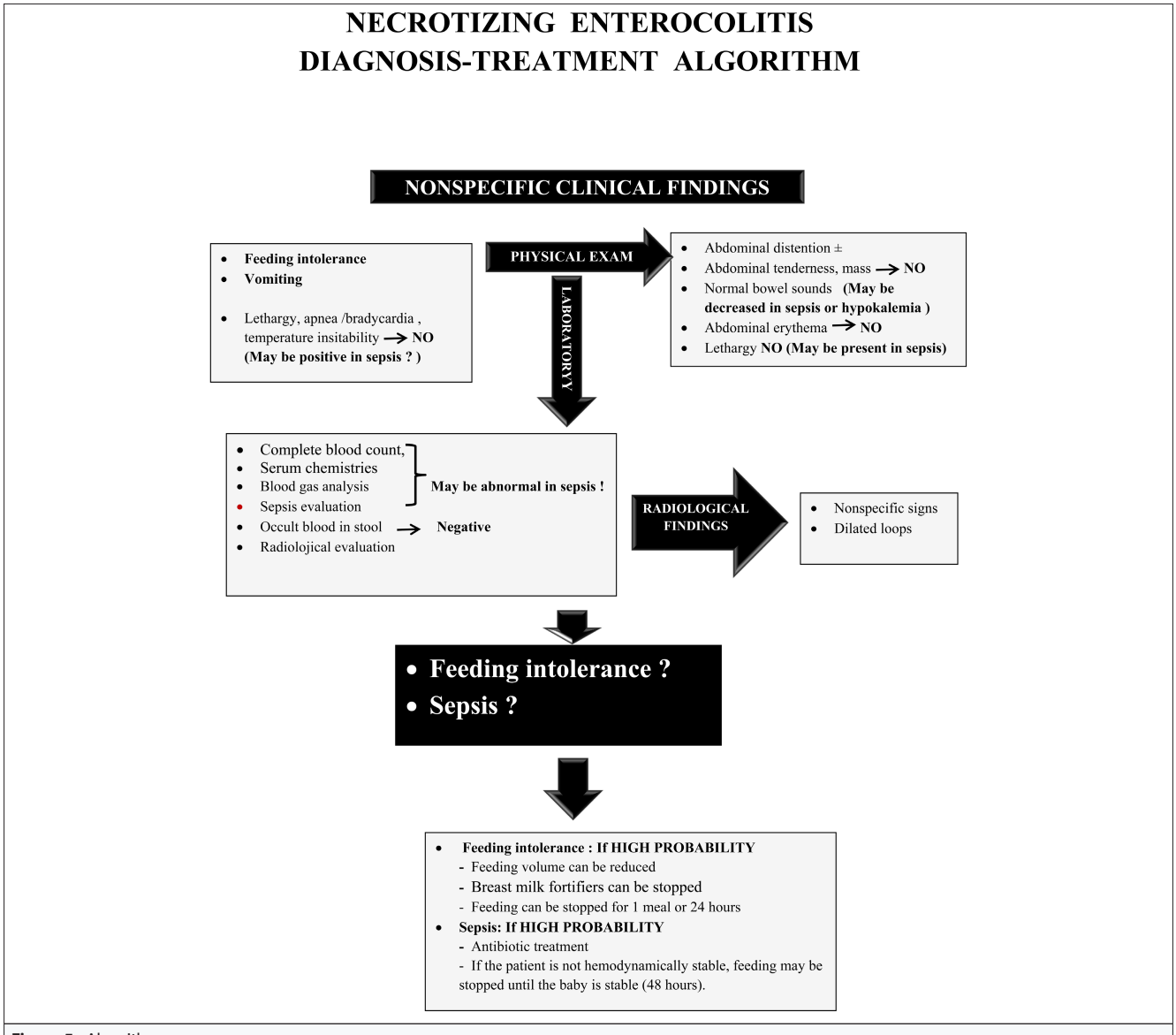

Figure 5. Algorithm.

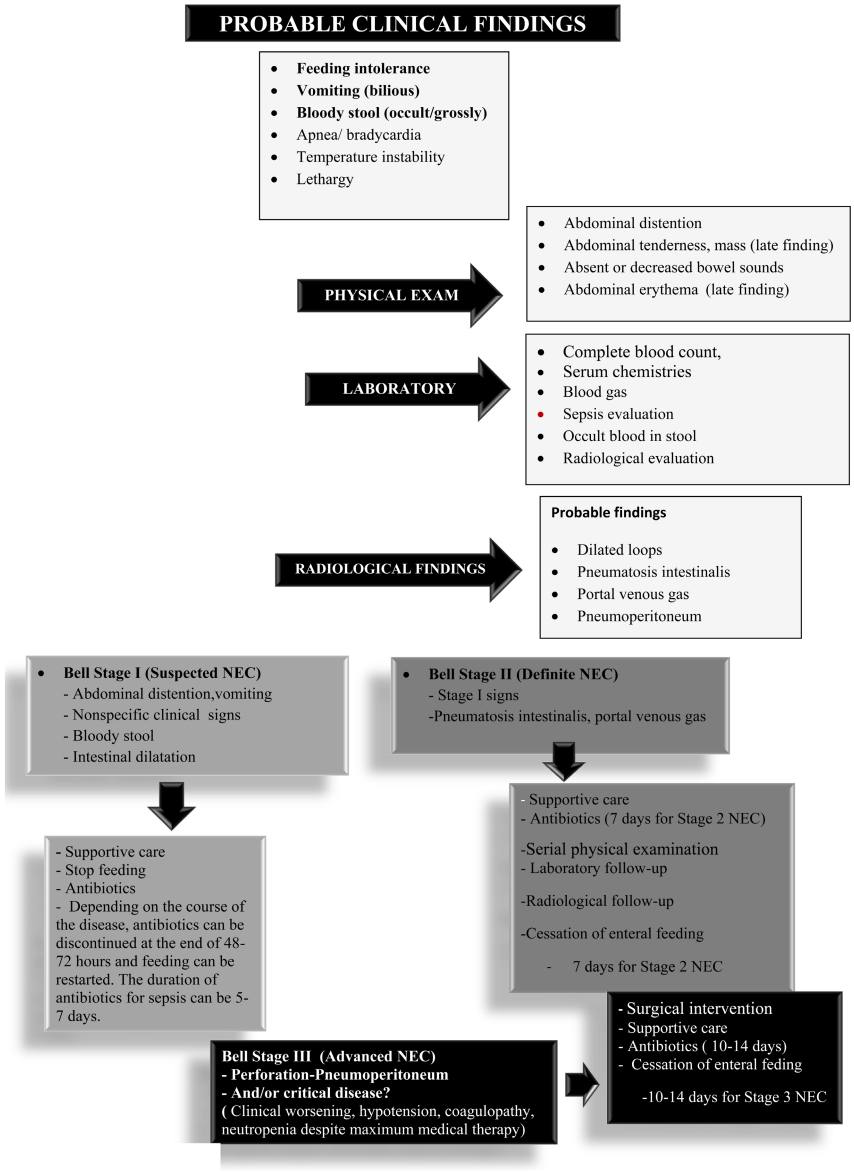

Figure 5. Algorithm (*Continued*).

Since complications are severe once the disease gets developed, prevention and early diagnosis are very important.

As there are different definitions of NEC, there are also different etiological factors, and each patient needs to be assessed with regards to the presence of those factors.

All the effort should be made to provide breast milk together with other preventive strategies.

Multidisciplinary follow-up is required for growth failure and gastrointestinal as well as neurological problems. Good nutrition and a good follow-up program with early intervention can help to decrease the severity of long-term complications.

The approach to NEC is summarized in the algorithm in Figure 5.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – E.E., C.T., H.Ö.; Design - E.E., C.T., H.Ö.; Supervision - E.E., C.T., H.Ö.; Resource - E.E., C.T., H.Ö.; Materials - E.E., C.T., H.Ö.; Data Collection and/or Processing - E.E., C.T., H.Ö.; Analysis and/or Interpretation - E.E., C.T., H.Ö.; Literature Search - E.E., C.T., H.Ö.; Writing - E.E., C.T., H.Ö.; Critical Reviews - E.E., C.T., H.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Gordon PV, Swanson JR, MacQueen BC, Christensen RD. A critical question for NEC researchers: can we create a consensus definition of NEC that facilitates research progress? *Semin Perinatol.* 2017;41(1):7-14. [CrossRef]

2. Koç E, Demirel N, Baş AY, et al. Early neonatal outcomes of very-low-birth-weight infants in Turkey: a prospective multicenter study of the Turkish Neonatal Society. *PLoS ONE*. 2019;14:e0226679.
3. Surmeli Onay OS, Korkmaz A, Yigit S, Yurdakok M. Hypoxic-ischemic enterocolitis: a proposal of a new terminology for early NEC or NEC-like disease in preterm infants, a single-center prospective observational study. *Eur J Pediatr*. 2020;179(4):561-570. [CrossRef]
4. Saroha V, Josephson CD, Patel RM. Epidemiology of necrotising enterocolitis: new considerations regarding the influence of and red blood cell transfusions and anemia. *Clin Perinatol*. 2019;46(1):101-117. [CrossRef]
5. Neu J, Modi N, Caplan M. Necrotizing enterocolitis comes in different forms: historical perspectives and defining the disease. *Semin Fetal Neonatal Med*. 2018;23(6):370-373. [CrossRef]
6. Overman Jr RE, Criss CN, Gadepalli SK. Necrotizing enterocolitis in term neonates: a different disease process? *J Pediatr Surg*. 2019;54(6):1143-1146. [CrossRef]
7. Kim JH. *Neonatal Necrotizing Enterocolitis: Pathology and Pathogenesis*. UpToDate; 2019.
8. Wertheimer F, Arcinue R, Niklas V. Necrotizing enterocolitis: enhancing awareness for the general practitioner. *Pediatr Rev*. 2019;40(10):517-527. [CrossRef]
9. Kim JH. *Neonatal Necrotizing Enterocolitis: Clinical Features and Diagnosis*. UpToDate; 2019.
10. Capriati T, Diamanti A, Ville de Goyet V. New nutritional and therapeutic strategies of NEC. *Curr Ped Rev*. 2019;15:92-105.
11. Goldstein GP, Sylvester KG. Biomarker discovery and utility in necrotizing enterocolitis. *Clin Perinatol*. 2019;46(1):1-17. [CrossRef]
12. Kim JH. Necrotizing enterocolitis and bowel ultrasound. *Clin Perinatol*. 2019;46(1):119-127. [CrossRef]
13. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am*. 1986;33(1):179-201. [CrossRef]
14. Naberhuis J, Wetzel C, Tappenden KA. A novel neonatal feeding intolerance and necrotizing enterocolitis risk-scoring tool is easy to use and valued by nursing staff. *Adv Neonatal Care*. 2016;16(3):239-244. [CrossRef]
15. Alganabi M, Lee C, Bindi E, Li B, Pierro A. Recent advances in understanding necrotizing enterocolitis. *F1000Research*. 2019;8:F1000. [CrossRef]
16. Hackam DJ, Sodhi CP, Good M. New insights into necrotizing enterocolitis: from laboratory observation to personalized prevention and treatment. *J Pediatr Surg*. 2019;54(3):398-404. [CrossRef]
17. Hong CR, Han SM, Jaksic T. Surgical considerations for neonates with necrotizing enterocolitis. *Semin Fetal Neonatal Med*. 2018;23(6):420-425. [CrossRef]
18. Thakkar HS, Lakhoo K. The surgical management of necrotising enterocolitis (NEC). *Early Hum Dev*. 2016;97:25-28. [CrossRef]
19. Robinson JR, Rellinger EJ, Hatch LD, et al. Surgical necrotizing enterocolitis. *Semin Perinatol*. 2017;41(1):70-79. [CrossRef]
20. Gupta A, Paria A. Etiology and medical management of NEC. *Early Hum Dev*. 2016;97:17-23. [CrossRef]
21. Christian VJ, Polzin E, Welak S. Nutrition management of necrotizing enterocolitis. *Nutr Clin Pract*. 2018;33(4):476-482. [CrossRef]
22. Autmizguine J, Hornik CP, Benjamin DK, et al. Best pharmaceuticals for children act-pediatric trials network administrative core committee. Anaerobic antimicrobial therapy after necrotizing enterocolitis in VLBW infants. *Pediatrics*. 2015;135:117-125.
23. Shah D, Sinn JK. Antibiotic regimens for the empirical treatment of newborn infants with necrotising enterocolitis. Cochrane database. *Syst Rev*. 2012;8:CD007448.
24. Carr JP, Burgner DP, Hardikar RS, Buttery JP. Empiric antibiotic regimens for neonatal sepsis in Australian and New Zealand neonatal intensive care units. *J Paediatr Child Health*. 2017;53(7):680-684. [CrossRef]
25. Ahle M, Ringertz HG, Rubesova E. The role of imaging in the management of necrotising enterocolitis: a multispecialist survey and a review of the literature. *Eur Radiol*. 2018;28(9):3621-3631. [CrossRef]
26. Munaco AJ, Veenstra MA, Brownie E, et al. Timing of optimal surgical intervention for neonates with necrotizing enterocolitis. *Am Surg*. 2015;81(5):438-443. [CrossRef]
27. Jones IH, Hall NJ. Contemporary outcomes for infants with necrotizing enterocolitis—a systematic review. *J Pediatr*. 2020;220:86.e3-92.e3. [CrossRef]
28. Mutanen A, Pierro A, Zani A. Perioperative complications following surgery for necrotising enterocolitis. *Eur J Pediatr Surg*. 2018;28(2):148-151. [CrossRef]
29. Hong CR, Fullerton BS, Mercier CE, et al. Growth morbidity in extremely low birth weight survivors of necrotizing enterocolitis at discharge and two-year follow-up. *J Pediatr Surg*. 2018;53(6):1197-1202. [CrossRef]
30. Fullerton BS, Hong CR, Velazco CS, et al. Severe neurodevelopmental disability and healthcare needs among survivors of medical and surgical necrotizing enterocolitis: a prospective cohort study. *J Pediatr Surg*. 2018;53:101-107.
31. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating lung maturation for women at risk for preterm birth. *Cochrane Database Syst Rev*. 2017;3(3):CD004454. [CrossRef]
32. Garg BD, Kabra NS, Bansal A. Role of delayed cord clamping in prevention of necrotizing enterocolitis in preterm neonates: a systematic review. *J Matern Fetal Neonatal Med*. 2019;32(1):164-172. [CrossRef]
33. Sekhon MK, Yoder BA. Impact of umbilical cord milking and pateurized donor human milk on necrotising enterocolitis: a retrospective review. *BMC Pediatr*. 2018;18(1):155. [CrossRef]
34. Askie LM, Darlow BA, Davis PG, et al. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev*. 2017;4(4):CD011190. [CrossRef]
35. Martini S, Aceti A, Galletti S, et al. To feed or not to feed: a critical overview of enteral feding management and gastrointestinal complication in preterm neonates with a patent ductus arteriosus. *Nutrients*. 2020;12(1):83. [CrossRef]
36. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev*. 2018;9(9):CD003481.
37. Huang X, Wang F, Wang K. Paracetamol versus ibuprofen for the treatment of patent ductus arteriosus in preterm neonates: a meta-analysis of randomized controlled trials. *J Matern Fetal Neonatal Med*. 2018;31(16):2216-2222. [CrossRef]
38. Cotten CM, Taylor S, Stoll B, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotising enterocolitis and death for extremely low birth weight infants. *Pediatrics*. 2009;123(1):58-66. [CrossRef]
39. Terrin G, Passariello A, De Curtis M, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012;129(1):e40-e45. [CrossRef]
40. Patel AL, Kim JH. Human milk and necrotising enterocolitis. *Semin Pediatr Surg*. 2018;27(1):34-38. [CrossRef]
41. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *J Perinatol*. 2007;27(7):428-433. [CrossRef]
42. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2018;6(6):CD002971.
43. Premkumar MH, Pammi M, Suresh G. Human milk-derived fortifier versus bovine milk-derived fortifier for prevention of mortality and morbidity in preterm neonates. *Cochrane Database Syst Rev*. 2019;2019(11):CD013145. [CrossRef]

44. O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250g: a randomized clinical trial. *Am J Clin Nutr*. 2018;108(1):108-116. [CrossRef]
45. Shah SD, Dereddy N, Jones TL, Dhanireddy R, Talati AJ. Early versus delayed human milk fortification in very low birth weight infants-a randomized controlled trial. *J Pediatr*. 2016;174:126-131.e1. [CrossRef]
46. Dermyshi E, Wang Y, Yan C, et al. The golden age of probiotics: a systematic review and metaanalysis of randomized and observational studies in preterm infants. *Neonatology*. 2017;112(1):9-23. [CrossRef]
47. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev*. 2017;8:CD001241. [CrossRef]
48. Gephart SM, Hanson C, Wetzel CM, et al. NEC-zero recomendations from scoping review of evidence to prevent and foster timely recognition of necrotising enterocolitis. *Matern Health Neonatol Perinatol*. 2017;3:23. [CrossRef]
49. Jasani B, Rao S, Patole S. Withholding feeds and transfusion-associated necrotizing enterocolitis in preterm infants: a systematic review. *Adv Nutr*. 2017;8(5):764-769. [CrossRef]
50. Pell LG, Loutet MG, Roth DE, Sherman PM. Arguments against routine administration of probiotics for NEC prevention. *Curr Opin Pediatr*. 2019;31(2):195-201. [CrossRef]
51. van den Akker CHP, van Goudoever JB, Shamir R, et al. Probiotics and preterm infants: a position paper by the ESPGHAN Committee on Nutrition and the ESPGHAN Working Group for probiotics and prebiotics. *J Pediatr Gastroenterol Nutr*. 2020;70:664-680.
52. He Y, Cao L, Yu J. Prophylactic lactoferrin for preventing late onset sepsis and necrotising enterocolitis in preterm infants: a PRISMA compliant systematic review and metaanalysis. *Medicine*. 2018;97(35):e11976. [CrossRef]