

Necrotizing enterocolitis (NEC) is one of the common gastrointestinal emergencies seen in the neonatal intensive care unit. The incidence of NEC varies among different centers, with endemic and epidemic occurrences. More than 85% of cases of NEC occur among preterm (<32 weeks' gestation) VLBW neonates. Studies from the developed countries report an incidence of 7% to 11% among VLBW infants.¹ The incidence of NEC among preterm (< 32 weeks' gestation) VLBW neonates in our unit in the year 2016 was 12%.

Risk factors for NEC: Prematurity (more than 90% occur in preterm infants), hypoxia, sepsis, abnormal colonization of the bowel, ischemic-reperfusion injury, umbilical arterial catheterization, H₂ blockers, broad spectrum antibiotics, and antenatally detected umbilical artery blood flow abnormalities (absent/reversed end-diastolic flow) are the common risk factors of NEC.

Exclusive breast milk feeding protects against NEC by lowering gastric pH, increasing intestinal motility, decreasing epithelial permeability, and altering the composition of intestinal bacterial flora. There is no increased risk of NEC with early introduction of feeds or faster rate of enhancement of feeds.^{2,3}

Type of milk and NEC: What is the evidence?

Meta-analysis of 6 RCTs comparing formula feeds versus human milk in preterm infants showed that preterm infants fed with formula had more than twice the incidence of NEC: typical RR 2.77 (95% CI 1.40 to 5.46).⁴

Pathogenesis

The pathogenesis of NEC is multifactorial with an immature host immunologic system, altered intestinal microbiome (dysbiosis), milk substrate and mucosal injury/inflammation playing key roles. The most common site of involvement is the distal small intestine and proximal large intestine. The

Table 23.1: Staging of NEC (modified Bell's staging)*

Stage	Systemic signs	Local signs	Radiological signs	Treatment
Stage I	Temperature instability, apnea, bradycardia	Increased pre-feed residuals, mild abdominal distention and, occult blood in stool (stage IA) or gross blood in stool(stage IB)	Normal or mild Ileus	NPO; consider antibiotics for 3 days pending culture report
Stage IIA	Same as stage I	Same as I plus absent bowel sounds, prominent abdominal distention, abdominal tenderness	Ileus, pneumatosis intestinalis	NPO, antibiotics for 7-10 days
Stage IIB	Same as stage I plus mild metabolic acidosis and thrombocytopenia	Same as IIA plus abdominal wall edema with palpable loops and tenderness	Same as IIA plus portal venous gas , with or without ascites	NPO, antibiotics for 14 days
Stage III A	Same as IIB plus hypotension bradycardia, mixed acidosis, DIC	Same as II with worsening abdominal wall edema, erythema and induration (signs of generalized peritonitis), marked tenderness	Same as IIB with definite ascites	Same as above; may require fluids upto 200ml/kg/d, inotropes, assisted ventilation, abdominal paracentesis
Stage III B	Same as IIIA with worsening shock, deterioration in laboratory values and vital signs	Same as IIIA	Same as IIB plus pneumoperitoneum	Same as above plus surgical intervention

*Adapted from Gordon *et al*

pathologic hallmarks are coagulation (haemorrhagic-ischemic) necrosis, inflammation and bacterial overgrowth.

Clinical features

NEC commonly presents as a fulminant and rapidly progressive illness; however, it may also present as a slow, paroxysmal illness with abdominal distension and features of sepsis and ileus (Table 23.1). In extreme preterm neonates, a high index of suspicion is required for early diagnosis.

The age of onset is inversely related to the postmenstrual age (PMA) at birth, with a mean of around 12 days and PMA of 29 to 31 weeks.¹ The common clinical features are

Systemic signs: These include respiratory distress with increased episodes of apnea/bradycardia and temperature instability; others include lethargy or irritability with poor feeding, decreased peripheral perfusion and pallor, acidosis, hypo/hyperglycemia, oliguria and bleeding diathesis.

Abdominal signs (usually predominate): These include increased gastric aspirates, abdominal distention or tenderness, blood in stools, peritonitis, abdominal wall erythema, vomiting (bile or blood-stained) and ascites.

Investigations

Laboratory findings: There may be anemia, neutropenia with a shift to left, thrombocytopenia, metabolic acidosis, hyponatremia, and occult blood in stool. Blood cultures are positive in up to 40% of cases. Severe refractory hyponatremia, persistent metabolic acidosis and thrombocytopenia comprise the classic metabolic triad in NEC.

Abdominal Xray: Both AP and left lateral decubitus (useful for detection of a small pneumoperitoneum) or cross-table lateral views (avoids the need to move and position these sick neonates) may be required for diagnosis. The common X-ray features include bowel wall edema, pneumatosis intestinalis (the radiologic hallmark; Figure 23.1), portal venous gas (Figure 23.2), gasless abdomen (indicating ascites), fixed position of

bowel loop on serial x-rays (same appearance of a dilated loop of bowel on radiography over 24 hours). The frequency of repeating x rays depends on the severity of NEC and may vary from 6 to 24 hourly and at the time of any clinical deterioration.



Figure 23.1: Pneumatosis intestinalis
(Arrow indicates intramural gas in bowel wall; the radiologic hallmark)

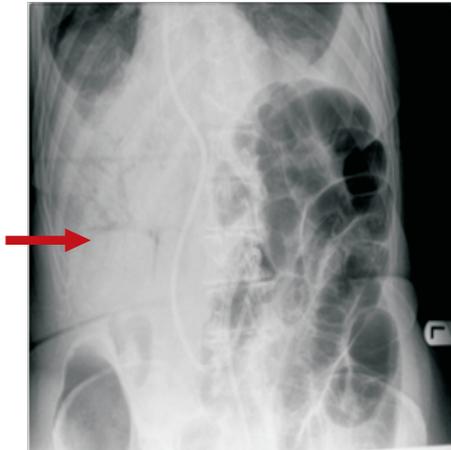


Figure 23.2: Portal venous gas
(Arrow indicates portal venous gas)

USG abdomen: May be helpful for detecting ascites, bowel wall thickness, and bowel wall perfusion; pneumatosis intestinalis and portal vein gas can also be detected.

Practical tip: X-ray abdomen

ELBW neonates often have only abdominal distension and ileus and are more likely to have pneumoperitoneum; pneumatosis intestinalis is more common after 30 wks PMA.⁶

Management

Prevention

- **Antenatal steroids:** Incidence of NEC is significantly reduced after antenatal steroids given to pregnant women with preterm labor or premature rupture of membranes.⁷
- **Standardized enteral feeding:** Minimal enteral nutrition and standard feeding guidelines have proven benefit in decreasing the incidence of NEC.⁸
- **Human milk feeding:** Newborns exclusively breastfed have a reduced risk of NEC.⁴
- **Probiotics:** Meta-analysis of 30 RCTs and 14 observational studies show a significant reduction in severe (stage II or more) NEC with a relative risk of 0.57 (95%CI 0.47-0.70).⁹ However, a recent large multicenter trial with *Bifidobacterium breve* strain showed no reduction in the risk of NEC or death.¹⁰ *We do not use probiotics for the prevention of NEC because of the very low incidence of severe NEC (stage 2 or more) in our unit.*
- **Lactoferrin:** Beneficial effects of breast milk are likely to be secondary to antimicrobial properties of lactoferrin. Lactoferrin, a glycoprotein, has been shown to attenuate lipopolysaccharide-mediated pro-inflammatory cytokine release from monocytic cells, and stimulate enterocyte proliferation, which is important in maintaining the integrity of the intestinal mucosa. Supplementation of lactoferrin with or without probiotics has been shown to reduce the incidence of late-onset sepsis and NEC. The results of ongoing trials will inform further practice regarding the use of lactoferrin for prevention of NEC.¹¹
- **L-arginine:** Arginine is a substrate for nitric oxide production and may help in prevention of NEC. Moderate quality evidence from three trials including 285 neonates showed a significant reduction in incidence of any stage

NEC (RR 0.38; 95% CI 0.23 to 0.64). However, given the small number of neonates enrolled, more trials are needed to make a definite recommendation regarding its use.¹²

Medical management

- All neonates with suspect/established NEC should be kept nil per oral with continuous gastric aspiration; volume-by-volume replacement of aspirates should be done with N/2 saline.
- Total parenteral nutrition may be required, particularly in stage II/III NEC.
- Remove umbilical arterial or venous catheters, if any (to prevent ongoing mesenteric intestinal ischemia).
- Appropriate respiratory support in form of CPAP or mechanical ventilation.
- Circulatory support: If there are features of shock, appropriate management with normal saline bolus and inotropes with monitoring of arterial blood pressure.
- Metabolic derangements like acidosis and electrolyte imbalances should be corrected.
- Blood cultures must be sent broad spectrum antibiotics as per NICU protocol (with anaerobic cover) when there is evidence of peritonitis or bowel perforation
- Pain control and minimal handling of the neonate are recommended
- Maintain hematocrit; arrange PRP and FFP if evidence of DIC
- Renal function monitoring: Monitor urine output, urea, creatinine, serum electrolytes and fluid management as indicated
- Serial monitoring with abdominal X-rays and abdominal girth monitoring are recommended
- Consultation with a pediatric surgeon for further management

Surgical management

Absolute indications for surgery

1. Pneumoperitoneum (indicating bowel perforation)
2. Presence of necrotic bowel (severe and persistent metabolic

acidosis and/or thrombocytopenia, persistent fixed loop on serial x-rays with lack of response to medical management)

The surgical options include

1. **Laparotomy:** The standard operation is laparotomy with resection of gangrenous bowel and enterostomy formation. Surgery can be resection and exteriorization or resection and primary anastomosis.
2. **Primary peritoneal drainage (PPD):** Consider PPD in ELBW neonates who are too unstable to undergo laparotomy

Laparotomy vs. PPD: What is the evidence?

Rao et al¹³ did not find any significant benefits or harms of peritoneal drainage over laparotomy. However, they included only 2 RCTs and had a small sample size of 185 neonates. The trials also did not distinguish isolated intestinal perforation from NEC. One trial found that 74% of neonates initially treated with primary peritoneal drainage required a rescue laparotomy.

Prognosis

The overall mortality of NEC ranges from 20% to 40%, but approaches 100% in neonates with the most severe form of the disease.⁷ Other complications in severe NEC requiring surgical intervention include intestinal strictures, short bowel syndrome, cholestasis and growth failure. There is also a significant risk of neuro developmental sequelae on follow up.¹⁴

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