Yorkshire and Humber Neonatal ODN (South) Clinical Guideline

Title: Necrotising Enterocolitis (NEC)

Author: Dr Aiwyne Foo, updated Dr Aarti Mistry Nov 2018

Date Written: October 2014

Review Date: March 2022

This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire and Humber Neonatal Operational Delivery Network (South). The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Best practice recommendations represent widely used evidence-based practice and high quality standards that all Neonatal Units across the Network should implement. Subsequent suggested recommendations may be put into practice in local units. However, alternative appropriate local guidelines may also exist.

A. Summary page

Necrotising enterocolitis (NEC) is a disease with high mortality in the preterm neonate.

- Preventive measures should always be part of care:
  - Early trophic feeding with breast milk
  - Following an incremental feeding regime. See Y&H Neonatal ODN (South) Feeding the preterm infant).
  - Avoid prolonged use of early empirical antibiotics
  - Careful application of blood transfusion
  - Use of multi-strain probiotics in infants < 33 weeks or <1500g

- Early symptoms may be non-specific and there should be a low threshold to investigate for this condition.

- Sick infants may require urgent resuscitation, stabilization with ventilatory and inotropic support, including need of fluids/blood products.

- Monitor haematological, biochemical, inflammatory markers; obtain blood cultures and start broad spectrum antibiotics.

- Consider early discussion with surgical team.

Diagnosis and Treatment of NEC

	Signs and Symptoms	AXR findings	Management
Suspected NEC	Abdominal Distension Feed intolerance Bilious Aspirates Unwell Increasing bradycardia and apnoea, desaturations Temperature instability Raised infection markers Decreasing neutrophil and platelet count	Normal Non-specific gaseous bowel loops.	Observe abdominal distension and feed intolerance closely Consider Nasogastric tube insertion to decompress bowel Holding feeds AXR Checking FBC, CRP and Capillary gas, Blood culture Consider broad spectrum antibiotics. To be reviewed at 36hrs with cultures and clinical assessment prior to re-administering feeds.
Medical NEC	Lactic acidosis Blood in stools	Distended bowels loops. Paucity of gas Pneumatosis Fixed dilated loops seen on serial AXR. Intramural gas	Stop feeds Nasogastric tube insertion to decompress bowel Serial AXR Close monitoring of inflammatory marker and examination of abdominal distension Broad spectrum Antibiotic 5-10 days Administration of parenteral nutrition via central access to maintain nutrition.
Failure of medical management (after 3-4 days) e.g. persistent ileus pattern, abdominal distension, AXR showing absence of bowel gas- consider elective discussion with surgical team			
Surgical NEC	Unwell Shocked Haemodynamically unstable Deteriorating clinical situation. Persistent abdominal distension with no improvement despite broad spectrum antibiotics.	Intraperitoneal gas Portal venous gas Ligamentum Flavum is visible	Stabilisation of haemodynamic status Referral to Surgical centre- laparotomy Early Intubation, ventilation, Inotropes, Fluids and Blood products maybe required

B. Full guideline

1. Background

Necrotizing enterocolitis is one of the most common gastrointestinal emergencies in the newborn infant. It is disorder characterized by ischaemic necrosis of the intestinal mucosa, with associated inflammation, invasion of enteric gas forming organisms and dissection of the gas into muscularis and portal venous system. The excessive inflammatory process in the highly immune-reactive intestine in NEC extend the effects of the disease systematically, affecting distant organs such as the brain, increasing risk of neurodevelopmental problems. NEC is can stage through the Bell Staging criteria, please refer to Appendix 1.

Necrotizing enterocolitis occurs in 1 to 3 per 1000 births. The survival rate in UK is 75% but mortality is inversely related to gestation and birthweight, 10-44% in infants < 1500gram and 0-20% in infants over 2500grams.

Risk factors for NEC:

- Prematurity
- Intrauterine growth restriction
- Very low birthweight
- Patent ductus arteriosus
- Indomethacin treatment
- Blood transfusion
- Lack of enteral breast milk

2. Aim

To provide, as far as possible, an evidence-based guide in managing NEC in the neonatal unit, from early recognition to surgical referral.

3. Making a Diagnosis

3.1 Symptoms

Classic NEC in a preterm (usually after 10 days of age)

- Feed intolerance
- Abdominal distension (may be shiny +/- periumbilical erythema)
- Bloody stools

Symptoms may progress rapidly, often within hours.

- Abdominal discolouration
- Intestinal perforation
- Systemic hypotension

Early symptoms may be non-specific:

- Increased episodes of bradycardia and desaturations
- Mild abdominal distension
- Feed intolerance e.g. large bilious or large bloody aspirates, vomiting
- Tachycardia
- Increased crying

3.2 Imaging

Early imaging signs

- Dilated loops of bowel
- Paucity of gas
- Gas-filled loops of bowel unaltered on repeated examinations (fixed loops)

More advance imaging signs

- Pneumatosis intestinalis
- Portal venous gas
- Pneumoperitoneum

Presentation with any of the above early symptoms should prompt a thorough clinical examination of the infant with appropriate investigations – see below

NEC-like symptoms also occur in term or late preterm infants, disease usually occurring in first week after birth, more often associated with other problems, e.g. maternal illicit drug use, intestinal anomalies, congenital heart disease and perinatal stress.[4,5]

Spontaneous perforation in preterm infants probably represents a different disease entity with a different pathogenesis.[6,7]

The more premature the infant, the later the disease occurs after birth.8

Diagnostic criteria using Bell's staging or Vermont-Oxford criteria both have similar short-comings since severe NEC can develop without meeting the advance criteria.9

4. Investigation & Treatment 1

Factors conferring a predisposition to NEC include genetic factors and several immature characteristics of the fetal intestine, including altered microbiota, inadequate intestinal barrier function, and an excessive inflammatory response.1,10-17

Management depends on clinical presentation (Table 1).

4.1 General Management

- Investigations include abdominal radiograph (AP +/- left lateral decubitus)+/- radiological opinion.
- Monitoring of white cells, differentials, platelet counts (sudden decreases suggest disease progression) and inflammatory markers; blood cultures; blood gases: electrolytes and lactate
- Medical intervention includes abdominal decompression, bowel rest and parenteral nutrition.
- Bowel rest, depending on degree of suspicion, severity of symptoms/signs may be a brief stopping of enteral feeds e.g. 24h (for unconfirmed NEC) or 7-10 days.
- Nasogastric tube on free drainage
- Start broad spectrum intravenous antibiotics – including anaerobic and gram-negative cover.

- Intensive care monitoring
- Appropriate resuscitation
- Ventilatory support
- Consider ventilation for infants on CPAP to avoid further abdominal distension.
- Cardiovascular assessment (HR, Blood pressure, Lactate)
- Low threshold for inotropic support
- Fluid resuscitation
- Strict fluid balance, monitor urine output, consider catheterization

- Support with blood products as required
- Early discussion with surgical team regarding on-going management, urgency of surgical assessment/intervention and the need for transfer – e.g. when not responding to/failure of medical management, where perforation/stricture is suspected.

4.2 Re-feeding after NEC

- In a clinically stable infant with unconfirmed NEC, consider restarting feeding after 5 days of nil by mouth
- In definitive NEC, consider restarting feeding after 10 days of nil by mouth
- Rate of feed increment no more than 30ml/kg/day (refer to Y and H (South) Feeding the preterm infant guideline)
- Use EBM or donor breast milk, if these unavailable, consider hydrolysed formula e.g. Pepti Junior
- After resolution of clinical and radiological features in medically managed NEC, if feeds cannot be established i.e. recurrent/large aspirates with abdominal distension etc plus dilated loops on plain AXR, surgical opinion should be sought to exclude a post-NEC stricture

Recommendations:

- **Suspected NEC in a clinically stable infant should be investigated and treated as NEC until proven otherwise.**
- **Suspected NEC in an unwell/unstable infant OR confirmed NEC in a clinically stable infant should be resuscitated, stabilized, investigated, monitored and treated for 5-10 days. Consider discussion with surgical colleagues +/- early transfer in cases not responding to medical management.**
- **Confirmed NEC in a sick/clinically deteriorating infant requires urgent resuscitation and stabilization, close monitoring of clinical, haematological and biochemical status; urgent discussion with surgical and neonatal colleagues and transport team.**

5. Prevention

5.1 Because of the fulminating nature of NEC, preventative approaches are extremely important:

- Avoiding rapid increases in feeding as this increases the likelihood of NEC.20
- However, complete withholding of feeds leads to prolonged use of parenteral nutrition, intestinal atrophy, parenteral nutrition associated cholestasis, increased permeability and inflammation, and late onset sepsis.21
- Exclusive use of human milk enterally may lower the incidence of NEC.22-24
- Prolonged empirical use of intravenous antibiotics increases the incidence of NEC.25

5.2 Probiotics

Evidence has amassed that demonstrates the use of probiotics can prevent the incidence of severe NEC RR 0.57 (0.47-0.7), mortality RR 0.77 (0.65-0.92) and late onset sepsis 0.88 (0.8- 0.97)[32]. Equivocal results from large studies such as PIPS study[34] which utilised Bifidobacterium contrasted with positive results from many other studies prompting assessment of type of probiotic used. Meta-analysis of strain-types demonstrates that multiple strains are more effective than single strains in reducing NEC (OR 0.36 (0.24-0.53)) and mortality (OR 0.58 (0.43-0.79)) supporting their use[33].
Multi-strain probiotics should be used routinely for babies born below 33 weeks' gestation or 1500g once infant is on a minimal feed volume of 1ml. Omit if the baby is nil by mouth or being treated for NEC. Discontinue at 34 weeks gestational age, unless feeds are poorly tolerated, and consultant decision is made to continue beyond this gestational age.

5.3 Prebiotics

These enhance the proliferation of endogenous flora such as bifidobacterial and appear to alter the consistency and frequency of stools, but their efficacy in prevention of NEC is unclear.

Recommendations

- **Early initiation of minimal enteral feeds of expressed human milk avoiding rapid increments: refer to Y&H Neonatal ODN "Feeding the Preterm Infant" guideline**
- **Avoid early prolonged use of antibiotics.**
- **Use of multi-strain probiotics to prevent severe NEC in infants < 33/40 or < 1500g**

6.0 Areas outside remit

6.1 Surgical management of NEC.

7.0 Audit criteria

Numbers of suspected and confirmed NEC
Preventive measures
Feed – type and rate of increment
Use of empirical antibiotics
Imaging
Medical management including: bowel rest (days), parenteral nutrition, antibiotics used (which and duration), monitoring of haematological, biochemical and inflammatory markers, support of other systems
Surgical referral
Outcomes

8.0 References

1. Neu J, Walker WA. Necrotizing Enterocolitis. N Engl J Med 2011;364:255-64
2. Bell MJ, Ternberg JL et al.Neonatal Necotizing Enterocolitis: therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7
3. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179-201
4. Martinez-Tallo E,Claure N et al.Necrotizing enterocolitis in full term or near term infants: risk factors. Biol Neonate 1997;71:292-8
5. Raboei EH. Necrotizing Enterocolitis in full term neonates: is it aganglionosis? Eur J Pediatr Surg 2009;19:101-4
6. Gordon PV, Attridge JT. Understanding clinical literature relevant to spontaneous intestinal perforations. Am J Perinatol 2009;26:309-16
7. Gordon PV, Swanson JR et al.emerging trends in acquired neonatal intestinal disease: is it time to abandon Bell's criteria? J Perinatol 2007;27:661-71
8. Neu J. Neonatal necrotizing enterocolitis: an update. Acta Paediatr Suppl2005;94:100-5
9. Epelman M, Daneman A et al. Necrotizing enterocolitis: review of state-ofthe-art imaging findings with pathological correlation. Radiographics2007;27:285-305
10. Martin CR, Walker WA. Intestinal immune defences and the inflammatory response in necrotizing enterocolitis. Semin Fetal Neonatal Med 2006;11:369-77
11. Fusunyan RD, Nanthakumar NN et al.evidence for an innate immune response in the immature intestine: toll-like receptors on fetal enterocytes.Pediatr Res 2001;49:589-93

12. Claud EC, Lu L et al. Developmentally regulated IkappaB expression in intestinal epitheliumand susceptibility to flagellin-induced inflammation. ProcNatl Acad Sci USA 2004;101:7404-8
13. Sharma R, Tepas JJ III et al. Neonatal gut barrier and multiple organ failure: role of endotoxin and proinflammatory cytokines in sepsis and necrotizing enterocolitis. J Pediatr Surg 2007;42:454-61
14. Morowitz MJ, Poroyko V et al. Redefining the role of intestinal microbes in the pathogenesis of necrotizing enterocolitis. Pediatrics 2010;125:777-85
15. Mshvildadze M, Neu J et al. Intestinal microbial ecology in premature infants assessed with non-culture based techniques. J Pediatr 2010;156:20-5
16. Crissinger KD. Regulation of hemodynamics and oxygenation of developing intestine: insight into the pathogenesis of necrotizing enterocolitis.Acta Paediatr Suppl 1994;396:8-10
17. Norwicki PT, Nankervis CA. The role of the circulation the pathogenesis of necrotizing enterocolitis. Clin Perinatol 1994;21:219-34
18. Davey AM, Wagner CL et al. Feeding premature infants while low umbilical artery catheters are in place:a prospective randomized trial. JPediatr 1994;124:795-9
19. Mally P, Golombek SG et al. Association of necrotizing enterocolitis with elective packed red blood cell transfusions in stable, growing premature neonates. Amm J Perinatol 2006;23:451-8
20. Anderson DM, Kliegman RM. The relationship of neonatal alimentation practice to the occurrence of endemic necrotizing enterocolitis. AM J Perinatol1991;8:62-7
21. Moss RL, Kalish LA et al. Clinicla parameters do not adequately predict
outcome in necrotizing enterocolitis: a multi-institutional study. J Perinatol2008;28:665-74
22. Meinzen-Derr J, Poindexter B et al. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. J Perinatol2009;29:57-62
23. Quigley MA, Henderson G et al. Formula milk vs donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev2007;4:CD002971
24. Sullivan S, Schanler RJ et al. An exclusive human milk-based diet is associated with lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr 2010;156(4):562.e1-567.e1
25. Cotten CM, Taylor S et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009; 123:58-66
26. Lin HC, Hsu CH et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics 2008;122:693-700
27. Tarnow-Mordi WO, Wilkinson D et al. Probiotic reduce all-cause mortality
in necrotizing enterocolitis: it is time to change practice. Pediatrics2010;125:1068-70
28. Alfaleh K, Anabrees J et al. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev2012;3:CD005496
29. Sherman PM, Cabana M et al. Potential roles and clinical utility of prebiotics in newborns, infants, and children: proceedings from a global prebiotic summit meeting. J Pediatr 2009;155:S61-S70
30. https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-necrotizing-enterocolitis-innewborns?source=search_result&search=necrotizing%20enterocolitis&selectedTitle=2~150

31. Pammi, Mohan, Suresh, Gautham Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database of Systematic Reviews 2017 John Wiley & Sons, Ltd,
32. The "Golden Age" of Probiotics: A Systematic Review and Meta-Analysis of Randomized and Observational Studies in Preterm Infants. Elda Dermyshi et al. Neonatology. 2017; 112: 9-23
33. Multiple strains probiotics appear to be the most effective probiotics in the prevention of necrotizing enterocolitis and mortality: An updated meta-analysis. Hung-Yang Chang 2017. PLoS ONE 12(2): e0171579.

34. Probiotics in Preterm Infants Study Collaborative Group. Bifidobacterium breve BBG001 in very preterm infants: a randomised controlled phase 3 trial. Costeloe K, Lancet. 2016. 13;387(10019):649-60.

Sources

- Bradford Royal Infirmary; Neonatal Guideline. S Oddie, S Wallis
- Probiotics guideline. Ashford and St Peter's Hospital. Dr P Reynolds.

C Appendices

1) **Bell's staging for NEC**
2) **Grading recommendation**

Appendix 1 - Modified Bell staging criteria for necrotizing enterocolitis (NEC) in neonates

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus
IB	Suspected	Same as above	Grossly bloody stool	Same as above
IIA	Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA	Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, Disseminated intravascular coagulopathy, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum

Appendix 2 - Grades of recommendation

Grade	
A	Requires at least one meta analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, and demonstrating overall consistency of results
B	Requires a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	Requires a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+