Introduction

Necrotising enterocolitis (NEC) is the most common gastrointestinal emergency in neonates. It is a disease of unknown aetiology with multi-factorial pathogenesis. A unifying hypothesis that may explain NEC is hypoperfusion in an immature gut as a result of a perinatal insult, either antenatal and/or postnatal. The circulatory changes are associated with mucosal injury, intestinal organisms and substrate (milk) breaching the mucosal barrier, as well as a complex interaction of inflammatory cascade as a response to the injury. 1,2 The newborn intestine has a low vascular resistance 3, and the mechanism of gut injury may be related to decreased ability of the immature gut to regulate blood flow.

INCIDENCE AND RISK FACTORS

Incidence

The incidence of NEC is reported between 0.3 - 3 / 1000 live births 1,2. The risk of developing NEC is inversely related to gestational age at birth with the extremely premature infant at greatest risk 2,4. At RPAH the incidence of NEC during the years 1995 - 2001 was 0.45 / 1000. It is estimated 10% of very low birth weight infants develop NEC. 1,2,4-6 NEC also occurs in term infants reported 0.05 / 1000 live births. 7,8

Risk factors

Prematurity and abnormal umbilical flows are found consistently to predispose to NEC. NEC is associated with many conditions that constitute increased risk, generally because they reduce mesenteric blood flow that may lead to intestinal hypoxia and injury.

Proven risk factors

1. Gestational age: Prematurity is the main risk factor 1,2,4,5
   - Infants < 30 weeks: NEC often occurs in the absence of a defined insult, the primary risk being gut immaturity itself.
   - Infants 31 - 36 weeks: a significant proportion of infants are growth restricted and there is a higher incidence of asphyxia. 4,6
   - Term infants: NEC is often secondary to a major predisposing event and/or associated with underlying congenital disease in 2/3, predominantly cardiac 9 and endocrine 7,9.

2. Blood flow abnormalities: Absent or reversed umbilical artery flow antenatally 10,11 and low systemic blood flow in the neonatal period. 12

3. Enteral Feeding: The majority of infants that develop NEC have been enterally fed. However, less than 10% of NEC occurs in infants who have never been fed.

4. Type of feed: NEC is rare amongst infants fed breast milk alone but it can occur. Prospective non randomised study 13 showed NEC is 6 -10 x more common among formula fed babies and 3 x more common in formula plus breast milk, compared to those that fed breast milk alone. The incidence of
Suggested risk factors:

1. **Intrauterine growth restriction**: 6 if associated with absent or reversed umbilical artery flow. 10,11
2. **Pathogenic organisms**: 2,4,16 The most frequently isolated bacteria are gram negative: *Klebsiella*, *E coli*, *Enterobacter* (These 3 are isolated in over half of cases), anaerobes: *Clostridia*, *bacteroides*, gram positive: *Staph epidermidis*, *Enterococci*. Virus and fungi have also been implicated. 17
3. **UAC**: NEC occurring with UAC is rare and does not have a significant effect on the incidence of NEC.18
4. **Congenital heart disease**: The incidence of NEC in these infants is 3%.7,9
5. **Perinatal asphyxia**: higher incidence in the more mature infants > 30 weeks.4
6. **No antenatal steroids**: Antenatal steroids given for preterm labour with rupture of membranes significantly decrease the incidence of NEC.19
7. **Polycythaemia** 4,20
8. **Exchange transfusion** 4,20
9. **Inflammatory mediators**: platelet activating factor (PAF) 21, imbalance of cytokines22, deficiencies of nitric oxide, gut trophic and growth factors. 22,23
10. On rare occasions NEC can develop in healthy term infants with no risk factors.

CONSEQUENCES

Pathology:

NEC affects all portions of the GIT most commonly the jejunum, terminal ileum and proximal colon. The gut with NEC shows mucosal and transmural coagulation necrosis, haemorrhage, inflammation, ulceration and reparative changes.24

Mortality:

Mortality rate of NEC overall is 20 - 40%. 1,2,5 It is the most common cause of death in infants undergoing surgery.

Intestinal sequelae:2

At discharge many infants have a high prevalence of adverse intestinal sequelae and remain at significant risk of under nutrition, recurrent illness, gastrointestinal complications, poor growth and recurrent hospitalisation. These are associated with:

- **Structures**: the most common long term GIT complication, present in up to 35% of infants who have had NEC. They occur in both surgically and medically treated NEC.25 The most common site is at the junction of the descending and sigmoid colon. Potential indicators of stricture formation are failure to thrive, feeding intolerance, altered stool pattern or bowel obstruction.
- **Short bowel syndrome**: seen in 25% of infants that undergo surgery.
- **Bowel obstruction**: in 5% of patients who have had surgery for NEC.
- **Cholestasis**: secondary to prolonged TPN 26
- **Uncommon sequale**: fistula, abscess, recurrent NEC, malabsorption, enteroctyst formation

Neurodevelopmental sequale:

NEC is significantly associated with increased neurodevelopmental morbidity independent of other factors
and is more common in infants who have required surgery compared with medically treated infants with NEC. 27-30

**Growth:**

Normal catch up growth is seen in infants with NEC who were managed conservatively. 29. There is an increased incidence of growth failure in infants who required surgery, developed short bowel syndrome and/or were on prolonged TPN. 28-30

**DIAGNOSIS**

**Clinical presentation:**

- NEC varies greatly, infants may have a sudden onset with rapid clinical deterioration or it may evolve slowly over a few days. Consider NEC if any of the following signs are present:
  - **Non - specific for GIT:** feed intolerance, abdominal distension, occult blood in stool
  - **Specific GIT:** increased abdominal distension with tenderness, abdominal wall oedema, decreased or absent bowel sounds, bile stained gastric aspirates, bloody stool.
  - **Systemic:** temperature instability, apnoea, persistent acidosis, thrombocytopenia, anaemia, neutropaenia and cardiovascular compromise such as hypotension, oliguria, shock.

- **Differential diagnosis** to be considered:
  - Sepsis with ileus
  - Bowel obstruction
  - Volvulus
  - Malrotation
  - Spontaneous intestinal perforation: 31-32 This is a distinct clinical entity in the VLBW infant, differentiated from NEC surgically by isolated perforation often at the terminal ileum with normal bowel. AXR has no evidence of pneumatosis intestinalis. Clinically it is often associated with systemic candidiasis. To be considered if early postnatal steroids have been given and the clinical picture is suggestive of NEC. 33
  - Systemic candidiasis: 34 clinical signs are often similar to NEC with abdominal distension seen in half these infants, metabolic disturbances, hypotension and thrombocytopenia.

**Investigations - Laboratory:**

- **FBC:** Anaemia, neutropaenia and thrombocytopenia are often seen. The early return of these indices to normal carries a good prognosis.
- **Blood film:** look for evidence of haemolysis and toxic changes
- **Electrolytes:** hyponatraemia
- **Arterial or venous blood gas:** for evidence of acidosis, hypoxia or hypercarbia.
- **Coagulation profile:** if there is active bleeding.
- **Blood cultures:** Positive blood cultures are found in less than 1/3 of cases. 4, 16 Bacterial and viral cultures may be helpful but not conclusive

**Investigations Imaging:**

Both a supine AP abdominal and left lateral decubitus Xray are essential for the diagnosis of suspected NEC. It is important to note that radiological findings associated with NEC are not seen in all infants.

**Xray findings include:**

- Dilated and thickened bowel loops +/- air-fluid levels.
- Pneumatosis intestinalis (intramural gas): the radiological hallmark of NEC.
• Pneumoperitoneum: best seen under the diaphragm in the left lateral decubitus AXR. Less common, on the AP film it is seen as a central collection of free air ("football sign").
• Persistently distended loop of bowel.
• Portal venous gas
• Gasless abdomen

Contrast studies: These are best avoided during the acute illness as there is a high risk of perforating. Due to the lack of evidence supporting contrast studies during the recovery phase, we suggest they be reserved for when there are concerns of late strictures.

TREATMENT GUIDELINE: What to use in the NICU at RPAH

Most infants with NEC can be managed conservatively but 30 - 50% will require surgical intervention. As there have been no controlled trials of treatment for NEC that have shown benefit, management is essentially supportive and based on empiric interventions.

Serial physical examinations and investigations should be done to guide treatment. Early surgical consultation is essential.

Bowel rest and nutrition:

Initial clinical management is directed at prevention of further injury to the gut

• Cessation of enteral feeding. Conventionally the duration of no enteral feed is usually 10 days. This is empirical with no available evidence to support this. Consider earlier recommencement of feed if gut function is returned to normal, ie, soft, non distended, non tender abdomen with normal bowel sounds and minimal gastric residuals.
• Gastric decompression with a large bore 8 -10F orogastric tube.
• Commencement of intravenous fluids
• Correction of electrolyte disturbances
• TPN should be commenced unless there is severe acidosis.
• Gradual reintroduction of feed, ideally this should be with breast milk. Following the re-introduction of feeds, up to 10% of infants show increased gastric residuals and abdominal distension.

Intravenous antibiotics:

• Broad spectrum intravenous antibiotic cover against gram positive and negative organisms, should be commenced as soon as the diagnosis is considered. Because of the prominence of anaerobic bacteria the routine inclusion of anti - anaerobic drug is suggested. Clinical trials for definitive management regimens are lacking, but therapy should be determined by the sensitivity of local organisms.
• The recommended antibiotic regime at RPAH is Vancomycin and Gentamicin. If there is clinical concern, Metronidazole may be added.
• The duration of antibiotic treatment is usually 7 - 10 days. Again this is convention without evidence to support this. Consideration to stopping earlier may be given if the baby is tolerating oral feeds and is clinically improved.

Fluids and cardiovascular support:

Many infants will be hypovolaemic as a result of capillary leak, third spacing and hypoalbuminaemia and may require fluid resuscitation. Link to fluids

• Crystalloid to be given as the initial fluid for volume expansion.
• Consider inotropes if not responding: Dopamine 10mcg/kg/min then dobutamine 10mcg/kg/min increasing up to 20mcg/kg/min
• Correction of thrombocytopaenia if platelets < 30
• Correction of anaemia with packed cells 15ml/kg. If there is haemolysis on blood film, do Tk Ag Activation test and give plasma free red blood cells with low titre Ag.
If there is active bleeding and/or abnormal coagulation profile: give Fresh Frozen Plasma 10 ml/kg and reassess.

**Respiratory support:**

Mechanical ventilation is required if there is increasing apnoea, oxygen requirements or increasing acidosis.

**Correction of acidosis:**

The acidaemia in NEC is mixed. Correct the respiratory component (hypercarbia and acidosis from hypoventilation) with appropriate ventilatory support. The metabolic component is from hypoperfusion and requires fluid. (see above)

**Analgesia:**

If required, commence morphine infusion at 10 - 20 microgram/kg/hr.

**Surgery:**

- **Consultation with a paediatric surgeon is essential** once the diagnosis has been considered. Surgeons from either The Children’s Hospital at Westmead or Sydney Children’s Hospital may be consulted, this needs to be discussed first with the neonatologist. Transfer of the infant to a Children’s Hospital may need to be arranged.
- **Indications for surgery:**
  - Clinical: Failure to respond to optimal medical management as evidence by persistent thrombocytopenia, leucopenia or leucocytosis, progressive neutropenia, severe GIT bleed, oliguria, hypotension, persistent acidosis or fixed abdominal mass.
  - Radiological: pneumoperitoneum, fixed loop on serial AXR, portal venous gas.
- There are two types of surgery performed for NEC: **Laparotomy** (resection of necrotic bowel, formation of enterostomy and mucosal fistula) and **peritoneal drainage** (PD). A meta analysis comparing all clinical trials (none were RCT’s) of PD and laparotomy for perforated NEC could not conclude which of the two techniques was the most effective, but found the mortality associated with surgery to be 35 - 55%. 36
- Currently, a multicentre, RCT (NET: Necrotising Enterocolitis Trial) 37 is enrolling patients with the aim to determine the best surgical management for perforated NEC in preterm infants. The NSW state coordinator is:
  - Dr Susan Adams (Paediatric Surgeon),
  - Sydney Children’s Hospital, Randwick. NSW. Australia.
  - Contact via SCH switchboard phone: 02 – 9382 1111

**Long Term Management of NEC:**

- Parents to have a working knowledge of the current and anticipated problems.
- Parents must be instructed about the signs of bowel obstruction.
- Medical +/- surgical follow up after discharge.
- Contrast studies should only be done if clinically indicated for stenosis.
- Appropriate developmental follow-up.

**INTERVENTIONS AND DIRECTIONS FOR FUTURE RESEARCH**

**Interventions effective in decreasing the incidence of NEC**

- **Breast milk**: is protective against NEC, exclusive breast milk, or breast milk and formula, are
associated with lower incidence of NEC.\textsuperscript{14, 15} The incidence of NEC is inversely related to the quantity of breast milk fed.\textsuperscript{14, 15}

- **Restricted fluid intake**:\textsuperscript{38}
- **Antenatal corticosteroids**:\textsuperscript{19}
- **Antenatal antibiotics**: in women with spontaneous preterm labour there is an overall decrease in incidence of NEC.\textsuperscript{39} Augmentin however, is not recommended as it is associated with an increased risk (non significant) of NEC.\textsuperscript{39-41}
- **Prophylaxis with oral aminoglycosides**:\textsuperscript{42} This reduces the incidence of NEC, however, is not recommended as it would only be effective in NEC caused by gram positive organisms and there are concerns about the risk of vancomycin resistant organisms.

### Interventions ineffective in decreasing the incidence of NEC:

- **Feeding Regimens**: The important role of enteral feeding as a key risk factor for the development of NEC, highlights the attempts to which manipulation of feeding has been done to prevent NEC. Systematic reviews addressing this include:
  - the delayed initiation of enteral feeding\textsuperscript{43}
  - slow versus fast rate of feed advancement\textsuperscript{44}
  - minimal enteric feeding\textsuperscript{45}
  - continuous nasogastric feeding versus intermittent bolus milk feeding\textsuperscript{14, 46}
  - fortifying human milk\textsuperscript{47}

  None of the above have showed any significant effect in decreasing the incidence of NEC, **however, they are considered to be safe clinical practices**.

- **Oral Immunoglobulin**: IgG or IgG/IgA combination, does not decrease the incidence of NEC.\textsuperscript{48} There are no RCT of oral IgA alone for the prevention of NEC.
- **Intravenous immunoglobulin**: Evidence from a multicentre trial of IVIG prophylaxis of neonatal infections did not demonstrate protection against NEC.\textsuperscript{49}
- **Indomethacin**: There is no significant difference in rates of necrotizing enterocolitis when Indomethacin is used for closure of PDA either as prophylaxis or treatment.\textsuperscript{50}

### Directions for future research:

- **Human milk banks (HMB)**: Pasteurised milk from screened donors is stored and given to predominately preterm infants. Currently, there are no HMB in Australia, but there are worldwide. Systematic review shows a significantly reduced risk of NEC in preterm or low birthweight infants enteral fed with donor human milk compared with formula milk feeding.\textsuperscript{51}
- **Erythropoietin (EPO)**: infants treated with recombinant EPO for anaemia of prematurity have a lower incidence of NEC.\textsuperscript{52}
- **Magnesium sulfate for maternal preeclampsia**: There is conflicting evidence for the role of antenatal MgSO\textsubscript{4} administration on the development of NEC in preterm infants.\textsuperscript{53, 54}
- **Inflammatory mediators and gut receptor imbalances**: are thought to be important in the pathogenesis of gut injury in NEC. Mechanisms that may be protective and decrease the incidence of NEC are via:
  - Dietary supplementation with magnesium and copper\textsuperscript{55}, probiotics (Bifidobacterium infantis and Lactobacillus acidophilus)\textsuperscript{56}, egg phospholipid\textsuperscript{57} and arginine.\textsuperscript{58}
  - Modulation of inflammatory mediators such as Nitroglycerine\textsuperscript{22} (as a Nitric oxide donor), cytokines\textsuperscript{22}, gut growth factors\textsuperscript{23}, platelet-activating factor (PAF) receptor antagonists\textsuperscript{24}, and cyclooxygenase COX - 2 inhibitors.\textsuperscript{59}
KEY POINTS

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<tr>
<th>Key Point</th>
<th>Level of evidence</th>
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<td>Prematurity 1,2,4-6 and umbilical artery flow abnormalities 10,11 are the main risk factors</td>
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<td>Antenatal corticosteroids are protective 19</td>
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<td>Breast milk is protective 1,13</td>
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<td>Serial clinical and radiological evaluation of the infant with early surgical consultation if NEC is considered</td>
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<td>Long term follow up is essential as gastrointestinal sequale and neurodevelopmental morbidity are common</td>
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REFERENCES:


53. Wiswell TF, Caddell JL, Graziani LJ, Komhauser MS, Spitzer AR. Maternally administered magnesium sulfate decreases the incidence of severe necrotizing enterocolitis in preterm infants: A prospective study.


Last Reviewed: July, 2003