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Great Ormond Street Hospital for Children



NHS Trust

Surgical Neonates

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Associated clinical guidelines/protocols:

- Fluid management
- Pentoxifyline

Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations.

They will not be repeated here.

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum

General Post operative care of neonates:

- Fluid management
- Sedation and analgesia
- Nutrition and weight gain
- Thermoregulation.
- Risk of IVH

Clinical conditions:

NEC: causes, diagnosis, medical & surgical management

Other surgical conditions covered "congenital anomalies requiring surgery"

Curriculum Notes for Year 1:

General Post-operative Care of Neonates:

The post operative care of neonates follows the general principles of neonatal intensive care: namely the support of the organ systems allowing healing, growth and maturation to occur while minimizing the risk of harm to the infant.

- **Minimal handling** – care is provided in the least invasive and disruptive way possible.
- **Positioning** – the infant is positioned to optimize diaphragmatic function and lung expansion. The developmental age is taken into consideration.
- **Ventilation.**
Ventilation is often required post operatively for several reasons: Pulmonary immaturity and immature respiratory drive in the preterm infant may necessitate ventilatory support. The FRC can be reduced following anaesthesia and in cases of abdominal distension (e.g. reduction of abdominal wall defects), which leads to increased work of breathing and respiratory distress. The use of higher levels of PEEP prevents atelectasis in these circumstances.
Ventilation is clearly indicated in cases requiring postoperative paralysis (e.g. long gap oesophageal atresia repair in which the anastomosis is under tension) and in those where mandatory analgesia causes central respiratory depression.

- **Fluid requirements and Renal support.**

The neonatal kidney has a limited ability to concentrate urine or to excrete a water or sodium load. Thus neonates are particularly vulnerable to both dehydration and fluid overload. ADH is secreted as part of the surgical stress response and this may become “inappropriate” in the postoperative setting.

The pre-operative physiological state has an important bearing on renal function postoperatively. Hypotension, low cardiac output, reduced circulating volume due to capillary leak and raised intra-abdominal compartment pressure in gastrointestinal surgical emergencies, all contribute to poor renal perfusion and the potential development of acute tubular necrosis postoperatively.

Therefore in general our fluid management entails:

- Restriction of crystalloid to 80mls/kg.
- Dextrose given in a concentration adequate to maintain appropriate blood glucose levels.
- Electrolytes added to the maintenance in amounts appropriate to maintain homeostasis, avoid sodium overload. Urine electrolyte concentrations may give objective evidence of losses.
- Intravascular volume/filling is given as colloid or blood products.
- Treat hypotension and ensure adequate intravascular volume in order to maintain renal perfusion.
- Treat suspected SIADH with fluid restriction
- Only use diuretics *after* the treatment of hypotension and any inadequate intravascular volume.

- **Cardiovascular support:**

The aim is to promote adequate tissue oxygenation and perfusion. Cardiac output is maintained by ensuring an adequate intravascular volume, myocardial contractility and heart rate.

Hypovolaemia may result from unexpected ongoing blood loss or fluid loss into the tissues (third spacing) or peritoneal cavity. Ongoing blood loss will be confirmed by a falling haematocrit and the surgeons should be immediately informed.

Tachycardia is an autonomic, compensatory response to hypovolaemia that attempts to maintain cardiac output. It also occurs in response to inadequate sedation and pyrexia.

Myocardial depression can occur secondary to anaesthetic and sedative agents, as well as being a recognized sequela of severe septic shock or SIRS. Severe tachycardia can exacerbate myocardial depression as poor coronary perfusion in the shortened diastole results in ischaemia.

The consequences of inotrope treatment on the splanchnic perfusion must be considered. All inotropic therapy will initially improve gut perfusion as they improve cardiac output, however, at higher doses, the risk of splanchnic vasoconstriction and hypoperfusion is increased.

- **Haematological support.**

Many infants undergoing emergency surgery for NEC may have DIC. The clotting profile will need to be normalized to prevent ongoing bleeding. In NEC the T Ag status should be determined prior to ordering blood products.

Limited erythropoiesis predisposes the preterm infant to anaemia. The critically ill surgical neonate has the additional stress of frequent blood sampling, blood loss in theatre, dilution effects occurring with fluid shifts and possible further suppression of myelopoiesis by drugs and sepsis.

- **Gastrointestinal and Hepatic support:**

There may be a prolonged ileus following gastrointestinal surgery. The stomach must remain decompressed by the constant drainage of gastric secretions. These losses should be replaced by intravenous saline (with added potassium) volume for volume. The perfusion of any stoma must be regularly observed.

The critically ill surgical infant is predisposed to jaundice for numerous reasons: immaturity of the liver, haemolysis, reduced gut motility, sepsis. These infants often have low plasma albumin and so have fewer binding sites for bilirubin. Levels of unconjugated bilirubin should be monitored and treated with phototherapy as indicated.

- **Analgesia.**
Continuous opiate infusion provides analgesia. I have included 2 reviews and a 3rd for interest^{1,2,3}
- **Thermoregulation.**
A neutral thermal environment is essential to prevent thermal stress and minimize oxygen consumption.
- **Avoid harm:**
Monitor drug levels of ototoxic drugs.
Monitor saturation and oxygenation, preventing both hypoxia and hyperoxia which contributes to the development of retinal damage (retinopathy of prematurity)

Necrotising Enterocolitis (NEC) :

A large proportion of our case mix includes neonates with Necrotising Enterocolitis.

Lee & Polin have written a review: "*Treatment and Prevention of NEC*"⁴

Henry & Moss discuss surgical management options: "Surgical therapy for NEC. Bringing evidence to the bedside"⁵

Diagnosis of perforations: "*Perforation*"⁶

Diagnosis/Evaluation:

Modified Bell's necrotizing enterocolitis (NEC) staging system⁷

Walsh's modified Bell NEC staging system is commonly used to assess NEC severity.

Stage	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, DIC, 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

Laboratory Studies

No specific pathogen has been found to have a consistent causal relationship	de la Cochetiere et al ⁸ ; Peter et al., 1999; Millar et al., 1996 ;
Insufficient evidence to support the use of stool patterns, presence of occult blood, or presence of specific pathogens as clinical indicators of NEC risk	Peter et al., 1999 [C]; Abramo et al., 1988 [C]; Andrews & Krowchuk, 1997 [D]).

Radiologic Studies:

The number of abdominal x-rays, the type of view(s), or the frequency & timing of abdominal radiographs have not been systematically studied with regard to influence on outcome or diagnostic validity. Inter-observer reliability of radiographic signs of NEC is low. Ultrasound may play a role in diagnosis – further studies need to be done¹⁰.

Primary Peritoneal Drainage:

Recently, primary peritoneal drainage (PPD) has been proposed as an alternative surgical treatment. A meta-analysis by Moss et al. also demonstrated comparable combined probability of survival for infants with perforated NEC who were treated with either procedure (67% in the LAP group vs 55% in the PPD group, $P=0.27$) even in the presence of a significant treatment assignment bias favouring the LAP group.¹¹

A recent multicentre RCT showed that laparotomy or peritoneal drainage does not influence survival, dependency on TPN and length of hospital stay in pre-term infants. In individual cases primary peritoneal drainage can be used as a temporizing measure to facilitate resuscitation prior to laparotomy.¹²

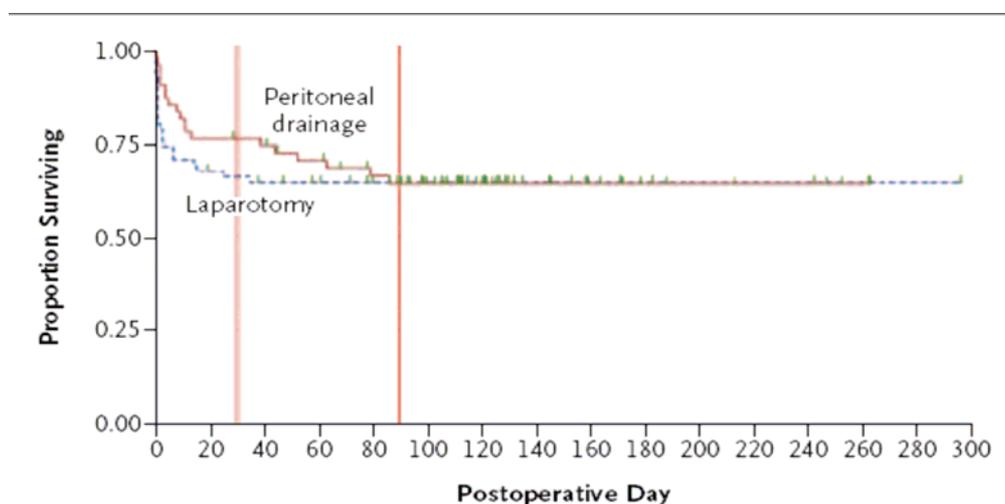


Figure 2. Kaplan–Meier Survival Curves for the Laparotomy Group and the Peritoneal-Drainage Group.

Survival curves were compared with the use of the log-rank test ($\chi^2=0.19$) and Cox proportional-hazards regression (0.66), adjusting for birth weight, sex, presence or absence of pneumatosis, presence or absence of ventilator dependence, and platelet count.

Moss et al New Engl J Med 2006; 354:2225-2234

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1. Mathew PJ, Mathew JL. Assessment and management of pain in infants. *Postgrad Med J.* 2003; 79: 438 – 443.
2. Berde CB, Sethna NF. Analgesics for the treatment of pain in children. *N Engl J Med.* 2002; 347:1094- 1103.
3. Wolfe AR. Pain, nociception and the developing infant. *Paediatr Anaesth* 1999;9:7-17.
4. Lee JS, Polin RA. Treatment and prevention of NEC. *Semin Neonatol.*2003;8; 449-459.
5. Henry MCw, Moss RL Surgical therapy for NEC. Bringing evidence to the bedside. *Semin Pediatr Surg* 2005;14:181-190.
6. Farrugia MK, Morgan AS, McHugh K, Kiely EM. Neonatal Intestinal perforation. *Arch Dis Child Fetal Neonatal Ed* 2003;8: 75
7. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am* 1986; 33:179–201.

8. De La Cochetiere MF et al .Early Intestinal Bacterial Colonization and Necrotizing Enterocolitis in Premature Infants: The Putative Role of Clostridium. *Pediatric Research*. 56(3):366-370, September 2004.
9. Di Napoli A, Di Lallo D,. Perucci CA, Schifano P, Orzalesi M, Franco F, De Carolis MP. Inter-observer reliability of radiological signs of necrotising enterocolitis in a population of high-risk newborns. *Paediatric and Perinatal Epidemiology* 18 (1), 80–87.
10. Faingold R et al. Necrotising Enterocolitis: assessment of bowel viability with color Doppler US. *Radiology* 2005; 235:587-594.
11. Moss RL, Dimmitt RA, Henry MC et al. A meta-analysis of peritoneal drainage versus laparotomy for perforated necrotizing enterocolitis. *J Pediatr Surg* 2001;36:1210–3
12. Moss et al. Laparotomy versus Peritoneal Drainage for Necrotizing Enterocolitis and Perforation. *New Engl J Med* 2006; 354:2225-2234

Information for Year 2 ITU Training (advanced):

Year 2 ITU curriculum

General Post operative care of neonates:

- Fluid management
- Immunology specific to surgical neonates

Clinical conditions:

- NEC: current research, prognostic factors, future therapies
- Short gut syndrome

Curriculum Notes for Year 2:

- **Metabolic and nutritional support.**
Please see review article "*Metabolic & nutritional support of the surgical neonate*".¹
- **Prevention and treatment of infection:**
The preterm infant is immunocompromised. Infection must be recognized early and treated vigorously. Adjunctive therapies such as intravenous immunoglobulin and pentoxifyllin may need to be considered see additional information below.

Necrotising Enterocolitis (NEC) :

Prognostic factors:

T antigen status: "*T antigen*"²

The significance of hyperglycaemia: "*Hyperglycaemia and NEC*"³

The significance of thrombocytopenia: "*Thrombocytopenia*" & "*Thrombocytopenia 2*"

The complications of NEC include:

Short Gut Syndrome "*Short gut Syndrome in Paediatric Patients*"

Long term TPN "*TPN and Immunity*" & "*TPN and Infection*"

Stricture formation.

NEC Preventative Measures:

Breast Milk

Infants who received human milk were 4 times less likely to have confirmed NEC compared to infants who received formula (relative risk [RR] 0.25, 95% confidence interval [CI*] 0.06 to 0.98). Studies show that providing human milk to twenty preterm infants will prevent one case of NEC

- McGuire, W 1; Anthony, M Y 2 Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. *Archives of Disease in Childhood Fetal & Neonatal Edition*. 88(1):F11-F14, January 2003.

Feeding strategies to reduce NEC:

The following strategies have all been researched by several clinical trials. None have shown to be effective.

Minimal Enteral Feeding	No Effect of: Dilute or full strength formula feedings providing <25 kcal/kg/day (37cc/kg/day) for >5 day (Tyson & Kennedy,2003) 0.5 to 1 mL/hr to extubation (McClure & Newell, 2000) 20 mL/kg/day, day 4 to 14 (Schanler et al., 1999) In all studies, controls were not fed by mouth
Timing of Initiation of Feeds	No Effect of: Early -- day 1 to 5 Late -- day 5 to 14 (Kennedy, Tyson, & Chamnanvanikij, "Early versus delayed," 1988)
Rate of Advancement of Feeds	No difference between; 10-20 cc/kg/day slow 20-35 cc/kg/day fast (Kennedy, Tyson, & Chamnanvanikij, "Rapid versus slow," 2000) 20 mL/kg/day X 10 day versus increase by 20 mL/kg/day to 140 mL/kg/day – <u>Decreased incidence of NEC</u> (Berseth, Bisquera, & Paje, 2003). Showed a decreased rate of NEC in infants maintained at 20 cc compared to those children advanced. Inclusion of this study did not alter results of the meta-analysis.
Transpyloric Versus Gastric Feeding	Insufficient evidence to support either: McGuire 2001
Bolus Versus Continuous Feeding	Insufficient evidence to support either: Premji 2003

- Kennedy KA, Tyson JE, Chamnanvanikij S. Early versus delayed initiation of progressive enteral feedings for parenterally fed low birth weight or preterm infants. *Cochrane Database Syst Rev* 2000; CD001970.
- Kennedy KA, Tyson JE, Chamnanvanakij S. Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infant. *Cochrane Database Syst Rev* 2003; CD001241
- Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2003;111:529–34.
- McClure, R J; Newell, Simon J Randomised controlled study of clinical outcome following trophic feeding. *Archives of Disease in Childhood Fetal & Neonatal Edition*. 82(1):F29-F33, January 2000.
- McGuire W, Anthony MY. Formula milk versus term human milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev* 2001; CD002971
- Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F147–51. (Premji & Chessell, 2003).

Umbilical Artery Catheters (UAC)

There is insufficient evidence to recommend a specific placement location for the tip of the umbilical artery catheter. Umbilical artery catheter position (high versus low) has not been found to effect the incidence of NEC.

- Umbilical artery catheters in the newborn: effects of position of the catheter tip. KJ Barrington Year: 1999. Cochrane

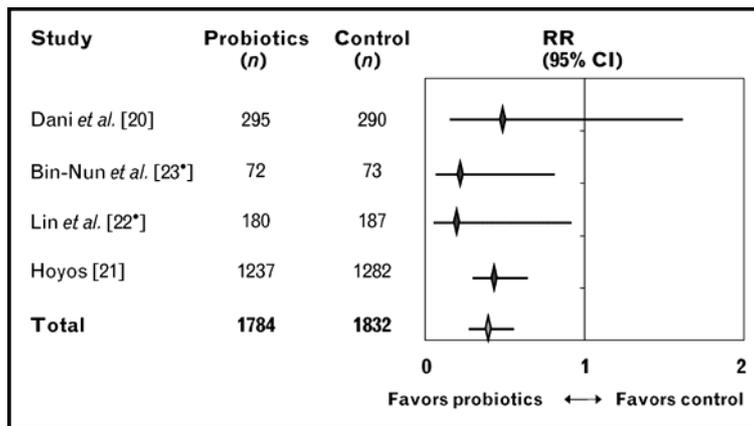
One small randomized trial found no difference in the incidence of NEC between infants fed early, with a UAC in place, and those in which feeds were delayed until 24 hours after UAC removal

- Davey AM, Wagner CL, Cox C, Kendig JW. Feeding premature infants while low umbilical artery catheters are in place: a prospective, randomized trial. *J Pediatr*.1994; 124 :795 –799

Probiotics

There is encouraging results so far to use of probiotics. It is unclear what this means for our population in GOSH NICU where children typically arrive with established NEC.

- Probiotics and neonatal intestinal infection. Cathy Hammermana, Michael Kaplana. *Curr Opin Infect Dis* 19:277–282.



Three of the four individual studies showed significant decreases in the incidence of NEC, and the overall result was significant. Relative risk (RR): 0.395 (95% CI, 0.279–0.559). x^2 : $P = 0.001$.

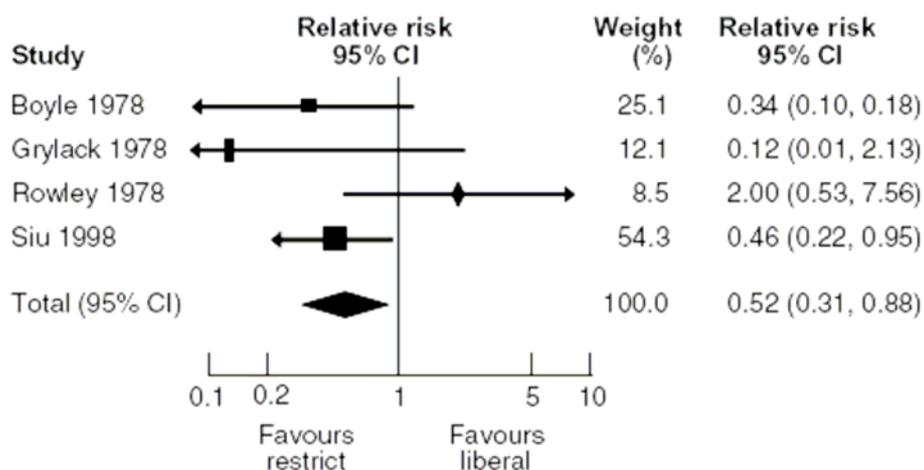
Only three of the four studies presented mortality data. Only one of the studies (Lin *et al.*) showed a significant decrease in mortality. The overall result was not significant. Relative risk (RR): 0.896 (95% CI, 0.709–1.132). x^2 : $P = 0.388$.

- Hoyos AB. Reduced incidence of necrotizing enterocolitis associated with enteral administration of *Lactobacillus acidophilus* and *Bifidobacterium infantis* to neonates in an intensive care unit. *Int J Infect Dis* 1999;3:197–202
Large observational study showed significant reduction of NEC
- Dani C, Biadaoli R, Bertini G, *et al.* Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. *Biol Neonate* 2002; 82:103–108
Large RCT did not show significant effect.
- Lin CH, Su BH, Chen AC, *et al.* Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005; 115:1–4.
Randomized, prospective trial demonstrating that probiotics prevent NEC and minimize its severity.
- Bin-Nun A, Bromiker R, Wilschanski M, *et al.* Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005; 147:192–196.
Randomized, prospective trial demonstrating that probiotics prevent NEC and minimize its severity.

Additional Prevention Strategies

Antibiotics

Results from a meta-analysis of 5 studies suggest that oral aminoglycosides decrease the incidence of NEC. However, lack of information on other outcomes including mortality and development of resistant bacteria precludes any recommendation. The likely efficacy must depend on local flora.



Bury RG, Tudehope D. Enteral antibiotics for preventing necrotising enterocolitis in low birthweight or preterm infants. *Cochrane Database Syst Rev* 2000; CD000405.

Amino Acid Supplementation	
<u>Glutamine</u>	<p>Cochrane review found that glutamine supplementation does not have a statistically significant effect on the incidence of necrotising enterocolitis (typical relative risk 1.02 (95% confidence interval 0.79 to 1.33); typical risk difference 0.00 (95% confidence interval -0.02 to 0.03).</p> <p>Poindexter BB, Ehrenkrantz RA, Stoll BJ, Wright LL, Poole WK, Oh W, et al. Parenteral glutamine supplementation does not reduce the risk of morbidity or late-onset sepsis in extremely-low-birthweight infants. <i>Pediatrics</i> 2004;113:1209-15.</p> <p>Vaughn P, Thomas P, Clark R, Neu J. Enteral glutamine supplementation and morbidity in low birth weight infants. <i>Journal of Pediatrics</i> 2003;142:662-8.</p>
Enteral arginine	<p>Only one eligible study was identified. The methodological quality of the included study was good. There was a statistically significant reduction in the risk of developing NEC (any stage) in the arginine group compared with the placebo group (RR 0.24 [95% CI 0.10, 0.61], RD -0.21 [95% CI -0.32, -0.09]). No significant side effects directly attributable to arginine were observed.</p> <p>Arginine supplementation for prevention of necrotising enterocolitis in preterm infants. P Shah, V Shah. <i>Cochrane</i>: 2004</p> <p>Amin HJ, Zamora SA, McMillan DD, Fick GH, Butzner JD, Parsons HG, Scott RB. Arginine supplementation prevents necrotizing enterocolitis in the premature infant. <i>Journal of Pediatrics</i> 2002;140:425-31</p>
Immunoglobulins	
Oral immunoglobulin G (IgG) or IgA/IgG combination	<p>In this review of the three eligible trials (including a total of 2095 neonates) the oral administration of IgG or an IgG/IgA combination did not result in a significant reduction in the incidence of definite NEC [RR 0.84 (95% CI 0.57, 1.25), RD -0.01 (95% CI -0.03, 0.01)], suspected NEC [RR 0.84 (95% CI 0.49, 1.46), RD -0.01 (95% CI -0.02, 0.01)], need for surgery [RR 0.21 (95% CI 0.02, 1.75), RD -0.03 (95% CI -0.06, 0.00)] or death from NEC [RR 1.10 (95% CI 0.47, 2.59), RD 0.00 (95% CI -0.01, 0.01)].</p> <p>Foster J, Cole M. Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates. <i>Cochrane</i>, CD001816</p>

<u>Intravenous IgG</u>	There were no statistically significant differences for mortality from all causes, mortality from infection, incidence of NEC, BPD and IVH or length of hospital stay. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. 2004, CD000361 Fanaroff AA, Korones SB, Wright LL, et al. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. <i>N Engl J Med</i> 1994;330:1107-13.
Supplemental Vitamin E	In those at greatest risk for NEC, studies suggest that supplemental vitamin E may increase the risk of NEC. (Brion, Bell, & Raghuvver, 2003)
Prenatal Indomethacin	There is insufficient evidence to recommend either use or avoidance of prenatal indomethacin related to risk of NEC. Parilla et al., 2000 ; Vermillion & Newman, 1999 ; Major et al., 1994 ; Norton et al., 1993
Postnatal Indomethacin	Evidence does not support an altered risk of NEC with use of indomethacin for prevention of intraventricular hemorrhage (Fowlie & Davis, 2003) or treatment of patent ductus arteriosus (PDA) (Malviya, Ohlsson, & Shah, 2003 ; Gersony et al., 1983 ; Cooke & Embleton, 2000

Treatment

Medications

There is insufficient evidence on benefit or risk regarding choice of antibiotic regimens or duration of antibiotic treatment of NEC

Primary peritoneal drainage

Recently, primary peritoneal drainage (PPD) has been proposed as an alternative to surgical treatment. A meta-analysis by Moss et al. also demonstrated comparable combined probability of survival for infants with perforated NEC who were treated with either procedure (67% in the LAP group vs 55% in the PPD group, $P=0.27$) even in the presence of a significant treatment assignment bias favouring the LAP group.

- Moss RL, Dimmitt RA, Henry MC et al. A meta-analysis of peritoneal drainage versus laparotomy for perforated necrotizing enterocolitis. *J Pediatr Surg* 2001;36:1210-3

A recent multicentre RCT showed that laparotomy or peritoneal drainage does not influence survival, dependency on TPN and length of hospital stay in pre-term infants. In individual cases primary peritoneal drainage can be used as a temporizing measure to facilitate resuscitation prior to laparotomy.

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1. Pierro A. Metabolic & nutritional support of the surgical neonate. *J Pediatr Surg*.2002;37:811-822.
2. Hall N et al. T cryptantigen activation is associated with advanced NEC. *J Pediatr Surg*. 2002; 37:791-3.
3. Hall N et al. Hyperglycaemia is associated with increased mortality and morbidity rates in neonates with NEC. *J Pediatr Surg* 2004;39:898-901.