Nutritional management in necrotising enterocolitis

Necrotising enterocolitis (NEC), a focus of intense research effort within the neonatal and scientific community, remains a significant problem for the preterm neonate. This review focuses on nutritional management strategies in the prevention and treatment of NEC.

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Key points

de Rooy L. Nutritional management in necrotising enterocolitis. *Infant* 2014; 10(3): 79-83.
1. The use of human milk and protocol-based management of feeding are evidence-based measures for the prevention of NEC.
2. The use of immunonutrition in NEC, while promising, requires further studies.
3. Nutrition should remain a key focus during the acute and convalescent phases of NEC.

Necrotising enterocolitis (NEC) is a devastating condition occurring in one in 1,000 live births, with an approximate incidence of 10% in extremely low birthweight (ELBW) infants[1]. Current incidence figures for the UK, as well as a national case definition for NEC, are uncertain but are the subject of an ongoing study by the National Perinatal Epidemiology Unit (NPEU)[2]. NEC is commonest in the preterm, as opposed to the term population. Term infants who develop the disease have different risk factors compared to preterm infants and these include hypoxic-ischaemic injury, hypotension, sepsis and congenital heart disease[1]. Mortality is between 20-30%, but is highest in the smallest and most premature infants and those requiring surgical management of the condition[3].

With advances in practice, premature infants are now surviving the early days of neonatal intensive care thereby increasing the population at risk for NEC. In addition, the timing of onset of the disease has been shown to correlate with gestational age, with infants at the limits of viability developing NEC at more than a month of age[4]. This can mean that parents are faced with a life-threatening illness at a time when they have started to hope and believe that their baby might survive.

NEC can occur in any part of the gastrointestinal tract, but in infants who require surgery or die the commonest sites are the terminal ileum, caecum, and ascending colon. The condition is characterised by a transmural inflammatory process, with later coagulative necrosis of the mucosa, mucosal ulceration, oedema and haemorrhage and possible perforation of the intestine. The pathogenesis of NEC, while not completely understood, is likely to involve mucosal injury of the gut, the presence of enteral feeds within the gut and the presence of bacteria or bacterial toxins[5]. Clinical presentation can be insidious with increased gastric residuals indicating reduced feed tolerance, or non-specific, with apnoea and desaturation. Pathognomonic features are abdominal distension and discolouration, blood per rectum, bile-stained gastric aspirates or vomits, and X-ray findings such as pneumatosis intestinalis and gas within the portal system. The disease can rapidly progress to profound shock requiring inotropic support, disseminated intravascular coagulation and death. Indications for surgical management include intestinal perforation, as indicated by the presence of free gas on the abdominal X-ray, or failure of medical management. Bell's staging has been traditionally utilised to classify severity of NEC (**TABLE 1**).

NEC remains the focus of intensive research efforts within the neonatal and scientific community. The special interest group for NEC (SIGNEC UK) held their first conference on NEC in July 2013, drawing together scientists and clinicians from around the world in an effort to share up-to-date and emerging knowledge around what remains, a significant problem for the preterm neonate[6]. The focus of this review will be on nutritional management strategies in the prevention and treatment of NEC.

Prevention

Prevention of NEC remains the 'holy grail' within neonatology: evidence-based nutritional interventions include the use of human milk, strategies for feed initiation and progression, and the use of probiotics and other nutritional supplements.

Stage	Systemic signs	Intestinal signs	Radiologic signs
I.A Suspected	Temperature instability, apnoea, bradycardia	Elevated gastric residuals, mild abdominal distension, occult blood in stool	Normal or mild ileus
I.B Suspected	Same as above	Same as above, plus bright red blood from rectum	Same as above
II.A Definite NEC Mildly ill	Same as above	Same as above plus diminished or absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis
II.B Definite NEC Moderately ill	Above plus mild metabolic acidosis and mild thrombocytopenia	Above plus definite abdominal tenderness, with or without abdominal cellulitis, or right lower quadrant mass, absent bowel sounds	Same as stage II.A with or without portal vein gas, with or without ascites
III.A Advanced NEC Severely ill, bowel intact	Same as stage II.B plus hypotension, bradycardia, severe apnoeas, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia, anuria	Above plus signs of generalised peritonitis marked tenderness, distention of abdomen, and abdominal wall erythema	Same as stage II.A with ascites
III.B Advanced NEC Severely ill, bowel perforated	Same as stage III.A	Same as stage III.A	Same as stage III.A with ascites plus pneumoperitoneum

TABLE 1 Modified Bell's staging criteria for necrotising enterocolitis.

Human milk

The use of human milk has long been known to be protective against NEC in a dose-dependent manner. In a study conducted in 1990[7] exclusively formula-fed infants were six to 10 times more likely to develop NEC than those fed breast milk alone. Infants receiving formula milk plus breast milk were three times more likely to develop NEC.

More recent work showed that infants weighing 700-1,500g who were given enteral feeds containing ≥50% mother's milk had a six-fold decrease in the risk of NEC compared to infants receiving <50% human milk feeds[8].

Another study compared infants weighing 500-1,250g receiving only human milk, with human milk-derived fortifier, to those receiving human milk and bovine-derived fortifier, or formula milk where no mother's milk was available[9]. This work showed that using an exclusive human milk-based diet, the number needed to treat (NNT) to prevent one case of NEC was 10. The NNT to prevent one surgical case of NEC was eight. While positive, there is an important caveat to this, namely the cost. Human milk-based fortifier costs between £3,500 and £6,000 per infant (costs from the manufacturer's press release); the approximate per infant cost for cows' milk-based fortifier is £250.

Speed of increase in enteral feeds

The preterm gut is ill-prepared for the task of absorbing all the nutrients required for growth and health. Fetal studies indicate that gastrointestinal motility begins in the second trimester and matures in the third trimester. Postnatal enteral feeding may enhance the development of intestinal motility in the preterm infant[10]. While the fetal gut resembles that of a newborn infant anatomically by 20 weeks' gestation, secretory and absorptive functions develop at different rates with the intestinal absorptive process only partially available before 26 weeks' gestation. Despite these considerations, a recent Cochrane review[11] found no evidence that delayed introduction of progressive enteral feeds prevented NEC in very low birthweight (VLBW) infants. In addition, the delayed introduction of enteral feeds may be related to a longer time needed to establish full enteral feeds, thereby prolonging the need for parenteral nutrition, with its attendant infectious and metabolic risks. However, how much and how fast to progress feeds remains uncertain.

In a recent review, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommended that feeds should be started within the first two days of life and be advanced by 30mL/kg/day in infants ≥1,000g[12]. In the UK, a randomised controlled trial (RCT) of two speeds of daily increments of milk feeding in very preterm or very low weight infants (SIFT) has just started recruitment[13]. Finally, the introduction of a standardised feeding regime (across a heterogeneous group of such regimes) was shown to be protective, with an 87% reduction in the risk of NEC[14].

Probiotics

Probiotics are 'helpful' bacteria that, when ingested, colonise the gut with normal intestinal flora, helping to suppress the overgrowth of potentially pathogenic bacteria. By manipulating the microbiome of the preterm gut, they are thought to impact upon the role that bacteria and bacterial toxins may play in the aetiology of NEC.

The use of probiotics to help prevent NEC in at-risk infants remains controversial: the ASPEN review[12] concluded that there were insufficient data to recommend the use of probiotics, despite all seven RCTs reviewed finding a lower incidence of NEC in the probiotic group. Challenges with the studies to date are that different probiotic organisms were used, for different durations and with little evidence of successful colonisation of the infant's gut. In addition, there are concerns

regarding bloodstream infections[15]. The UK's Probiotic in Preterm babies Study (PiPS) has completed recruitment and data collection, and preliminary results will be presented at the end of May 2014. This study, which aims to investigate an unselected group (ie both human milk and formula fed infants) at highest risk of NEC and sepsis, will hopefully help answer some of the outstanding questions regarding probiotic use for the prevention of NEC[16].

Prebiotics

Gibson and Roberfroid[17] coined the term 'prebiotic' to describe a non-digestible food component that benefits the host by stimulating the growth and/or activity of normal commensal bacteria in the colon. Oligosaccharides in human milk pass through the small intestine into the colon, where they act as substrates for probiotic bacteria, such as bifidobacteria and lactobacilli, in this way promoting the growth of helpful bacteria without the need to ingest live bacteria. A recent review examined seven RCTs involving 417 infants, and found that prebiotics are well-tolerated by preterm infants and also resulted in significantly increased bifidobacteria counts in the stool[18]. However, there were no beneficial effects shown on prevention of NEC, decreased incidence of late onset sepsis or shorter time to establish enteral feeds. Prebiotics are a standard ingredient in the leading brands of preterm formula milks available to UK neonatal units and they occur naturally in the preferred feed for all infants; mother's milk.

Immunonutrition

Glutamine

Glutamine is the most abundant amino acid in the muscle and plasma of humans. While normally non-essential in adults, it may become conditionally essential during illness and metabolic stress and may be a conditionally essential nutrient for preterm and VLBW infants, who may undergo prolonged periods of metabolic stress and have low protein and energy reserves. It would seem biologically plausible that glutamine supplementation at times of stress may help support metabolism and ameliorate the associated muscle tissue breakdown. In addition, glutamine is thought, along with a number of other substances such as arginine and n-3 fatty acids, to be an immunonutrient – a nutritional substance that can modulate the immune and inflammatory responses. However, despite some early positive results, glutamine supplementation has not been shown to be helpful to critically ill adults in the recently published REDOXS trial[19]. In newborn infants, results seem conflicting. A large RCT found no difference in NEC incidence between groups receiving either glutamine supplemented parenteral nutrition or standard parenteral nutrition[20]. There is some evidence to suggest that enterally administered glutamine may help with the gut's integrity and immune function[21]. However, some smaller trials looking at enteral glutamine supplementation[22] have shown benefit, with others demonstrating no clear evidence of benefit[23].

Arginine

Arginine is another strong contender as an immunonutrient as:

- it is a precursor of nitric oxide, a potent regulator of blood flow and immune function
- animal experiments have shown that it decreased thymus involution associated with trauma, promoted thymus cellularity and encouraged wound healing[24]
- supplementation has been shown to improve intestinal barrier function and vascular development in adult pigs[25]
- rodent models have shown intestinal recovery after ischaemia-reperfusion injury with arginine supplementation[26].

In humans, arginine supplementation increased blood lymphocyte proliferation in response to mitogens and promoted wound healing[27]. However, the step from basic science and animal work to applied studies in humans has proved disappointing: a recent review of immune modulating diets (IMDs) in critically ill adults found no effect of IMDs on mortality or length of stay (this included studies which looked at diets containing glutamine, arginine and fish oil, alone or in combination). There was, however, an effect on infection in that IMDs appeared to reduce the incidence of new infections[28]. In preterm infants, there are two studies to date, which examine the issue of whether arginine supplementation can prevent NEC. The first study looked at prophylactic administration of arginine to VLBW infants of <32 weeks' gestation[29]. The results show a decrease in the overall incidence of NEC in the arginine group. However, there was no statistically

significant reduction in Bell's stage II disease, arguably the outcome of interest. In work from a pilot study in which prophylactic enteral arginine supplementation was given from day three of life, there was a significant decrease in the incidence of Bell's stage III disease in the intervention group[30]. However, the combined incidence of Bell stage II and III NEC in the group not receiving arginine seemed higher (23%) than would be expected. Also, more infants in the unsupplemented group received preterm formula rather than human milk, although the difference was not significant.

n-3 Polyunsaturated fatty acids

Polyunsaturated fatty acids of the n-3 series have been shown to modulate the immune and inflammatory response. Work from a rat model of NEC supplemented with long-chain polyunsaturated fatty acids (LCPUFA) has shown a significantly reduced incidence of NEC[31]. However, the ASPEN review[12] concludes that LCPUFA may predispose infants to NEC, based on an examination of a single study comparing neurodevelopmental and growth outcomes for infants fed formula milk, formula milk supplemented with LCPUFA or mother's milk[32]. In the LCPUFA supplemented group there were five cases of NEC (5.2%) compared to two (2%) cases in the unsupplemented formula fed group, and none in the mother's milk group. The differences between the formula fed groups all but disappeared when two infants who were fed <20mL of the supplemented formula, and one infant who received no formula milk prior to developing NEC were excluded.

In a trial examining the effect of n-3 LCPUFA on preterm infant visual acuity and growth, a non-significant trend towards more cases of NEC was observed in the LCPUFA supplemented formula fed group[33]. It is noteworthy that these trials were not designed to answer the question of whether the use of a nutritional supplement of LCPUFA would help prevent or increase the risk of NEC in the preterm infant. In order to answer this question, the following is required:

- a large study powered to detect differences in rates of NEC between the groups
- a better understanding of the current intake of LCPUFA by the human milk fed infant

■ consideration of novel methods of supplementation of the human milk fed infant, such as maternal dietary manipulation.

Treatment

Effective treatments for NEC remain elusive. To date, there are no treatments that can modulate disease outcome or halt disease progression. Currently treatments are non-specific and consist of:

■ bowel rest, with gastric decompression
■ antibiotics
■ intensive care support, including ventilation and inotropic support
■ surgical management, if needed.

Is it possible that optimal nutritional management during and after NEC may ameliorate the disease course and impact on short- and long-term outcomes? In metabolic terms, infants are not merely scaled down adults: a newborn infant on enteral feeding requires 100-120kcal/kg/day, compared to the 60-80kcal/kg/day required by a 10-year-old child, and the 30-40kcal/kg/day required by an adult. Of this total of 100-120 kcal/kg/day, approximately 50-70kcal/kg/day will be needed for growth.

Surgical trauma significantly alters energy metabolism in the adult. In 1942, Cuthbertson published a classical description of a brief 'ebb' phase immediately after injury, followed by a 'flow' phase with a corresponding decrease and then increase in resting energy expenditure (REE), which could last for several days[34]. The endocrine changes orchestrating this response consist of a rise in catecholamines, glucagon and cytokines during the ebb phase followed by a rise in cortisol during the flow phase, with relative insulin resistance combining to produce a catabolic state post injury or stress[35]. The induced hypermetabolic state releases substrates required by essential organs and healing tissues.

There are relatively few studies investigating the changes in REE post injury or stress in infants[36], and fewer still in neonates. A study in neonates undergoing abdominal surgery showed a moderate and immediate elevation in REE, with a rapid return to baseline within 12-24 hours[37]. Neonates do not enter a prolonged hypermetabolic state post surgery[38,39]. The changes in whole body protein flux, protein synthesis and amino acid oxidation do not seem to occur in infants, leading to the hypothesis that
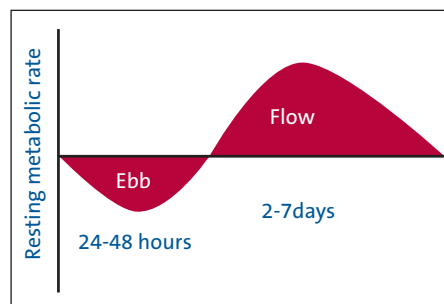

FIGURE 1 The ebb and flow phase in the postoperative adult, as described by Cuthbertson (1942)[34].

infants are able to divert energy and protein from growth, thus avoiding the hypermetabolism seen in adults[40]. In adult patients, it is common practice to multiply a basal estimate of energy requirement by a stress factor reflecting disease severity, in order to arrive at an estimate of energy requirement[41]. In neonates it seems that such an upwards adjustment is not necessary, and may even be harmful, given that the hormonal milieu is set for catabolism, and not for growth, even if enough energy and protein is provided. It seems reasonable in the acute phase of illness, pending further evidence, to provide neonates with sufficient energy for maintenance metabolism, and sufficient nitrogen to prevent a negative nitrogen balance. As the enteral route is not available in the acute inflammatory phase, this would amount to a parenteral energy intake of 40-70kcal/kg/day[42], with a protein intake of 1.2g/kg/day. Energy should be supplied as carbohydrate and lipid, with 25-40% of non-protein calories provided using lipids[43]. Even these low intakes may be a challenge in the critically ill infant, where fluid restriction due to poor renal function may only leave minimal volumes available for nutrition.

Recovery, as indicated by a reduction of acute phase reactants such as C-reactive protein (CRP), may precede the mobilisation of fluid which accumulates in the tissues during the acute phase of the illness. This may make liberalisation of fluid intake problematic. However, as nutrient requirements will gradually increase to premorbid levels during the recovery phase, it is important to try and keep pace with the infant's changing needs. Smaller volumes of more concentrated parenteral feeds may be required during this period.

There is little agreement and even less evidence when considering when and how

to re-introduce feeds after NEC. Most clinicians choose a nil by mouth time of between seven and 14 days, depending on the severity of the illness. There is evidence to show that prolonged fasting may lead to atrophy of the gut epithelium, with increased risk of feed intolerance and bacterial translocation[44]. In a study looking at surgically managed infants with NEC, a normal postprandial surge in secretion of gastrointestinal hormones was demonstrated[45]. A review of practice, from 1997 onwards, looked at early feeding after NEC, guided by the ultrasonic detection of gas bubbles within the portal vein[46]. In the early feeding group, feeds were re-started on day 4 (median, range 3-10), compared to the late group where feeds were re-started on day 10 (median, range 8-22). Early feeding was associated with a significantly shorter time to reach full feeds, reduced duration of central venous access and a shorter hospital stay. While encouraging, this study uses a retrospective control group and is underpowered to detect differences in recurrence rates of NEC.

In another study, 47 neonates with Bell stage II NEC were managed either with early feeding (30 infants, 64%, fasted for <5 days, range 1-4 days) or late feeding (17 infants, 36%, fasted for >5 days, range 6-16 days)[47]. One infant (3%) in the early group and four (24%) in the late group developed post-NEC bowel stricture. One (3%) and two infants (12%) suffered NEC relapse; none and five (29%) infants developed catheter-related sepsis, in the early and late groups respectively. Overall, early feeding after NEC appeared both safe and associated with lower morbidity. Data were collected by a standardised questionnaire across a number of different centres and analysed retrospectively.

It would seem biologically plausible that human milk, containing growth factors and immune modulating factors, would be the ideal 'early feed' after NEC. However, both early feeding and early feeding using human milk after NEC, await substantiation in further trials.

Conclusion

The use of human milk and a standardised feeding guideline are evidence-based measures for the prevention of NEC that can be utilised in neonatal units immediately. Interventions such as immunonutrition require further evidence before recommendations for practice can

be made. During the acute and recovery phases of NEC, meticulous attention should be paid to nutrition using current knowledge of requirements of the preterm infant in health and disease, in order to obtain the best possible outcome.

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