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Intestinal failure following necrotizing enterocolitis: A clinical approach

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A B S T R A C T

Intestinal failure is a recognized complication of surgically-managed necrotizing enterocolitis (NEC). Functional adaptation of remaining bowel means that many children are eventually able to achieve enteral autonomy. Integrated multidisciplinary care in the early post-operative phase is key to long-term success. The objective of this review is to outline a clinical approach to management of intestinal and nutritional complications experienced by children following intestinal resection for NEC.

1. Introduction

Intestinal failure (IF) in children is defined as a reduction in functional intestinal mass below that which is necessary for adequate digestion and absorption of fluid and nutrients required for healthy growth [1]. Surgical resection for necrotizing enterocolitis (NEC) may be associated with significant loss of mucosal surface area, and is one of the commonest causes of IF. Short (intra-operatively-measured) residual small intestinal length, resection of the ileocaecal valve and colectomy are adverse prognostic indicators [2]. The remaining small intestine undergoes a process of structural and functional adaptation [3]. Objectives of post-surgical management of NEC are to promote this adaptation, protect and preserve other organ system functions and to carefully monitor nutritional and clinical parameters during the recovery phase. The aim is to achieve enteral autonomy, ideally via oral feeding, which remains a realistic goal for most patients. However, close, personalized and proactive clinical management will be required during what can be a turbulent journey. Clinical approaches to IF in infancy are not underpinned by a strong evidence base. Indeed, a recent systematic review found no studies pertaining to the management of IF in children of high methodological quality [1]. This review aims to present a clinically useful guide, based on the available evidence and our clinical experience, to managing the post-surgical gastroenterological and nutritional care of infants recovering from NEC, and to highlight potential areas of future research.

2. Initial nutritional management of the post-NEC baby

Optimizing growth and nutrition is a fundamental aspect of neonatal medicine. However, the specific complications faced by infants who have undergone extensive intestinal resection may persist long after they have 'graduated' from the neonatal unit. Therefore multidisciplinary input from a dedicated nutrition support team should be provided from as early as practicable following return from the operating theater [4]. This should involve representatives from neonatal medicine, pediatric gastroenterology, pediatric surgery, parenteral nutrition (PN) pharmacy, dietetics, and speech & language services. Involvement of junior medical and nursing staff as well as parents is key, since optimal outcome will depend on situational understanding from all individuals making day-by-day clinical decisions, observing infant feeding and fluid balance and assessing clinical wellbeing.

A first objective should be to define a clear set of individualized parameters and goals for nutrition. This should include a statement of specific total fluid and macro/micronutrient requirements, along with a clear plan for enteral feed provision, including criteria for feed type and rate modification.

Parenteral feeding is essential following surgery, to provide the substrate for tissue repair and catch-up growth, and to minimize depletion of the infant's nutrient stores. Choice of parenteral nutrition composition will depend on local availability. There has been significant interest in the use of fish oil-based or blended lipids for primary prevention and rescue of intestinal failure-associated liver disease. Although benefit over and above lipid restriction has not been demonstrated in large controlled trials, several studies have pointed to clinically relevant improvements in the context of established intestinal failure-associated liver disease, and they are now widely used both in this context and prophylactically [1,5,6].

The rate and timing of enteral feed reintroduction will depend on the nature and extent of surgery, and on the clinical status of the infant. Recurrence of NEC may occur in 5–10% of cases, and is associated with very poor outcome [7]. The low primary NEC risk associated with early initiation and rapid advancement of enteral feeds in stable

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premature infants cannot be directly extrapolated to the post-surgical scenario [8,9]. More cautious approaches may be required. However, early initiation of feeding after gastrointestinal surgery has been shown to be safe in other settings, and there are theoretical benefits of enteral feeding to promote early intestinal adaptation [10,11]. Implementation of clear guidelines on feed advancement can decrease time on PN without compromising safety [12].

The optimal feed to reintroduce is mother's breast milk where available, because it contains a wide array of trophic, immunomodulatory and prebiotic factors. Oral rehydration solutions are often trialed before milk but there is no evidence of benefit of such an approach and it should not delay the initiation of enteral nutrition. If breast milk is unavailable or insufficient, a hydrolyzed milk formula would usually be preferred. The rationale is that in small series, children with intestinal failure were found to be at higher risk of non-IgE-mediated cows' milk protein allergy [13,14]. Indeed, recent studies have suggested that NEC itself may be associated with an aberrant immune response to cows' milk [15]. Although it has also been suggested on theoretical grounds that hydrolyzed or elemental formulae might be less effective in promoting intestinal adaptation, this has not been borne out by a recent study using a piglet model of short bowel syndrome [16]. Beyond protein, infants will usually need to be fed with a formula containing a mix of long- and medium-chain triglycerides (LCT/MCT). LCT are the richer energy source but children with IF often have some degree of fat malabsorption and are at risk of developing steatorrhea, whereas MCT are soluble in water and are more readily absorbed. There is no specific rationale for avoiding lactose, though lactose-free formulae are frequently employed and may be trialed in the event of feed intolerance (see below).

3. Transitioning from post-NEC to IF

Some infants who have required surgery for NEC will be able to progress to full enteral feeding within a matter of days following the reintroduction of milk. However, a proportion, especially those who have undergone large resections or who have other risk factors, will require long-term parenteral nutrition due to IF [2]. The medical and nutritional care of such children has been described in terms of two or more distinct phases [17,18]. At first, the clinical priority is to minimize fluid shifts, dehydration and electrolyte imbalances that may result from large-volume diarrhea and stoma losses. Intensive clinical and biochemical monitoring is required to guide PN, water and specific electrolyte provision. Stoma losses greater than 30 ml/kg/day will usually be replaced following careful assessment of hydration status. While intestinal transit time may initially be slow, as surgical ileus resolves the interruption of neuro-hormonal communication between the stomach and intestines results in rapid gastric emptying with hypersecretion of fluid and acid that should be treated with a histamine receptor 2 (H2)-antagonist and/or proton pump inhibitor [19].

In this acute phase, the benefits of feed advancement need to be balanced against the risk of worsening malabsorption and osmotic diarrhea. The development of feed 'intolerance' characterized by vomiting, increasing naso-gastric aspirates, and abdominal distension may occur. Sometimes modification of the feed type, for example towards a more extensively hydrolyzed protein formula, amino acid formula or a specifically tailored feed made up from modular components, may improve tolerance.

Infants with IF secondary to NEC are likely to have required at least a period of invasive ventilation as well as longer-term naso/orogastric tube feeding. These exposures predispose to oro-mucosal sensitization and the development of oral aversion, which can be a major complication in later life. Strategies designed to minimize negative experiences (e.g. nasal, rather than oral, endotracheal tube placement) and promote positive behavior (e.g. with non-nutritive sucking even where oral feeding is contraindicated) should be considered as early as possible. Breast or bottle feeding should be started at the earliest opportunity, and solid oral feeds should be introduced as they are developmentally appropriate [20].

4. Management of established IF

The second phase of IF management involves maintaining optimal long-term nutrient provision while giving time for intestinal adaptation to progress (which may take several years), whilst avoiding complications. Care can be divided into several domains:

4.1. Managing motility

Disordered gastrointestinal motility is a major cause of morbidity in post-NEC IF. Damage to the enteric nervous system, which controls peristalsis, leads to disruption of the normal pattern of enteral bolus feeding. Mechanical abnormalities such as loss of the ileo-caecal valve or post-surgical strictures can result in either fast or slow intestinal transit time [21]. Specific problems may be partly determined by the location of resection or injury, for example the colon is the major site of water absorption in the GI tract so children with reduced colonic length will have loose stools. Bile salt malabsorption can contribute to diarrhea post ileal resections, but can be unpredictable. It can be managed with a bile acid sequestrant such as colestyramine. For managing fast transit time, Loperamide is preferred to opioid agents because there is some evidence it supports more-efficient electrolyte absorption and causes fewer central side-effects [17].

Clinicians should be aware that acute changes in motility, for example increasing in stoma losses or reduced output with abdominal distension, can signal serious underlying pathology. Comprehensive re-evaluation is essential, with consideration of sepsis (either catheter-related or via the gut), small intestinal overgrowth (see below), or surgical complications.

4.2. Nutritional monitoring

Patients receiving long-term PN are at high risk of micronutrient abnormalities without regular monitoring and individualized prescriptions [22]. Our center's schedule for routine micronutrient monitoring in stable patients on PN is shown in Table 1. Iron, zinc, copper and vitamin D are among the more common deficiencies [23,24]. Manganese levels are frequently high and have been associated with central toxicity due to basal ganglia deposition [25]. Because manganese is subject to biliary excretion, close monitoring in children with IF-associated liver disease is particularly important [26].

Routine anthropometry including length and head circumference should be used to guide macronutrient intake, with an objective to achieve growth on the infant's birth centile. Over-feeding is likely to

Table 1
Suggested schedule for nutritional monitoring of stable children on long-term parenteral nutrition.

Analyte	Frequency
Sodium, potassium, urea, creatinine, phosphate, magnesium, calcium	Monthly (adjust according to clinical status)
Zinc, amylase	1–3 monthly
ALT, AST, ALP, GGT, albumin, bilirubin	3 monthly
Triglycerides, cholesterol	3 monthly
Urinary sodium, potassium, bicarbonate	3 monthly
Selenium, vitamins A and E, vitamin D	3 monthly
Manganese	3 monthly
Vitamin B (thiamine status)	3 monthly
Copper	3 monthly
Thyroid function tests	3 monthly (annually when stable)
Parathyroid hormone	Annually
Vit B6	3 monthly
Full blood count	Monthly
Vitamin B12, folate, ferritin, iron	3 monthly
Clotting: PT, PTT	3 monthly