Nutritional Management of Inflammatory Bowel Disease

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Introduction

While similar in many respects, the inflammatory bowel diseases (IBD) can be classified based on certain distinctive endoscopic and histological characteristics. Clinical manifestations also vary between Crohn disease (CD) and ulcerative colitis (UC), including their impact on nutritional status. Therapeutic options aim to control the disease and prevent adverse outcomes [1]. In the treatment of IBD in children, nutrition and growth outcomes are critical indicators of overall well-being and therapeutic success.

A history of weight loss or poor weight gain is a very common symptom at presentation particularly with CD and severe UC [2]. Linear growth impairment is reported even before the onset of intestinal symptoms in almost half of pediatric patients with CD [3]. Given the early age of onset, such impairment of growth is particularly problematic, with subsequent impact on onset of puberty, self-esteem, and quality of life.

In addition to a multitude of pharmacologic approaches to therapy, there is extensive evidence supporting the efficacy of nutritional therapy in CD. Despite the obvious advantages including the direct impact on growth, nutrition and the avoidance of adverse drug effects, nutritional therapy has not been as widely accepted in North America as other parts of the world [4]. Since linear growth and bone disease have been addressed in alternate chapters, this chapter will focus on nutritional deficiencies and the role of nutritional management in the treatment of IBD.

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Nutritional Impairment in Pediatric Inflammatory Bowel Disease

Malnutrition is common in IBD. Several cohort studies have demonstrated weight loss, or poor weight gains at the time of initial diagnosis of CD. Griffiths et al. reported 80% of the 386 children diagnosed with CD over a period of 10 years had a history of weight loss [1]. A recent Danish prospective population-based cohort study reported children with CD had poor nutritional status at diagnosis compared with the general pediatric population [5]. Among Australian children, a case–control study by Aurangzeb et al. to assess the nutritional status found that children with newly diagnosed IBD had lower mean body mass index (BMI) Z-scores and weight-for-age percentiles than controls [6].

Weight loss is seen less commonly, particularly through the course of established UC, but has been seen in up to 65% of children at diagnosis [2]. Kugathasan et al. conducted a systematic review of 783 children with newly diagnosed IBD from two prospective inception cohorts to examine BMI status at presentation. Most children with CD and UC had a BMI in the normative range (5–84%). Low BMI (<5%) was seen in 22–24% of children with CD and 7–9% of children with UC [7].

Several interrelated factors contribute to growth impairment in IBD. Chronic suboptimal nutrition has long been implicated as a cause of growth retardation [2,8–12]. In addition, direct growth-inhibiting effects of pro-inflammatory cytokines (such as TNF-α) released from the inflamed intestine have been more recently recognized for their role in growth impairment, as well as indirectly by resulting in anorexic effects and early satiety [13]. Symptoms including

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nausea, abdominal pain or diarrhea in association with meals also limits caloric intake. Localization of disease in the small bowel may lead to partial obstruction and early satiety. Small intestinal involvement may also lead to disaccharide intolerance resulting in shorter gut transit times, pain and exacerbation of diarrhea. Malabsorption of food components and the diversion of calories to sites of gut inflammation may also lead to impaired weight gain and growth [14]. Thus, enhancement of growth is best achieved through control of intestinal inflammation and assurance of adequate nutrition [15,16].

Caloric Requirements, Energy Intake, and Body Composition in Children with CD

Energy Requirements and Dietary Intake

The impact of CD on growth and body composition is determined by an interaction between the duration and severity of the inflammatory disease process, genetic predisposition and the extent to which the demands for energy and nutrients are met. There is conflicting data from studies reporting resting energy expenditure (REE) in children with CD. In comparison to healthy controls Azcue et al. [17] reported no difference in REE per unit of lean body mass in patients with CD, while Zoli et al. [18] found elevated REE in growing children with CD. Surprisingly, the latter study did not reveal any further increase in REE with relapse of disease, and suggested that energy may be "diverted" from growth to disease activity during relapse.

It is imperative that the management of children and adolescents with CD combines the control of inflammation whilst providing optimal nutrition support with adequate protein and sufficient calories to support growth. The mean energy intake of patients with CD during relapse has been found to be up to 420 kcal per day lower than age-matched controls [13]. In a study by Thomas et al. 71% of children consumed less energy with protein intake differing significantly compared to age-matched controls [13]. While all of the studied patients with CD increased their caloric intakes when in remission, others have shown that despite being asymptomatic, the mean caloric intake of children and adolescents with CD was 82% of expected for height age [8].

Pons et al. [19] recently evaluated the dietary intake of 41 children with CD (18 active, 23 in remission) and compared them with the intakes of 22 age-matched control children without IBD. Comparison was also made to Australian recommended daily intake (RDI). Dietary intake was defined by a food frequency questionnaire. The energy intakes of the children with CD were less than the estimated energy requirements regardless of disease activity. Fat and carbohydrate intake were found to be lower in CD patients than in controls, while protein intake was similar in patient and control groups [19].

Body Composition

Several studies have confirmed that children with CD have significant deficits in lean body mass (or fat free mass), which is consistent with cachexia [17,20–22]. Wiskin [21] recently found that fat free mass was related to disease activity regardless of changes in weight and concluded that weight or BMI may mask deficits in lean tissue in the presence of normal or increased proportions of body fat. Sylvester et al. [23] studied the effects on lean mass and body composition longitudinally over 2 years and found that BMI improves with treatment in children with CD whereas Fat Free Mass Index (Fat Free Mass/height^2) does not, and raises significant concerns on long-term impact of disease on growth and bone health [23].

Gender can also influence body mass composition, as reported by Thayu et al., who studied the body composition of 74 children with CD at diagnosis. She found that boys with CD at diagnosis had significant fat free mass deficits consistent with cachexia, whereas girls demonstrated both fat mass as well as fat free mass deficits consistent with wasting [22].

The clinical significance of lean mass deficits in children with CD is not known; however, lean mass deficits may be associated with poor physical functioning and greater infection risk during childhood and compromised peak bone mass by young adulthood.

Because of the difficulty ensuring adequate energy and nutrient requirements of children with IBD, particularly during flares, active monitoring of nutritional status must be undertaken throughout childhood, but especially in adolescence. Hannon et al. demonstrated that in stable adolescents with CD, enteral nutrition promotes anabolism by suppressing proteolysis and increasing protein synthesis [24]. Thus, where indicated, aggressive nutritional intervention should be initiated before puberty, whether disease is active or in remission, to correct the energy deficits and maximize growth potential.

Micronutrient Deficiencies

Dietary intakes of children and adolescents with IBD may be compromised in micronutrient content in addition to protein and energy. Specific micronutrient and vitamin deficiencies are encountered more commonly with CD than with UC. Hendricks et al. [9] compared a group of adolescents with CD and growth failure with a control group of adolescents with CD who were growing normally. Mean serum ferritin levels were significantly decreased in both groups and mean plasma zinc levels were borderline low in the growth failure group and low in the control group. Dietary zinc intake was below the Recommended Daily Allowance (RDA) in 88% of the group with growth failure and 44% of controls (64% combined) and less than 75% of the RDA in 41% of all adolescents with CD. Dietary iron intake was also below the

RDA in 24% of all adolescents with CD, with one adolescent in the growth failure group consuming less than 75% of the RDA. One-third of adolescents were consuming less than 75% of the RDA for calcium [9]. In evaluation of 41 children with CD compared to age-matched controls, calcium intake was significantly less than the Australian RDI and iron intake approached less than RDI [19]. Most recently, Levin et al. retrospectively assessed vitamin D in a group of 78 Australian children with IBD (70 CD, 5 UC, 3 IBDU) and explored associations between vitamin D status and clinical factors. Using a level of 50 nmol/L or less to indicate deficiency and 50–75 nmol/L to indicate insufficiency, 19% of children were vitamin D deficient and 38% were insufficient respectively. Levels were not found to be associated with disease location or use of immunosuppressive drugs. Children with vitamin D deficiency had significantly greater corticosteroid exposure than those with normal status [25].

Other studies of micronutrient intakes in CD have found mean intakes of zinc, copper, iron, calcium, folic acid, vitamin C, and vitamin D to be significantly ($p < 0.05$) lower than age-matched controls and RDAs [13]. Essential fatty acid status may also be altered, in association with low BMI and disease activity [26]. Malabsorption of fat soluble vitamins can be an issue in patients with ileal disease [27,28]. Gerasimidis et al. recently looked at the impact of exclusive enteral nutrition (EEN) on body composition and circulating micronutrients in plasma and erythrocytes of 17 children with active CD. At baseline, several children presented with suboptimal concentrations of carotenoids, trace elements, vitamin C, B6, and folate in plasma but not in erythrocytes [29].

Despite how well recognized the occurrence of nutritional deficiency is in IBD patients, only ESPEN has recommended nutritional deficiency screening in this population [30]. The extent of micronutrient deficiency screening and whether or not to supplement a child's diet should be considered on an individual basis, following dietary assessment, as firm recommendations for vitamin and mineral supplementation await future studies [15]. Kleinman and colleagues [31] have suggested that patients should be recommended a multivitamin/mineral to meet 100–150% of the RDA when dietary intake is less than expected.

Elevated BMI in IBD

Although most emphasis of the nutritional aspects of IBD is focused upon impaired nutritional status, the increasing rate of childhood obesity is also relevant in children presenting with acute IBD. Several cohorts have observed that children with IBD are at comparable risk of overweight and obesity as the general population.

Sondike and colleagues [32] reported this phenomenon in a group of 166 children from Wisconsin, USA. Sixteen (12%) of a group of newly diagnosed children with CD were overweight (BMI > 85%) or obese (BMI > 95%). This feature was also evident in the children diagnosed with UC: 17.6% of these 34 children were overweight or obese. Observations by Kugathasan et al. from two large multicenter North American cohorts revealed 10% of children with CD and 20–30% of children with UC had a BMI at diagnosis consistent with overweight or risk for overweight [7].

Most recently, another large multicentre cohort of 1,598 children with IBD found that approximately one in five children with CD and one in three with UC are overweight or obese [33]. Rates of obesity in UC are comparable to the general population. Attempts to evaluate whether overweight and obese status is associated with patient demographics or disease characteristics found that socio-demographic risk factors for obesity in the IBD population were similar to those in the general population. Prior IBD-related surgery was the only disease characteristic associated with overweight and obesity in children with CD (OR 1.73, 95% CI: 1.07–2.82) [33].

General Management of Nutrition in IBD

Monitoring Nutritional Status

Assessment for under- (or over-) nutrition is an essential component of medical care of children with IBD. At a minimum, screening should include measurement of body weight and height for age, with calculation of BMI. Nutritional status can be expressed in terms of the degree of height deficit (shortness), weight deficit (underweight or lightness) or relative weight for height or BMI for age (thinness). Each component captures a different aspect of growth and interpretation is further complicated during puberty when differences in measures for thinness can be driven by changes in lean muscle and/or fat [21]. Growth parameters should be routinely collected and graphically recorded on standardized charts. It is important to obtain information on familial growth patterns, particularly parental heights, as well as pre-illness measurements to assess growth potential and the impact of disease on growth, respectively.

Ongoing assessment of nutritional status includes history, physical examination, and laboratory testing. History should attempt to obtain information on appetite, weight changes and dietary intake (often with the assistance of a registered dietician), as well as identification of medications as well as nutritional or herbal supplements, including vitamins and minerals. Review of psychosocial factors such as economic and cultural or environmental influences may be useful.

Physical examination, in addition to growth parameters and BMI, should include anthropometric assessment of body habitus along with recordings of sexual maturation by Tanner

staging. Examination may reveal signs of generalized malnutrition or specific nutrient deficiencies.

Laboratory tests are valuable in assessment of specific nutrient deficiencies; however, some measures of nutritional status can also be affected by inflammation (e.g., serum albumin, ferritin). Serum pre-albumin has a much shorter half-life (2 days) than does albumin (18–20 days) and may be more useful in the assessment of nutritional status changes with nutritional support [34].

Other potential tests of nutritional status are urinary creatinine:height ratio or 3-methyhistidine determinations which reflect somatic (muscle) protein status, and 24-h urine urea nitrogen which reflects protein catabolism. However due to the difficulty obtaining accurate specimens and assumptions required for interpretation, these lab tests are not used in routine clinical practice. Additional research techniques for assessment of nutritional status are dual energy X-ray absorptiometry [20], bioelectric impedance analysis and total body electrical conductance to determine total body water and fat mass and isotopic labeling of various molecules to determine energy expenditure and metabolic turnover rates [15].

Serum leptin may also have a role in nutritional assessment as a marker of fat stores [35–37] and has been found to be lower in children with severe protein energy malnutrition [38]. Controversy exists in the literature regarding the correlation of leptin levels with inflammation or whether it simply reflects nutritional status regardless of underlying disease. Hoppin et al. found no difference in serum leptin levels between children with IBD and controls and concluded that serum leptin levels depend on BMI and sex and not on disease activity or severity [39].

Aurangzeb et al. explored the relationship between leptin and BMI in newly diagnosed children with IBD in comparison to controls. Significantly lower mean serum levels were found in 28 newly diagnosed IBD patients compared to 56 controls (2.32 pg/mL+/−1.88 vs. 5.09 pg/mL+/−4.86, $p+0.009$). In this group of children with IBD, leptin levels did not correlate with the degree of inflammation, as defined by serum markers of inflammation [6]. Further studies are required to elucidate the role of leptin in nutritional assessment of IBD patients.

Following diagnosis of IBD, there are numerous ongoing aspects of nutritional management to address. Nutritional issues relating to therapy may arise. The use of steroids often leads to increased appetite and commonly alters fluid balance with initial fluid retention and weight gain that only partially reflects improvements in underlying nutritional status. Steroids are clearly linked with impaired bone mineralization, with enhanced resorption and decreased new bone formation [40,41]. Adequacy of calcium and vitamin D intake must be reviewed regularly. Inhibition of linear growth and altered final height, due to suppression of insulin-like growth factor-1 (IGF-1), is also a feature of daily corticosteroid therapy [42]. Other medications may interfere with the absorption of specific micronutrients. Sulfasalazine may interfere with folate metabolism by reducing absorption, however, daily supplementation does not appear necessary [43]. In contrast, folate supplementation is required when the immunosuppressive drug methotrexate is used, as this drug acts to inhibit the conversion of folate to the active moiety tetrahydrofolate [44].

Questions related to nutrition and which foods to avoid are amongst the commonest raised by families both at diagnosis and in routine follow-up. Rigorous scientific study has not been performed and evidence to support the use of diets with specific carbohydrates or elimination of specific food groups is unavailable, despite isolated case reports of clinical efficacy [45]. A controlled study of a high fiber, low sugar diet compared with a low fiber, unrestricted sugar diet found no difference in the clinical course of adult patients in remission [46]. Low residue diets are also ineffective in the treatment of inflammation [47]. In the event of intestinal obstruction or transient abnormalities of digestion such as disaccharide intolerance in those with severe small bowel disease, short-term dietary restrictions may be required to alleviate symptoms [15,48].

The current consensus from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) is that diets of children with CD should be well balanced, based on the Food Guide Pyramid and follow dietary reference intakes [15]. Brown et al. recently created a "global practice guideline" which attempted to consolidate the existing information regarding diet and IBD proposed by medical societies or dietary guidelines from patient-centered, IBD-related organizations. The dietary suggestions included nutritional deficiency screening, avoiding foods that worsen symptoms, eating smaller meals at more frequent intervals, eliminating dairy if lactose intolerant, limiting excess fat, reducing carbohydrates and reducing high-fiber foods during flares. Enteral nutrition was recognized as being recommended for CD in some parts of the world more often than others (e.g., more in Japan than in the USA) [49].

Overall, CD, in contrast to UC, can have a tremendous and long-lasting impact upon nutritional status but can also be successfully treated with nutritional therapy. Minimal evidence exists for the treatment of UC with enteral nutrition. Wedrychowicz et al. recently evaluated the effect of EEN on endothelial growth factor (VEGF) and transforming growth factor beta 1 (TGF-β1) in both UC and CD [50]. However, due to the concomitant use of antibiotics and 5ASA in this study, the role of EEN in UC is impossible to determine from this study. Therefore, the remainder of this chapter will focus on the nutritional impact and management of CD.

History of the use of EEN in CD

The effectiveness of elemental diets was originally identified in 1973 by Voitk when it was used in CD to provide preoperative nutritional support [51]. The first controlled study of adults with CD determined that an elemental diet was equally effective in the induction of remission as corticosteroids [52]. The role of EEN in pediatrics, where EEN had the important additional benefit of supporting growth, was first reported by Sanderson and colleagues in 1987 [53].

The type of EEN utilized has evolved from the initial use of elemental feeds by nasogastric tube towards using polymeric feeds which have better palatability and the option of oral administration. Although still the subject of some debate practice has moved towards the use of EEN for any disease location in the gastrointestinal tract. The ideal formula composition of EN continues to be explored in an attempt to optimize acceptance, remission rates, and shed light on the mechanism of action.

Postulated Mechanisms of Action of EEN in CD

Our understanding of the mechanisms by which the beneficial effects of EEN are achieved in active CD remains incomplete. Various mechanisms have been proposed over time. Recent data supports several of these.

Postulated mechanisms include relative gut rest, avoidance of allergenic elements, nutritional mechanisms, alteration of the intestinal microflora, and specific anti-inflammatory effects. Gut rest does not appear to be a complete explanation as complete gut rest, with total parenteral nutrition and nil by mouth, does not lead to enhanced rates of remission. Avoidance of dietary allergens also does not seem to explain the effects of EEN fully as the benefits of EEN are shown to the same whether an elemental or polymeric formula (PF) is utilized. Recent studies have focused upon changes in the intestinal microflora, direct anti-inflammatory activities, and effects upon gut barrier function.

The Intestinal Microflora

The intestinal flora plays a central role in the pathogenesis of IBD, although current data does not indicate any one species as being causative on its own. The impact of EEN upon the intestinal microflora has been examined in human settings and in an animal model of IBD.

Two early studies used molecular techniques to examine the impact of EEN upon the flora in the context of IBD [54,55]. These reports illustrated changes in the flora consequent to the introduction of the enteral formula. A more recent study employed a more comprehensive molecular approach (Denaturing gel gradient electrophoresis–DGGE) with a wider selection of probes, enabling a broader profile of the changes [56]. This study showed a reduction in the diversity of the bacterial species and changes within all the main bacterial groupings. These changes were sustained, with effects well beyond the period of EEN alone.

Data from an animal model of CD complements these data. Using an IL-10 knock-out model of gut inflammation, a Japanese group assessed changes after the administration of elemental formula [57]. The bacterial diversity and bacterial number were both reduced in those animals given the formula compared to a control group with normal mouse diet.

Two recent studies have also assessed patterns of the intestinal flora consequent to enteral feeding in non-IBD contexts. Smith et al. [58] assessed changes in bacterial composition in the stomach and duodenum of adults receiving enteral formulae via a gastrostomy for various noninflammatory indications. Higher levels of bacterial DNA were found in the upper gut after enteral feeding. The fecal flora was not examined in this patient group.

A second study examined the fecal microflora in a small group of adults requiring exclusive nasogastric feeding for a variety of medical reasons [59]. Individuals with IBD were excluded from the study. The subjects provided stools at the start, during and at the end of a 14-day period of enteral feeds. Molecular methodology was employed to assess the flora (fluorescence in situ hybridization). Overall the investigators did not observe consistent changes in the microflora during this short period. However, they did note changes in particular groups of organisms in the individuals who developed diarrhea secondary to the enteral feeds. However, these effects differed to those seen consistently in individuals with IBD.

Anti-Inflammatory Activities

Meister et al. [60] demonstrated in vitro anti-inflammatory activities of formulae in a series of experiments using explants (short-term culture of colonic tissue samples obtained endoscopically). These samples were incubated directly with an elemental formula, or maintained in a control situation. The production of interleukin (IL)-1-β, IL-1-receptor antagonist, and IL-10 were used as indicators of cell responses. The cells incubated with formula lead to an increase in the ratio between IL-1RA and IL-1-β, compared to the control cells ($p < 0.05$). These changes were also evident when full protein-based formulae were employed. Further, these changes were not observed in biopsies taken from individuals with UC or with non-inflamed IBD tissue.

More recently, an in vitro model of intestinal cells has been used to elucidate the anti-inflammatory effects of

formulae [61]. These experiments utilized established colonic epithelial cells lines, which were stimulated with one or more pro-inflammatory cytokine to replicate intestinal inflammatory events. Polymeric formulae were then used to rescue or to prevent the cellular response to this inflammatory insult, with interleukin (IL)-8 utilized as an indicator of epithelial response. The effect of adding PF to this model was assessed in a series of different ways, with particular use of a two-compartment model whereby the PF was separated from the inflammatory cytokine. Experiments using this model demonstrated that PF lead to alteration of the inflammatory effects of TNF-α (reduced levels of IL-8), and suggested alteration of cellular signal transduction pathways as a mechanism for this [61].

Epithelial Barrier Function

Disruptions to barrier function, measured as altered intestinal permeability, are demonstrated in individuals with CD [62]. It is unclear whether these are primary events, or are consequent to inflammation. Data showing similar alterations in permeability in asymptomatic first-degree relatives of people with IBD suggests that these could be primary changes, which could thereby predispose to the development of inflammatory changes in some individuals [63].

Intestinal permeability improves with resolution of inflammation [64] including following EEN [65]. Recent in vitro studies have explored these mechanisms further [66]. These studies employed an in vitro model of inflammation similar to that described above, whereby intestinal epithelial cell monolayers were stimulated with pro-inflammatory stimuli and then rescued with PF. Using an Ussing chamber, these experiments demonstrated that EEN lead to complete reversal of cytokine-induced changes in trans-epithelial resistance, short circuit current and horse-radish peroxidase flux. In addition, PF was shown to correct cytokine-induced changes in tight junction proteins and key mediators of tight junction function. Although the molecular mechanisms of these detailed observations are not yet defined, these findings provide significant clues to the activity of EEN in vivo. More work is required to clearly define the molecular events behind these important observations, and also to translate these in vitro findings to an in vivo situation.

Effectiveness of EEN Therapy in CD

Induction of Remission

There have been numerous open and comparative studies evaluating the use of EEN with elemental formulae in adults [67–70] and children [53,71,72] with CD. Individual studies comparing the effectiveness of EEN for the induction of remission of CD have varied considerably in their results with remission rates ranging from 20 to 84%. This apparent discrepancy may stem from differences involving study populations (e.g., ages, disease activity), interventions (e.g., route of administration), outcome assessments (disease activity measures), and methodology (e.g., sample size, blinding, randomization). In three meta-analyses, investigating the use of EN in CD, steroids were found to be more effective in the induction of remission [73–75]. The most recent Cochrane meta-analysis comparing induction of remission by corticosteroids (160 patients) vs. EEN (192 patients) yielded a pooled odds ratio (OR) of 0.33 (95% CI: 0.21–0.53) favoring corticosteroid therapy (39). However, these analyses involved predominantly adult studies of varying quality. A recent well-conducted pediatric randomized controlled study [76], added to the latest meta-analysis allowed for a sensitivity analysis of high-quality studies based on the Jadad scale [77]. The two high-quality studies had conflicting results, one favoring steroid therapy [78] and one favoring EEN [76] though neither study demonstrated statistically significant differences. Combining these high-quality studies in a subgroup analysis resulted in 34 patients treated with EEN (both polymeric) and 35 treated with steroids. The OR was 1.18 (95% CI: 0.37–3.70). The question of equivalent or superior efficacy of steroids to EEN in children is also raised by Heuschkel et al. who combined in meta-analysis the data accrued in controlled trials conducted exclusively in children and adolescents [79]. They concluded that nutritional treatment and conventional corticosteroids are equally effective in a pediatric population, even if not in adults. However, to reach this conclusion, their NNT was 182 patients to detect a 20% difference in treatment effects. The actual number they had from five randomized controlled trials was only 147 children and hence, they included two nonrandomized trials to reach the desired sample size.

In summary, existing studies and meta-analyses suggest that the benefits of EEN may differ between children and adults, and therefore other risks and benefits must be factored into the therapeutic decision pathway. In addition, Day et al. have identified poor compliance resulting in inadequate volume of EEN received as a major reason why some patients did not achieve remission [80].

Maintenance of Remission

Following the induction of remission, use of EN as maintenance therapy may have additional benefits to prolonging remission, including delaying the requirement for further therapy (i.e., steroids) and optimizing growth and nutrition. Most often maintenance EN is practiced in combination with maintenance medical therapy, but limitations of adherence may similarly impact enteral therapy as it does medical therapy.

To date, the majority of the literature on maintenance of remission of CD with EN therapy has been in adult patients, mostly arising from multiple centers in Japan. There is a smaller and older body of work in pediatrics.

Maintenance of Remission with EN in Adults

Akobeng and Thomas [81] conducted a Cochrane review of enteral nutrition for maintenance of remission in CD. They identified only two maintenance studies in adult patients which were randomized-controlled studies, one where the comparison groups were two types of formula (elemental vs. polymeric) [82], and another were a maintenance EN regimen was compared with regular diet [83]. Verma and colleagues studied 33 adult steroid-dependent CD patients in remission, who were randomized to elemental ($n=19$) vs. polymeric ($n=14$) formula, and followed for maximum of 12 months. Fourteen or 43% of the total population remained in remission and off corticosteroid at 12 months, with no significant difference in relapse rates noted between the two formula groups [82]. They did not identify any disease or patient-related factors which predicted response to enteral nutrition, however, their sample size was small limiting their ability to make meaningful comparisons. Although no "toxicity" was encountered per se, six (18%) of patients withdrew within 2 weeks of study start due to intolerance to feeds related to smell or taste problems.

Takagi [83] studied 51 adult patients in remission who were randomized to receive a half elemental diet ($n=26$) or a free diet group ($n=25$). The half elemental diet group were required to take half the daily caloric allowance as an elemental formula (either orally or via a nasogastric tube). While there were some restrictions placed on the caloric intake of the other "half" of their diet (aided through use of semi-weighed food diaries), there were no specifications for its composition. This was one of many Japanese studies which has looked at the question of maintenance EN however, and as such, the unrestricted free diet is likely different from the equivalent Western diet. The authors in the Takagi study chose a primary outcome of relapse over a 2-year period [83]. The study was stopped before achieving the 2-year follow-up for all participants because the relapse rate in the half elemental diet group was significantly lower than that in the free diet group (34.6 vs. 64%) after a mean follow-up of 11.9 months.

Yamamoto [84] carried out a systematic review examining EN for the maintenance of remission in CD. They included studies where EN was compared with another therapy, thus the study by Takagi [83] was included, but not the study by Verma and colleagues [82]. They did not limit their review to RCTS, so three prospective nonrandomized trials [85–87], and six retrospective studies [88–92] were included. The number of patients included in most of these studies was small. One of the ten studies included pediatric patients alone [89]. Eight of ten studies were conducted in Japan. Knowledge of the country of origin for a study is important when interpreting the results and assessing generalizability. In Japan, EN has a central role in the management of CD. In all but one of the eight Japanese studies included in the systematic review, an elemental formula was used, and also in a majority of studies, the oral component of the diet was a low fat diet. The impact of this dietary approach, compared with a maintenance PF and/or traditional Western diet has not been directly studied. The contribution of the low fat diet, and elemental formula with a relative low fat component, may be a relevant factor in light of the work by Bamba et al. who suggested that a lower fat diet may be an important factor related to the efficacy of EN in CD [93]. Another factor when reviewing EN studies from Japan is that virtually all participants with CD are on a 5ASA preparation, as this is viewed as a standard of care for maintenance [84]. Because all participants are exposed to this intervention, it would not be expected to bias the findings relative to the EN outcomes. Additionally azathioprine was used by a number of study participants, but as is the case with 5ASA, overall its use seemed to be balanced between the treatment and comparison groups in the studies, thereby limiting the bias this concomitant therapy might have introduced.

In the systematic review by Yamamoto [84], the authors broke down the studies by whether the patients had achieved a medically or surgically induced remission. Interestingly, different from what would be seen in studies conducted in North America, for those studies with patients who entered from a medically induced remission, the majority of patients went into remission with total parenteral nutrition or EEN. Regardless of the method of induction of remission (medical or surgical), the outcomes for the ten included studies showed benefit of EN for maintenance of remission (48–95%) over the non-EN comparison groups (21–65%) [84]. In four studies the impact of dose of EN on remission rates was evaluated [88,90,92]. They found that higher amounts of enteral formula were associated with higher clinical remission rates. Another interpretation of these findings could be that patients with less active disease tolerated the enteral feeding better and, therefore, reached greater intakes than those with more active disease. Thus patients with milder disease may tolerate the nutrition better, rather than the higher intake being a predictor of maintenance of remission. As well, because there was no standard approach to "dosing" used in these studies, at this time no clear recommendations can be made regarding the minimum dose of EN required to optimally maintain remission.

Maintenance of Remission with EN in Pediatrics

Maintenance EN programs have been provided in various forms: overnight NG feeds in conjunction with normal

daytime eating, short intervals of exclusive NG feeds every few months interspersed with regular diet, or as oral supplements in addition to oral eating through the day. Two Canadian groups have considered the first two approaches [89,94]. Researchers at the Hospital for Sick Children in Toronto, Canada, reported on 28 children who after entering remission with EEN had subsequently continued overnight supplementary NG feeds in addition to normal diet in the daytime [89]. They were compared with 19 children in whom EEN successfully induced remission but who opted to discontinue nocturnal elemental feeding. At 12 months 43% (12/28) receiving nocturnal EN had relapsed compared with 79% (15/19) who had discontinued supplemental elemental feedings ($p<0.02$). A second group, from Montreal, Quebec published a report utilizing a different approach to EN feeds, with intermittent intensive periods of nutritional therapy (EEN) [94]. This small study included eight children with CD and associated growth failure who were given intensive exclusive periods of formula for 1 month out of every 4 months. Disease activity markers fell in this group over time and in comparison to a control group who did not receive this intensive therapy. These eight children, managed with intensive nutritional therapy, also had significant catch up growth [94].

EN in Combination with Medical Therapy

Thus far, there is minimal scientific evidence available on the role of EN with medical therapy particularly for the maintenance of remission. Two studies, both from Japan, exist on the combined use of EN in patients receiving infliximab [95,96]. Tanaka et al., in a study aiming to investigate the efficacy and safety of infliximab in Japanese patients, also examined the effect of concomitant EN. Their results suggested higher response rates to infliximab in patients receiving concurrent EN at 16 weeks, but confirmation by randomized controlled trial is necessary. A more recent study by Yamamoto and colleagues [96] prospectively evaluated whether the addition of maintenance EN to biologic therapy impacted the relapse rate. They studied 56 patients who had achieved clinical remission with infliximab induction therapy, with 32 of these patients receiving concomitant EN (elemental diet infusion during the night, and a low fat diet during daytime), while the remaining 24 patients received neither nutritional therapy nor food restriction. On an intention-to-treat basis, no significant difference was noted between the groups (25 patients in EN group (78%) and 16 patients in the non-EN group (67%) remained in remission, $p=0.51$). The study did not report power calculations for their primary outcome, but was likely underpowered to determine a difference.

No studies have been conducted to examine the use of immunomodulators and EEN in children with newly diagnosed CD but Buchanan et al. reported it difficult for patients to continue supplemental nutrition for maintenance or remission and therefore used a strategy of early introduction of azathioprine for maintenance of EEN-induced remission [97]. A steroid-free algorithm of therapy would be an attractive therapeutic option particularly in children. Further long-term study of the combination and synergistic effects of enteral nutrition and medical therapy particularly for maintenance of remission and mucosal healing are needed.

Additional Effects and Proof of Efficacy of EEN

EEN and Mucosal Healing

For some time the treatment goals for the management of active CD have focused on the induction of remission, judged in clinical (resolution of symptoms) and biochemically (normalization of altered inflammatory markers) terms. More recently it has become clear that the goal of treatment should be the achievement of mucosal healing. Mucosal healing in both CD and UC is clearly associated with improved long-term outcomes [98]. Persisting inflammatory changes are likely to contribute to poor growth in children and are also associated with an increased risk of subsequent disease relapse [99]. Mucosal healing may also influence disease progression, and extra-intestinal disease patterns.

Both EEN and infliximab are shown to lead to high rates of mucosal healing in CD: more so than other therapies used to induce remission (such as corticosteroids [100]).

At the turn of the century, Fell and colleagues [101] undertook a prospective assessment of mucosal healing in a group of children treated with EEN. These 29 children with active CD were treated with a PF. In addition to baseline endoscopic assessment, repeat colonoscopy was completed after 6–8 weeks time in order to judge endoscopic and histologic changes. EEN lead to clinical remission in 79% of these children. Overall there was significant endoscopic improvement in these children. A one-point improvement in the colonoscopy grading score was seen in the ileum and colon ($p<0.0001$ and $p<0.001$, respectively). Eight of the children achieved mucosal healing in the ileal region, whilst eight also had colonic mucosal healing.

More recently the results of two prospective Italian studies show the enhanced rates of mucosal healing following EEN comparing to corticosteroids [76,102]. Berni-Canani and colleagues [102] evaluated the responses in children managed with EEN or corticosteroids. Thirty-seven children

were treated nutritionally for 8 weeks with various different formulae (polymeric, semi-elemental, and elemental) whilst ten received corticosteroids. Clinical remission rates were similar in the two groups (86.5% vs. 90%, respectively), but mucosal healing rates were quite different. Twenty-six of the 37 children treated nutritionally had mucosal improvements and seven of them had complete mucosal healing. In contrast, just four of the steroid group had improvement noted, and none had mucosal healing.

In a second Italian study, children with active CD were allocated to receive either EEN (PF) or corticosteroids. Baseline colonoscopic assessment was followed by repeat colonoscopy at 10 weeks. Fourteen (74%) of the 19 children treated with EEN had mucosal healing. In contrast, mucosal healing was achieved in just 6 (33%) of the 18 children treated with corticosteroids ($p<0.05$).

Data from adult patients also clearly demonstrate high rates of mucosal healing consequent to EEN. Yamamoto et al. [103] assessed the mucosal changes following an elemental formula in 28 adults with active CD. In this series of patients treated with EEN, clinical remission was seen in 71%. Furthermore, endoscopic healing or improvements were documented in 44% and 78% of patients, respectively.

Mucosal healing with EEN does not appear to be dependent on the type of formula utilized. Benefits have been documented with elemental [102–104] or polymeric formulae [76,101].

Coincident with promoting healing of the inflamed mucosa, EEN is also shown to lead to changes in levels of inflammatory mediators. Several reports published in the final decade of last century demonstrated that EEN lead to reduced mucosal production of pro-inflammatory cytokines (especially TNF-α and interleukin-2) [104,105] and prompted down-regulation of pro-inflammatory genes measured within the intestinal mucosa [101,106]. In addition, Fell et al. [101] also demonstrated increased levels of TGF-β mRNA, consistent with increased production of this anti-inflammatory cytokine. Yamamoto and colleagues [103] also showed that the mucosal levels of multiple proinflammatory cytokines fell to control levels consequent to treatment with an elemental formula. The ratio between IL-1β and IL-1ra within the mucosa also normalized.

Overall these data clearly show alterations in levels of inflammatory mediators within the mucosa following treatment with EEN. The full implications of achieving mucosal healing with EEN in children are not yet well defined. Maintenance EN may have a role in maintaining the levels of mucosal healing. It is also not clear if mucosal healing with one therapy (such as EEN) is different to that achieved by another agent (e.g., steroids). Furthermore, treatment protocols have not yet evolved to stratify maintenance therapy upon the level of mucosal healing.

EEN and Changes in Fecal Markers of Inflammation

Various proteins measured in the stool are valid markers of the level and extent of gut inflammation [107]. The most well-known markers are calprotectin and lactoferrin, but others include S100A12 and osteoprotegrin (OPG).

A recent study measured fecal calprotectin (FC) levels on multiple occasions during and following a course of EEN in 15 children [108]. The children received a PF and clinical disease activity was defined by determination of Pediatric CD activity Index (PCDAI) scores, with a score of 10 or less being judged as clinical remission. FC levels fell only in the children who were in clinical remission by the end of the period of EEN, but FC levels were normalized in only one child. Interestingly, the FC level after 1 month of EEN was associated with clinical response at the end of EEN, suggesting a predictive value at this time.

The levels of S100A12 (a protein related to calprotectin) were evaluated in a small group of Australian children managed with EEN for active CD [109]. Levels fell in the subset of children who achieved clinical remission and normal CRP.

Recent work showed that EEN treatment also led to reductions in levels of another fecal inflammatory marker, OPG [110]. Levels of OPG fell to around 25% in response to 6 to 8 weeks of EEN (1,994 ± 2,289 pg/g at baseline to 406 ± 551 pg/g after EEN: $p=0.002$). The value of this marker in predicting response to EEN or in correlating with mucosal healing has not yet been determined.

EEN—Nutritional Status and Growth

Along with improvements in disease activity, weight and growth improvements are also commonly seen with EEN. Numerous studies show improved weight gains, whilst some have illustrated changes in specific nutritional markers. Several studies have suggested that nutritional improvements occur at different times to changes in specific inflammatory markers. These studies demonstrate that improvements in nutrition do not correlate with the timing of normalizing inflammatory markers [34,111]. It is not clear whether the nutritional changes are essential to achieve anti-inflammatory improvements. However, satisfactory weight gains are associated with response to EEN, illustrating the importance of these events [80].

Insulin-like growth factor (IGF)-1 is a key mediator of growth hormone signaling. Alterations in this protein occur due to the effects of cytokines (reduced hepatic production secondary to interleukin-6) and are commonly observed in active CD. A number of studies illustrate early increases in IGF-1 and its related binding protein (IGF-BP3) after

commencement of EEN [112; unpublished data, Day et al.]. IGF-1 levels rose after just 7 days of EEN in a small group of 12 children [111].

Detailed nutritional assessments, including body composition analysis, have been conducted in individuals receiving EEN. One key study evaluated body composition using multiple direct methods to define fat, water, total body protein, and potassium [113]. A group of 30 individuals with CD were assessed before and after 3 weeks of EEN. Within this short time, increased weight was linked with proportionate increases in body fat, protein, and water. Another study documented changes in body compartments in a group of Canadian children [17]. Body water, lean body mass, and height increases were observed in the children who had received EEN, but not in a comparison group treated with corticosteroids. EEN has been shown by other authors to promote anabolism consequent to suppression of proteolysis and enhanced protein synthesis [14,24].

These changes in nutrition manifest in weight gains during EEN. The average weight gain in a group of Australian children treated with 6–8 weeks of EEN in Australia was 4.7 ± 3.5 kg [80]. In addition, weight Z-scores increased over the duration of EEN from −0.2767 ± 0.9707 to 0.1866 ± 0.8024 ($p = 0.0016$). Weight standard deviations scores increased after 8 and 16 weeks ($p < 0.05$) in a small cohort of 14 UK children with mean age of 12.5 years [112]. Studies do report variable weight gains, however [76,114].

EEN is also noted to have a positive benefit upon linear growth, with improved height velocity even within a short period of time [13,53]. In a meta-analysis, Newby and colleagues [115] illustrated a significant improvement in height velocity Z-scores with EEN compared to outcomes after treatment with corticosteroids. In the afore-mentioned Australian study, children receiving EEN gained up to 3 cm during the 8-week course of EEN; however, there was no change in height Z-scores across the whole group [80].

EEN and Bone Health

CD is associated with reductions in bone mineral density, which can lead to osteopenia and increased fracture risk. EEN appears to have benefits upon bone health.

Whitten et al. [116] evaluated serum markers of bone turnover in a group of children with active newly diagnosed CD who were treated with PF as sole therapy to induce remission. Serum levels of bone resorption and bone production were measured at baseline and then again after 6–8 weeks of EEN. Control data was obtained from a group of children without IBD with normal growth patterns. Serum levels of C-terminal telopeptides of Type-1 collagen (CTX), a marker of bone resorption were elevated at baseline and fell during therapy ($p = 0.002$). In addition, levels of bone-specific alkaline phosphatase, a marker of new bone formation were low at baseline, but rose significantly during therapy ($p = 0.02$). This study did not include evaluation of other aspects of bone health or bone densitometry.

A more recent study has evaluated the impact of EEN upon vitamin D, an important factor involved in bone health [25]. This study retrospectively evaluated levels of vitamin D in 78 children with CD. A subgroup ($n = 38$) had been treated with EEN at diagnosis. These children treated with EEN had higher levels of vitamin D than a comparison group of 17 children treated with corticosteroids after diagnosis ($p = 0.04$), suggesting that EEN provided a protective effect for this aspect of bone health.

Although these data suggest that EEN provides beneficial effects for bone health in children with CD, further studies are required to confirm these benefits. Prospective studies of bone mineral density in children treated with EEN or other therapies (especially corticosteroids) would be helpful.

There are no reports of the long-term impact on bone health in patients who received induction of remission using EEN, nor with patients continued on maintenance EN. Prospective studies which evaluate serum bone markers and evaluate bone density outcomes over time are required to assess the potential impact of EN on this complication of active CD.

EEN and Quality of Life

Impaired QOL is well recognized in children with CD. The IMPACT questionnaire was developed and validated several years ago as a disease-specific tool to measure QOL in pediatric IBD [117]. Given the importance of eating and food in many cultures and the disruption of these usual patterns during treatment with EEN, there has been some concern that EEN could further impair QOL in these children. The influence of EEN upon QOL has been examined in just a small number of studies in children and adults.

An initial report on the effects of EEN upon QOL and functioning was published by a French group [118]. This study involved 30 children with active CD: half of the group were treated with EEN via a NG tube, whilst the other half of the group was given corticosteroids. The children were assessed by an adaptation of the IBD Questionnaire and underwent a series of psychological assessments, including a psychological interview. A disease-specific pediatric scoring tool was not utilized in this cohort.

The authors showed that the children managed with EEN overall had improvements in their well-being. Several reported concerns about feeling different, disruptions to family routines and the cosmetic effects of the NG tube itself. The children managed with EEN had better scores of anxiety and depression measures than those treated with corticosteroids.

Both groups had disruptions to daily activities such as school absences.

A study from the United Kingdom looked specifically at QOL in a group of 26 children with active CD who were all managed with EEN [119]. This study reported remission rates and measured QOL using the IMPACT II questionnaire. Almost 90% of these children entered remission with EEN. Overall 24 of the 26 children had improved QOL scores during this therapy. In this group of English children, the use of NG tubes to provide the formula didn't impact adversely upon QOL.

In contrast to these findings, Hill et al. [120] found that the use of EEN was associated with lower QOL scores in their evaluation of children in their Australian center. This study involved the repeated assessment of various variables, including QOL and disease activity, at diagnosis and then six-monthly in 41 children (with 186 assessments in total). Nine children had assessments whilst receiving EEN: these children were noted to have lower QOL scores than other children on no treatments or those on other medical therapies. However, the group treated with EEN was also those with highest disease activity scores and lowest nutritional parameters. Furthermore, multiple regression analyses showed that the only independent factor for prediction of QOL in the overall group was disease activity.

These data relate to the use of EEN as therapy for active disease. The ongoing influence of maintenance EN upon QOL has also been assessed in a large group of Japanese adults with known CD [121]. Ninety-five of the 126 patients included were receiving EN as maintenance therapy at the time of the assessment. The investigators used the adult IBD Questionnaire to assess QOL scores. In addition to QOL, other parameters were evaluated. Overall, this study showed that disease activity affected QOL, whilst nutritional treatment improved QOL. Overall scores and subscores for bowel and systemic symptoms were better in the patients with long-standing disease who were receiving maintenance EN.

At present the overall impression of the available data is that the net benefits of EEN upon QOL are positive, likely consequent to improved energy and improved disease control. However, these data are not yet comprehensive and further study is required to more fully understand the relationships between nutritional therapies and QOL in children with CD.

Postoperative Effects

Limited data from Japan exists on the impact of enteral nutrition on postoperative recurrence of CD. Initial intraoperative enteroscopic evaluation by Esaki suggested prophylactic effects of enteral nutrition on postoperative recurrence of small intestinal CD [92]. Yamamoto et al. studied the impact of long-term enteral nutrition on the clinical and endoscopic recurrence rates in a prospective, nonrandomized, parallel, controlled study of 40 adults who underwent resection for ileal or ileocolonic CD. Twenty patients continuously received enteral nutritional therapy (EN group) overnight via nasogastric tube and had a low fat diet during the day. The 20 controls had neither nutritional therapy nor food restriction (non-EN group). Six months after operation, five patients (25%) in the EN group and eight (40%) in the non-EN group developed endoscopic recurrence but the difference did not achieve significance. At 1 year, a significant difference was found in both clinical recurrence (5% in the EN group vs.35% in the non-EN group) and endoscopic recurrence rates (30% in the EN group vs. 70% in the non-EN group) [87]. This preliminary work in the postoperative setting supports the effectiveness of enteral nutrition but additional studies are required to replicate this effect or determine regimens of postoperative EN use that would optimize long-term compliance.

Adverse Effects of Enteral Nutrition

There are very few adverse effects associated with the use of EN. Loose stools may be reported, particularly in those with predominantly colonic disease distribution. Nausea and constipation are less commonly reported [101].

A cross-sectional Japanese study in adults has reported a risk of selenium deficiency in patients with CD being treated with EN. Selenium concentrations were measured and compared in 29 patients with CD treated by EN, 24 patients with CD who were not being treated with EN and 21 healthy controls. Selenium levels were only decreased in CD patients receiving EN and were inversely correlated to the duration and daily dose of EN. Clinical manifestations of selenium deficiency were only found in one patient [122]. A European study examining the effect of exclusive EN on antioxidant concentrations in childhood CD reported conflicting results with respect to selenium. Mean selenium concentrations of the cohort increased significantly from 0.82 μmol/L to 1.14 mmol/L ($p<0.001$). There were however, significant reductions in mean concentrations of vitamin C and E [123]. A recent study on the impact of EEN on circulating micronutrients resulted in improved concentration for several nutrients but interestingly, more than 90% of patients had depleted concentrations of all carotenoids, which later improved on normal diet [29]. Multiple factors including differences in age groups, disease activity, nutritional status and EN formulae may all impact on vitamin and antioxidant levels and the disparate results of the above studies. Further investigation of potential adverse effects at the micronutrient level is required.

Another potential biochemical side effect reported to occur with EEN is transient elevation of transaminase enzymes. Schatorje et al. [124] performed prospective follow-up of liver enzymes in 11 new consecutive children who were primarily treated with EEN for 6 weeks. Liver enzymes were measured before starting EEN and after 3, 6, and 12 weeks. Overall, nine of eleven patients developed a marked elevation of aspartate transaminase (AST) and ten had an elevated alanine transaminase (ALT) peaking at 3 and 6 weeks. GGT was slightly elevated in three patients during therapy, including two boys with either preexisting or persistent raised transaminases. Alkaline phosphatase and bilirubin remained normal. The mean follow-up period was 2.1 years (1.0–3.5 years). None of the patients developed liver disease during follow-up, and liver biopsy was therefore not performed [124]. However, subsequent to this publication, a letter to the editor by Lemberg et al. reviewing transaminase results in their published cohort of 12 children with newly diagnosed CD managed with 8 weeks of EEN showed conflicting data from Shatorje et al. ALT levels were borderline elevated in only two of their patients at 3 weeks of EEN and one patient at 8 weeks of EEN therapy [125].

At diagnosis, all of the markers were within normal ranges. After 2–3 weeks of EEN, the average AST levels were 26.2. Subsequent means were 25 at 8 weeks and 16.8 at 1–2 months after EEN. Average ALT levels rose initially to 21.9 U/L and were subsequently 21.2 at 8 weeks and 14.2 at 1–2 months after EEN. ALT levels were above the upper range of normal (45 U/L) at 2–3 weeks in only two children (51 and 48, respectively) and at 8 weeks in one child (48 U/L). GGT levels did not change and liver disease did not develop in any of the patients. Thus, the effect of EEN on the liver is unclear from existing data. Further prospective investigation is required to clarify the effects of EEN on transaminase levels.

Severe adverse events related to EN are rare. To date there are three case reports of refeeding syndrome consequent to the use of EEN in CD [126,127]. The two most recent cases reported by Akobeng et al. occurred within days of starting EEN in severely malnourished children [127]. Although rare, it is important for clinicians to be aware of refeeding syndrome and to identify and monitor patients at risk.

Factors Affecting Response to EEN

Disease-Related Factors

Disease Duration

Several studies suggest higher efficacy of EEN in children with newly diagnosed CD over those with established disease duration. A multicenter North American study using a semi-elemental formula showed a remission rate of 83% in children newly diagnosed with CD [128], compared to a response rate of 50% in children with previously diagnosed CD. An Australian retrospective study found 12 of 15 (80%) children with newly diagnosed CD entered remission, defined by PCDAI, compared to 7 of 12 (58%) children, who had been diagnosed with CD for a mean of 3.2 years [80]. The latter study also showed that although some children in this group did not enter remission, each had reductions in pediatric Crohn's disease activity index (PCDAI) and each had nutritional improvements.

Disease Location

Disease location has often been considered to potentially influence the effectiveness of EEN. Several early reports suggested increased efficacy when there is small bowel involvement [90,129] and a trend towards earlier relapse in those with isolated colonic involvement [129]. Yet, Afzal et al. [114] demonstrated, in a prospective study of 65 children with acute intestinal CD treated with exclusive polymeric diet, that even the patients with disease limited to the colon had remission rates of 50%, albeit much lower than those with ileocolonic (82% remission rate) or ileal disease (91.7% remission rate).

A recent study by Buchanan and colleagues [97] using carefully defined phenotypic classification in 110 patients on EEN found no significant differences in the remission rates based on disease location. This is supported by a retrospective study by Rubio et al. who recently compared remission rates according to route of administration, and found that the site of disease activity had no impact on response to nutritional therapy [130]. Disease location could not be examined by the meta-analysis by Zachos et al. due to insufficient data [75]. Thus, until the influence of disease location on response to EEN is more clearly delineated, it is reasonable to recommend it for all patients with CD regardless of disease site.

EEN-Related Factors

Polymeric Vs. Elemental/Semi-Elemental Diets

Nutritional therapy is classified by the nitrogen source derived from the amino acid or protein component of the formula. Elemental diets are created by mixing of single amino acids and are entirely antigen-free. Oligopeptide or semi-elemental diets are made by protein hydrolysis and have a mean peptide chain length of four or five amino acids which is too short for antigen recognition or presentation. Polymeric diets contain whole protein from sources such as milk, meat, egg, or soy. They can be classified more simply as elemental (amino acid-based), semi-elemental (oligopeptide), and polymeric (whole protein) diets.

Although elemental diets were used in the initial studies focusing upon the nutritional treatment of CD, subsequent

studies in both children and adults have compared these elemental diets to polymeric diets [78,101,131,132]. Comparisons between any combination of the different protein sources when combined in meta-analysis [75] have shown no significant difference in effectiveness. Similarly, one study comparing polymeric diets differing in glutamine enrichment showed no difference in remission rates [133].

Fat Composition

In more recent years, several trials have been conducted to investigate the importance of fat composition [93,134–136], building on the hypothesis that the proportion or type of fat in an enteral feed could affect the production of pro- or anti-inflammatory mediators. Two trials, Leiper et al. [135] and Sakurai et al. [136] investigated the effect of low vs. high long chain triglyceride (LCT) content, and differing amounts of medium chain triglycerides, respectively, in adult patients and showed no difference in effect. Another study by Bamba et al. [93] comparing diets of low (3.06 g/day), medium (16.56 g/day), or high fat (30.06 g/day) content showed higher remission rates in the lowest fat group. By intention to treat analysis, remission was achieved in 8 of 11 patients (72.7%) of the low fat group, 4 of 13 (30.8%) of the medium fat group, and 2 of 12 (16.7%) of the high fat group. However, all of these studies were flawed by either small sample sizes, high dropout rates or unvalidated activity indices used to define remission. When studies evaluating fat composition were combined by meta-analysis [75], a non significant trend favoring very low fat and low LCT content has been demonstrated. However, these results should be interpreted with caution due to statistically significant heterogeneity and small size which may have lacked statistical power to show differences should they exist. In addition, subgroup analyses could not be performed based on the n6 or n9 fatty acid composition in the feeds due to significant heterogeneity. The possibility that fat composition influences immunomodulatory or anti-inflammatory effect in active CD warrants further exploration with larger trials. In summary, no specific formula composition of EN diets has been conclusively shown to influence induction of remission in active CD.

Exclusive Vs. Partial EN

The question of whether supplementary EN could be considered instead of exclusive EN was explored in a randomized controlled pediatric trial by Johnson et al. [137]. This study showed that the combination of partial EN (50% of energy requirements) with normal diet lead to a substantially lower rate of remission compared to the use of exclusive EN (100% of energy requirements) (15% in PEN vs. 42% in EEN; $p<0.035$).

Gupta et al. [138] have recently retrospectively examined a novel protocol providing patients with 80–90% of caloric needs by EN and allowing consumption of remaining calories from a normal diet. Fifteen of 23 (65%) of the patients receiving the novel partial EN protocol achieved remission [138]. Further prospective clinical trials are needed to confirm these findings and to clarify what proportion and type of calories from normal diet would benefit compliance rates without compromising effectiveness at inducing remission.

Duration of Therapy

The duration of EEN therapy ranges from 2 to 10 weeks in published trials and varies substantially in different parts of the world. The early effects of EN have been achieved over the first 4 weeks of therapy. Additional later effects in the fourth to eighth week of therapy may include further anti-inflammatory and nutritional benefits [80].

Delivery of EEN

Route of Administration of EEN

EEN can be administered by various different routes, such as oral, nasogastric (NG) or via a gastrostomy tube. The choice of route of administration will often be dependent on clinical judgement, and reflects local practice, tolerance of formulae, and patient choice. Elemental or semi-elemental formulae may be more difficult to take orally. Since polymeric formulae have the same clinical benefits, lower cost, and better palatability (allowing for oral administration), they may be associated with increased interest, tolerance, and compliance of EN therapy, which remains the greatest challenge of this form of therapy. However, while, generally children will accept the oral route more than the NG route, oral feeding may lead to greater difficulties over time as the child tries to maintain sufficient volume over a longer period of time. Rubio et al. [130] have retrospectively reviewed 106 patients treated with either fractionated oral or continuous enteral feedings and found that both routes were efficacious in inducing remission and mucosal healing. After 8 weeks of EEN, 34 of 45 (75%) achieved remission in the oral group and 52 of 61 (85%) in the enteral nutrition group ($p=0.157$). All patients showed a significant decrease in disease severity assessed by PCDAI, and significant improvements in anthropometric measures and inflammatory indices. Weight gain was greater in the enteral group ($p=0.041$) [130].

Some reports refer to the practice of routine placement of a NG tube at the start of the course of EEN and then encouragement of oral intake so that children end up with removal of the tube and ongoing oral feeds [139]. On the other hand, children who struggle with tolerance soon after commencing a period of EEN orally can subsequently be switched to NG administration [97].

Approach to Reintroduction of Normal Diet

Following the completion of the course of EEN, the next step will be the recommencement of normal regular diet. This phase of treatment can be conducted in different ways, and there has not yet been a formal evaluation between these protocols. An international review of protocols in different units illustrated the range of approaches [140]. Overall, the time taken to reintroduce a normal diet (following a 6- to 8-week period of EEN) at these pediatric units varied from 1 to 12 weeks.

One of the most accepted approaches to reintroduce normal diet is a gradual introduction of food quantity while formula volume is progressively decreased [140]. This approach entails the introduction of a meal every 2–3 days whilst reducing the volume of formula with the introduction of each meal, so that the adjustment takes place over 7–10 days time [80,97]. Although not formally evaluated in this setting, this approach has been well accepted with very few children having disruptions to the reintroduction of normal diet [personal observations, A. Day].

One group has reported the immediate introduction of food while formula volume is decreased to overnight feeds [141]. A further approach has involved the use of a low-allergen diet, with new low-allergen foods (initially lamb, potato, chicken or rice) introduced every 2 or 3 days, followed by the progressive reintroduction of other foods and food groups [142]. This method of returning to a normal diet was recently evaluated in 100 patients and no clear benefits were demonstrated [143].

Geographic Variability and Barriers to Utilization of EEN

There is significant geographic variation in the practice and recommendations for EEN as primary therapy in the management of children with Crohn's disease [49]. In Europe and Japan, guidelines recommend EEN as a first-line therapy for induction of remission in children with Crohn's disease [144,145]. The variation in use is noted between and within different countries across the world [4,146–148]. In an early study by Levine et al. [4], significant variations in the use of EEN were reported in a trans-Atlantic survey of 167 physicians from the United States, Canada, Western Europe, and Israel. In that study, while 4% of North American pediatric gastroenterologists used EEN regularly, 62% of European practitioners reported regular use. These European numbers were echoed in a report from a survey of Swedish pediatric GI units, which showed that 65% of the units used EEN as their primary therapy in newly diagnosed CD [146]. The variation in practice amongst North American pediatric gastroenterologists was revisited recently in a survey of 326 NASPGHAN members from North America (86% USA, 14% Canada) [148]. They reported that 31% of respondents never used EN, 55% reported sparse use, and 12% reported regular use. Physicians in Canada reported significantly more use than in America ($p<0.001$). Variations in EN use within a country were also demonstrated in a study of Australian pediatric gastroenterologists by Day et al. [147]. In both the North American and Australian studies currently working and previously working in a center where EEN was used were important factors for both the perceived appropriateness of EEN and the regularity of its use. North American pediatric gastroenterologists reported that concerns about adherence were the main disadvantage of EEN and provided a barrier to wider usage. Australian respondents also commented that adherence was a concern but cited other issues including cost and resource demands. Both of these surveys noted that experience with EEN during gastroenterology training related to current use and confidence with EEN.

While this preliminary work has attempted to explore physician factors to explain use of EEN, currently no studies have assessed factors influencing patient or parent acceptance. Patient, family and societal/cultural factors undoubtedly play a role in the acceptance and use of EEN. From personal experience, the fear of corticosteroid related side effects, the cost of EEN (which is rarely covered by insurance plans in many countries), concerns over giving up conventional foods, poor palatability of formulas and fear of tube feedings are some of the reasons patients and/or parents give for not choosing EEN [149].

Another potential barrier to the incorporation of EN as a realistic therapeutic option are adequate resources to support an EN program. There are no published studies which have delineated the optimal resources required. A recent clinical report on EN as primary therapy in pediatric CD from the NASPGHAN highlighted several issues of importance [149]. Attitudes among the health care staff that promote the use of EN and the center's experience appear to play a large role [148]. Dedicated dieticians are fundamental to an EN program, determining appropriate nutrient intake and in administration of the program. Nursing support with experience in administering and teaching care of tube feedings and use of the feeding pumps is necessary for those who are unable to tolerate oral formula. Formula cost is also an important consideration, particularly when semi-elemental or elemental formulas are chosen, and they are providing sole source nutrition during the period of exclusive EN feeding. Also, formula costs may not be covered by the relevant health system or drug insurance plans. In some jurisdictions coverage may be obtained if formula is delivered by a tube, either NG or gastrostomy tube. The high cost is likely to be a barrier to utilization of this therapy.

Conclusions

Nutrition is an important component of the management of IBD in children and adolescents. Successful use of EEN as a form of therapy, specifically for CD, requires a dedicated multi-disciplinary team of nurses, dieticians, social workers, and medical staff to support children and families during therapy. Pediatric gastroenterologists must consider EEN in the therapeutic decision process since it yields all of the target outcomes of interest in the management of CD including alleviation of symptoms, mucosal healing, correction of nutritional deficiencies, optimization of growth, and normalization of quality of life, without adverse effects encountered with most pharmacologic therapies. Further work on the mechanism(s) of action of EN will likely shed light on the pathogenesis of IBD.

A remaining challenge is the difficulty in maintaining remission as many patients do not welcome repeated restrictions on normal eating. Potential avenues of future study will likely include exploration of nutraceuticals and nutrients that have pharmacologic properties, such as the ability to induce immunomodulation, or, the development of designer formulae in alternative forms such as solid food in order to improve acceptance and palatability [150]. Alternatively, the combination of enteral and drug therapy with immunomodulators to maintain remission warrants further study.

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