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Nutrition in Paediatric Inflammatory Bowel Disease:

A Position Paper on Behalf of The Porto IBD Group of ESPGHAN

Erasmo ***Miele***[1]*, Raanan* ***Shamir***[2]*, Marina* ***Aloi***[3]*, Amit* ***Assa***[2]*, Christian* ***Braegger***[4]*, Jiri* ***Bronsky***[5]*, Lissy* ***de Ridder***[6]*, Johanna C.* ***Escher***[6]*, Iva* ***Hojsak***[7]*, Sanja* ***Kolaček***[7]*, Sibylle* ***Koletzko***[8]*, Arie* ***Levine***[9]*, Paolo* ***Lionetti***[10]*, Massimo* ***Martinelli***[1]*, Frank* ***Ruemmele***[11]*, Richard K.* ***Russell***[12]*, Rotem* ***Sigall Boneh***[9]*, Johan* ***van Limbergen***[13]*, Gigi* ***Veereman***[14]*, Annamaria* ***Staiano***[1]*.*

1. Department of Translational Medical Science, Section of Pediatrics, University of Naples “Federico II”;
2. Institute for Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel;
3. Pediatric Gastroenterology and Liver Unit, Sapienza University of Rome, Rome, Italy;
4. Division of Gastroenterology and Nutrition, University Children's Hospital Zurich, Zurich, Switzerland
5. Gastroenterology and Nutrition Unit, Department of Paediatrics, 2nd Faculty of Medicine, Charles, University and Motol University Hospital, Prague, Czech Republic

6. Department of Paediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands;
7. Department of Gastroenterology, Children Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia;
8. Dr. von Hauner Children's Hospital, Ludwig Maximilians University Munich, Germany;
9. Wolfson Medical Center, Sackler School of Medicine, Tel-Aviv, Israel;
10. Meyer Children Hospital, University of Florence, Florence, Italy;
11. Université Sorbonne Paris Cité, Université Paris Descartes, and Assistance publique-hôpitaux de Paris, Hôpital Necker-Enfants malades, Service de gastroentérologie pédiatrique, Paris, France;
12. Department of Paediatric Gastroenterology, The Royal Hospital for Children, Glasgow, Scotland;
13. Department of Pediatrics, Division of Pediatric Gastroenterology & Nutrition, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada;
14. Department of Paediatric Gastroenterology and Nutrition, University Hospital Brussels, Free University Brussels, Belgium.

Corresponding Author: Annamaria Staiano, MD

Department of Transitional Medical Science,

Section of Pediatrics

Via S. Pansini, 5

80131 Naples, Italy Phone & Fax: .39.(0)81.7462679

E-mail: staiano@unina.it

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Abstract

Background and aims: A growing body of evidence supports the need for detailed attention to nutrition and diet in children with IBD. We aimed to define the steps in instituting dietary or nutritional management in light of the current evidence and to offer a useful and practical guide to physicians and dieticians involved in the care of paediatric IBD patients.

Methods: A group of 20 experts in paediatric IBD participated in an iterative consensus process including 2 face-to-face meetings, following an open call to ESPGHAN Porto, IBD Interest and Nutrition Committee. A list of 41 predefined questions was addressed by working subgroups based on a SR of the literature.

Results: A total of 53 formal recommendations and 47 practice points were endorsed with a consensus rate of at least 80% on the following topics: nutritional assessment; nutrition as a primary therapy of paediatric IBD; macronutrients needs; trace Elements, minerals and vitamins; probiotics and prebiotics; specific dietary restrictions; dietary compounds and the risk of IBD.

Conclusions: This position paper represents a useful guide to help the clinicians in the management of nutrition issues in children with IBD.

Keywords: nutrition; IBD; enteral nutrition; Nutritional therapy; paediatrics; Ulcerative colitis; Crohn's Disease

What is known

- A growing body of evidence supports the need for detailed attention to nutrition and diet in children with IBD;
- Despite the increasingly recognized importance of the issue, no speficic paediatric dietary guidelines has been published to date.

What is new

- We provide clear recommendations to better define the steps in instituting nutritional management in light of the current evidence;
- This position paper represents a useful practical guide to help physicians and dieticians involved in the care of paediatric IBD patients.

Exclusive Enteral Nutrition

What is the efficacy of EEN for the induction of remission of Paediatric CD?

Statement:

- EEN has the same efficacy as oral steroids in the induction of remission of children with active luminal CD (EL 1).
- EEN may be re-used during the course of disease in case of relapse (EL 2).

Although no placebo-controlled randomized controlled trial (RCT) of EEN have been conducted, several RCTs summarized in 3 different meta-analyses, established the efficacy of EEN for the induction of remission in children with CD (177-179). As stated in the most recent guidelines on the therapeutic management of paediatric CD (45), the overall combined remission rate for EEN is 73% (relative risk (RR) 0.95, 95% confidence interval (CI) 0.67–1.34 (178) and RR 0.97, 95% CI 0.7–1.4 (179)). After the publication of the last meta-analysis, 1 RCT and some other prospective studies were published replicating the previous results (180-183). The overall conclusion is that EEN has the same efficacy in the induction of remission as corticosteroids. Recently, the efficacy of EEN has been confirmed in comparison to biological therapy. Lee et al. enrolled 90 consecutive children with an active CD in a prospective study. Patients received EEN, Infliximab or Partial Enteral Nutrition (PEN) as therapy for induction of remission (184). Clinical response was achieved in 88% of children treated with EEN, 84% of those receiving biological therapy and 64% in children undergoing PEN (184).

In conclusion, considering all the benefits of EEN and taking into account the side effects of steroids, EEN should be considered as the first line therapy to induce remission in paediatric luminal CD (45).

Few retrospective studies evaluated the efficacy of a second course of EEN as induction therapy during the course of the disease. Remission rates ranged from 58.3% to 80% (185-188). In the most recent retrospective study including 52 children, Frivolt et al. reported a 92% of remission rate after the first cycle of EEN and 77% after a second cycle of EEN; although a second cycle was used in only 26 children (188). These data confirm that if the compliance of the patients is maintained, EEN may be successfully reused during the subsequent course of the disease for future relapses.

Type of formula and delivery mode

Statement:

- The use of standard polymeric formula, with a moderate fat content, is recommended unless other conditions are present (e.g. cow's milk protein allergy) (EL 1).

Practice Points:

- There is no evidence that the dietary source of proteins affects the efficacy of EEN.
- Initially the formula should be administered orally. A nasogastric tube may be used when there is failure to achieve adequate oral intake.

The source of proteins seems not to affect the efficacy of EEN. Indeed, numerous studies have compared the efficacies of different types (elemental, semi-elemental, oligomeric or polymeric diets) of enteral formulas in the management of active CD with no significant results (189-191). This was further confirmed by a Cochrane meta-analysis of 10 trials showing no statistically significant difference between patients treated with elemental and non-elemental diet (192). Therefore, unless cow's milk protein allergy (CMPA) coexists, polymeric formula should be preferred considering the better palatability and the lower costs (193). Given the pro-

inflammatory properties of some lipids, fats' composition of formulas has been postulated as one of the possible mechanism to explain EEN efficacy. Although, no studies have been published in paediatrics, 2 adults' trials demonstrated no differences when increasing medium chain triglycerides (MCT) (194) or monounsaturated fatty acids (MUFA) content in the formulas (195). Similarly, a sub analysis of a Cochrane demonstrated no differences in induction of remission of CD between low fat and high fat formulas (48). Finally, the addition of metabolites with anti-inflammatory properties such as glutamine (68) or omega-3 (117, 118) has not given positive results and should not be recommended.

To date, few formulas with the adequate caloric intake are available and successfully used for delivering EEN in children. However, no comparison study in terms of effectiveness has been performed so far.

No differences in term of efficacy have been observed between oral EEN and continuous administration through a nasogastric tube (182). Considering that the use of a nasogastric tube may decrease the improvement of quality of life achieved with EEN (196), oral feeds should be preferred. A nasogastric tube should be positioned if adequate caloric intake could not be achieved orally (45).

Duration and reintroduction of foods

Statement:

- EEN is recommended for a period of at least 8 weeks (EL 1).

Practice points:

- There is still insufficient evidence to recommend a standard food reintroduction scheme. In the absence of evidence we suggest a gradual reintroduction of the foods, with a concomitant reduction of the formula over a 2–3 week period.

There is no evidence regarding the precise duration of EEN. Duration of EEN in clinical studies varied from 2 to 12 weeks, with majority using 6-8 weeks (197). Symptoms usually improve after a few days on EEN and mucosal healing was demonstrated after 8 weeks (198). In accordance with the last CD guidelines we suggest that EEN induction therapy should last at least 6 weeks (45).

There is no evidence to guide reintroduction of normal food after the EEN. Recently, Faiman et al. conducted a retrospective study comparing a standard food reintroduction over 5 weeks versus a rapid reintroduction over 3 days (199). No significant differences were observed in terms of relapse rate and maintenance of remission over 1 year. The authors concluded that due the better tolerability, a rapid reintroduction should be preferred (199). However, this study suffers several limiting factors; it was retrospective and had very high drop-out (20 out of 31 children with slow introduction and 19 out of 33 were included in the analysis). In the absence of more solid evidences, a gradual food reintroduction with concomitant decrease of formula volume over a 2–3 week period, as suggested in CD guidelines (45), should still be the preferred approach.

Location and behaviour of disease

Statement:

- EEN should be recommended in all cases of active luminal disease irrespective of the GI tract location (EL 2).

Practice points:

- There is insufficient evidence to recommend EEN for isolated oral or perianal disease and for extra-intestinal manifestations.

Opposing data exist regarding the efficacy of EEN and CD disease location. Previous studies (198, 200) suggested a better efficacy of EEN in patients with ileal involvement compared to isolated colonic disease. However, more recent data demonstrated no significant differences between isolated colonic disease and small bowel CD (182, 185). Particularly, in the retrospective study from Rubio et al. which included 106 CD patients, no significant difference was observed regarding location of disease (182). Conversely, another retrospective analysis including 114 children reported that individuals with isolated terminal ileal disease (n=4) had lower remission rates than other locations (p=0.02) (181). In the absence of better scientific evidence, these data support the conclusions of the Cochrane meta-analysis, which suggested the use of EEN in all paediatric CD patients with luminal disease, irrespective of the disease location (177).

To date there are no data to support the use of EEN in patients with isolated extraintestinal manifestations or oral disease. Efficacy of EEN for active perianal disease was reported only in a small case series (201).

Side effects

Practice points:

- Clinicians should be aware of the risk of refeeding syndrome in severely malnourished children.

- Other possible side effects include: nausea/vomiting, diarrhoea, abdominal discomfort, bloating.

EEN is associated with minimal and temporary side effects. Most common reported are nausea, diarrhoea, constipation, abdominal pain and bloating (202). Borrelli et al. reported that 4 out of 17 patients (23.5%) had mild gastrointestinal side effects (203). The only severe reported adverse event was refeeding syndrome. Refeeding syndrome is defined as a potentially fatal metabolic complication causing shifts in fluids and electrolytes (especially hypophosphatemia) that may occur in severely malnourished patients after the start of refeeding (204). Refeeding syndrome has been described in 3 case reports in very malnourished CD children (205, 206). Therefore, the awareness of a clinician for this life-threatening complication is essential, since the risk of refeeding syndrome can be dramatically decreased by a slow increase of EEN (volume and concentration) over several days, starting with reduced caloric intake [last known intake or 50-75% of the resting energy expenditure (REE)] and advancing only when there are no significant electrolyte abnormalities.

What is the efficacy of EEN for the maintenance of remission of Paediatric Crohn's disease?

Statement:

- There is no evidence for using EEN as a maintenance therapy (EL 4).

Practice Point:

- Due to the highly demanding adherence, EEN should not be considered as an option for long-term maintenance therapy.

No study has evaluated the role of EEN for the maintenance of remission in children with CD. Due to the low compliance of patients after the induction cycle, we do not recommend EEN for the maintenance of remission in children with CD.

What is the efficacy of EEN for the induction and maintenance of remission of Paediatric Ulcerative Colitis?

Statement:

- EEN is not efficacious in the induction and maintenance of remission of paediatric UC (EL 4).

What is the efficacy of EEN on mucosal healing of paediatric Crohn's disease?

Statement:

- EEN promotes mucosal healing (EL 2).
- EEN also promotes transmural healing in a proportion of patients.

Effect of EEN on mucosal healing was investigated by 7 studies (182, 196, 198, 203, 207-209) where endoscopy was performed 8 or 10 weeks after initiation of EEN. All studies found improvement in mucosal inflammation and complete mucosal healing was found in 19-87% of patients. Two studies, one open label RCT (203) and other retrospective study (209) compared mucosal healing between children treated with corticosteroids and with EEN. Both studies found significantly higher rate of mucosal improvement in EEN group (42% vs. 87% and 0 vs.19%). Furthermore, there is evidence that early endoscopic response is associated with reduced relapses, hospitalization and need for anti-TNF treatment at 1 year of follow-up (208). In 3 out of 14 (21 %) children EEN was even able to induce complete transmural remission of ileal CD (208).

What are the long-term outcomes of EEN?

Statement

- EEN improves nutritional status (EL 2) and QoL (EL 3).
- There is insufficient evidence at present to show EEN improves long term bone health (EL 4)

a) Remission duration

Remission duration after EEN is not well determined. Overall 11 studies (180, 186-188, 193, 198, 199, 209-212) reported relapse rate in the longer period of time (10 months to 7 years). Relapse rate ranged from 42%-67% in the first year (188, 193, 199, 210, 212) and 58%-68% at 24 months (180, 187, 212). Median time to first relapse ranged from 6.5 to 12.7 months (186-188). Duration of remission after induction with EEN vs. corticosteroids was assessed by 3 studies and results were contradictory; Thomas et al. found shorter remission duration after EEN (211), but two more recent studies found longer duration of remission if EEN was used as a first line induction therapy (209, 210). Furthermore, although it did not report difference in remission duration after EEN or corticosteroids, one study reported protection against relapses in EEN group during the 24 months period (212). These results, however, should be interpreted with caution due to their retrospective nature and high possibility of other confounding factors.

b) Growth and bone health

All studies investigating weight change during EEN treatment reported positive effect of EEN on weight. Three studies showed an increase in lean body mass (53, 213, 214). Results on height increase are conflicting. Some studies reported height velocity increased immediately after the EEN treatment (203, 208, 209, 215). Furthermore, there

is no agreement on long term results; retrospective studies with no comparative cohort found no significant long term improvement in height Z score (186-188); studies which compared EEN and corticosteroids found conflicting results: 2 studies (211, 216) found better growth rate if EEN was used as a primary induction therapy and one showed no difference (217).

The influence of EEN on bone health has been investigated by 3 studies (214, 217, 218). Werkstetter et al. (214) prospectively evaluated data on bone quality using peripheral quantitative computed tomography (pQCT) and found improved bone metabolism within 3 months of starting EEN with no further normalization afterwards (one year of follow up). EEN therapy also normalized markers of bone turnover 8 weeks after EEN introduction (218). After a follow up of one year EEN group had a non-significant improvement in bone mineral density (BMD) assessed by DXA (217).

c) Quality of life (QoL)

Two studies evaluated QoL after the treatment with EEN both showing improvement in QoL scores after EEN (184, 196). Additionally, patients who received EEN comparing to partial EN and antiTNF therapy had similar improvement in QoL scores (determined by IMPACT score) (184).

Partial Enteral Nutrition

Definition

Partial enteral nutrition (PEN) is defined as providing subjects with a nutritionally balanced liquid formula while continuing to eat an unrestricted or exclusion diet.

What is the efficacy of PEN for the induction of remission of Paediatric Crohn's disease (CD)?

Statement:

- PEN alone should not be used for induction of remission (EL 2)

Practice points:

- PEN in isolation is not efficacious to induce remission in the majority of patients.
- Supplementation with a standard polymeric formula, in addition to conventional induction treatment may be considered.

Johnson et al showed in a RCT the superiority of exclusive enteral nutrition (EEN) over PEN in clinical remission rates defined using the Paediatric Crohn's disease activity index (PCDAI) as the primary outcome measure at 6 weeks (10/24 [42%] vs.4/26 [15%], respectively, p = 0.03). In this study, PEN provided an average of 47% of total energy requirements (range 39–58%). (219)**.** Additionally, a recent prospective study of children initiating PEN, EEN, or anti-TNF therapy for active CD, confirmed that each therapy improved symptoms, but EEN and anti-TNF therapies were significantly superior to PEN providing between 80-90% of estimated calories needed for inducing mucosal healing (184). In a retrospective cohort of 28 children with CD, supplementation with polymeric formula, plus conventional treatment, was associated with a decrease in PCDAI whereas children who were not on supplementation did not (220). Gupta et al administered formula overnight to deliver 80-90% of overall needs with the remaining 10% to 20% of their caloric needs came from an unrestricted diet of small meals or snacks during the day. This was effective for the induction of remission in paediatric patients with CD (221). More recently, Sigall-Boneh et al proposed a dietary intervention in mild-to moderate CD, based on 50% PEN and a structured exclusion diet which led to remission in 70% of children. (222).

What is the efficacy of PEN for the maintenance of remission of Paediatric CD?

Statement:

- PEN is a treatment option to maintain remission in selected patients with mild disease and low risk of relapse (EL 4).

What is the optimal daily amount and recommended duration of PEN for the maintenance of remission of Paediatric CD?

- The optimal daily amount and the duration of partial enteral nutrition that needs to be consumed to be effective are unknown (EL 4)

Practice points:

- A long or short-term PEN course, in addition to unrestricted normal or specific food diet may be offered in order to prolong the period of remission in patients who are on no other maintenance treatment for Crohn's disease.

Long-term enteral nutritional supplementation, in addition to unrestricted normal or specific food diet, such as low fat diet; may prolong the period of remission and reduce relapse rates in patients with CD. There is limited research evidence relating to maintenance EN as a treatment for paediatric CD patients, with many of the best studies being performed in adults (223). Yamamoto et al performed a systematic review in adult CD, including 10 studies: one RCT, three prospective non-randomized trials and six retrospective studies. The clinical remission rate was significantly higher in patients receiving PEN in all seven studies comparing PEN to non-supplementation (223). Additionally, in two studies, PEN showed reduction in endoscopic

disease activity. There are a smaller number of paediatric studies. Wilschanski et al showed retrospectively that providing PEN (nocturnal nasogastric supplements), without restriction of normal diet, after successful treatment with EEN, was associated with prolongation of remission and improved linear growth. (224). Duncan et al. Demonstrated that a sub group of patients can successfully continue PEN supplements post induction of remission with EEN as an effective maintenance treatment and had 1 year remission rates matching thiopurines. PEN therefore seems a useful strategy in a sub group of patients especially in those who are not commencing azathioprine or similar maintenance treatments (225). In contrast to the previous studies suggesting the efficacy of PEN, Knight et al reported that the intake of maintenance enteral feeding was not associated with significantly decreased relapse rate (186).

In adult studies investigating the impact of the quantity of enteral formula on clinical remission, higher amounts of enteral formula (35-50%) were associated with higher remission rates. (226, 227). In children the proportion of PEN varies between studies. It is clear that further studies are needed to find appropriate amount, duration, timing of PEN (186).

PROBIOTICS AND PREBIOTICS IN IBD

What is the clinical efficacy and safety of probiotics, when compared to no treatment, placebo, pharmacological treatment or alternative non-pharmacological treatment in the induction and maintenance of remission of paediatric UC and CD?

Statements:

- There is limited evidence in favour of using VSL#3 or L. reuteri ATCC 55730 as adjuvant to standard therapy for induction of remission in mild to moderate paediatric UC (EL 2)
- There is evidence in favour of using VSL#3 or E.coli Nissle as an alternative to 5-ASA therapy in maintenance of remission in mild to moderate paediatric UC especially in mesalazine intolerance (EL 2)
- *VSL#3* has shown efficacy for maintaining antibiotic-induced remission in pouchitis and for preventing it in adults (adult EL 2; paediatric EL 5)
- We do not recommend the use of probiotics in the induction or in the maintenance of remission of paediatric CD (EL 2).

Practice points:

- Probiotics should be used with caution in patients with central venous catheter or in immunocompromised patients.
- Results from clinical trials are strain-specific and should not be extrapolated to other bacterial strains.

High quality studies on the effect of probiotics in paediatric IBD are limited, with only three RCTs two in UC (228, 229) and one in CD (230). Some extrapolations can be made from adult data (231-242) but these have limited applicability in the paediatric population.

Ulcerative colitis

Oliva et al. showed an effect on decrease of both endoscopic (Mayo score) and histological score during 8 weeks of follow-up in group of paediatric patients treated by rectal enema containing *L. reuteri ATCC 55730* in addition to mesalazine treatment, but not in placebo arm in mild to moderate active distal paediatric UC (229). Miele et al. has shown *VSL#3* to be superior to placebo in both induction and maintenance of remission (1 year follow-up) when added to standard treatment in paediatric newly diagnosed UC (228).

An open label study of *VSL#3* in induction of remission in children with mild to moderate active UC (243) and another small study on *E.coli Nissle* showing efficacy comparable to 5-ASA in maintenance of remission in paediatric UC (not an RCT) (244) were excluded.

In adults, neither ECCO (232) nor Cochrane review (235) recommend probiotics for induction of remission of mild-to-moderately active UC, despite some studies showing some effect of *VSL#3* (228, 245-248). There are no relevant data on probiotics in treatment of acute severe colitis (249).

Based on several RCTs and in accordance with systematic reviews (236, 250), ECCO recommend *E coli Nissle* as an effective alternative to 5-ASA for maintenance therapy in adult UC (232).

Current paediatric UC guidelines (251) conclude in accordance with the Cochrane review (237) that there is insufficient evidence to recommend routine use of probiotics for induction or maintenance of remission in paediatric ambulatory UC patients. However, some probiotics (*VSL#3, E.coli Nissle*) may be considered in children with mild UC intolerant to 5-ASA, or as an adjuvant therapy in those with mild residual activity despite standard therapy. Therapy with *VSL#3* has also shown efficacy for maintaining antibiotic-induced remission and for preventing pouchitis in adults (238, 240, 241). Recently, the probiotic mixture VSL#3 has changed

manufacturer and although it contains the same bacteria, its efficacy under the new manufacturing conditions has not yet been scientifically tested in IBD clinical trials.

Crohn´s disease

Only one relevant paediatric study was identified showing that *LGG* is not superior to placebo in addition to standard maintenance therapy in paediatric CD (230). Moreover, a meta-analysis has even concluded that LGG may increase incidence of relapse in children (252). Also, Saccharomyces Boulardii has not shown any efficacy in preventing of relapse in CD adult patients in remission of disease (253). Current paediatric CD guidelines (45) as well as adult ECCO guidelines (233) and Cochrane review (239) are in accordance that there is no significant benefit of probiotics for reducing the risk of relapse compared to standard maintenance therapy.

What is the clinical efficacy and safety of prebiotics, when compared to no treatment, placebo, pharmacological treatment or alternative non-pharmacological treatment in the induction and maintenance of remission of UC and CD?

Statement:

- There is no evidence to the use of prebiotics and/or synbiotics in the induction and in the maintenance of remission of paediatric UC (Adult: EL 2; Paediatric: EL 5) and CD (Adult: EL 2; Paediatric: EL 5).

There are very few data on the effect of prebiotics and synbiotics in paediatric IBD, with no

published clinical trial. The majority of data in adults are limited by the small sample size, short duration and high drop-out rate (254-261). A systematic review of RCT published in 2015, based on major limitations of the studies, including different agents used, sample size and methodological issues, concluded that there is inconclusive evidence of a beneficial role of prebiotics and synbiotics in IBD (262).

What is the clinical efficacy and safety of dietary fibers, when compared to no treatment, placebo, pharmacological treatment or alternative non-pharmacological treatment in the induction and maintenance of remission of UC and CD?

Statements:

- Based on adult studies, fiber supplement intervention may be effective in the management of UC and pouchitis (Adult: EL 2; Paediatric: EL 5).
- There is no evidence to support high-fiber or low-fiber diet in CD (Adult: EL 2; Paediatric: EL 5).

Practice points:

- A possible effect of fiber supplementation associated with standard therapy has been reported in maintenance of remission (psyllium fiber), in active UC (germinated barley fiber) and in maintenance of remission in pouchitis (inulin-enriched oral supplement).
- Fiber restriction should not be recommended in patients with IBD without evidence of stricturing phenotype.

The scientific rationale of using dietary fiber in IBD relates to the production of metabolites (i.e. SCFAs, particularly butyrate) and a beneficial influence on gastrointestinal functions (263). Although no specific paediatric study has been performed, several trials in adults have evaluated the effectiveness and mechanisms of action of fiber in IBD. Based on the published RCT in adults and on 3 systematic reviews, there is limited evidence for the effectiveness of fiber supplementation in active UC and in maintenance of remission in UC and pouchitis (254, 255, 264-275). Data in active UC are conflicting, with few studies reporting a possible effectiveness of fiber supplementation and others no effect on disease outcomes (8,10,14)

Dietary intervention studies didn't show any significant benefit of high versus low-fiber diets in CD (264, 265, 270-272). Based on the current evidences, no dietary fiber restriction should be recommended to patients with IBD without evidence of stricturing phenotype, although monitoring of potential fiber intolerance intake should be performed (263).

SPECIFIC DIETARY RESTRICTIONS FOR PAEDIATRIC IBD

Statement:

- Elimination or restrictive diet in children/adolescents with IBD should not be recommended unless potential benefits outweigh potential risks of the diet (EL 4).

Several diets restricting one or more foods from the diet have been advocated for paediatric and adult patients with IBD to improve symptoms and/or inflammation (274, 276-279). In general, restrictive diets may influence nutritional status, psychological and quality of life. Nutritional restriction may result in unbalanced food intake with deficiency of certain macro- and

micronutrients, which may have negative short and long-term effect, particularly on the growing and developing child. While adults can decide on a specific diet for themselves children depend on the decision and support by their caregivers. Diets should only be considered if they have proven benefit in reducing inflammation, symptoms or both. A list of reported diets is provided in Table 2.

Specific carbohydrate diet (SCD)

Statement:

- A SCD for induction or maintenance of remission in PIBD patients should not be recommended (EL 4).

Practice points

- SCD is an unbalanced diet due restriction of most carbohydrates leading to high protein and high fat intake which has been associated with risk of CD and UC.
- More evidence on the benefit of SCD from RCTs is needed before such a dietary restriction can be recommended to paediatric IBD patients.

The SCD restricts all carbohydrates (starch, polysaccharides and disaccharides) except monosaccharides (glucose, fructose, and galactose). The hypothesis behind is that di- and polysaccharides are poorly absorbed resulting in overgrowth of bacteria and yeast with increased mucus production, small bowel injury and malabsorption. Two retrospective chart reviews of 7 and 26 children with IBD on a SCD showed improvement of symptoms and anthropometry (280, 281). Nine children with CD were prospectively enrolled in a trial of SCD while continuing their normal medication. Lab values, PDCAI and videoendoscopy scores improved, however there was no control group and total energy given was higher compared to the normal diet before

starting SCD(282). Before there is more evidence in favour of a SCD it cannot be recommended in children with IBD.

Lactose free diet (LFD)

Statements

- Symptoms of lactose malabsorption (abdominal pain, bloating, and diarrhoea) overlap with symptoms of active IBD (EL 4).
- A diet with reduced lactose intake with monitoring of symptom improvement may be initiated in children/adolescents with IBD and symptoms suggestive of lactose malabsorption (EL 3).

Practice points

- IBD patients should be counselled not to avoid dairy product, but to reduce high lactose containing products and/or to use lactase treated products or enzyme replacement if lactase deficiency is suspected or intolerance is observed by the patient. If dietary calcium intake is low, calcium supplementation should be considered (283).

Hypersensitivity to lactose (lactose intolerance) results from primary or secondary deficient hydrolysis of lactose in the small intestine by the brush border enzyme lactase phlorizin hydrolase. The population proportion of people who are homozygous for the primary or adult onset of lactase deficiency varies from less than 10% in white Northern Europeans to >80 to 90% in regions of Asia and Africa**.** Several studies in different populations showed that the primary genetic form of lactose intolerance occurs in the similar frequencies as in the respective control population with the same ethnic background (healthy controls and non-IBD relatives).

Secondary lactose intolerance with lactase deficiency is due to multiple causes resulting in damage of the microvilli of the intestinal mucosa (e.g. inflammation, ulceration, bacterial overgrowth) or reduction of the intestinal surface (resection). A few recent studies in children (284, 285) have shown that IBD patients, particularly with small bowel CD, are more frequently lactose intolerant compared to healthy controls, when assessed by breath testing, symptoms and measurement of brush border enzyme activity. Risk of vitamin D deficiency and low Ca intake with negative impact on bone health has to be taken into account.

Diet low in fermentable oligo-, di- and mono-saccharides and polyol (FODMAPs)

Statement:

- A low FODMAPs diet should not be recommended for induction to remission in children/adolescent with IBD (EL 5).

Practice points

- A strict low FODMAP diet is highly restrictive
- It may improve IBS symptoms for patients without evidence of inflammation. However, it may decrease diversity and induce dysbiosis.
- FODMAP diet may be responsible for nutrient deficiencies (Ca, Folate, Thiamin, Vitamin B6) and cannot be maintained for a long period of time. Dietary counselling is strongly advised.

Mono, Di- and polysaccharides and polyols are poorly absorbed resulting in increased intestinal permeability and increased functional symptoms (abdominal pain, diarrhoea and bloating) in

patients with IBD (286). A few open non-blinded pilot studies improved functional gastrointestinal symptoms in adult IBD patients (287, 288). No paediatric data are available. The diet is low in fiber serving as prebiotics, with potential negative effects on the microbiome and metabolome (289) and a risk of nutrient deficiencies.

Crohn's disease exclusion diet (CDED)

Statement:

- A CDED cannot be recommended as induction therapy due to insufficient evidence (EL 4)

Practice points

- More evidence on the benefit and safety of CDED from RCTs is needed before such a dietary treatment can be recommended to paediatric IBD patients.

The diet is based on exclusion of multiple dietary components (290), and was evaluated for induction of remission in 34 children and 13 adults with mild to moderate CD. The investigators used the diet in conjunction with 50% of caloric intake from one of two polymeric formulas. Remission by week 6 was achieved in 70% of patient, with significant drop in CRP and ESR at both week 6 and week 12, with normalization of CRP in 70% of those entering remission (222). Fifteen patients in remission at week 6, continued dietary restriction and performed a follow up evaluation for mucosal healing, 11/15 achieved complete mucosal healing. This diet is currently being evaluated in a multinational multi-center randomized controlled trial.

Other restrictive diets

Several other diets have been suggested for treatment of active CD or UC including the Paleolithic diet, a vegan diet, a gluten free diet, a diet based on IgG4 testing against foods with excluding foods with high titers (278). In the latter diet the most common foods excluded were milk, beef, pork and egg. The authors reported an improvement in the symptom score compared to a control group on a sham elimination diet, however there was no significant improvement in faecal calprotectin or CRP (291). None of these diets should be recommended to children and adolescents with IBD at present.

7. DIETARY COMPOUNDS AND THE RISK OF IBD

Definition

Dietary compounds with proven effect on the intestinal barrier function directly or indirectly via the modification of the intestinal microbiota potentially implicated in triggering inflammatory or immune-mediated responses leading to IBD

Practice points:

- Avoidance of "westernized" food (high fat, high protein, high sugar, low in fruit and vegetables) identified in epidemiological studies as risk factor for the development of IBD might be considered
- Avoidance of high fat diet (including saturated milk fats) in patients with IBD might be considered

- Avoidance of food or beverages containing large amounts of emulsifiers (i.e. sauces, fast foods, margarines, ice-creams) might be considered

The complex interaction of diet with the host's immune system (directly or indirectly via intestinal microbiota) is a key part in the development of chronic inflammation, the hallmark of IBD. When considering IBD and diet, there are two different aspects: 1) to identify pre-illness dietary patterns/habits that confer a risk to develop IBD in susceptible individuals 2) to identify alimentary factors that impact on the inflammatory state of patients. However, epidemiological or cohort data indicating specific dietary elements as risk factors for developing IBD are often used as indirect evidence to recommend specific nutritional interventions to treat IBD.

Several epidemiological studies discuss a positive correlation between western life style (western diet with high amounts of unsaturated fatty acids, of proteins, a high sugar loads and low vegetables and fruits intake) and the risk of developing IBD (292) (293): A paediatric study confirmed recently a profound imbalance in fat, vegetables and fruits consumption and the development of CD favouring this hypothesis (294). This is in line with adult data from Japan (295, 296) or UK (297) indicating that an increased consumption of trans-unsaturated fatty acids increases the risk of developing UC. However, a prospective cohort study from France failed to show any effect of fat or sugar intake, but the same study identified high protein intake (animal and fish proteins) as positively correlated to the risk of developing IBD (both CD or UC) (298), in keeping with the results of Shoda et al (295) who previously identified a weak positive correlation between high animal and fish protein intake and the risk to develop IBD. Increased dietary fiber intake has been associated with a lower risk of developing CD, but not UC (299). Recently, the results from EPIC study confirmed that high consumption of sugar and soft drinks and low consumption of vegetables are associated with adult UC risk (300).

Important experimental data support the hypothesis that food additives, such as emulsifiers or food thickeners (carboxymethyl cellulose (CMC), carrageenan, polysorbate (P)-60 or P-80, xanthan gum) can have detrimental effects on intestinal homeostasis. In vitro, as well as in vivo analyses with CMC or P60 or P80 revealed that these emulsifiers alter the mucosal epithelial barrier directly or via a change of the intestinal microbiota biodiversity. They can modify the mucosa-adherent biofilm and the conditions for adhesion and translocation of mucosal bacteria. Chassaing et al. (301) recently confirmed in an experimental model that two commonly used emulsifiers CMC and P80 create low-grade inflammation in WT and in genetically susceptible animals severe colitis, completing previous experimental work (302, 303). It is important to note that western diet (fast food and sweet beverages) is rich in emulsifiers. Roberts and colleagues (304) highlighted recently that they observed a clear correlation between annual emulsifier consumption (in food and beverages) and the incidence of IBD, in line with previous studies (293). In the same line, high margarine (rich in emulsifying agents and hydrogenated fats) was identified by independent studies as being positively correlated with the development of UC and in some studies with CD (305, 306).

DISCLAIMER

ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians.

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Table 1. Estimated Energy Requirements

Male and female 4-18 years	**% of total calories per day**	**RDA/AI**
Protein	10-30%	**Varies on the basis of age and gender**
Carbohydrate	45-60%	ND
Fat	40% 6-12 months 35-40% 1-3 yrs 20-25% >4 years	ND

Based on the following European Food Security authority (EFSA) recommendations:

1-https://www.efsa.europa.eu/it/efsajournal/pub/2557

2-https://www.efsa.europa.eu/it/efsajournal/pub/1462

3-https://www.efsa.europa.eu/it/efsajournal/pub/1461

Table 2. Exclusion diets and related risks in Inflammatory Bowel Disease

Exclusion diets	Not allowed foods	Risk*
Ovo-lacto-vegetarian	Meat, Fish	None
Lactose free (reduced)	Animal milk /products high in lactose	None, if dairy products low in lactose are not avoided
Vegan	All foods from animals	Low vitamin A, B12, D, Zinc, low protein intake
Paleolithic diet	Potatoes, legumes, cereal grain, domesticated meat, all dairy products, juices, soft drinks, refined sugar	Increased fats intake Hypocalcemia
Spec. carbohydrate diet	Mono-, disaccharides, potatoes, Yams, legumes, canned products, cereal grains, milks, sweets, margarine, beer	Reduced caloric intake, B and D Hypovitaminosis, hypocalcemia and hyposideremia
Low FODMAP diet	Mono-, di- oligosaccharides, fiber, wheat, rye, many fruits and vegetables, milk	If long-term, reduction of Calcium, Folate, Thiamin, Vitamin B6
CD exclusion diet (50% polymeric formula)	Dairy products except the allowed formula, margarine, gluten, processed and smoked meat and fish, canned products, yeast, soy, potato or corn flours, soft drinks, fruit juices, alcoholic beverages, coffee, chocolates, cakes, cookies, gums. .	None
IgG4 based exclusion	Individual, mostly dairy, egg, pork, beef	Depending on the excluded foods

*Possible nutritional risks in children undergoing diets without nutritional advise.