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ESPEN Guideline

ESPEN guideline on Clinical Nutrition in inflammatory bowel disease

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SUMMARY

The present guideline is an update and extension of the ESPEN scientific guideline on Clinical Nutrition in Inflammatory Bowel Disease published first in 2017. The guideline has been rearranged according to the ESPEN practical guideline on Clinical Nutrition in Inflammatory Bowel Disease published in 2020. All recommendations have been checked and, if needed, revised based on new literature, before they underwent the ESPEN consensus procedure. Moreover, a new chapter on microbiota modulation as a new option in IBD treatment has been added. The number of recommendations has been increased to 71 recommendations in the guideline update. The guideline is aimed at professionals working in clinical practice, either in hospitals or in outpatient medicine, and treating patients with IBD. General aspects of care in patients with IBD, and specific aspects during active disease and in remission are addressed. All recommendations are equipped with evidence grades, consensus rates, short commentaries and links to cited literature.

1. Introduction

Inflammatory bowel disease (IBD), predominantly ulcerative colitis (UC) and Crohn's disease (CD), is now common in the entire developed world.

Malnutrition can occur as well in UC and CD, but is a considerably greater problem in CD given its capacity to affect any part of the gastrointestinal tract, unlike UC, which is restricted to the colon and has few direct malabsorptive effects [1]. As in adults, malnutrition is prevalent in pediatric IBD, mainly in active disease and more in CD than in UC. In both UC and CD malnutrition may be the result of reduced oral intake, increased nutrient requirements, increased

Abbreviations: 5-ASA, 5-aminosalicylic acid; BMI, body mass index; CD, Crohn's disease; EN, enteral nutrition; FMT, fecal microbiota transplantation; FODMAP, fermentable oligo-di- and monosaccharides and polyols; IBD, inflammatory bowel disease; ONS, oral nutritional supplements; PN, parenteral nutrition; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; SIBO, small intestinal bacterial overgrowth; UC, ulcerative colitis.

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gastrointestinal losses of nutrients, and occasionally from drug–nutrient interactions [1]. The severity of malnutrition in IBD is influenced by the activity, duration and extent of the disease, and particularly to the magnitude of the inflammatory response which drives catabolism and is anorexigenic. Patients with CD remain at risk even when their disease appears quiescent, whereas patients with UC generally develop problems only when the disease is active [2]. Since patients with IBD constitute a high-risk population for malnutrition, they need screening for malnutrition, with its subsequent assessment and management. Nutritional care is clearly important in the treatment of patients with IBD and includes prevention of malnutrition and micronutrient deficiencies, prevention of osteoporosis, and, in children promotion of optimal growth and development. Nutritional care is clearly important in the treatment of patients with IBD and includes prevention of the treatment of malnutrition and micronutrient deficiencies, prevention of osteoporosis, and, in children promotion of optimal growth and development [3–7].

Obesity has not been associated with IBD in the past. However, this changes now, since the obesity epidemic does not stop in the IBD population and, even more important, obesity might worsen the outcome of IBD, as suggested by some recent publications. Obesity at diagnosis was more common in subjects with CD versus UC and increasing degrees of obesity were associated with increased risk [8]. Low BMI at diagnosis was also associated with risk of CD versus UC resulting in a U-shaped relationship between BMI and risk of CD [8]. A more recent publication found that obesity is associated with decreased rates of disease remission and increased risk of complicated disease course in CD over a six-year follow-up period. No effects were seen on disease progression and index treatment failure neither in CD nor UC [9]. These findings are based on a cohort of 3075 patients, the prospective Swiss inflammatory bowel disease cohort, in which 325 patients (10.6%) were obese, namely, 194 CD patients, 131 UC, and inflammatory bowel disease-unclassified patients. Disease activity scores were elevated in obese CD, but not UC patients. Moreover, obese CD, but not UC patients were less likely to be in remission. In a multivariate regression model, obesity was negatively associated with disease remission in CD (odds ratio 0.610, 95% confidence interval 0.402–0.926, $p = 0.020$), but not UC [9].

The gut microbiota is a new topic also in IBD and has been now included in the present guideline update (chapter 8). Although a close link between the gut microbiota and its metabolites on the one side and the pathogenesis of IBD on the other [10,11], recommendations for clinical practice cannot easily be deduced from such knowledge [12], Nevertheless, recommendations about the usage of probiotics, prebiotics and antibiotics as well as fecal microbiota transplantation (FMT) are presented in the present guideline update – however, currently mostly negative recommendations.

2. Methods

2.1. General methodology

The present guideline was developed according to the standard operating procedure for ESPEN guidelines [13]. The guideline is an updated version of the "ESPEN guideline: Clinical nutrition in inflammatory bowel disease" that was developed in 2016 by Forbes et al. [14]. The present guideline update was developed by an expert group representing different professions including dietitians (DVB, NW), nurses (PB), pediatricians (JE, RS), physicians (SCB, AF, XH, CLH, FJ, ZK, JO, SS, KS), and surgeons (SK, AW).

Following the standard operating procedures for ESPEN guidelines and consensus papers, the first development step of this guideline was to check the 2016 PICO questions check for further applicability and extension. PICO questions are designed to address specific **p**atient groups (or **p**roblems), **i**nterventions, **c**ompare different therapies, and be **o**utcome-related [13]. In total, the 2022 guideline update consists of 28 PICO questions divided into seven main chapters entitled "prevention of IBD", "general aspects of nutrition in IBD", "dietetic recommendations in active disease", "medical nutrition therapy in active IBD", "surgical aspects of nutrition in IBD", "microbiota modulation", and "dietetic and other recommendations specific for the remission phase". To answer these PICO questions, a literature search that covered the period since the last guideline was performed to identify suitable meta-analyses, systematic reviews, and primary studies (for details see below, "search strategy"). Each PICO question was allocated to subgroups/experts for the different topics and, initially, 85 recommendations answering the PICO questions were formulated. The grading system of the Scottish Intercollegiate Guidelines Network (SIGN) [15] was used to grade the literature. The allocation of studies to the different levels of evidence is shown in Table 1. Supporting the recommendations, the working group added commentaries to explain their basis.

The grades of recommendation were decided according to the levels of evidence assigned (Table 2). In some cases, a downgrading from the generated grades of recommendation was necessary based on the levels of evidence according to Tables 1 and 2, e. g. due to a lack of quality of primary studies included in a meta-analysis. Such cases are described in the commentaries accompanying the respective recommendations. The wording of the recommendations reflects the grades of recommendations since level A is indicated by the use of the word "shall", level B by the word "should" and level 0 by the word "can" or "may". The good practice points

Table 1
Definition of levels of evidence.

1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

According to the Scottish Intercollegiate Guidelines Network (SIGN) grading system [15]. RCT, randomized controlled trial.

Table 2
Definition of grades of recommendation [13].

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points/expert consensus: Recommended best practice based on the clinical experience of the guideline development group

Table 3
Classification of the strength of consensus.

Strong consensus	Agreement of >90% of the participants
Consensus	Agreement of >75–90% of the participants
Majority agreement	Agreement of >50–75% of the participants
No consensus	Agreement of <50% of the participants

According to the AWMF methodology [16].

(GPP) are based on experts' opinions due to the lack of studies, for which the choice of wording was not restricted.

Between 29th March and 19th April 2022, an online voting (Delphi round) on the recommendations was performed using the guideline-services.com platform. All ESPEN members were invited to agree or disagree with the recommendations and to provide comments. A first draft of the guideline was also made available to the participants on that occasion. Seventy-three recommendations reached an agreement >90%, 12 recommendations reached an agreement of >75–90%, and one recommendation an agreement <75%. Those recommendations with an agreement higher than 90% (indicating a strong consensus, see Table 3) were directly passed, and all others were revised according to the comments and voted on again during a consensus conference that took place online on 25th April 2022. Seven recommendations that originally had received more than 90% agreement were also voted on during the consensus conference due to major changes in wording. During the consensus conference, six recommendations were deleted, recommendations were also merged, and one recommendation was transformed into a statement resulting in an additional reduction of eight recommendations. Therefore, the final guideline comprises 71 recommendations. At the consensus conference, all recommendations but five received an agreement higher than 90%. To support the recommendations and the assigned grades of recommendation, the ESPEN guideline office created evidence tables of relevant meta-analyses, systematic reviews (randomized) controlled trials, and cohort studies. These evidence tables are available online as supplemental material to this guideline.

2.2. Search strategy

The literature search was conducted by the working group members between October and December 2021 with an update search shortly before the Delphi round in March 2022. The search strategies used are available online as supplemental material to this guideline.

3. Prevention of IBD

Are there any specific dietetic recommendations, because diet promotes IBD or protects against IBD?

Recommendation 1.

A diet rich in fruit and vegetables, rich in n-3 fatty acids, and low in n-6 fatty acids is associated with a decreased risk of developing IBD and is therefore recommended.

Grade of recommendation 0 – Strong consensus 96% agreement.

Commentary.

Smoking, antibiotic use, and diet are potentially reversible risk factors for IBD. Many studies have evaluated the effect of diet on the risk of developing IBD. However, most of them are retrospective case–control studies. In 2011 Hou et al. published the first systematic review entitled "Dietary Intake and Risk of Developing IBD" [17]. They used guideline-recommended methodology to evaluate the association between pre-illness intake of nutrients (fats, carbohydrates, protein) and food groups (fruits, vegetables, meats) and the risk of subsequent IBD diagnosis. Nineteen studies were included, encompassing 2609 patients with IBD (1269 with CD and 1340 with UC), and over 4000 controls. The main results are: (i) increased risk of developing UC and CD with high intake of polyunsaturated fatty acids (PUFAs), n-6 fatty acids, and meats, (ii) decreased risk of CD, but not UC, with high intake of dietary fiber (>22 g/d) and fruits.

Fiber, fruit, and vegetables [18]: Compared to women with the lowest energy-adjusted fiber intake, intake of fiber in the highest quintile (median 24 g/d) was associated with a significant reduction in risk of CD [HR 0.59, 95% CI 0.39–0.90] but not UC. In a meta-analysis including a total of 14 case–control studies [1], consumption of vegetables was negatively associated with the risk of UC (OR = 0.71), but not with CD (OR = 0.66). Higher consumption of fruit was negatively associated with the risk of UC (OR = 0.69) and CD (OR = 0.57).

Dietary fat [2]: Cumulative energy-adjusted intake of total fat, saturated fats, unsaturated fats, n-6, and n-3 PUFA were not associated with risk of CD or UC. However, greater intake of long-chain n-3 PUFA was associated with a trend toward a lower risk of UC (HR 0.72). In contrast, a high long-term intake of trans-unsaturated fatty acids was associated with a trend towards an increased incidence of UC (HR 1.34).

In the EPIC study, 229,702 participants were recruited from nine European centers between 1991 and 1998 [3]. At recruitment, dietary intakes of docosahexaenoic acid and fatty acids were measured using validated food frequency questionnaires. In a nested case–control analysis, each participant who developed incident UC (n = 126) was matched with four controls. The highest quartile of intake of linoleic acid was associated with an increased risk of UC (OR 2.49) with a significant trend across quartiles (OR 1.32 per quartile increase).

Apart from this recommendation, there are no other nutritional concepts proven to protect against IBD.

Recommendation 2.

Ultra-processed food and dietary emulsifiers such as carboxymethylcellulose could be associated with an increased risk of IBD and, therefore, generally, such exclusions can be recommended.

Grade of recommendation 0 –Strong consensus 100% agreement.

Commentary.

Recent pilot studies suggest that processed food and especially ultra-processed food might be a risk factor for the development of IBD [19,20]. The International Organization for the Study of Inflammatory Bowel Diseases, therefore, recommends decreasing ultra-processed food in patients with IBD [21].

The pro-inflammatory effect of carboxymethyl cellulose has been demonstrated in preclinical studies and recently in healthy subjects [22]. Although the data seem preliminary, a cautious recommendation of avoidance seems to be justified, especially since only a few dietetic recommendations can be made for IBD prevention.

Should breastfeeding be recommended, because it protects against IBD?

Recommendation 3.

Breastfeeding should be recommended because it is the optimal food for infants and it reduces the risk of IBD.

Grade of recommendation B – Strong consensus 96% agreement.

Commentary.

Systematic reviews from 2004 to 2009 concluded strongly in favor of breastfeeding [4,5] and subsequent studies have reinforced this interpretation. A case–control study from New Zealand

reported that breastfeeding was protective against IBD (CD OR 0.55 95% CI 0.41–0.74, UC OR 0.71 95% CI 0.52–0.96) with a duration-response effect [6]. Comparable data were reported from a Danish cohort study, in which breastfeeding for more than six months decreased the odds of IBD (OR 0.50, 95% CI 0.23–1.11) [7]. Two further publications confirmed this relationship, one from the US and another from Asia-Pacific [23,24]. Breastfeeding for around six months or longer is desirable in all infants [25].

4. General aspects of nutrition in IBD

What is the risk of malnutrition in IBD; what are the consequences?

Recommendation 4.

Patients with IBD are at risk and therefore should be screened for malnutrition at the time of diagnosis and thereafter on a regular basis.

Grade of recommendation GPP – Strong consensus 100% agreement.

Recommendation 5.

Documented malnutrition in patients with IBD should be treated appropriately because malnutrition worsens the prognosis, complication rates, mortality, and quality of life.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary for 4 and 5.

Adults with IBD are at increased risk of malnutrition, with deficits more common in patients with CD than with UC [26,27]. This reflects the poor dietary composition and food avoidance before diagnosis, but also in follow-up [28–30], albeit at a lower frequency [31]. The risk of malnutrition can be assessed with validated screening tools [32,33].

Patients with obesity (who now represent up to one-fifth of patients with IBD [34]) may have covert deficits in lean body mass which may be unmasked by assessment of body composition. Patients with obesity may therefore be at increased risk (for example readmission after an exacerbation [35]), despite a possible protective effect more generally [36,37].

Patients with active IBD, particularly those whose disease is poorly responsive to medical therapy, and those embarking on surgery are at the highest risk of poor nutrition [38].

Malnourished patients with IBD are more likely to have exacerbations of the IBD itself [39,40], are more likely to be admitted to hospital [41,42], and more likely to suffer severe infection [43]. In hospitalized patients, malnutrition is an independent risk factor for venous thromboembolism [44], non-elective surgery [42,45], longer duration of admission (generally and after surgery) [26,45] for more numerous and more severe postoperative complications [46,47], and increased mortality [26,48].

Malnutrition in childhood CD is common at diagnosis and may persist despite treatment of the disease [49–51]. Children with UC are also at risk of poor nutrition, but nutritional deficits may not be immediately obvious from basic anthropometric data [52]. Although a variety of screening tools exists, the tools are not good at discerning different levels of nutrition risk in children with IBD [53]. Poor nutrition in childhood IBD contributes to disrupted pubertal development and impaired growth velocity which may lead to short stature in adulthood. Growth failure is thus of particular importance in pediatric IBD, reflecting the combination of inflammation and chronic malnutrition [54]. As in adults, malnutrition may contribute to a higher risk of exacerbations [55], postoperative complications [56], and prolonged length of stay [57]. Obesity in childhood IBD appears a more adverse factor than in adults [40].

Do patients with IBD have altered energy requirements?

Recommendation 6.

In general, energy delivery should be 30–35 kcal/kg/day, since the energy requirements of patients with IBD are similar to those of the healthy population. If there is a clinical suspicion of a different energy requirement in particular disease states, individual energy requirements should be determined using indirect calorimetry and an individual physical activity factor.

Grade of recommendation GPP – Strong consensus 95% agreement.

Commentary.

Although energy requirements of patients with IBD are mostly similar to those of the healthy population, particular disease states such as hypermetabolism, of acute inflammation may increase energy demands, especially in UC, while patients with active CD and catabolism have a reduced resting energy expenditure. Even if the resting energy expenditure is increased, its contribution to the total energy expenditure is often offset by a concurrent reduction in physical activity. Similar (and perhaps stronger) observations apply to children and adolescents. Energy should be provided accordingly.

Ulcerative colitis: There are relatively few studies examining energy expenditure in patients with UC, and none of them includes a large number of patients. In general, there do not appear to be major differences in overall energy expenditure compared to control populations. Although increased catabolism is an inevitable consequence of acute inflammation, it is frequently offset by decreased physical activity resulting in “normal” total energy expenditure. There may however be an increase in total energy expenditure in patients with acute UC and acute severe UC when compared to the total energy expenditure in remission and adult controls [58–60]. Significant reduction in dietary intake is common in acute severe UC and important negative energy balance may result [61].

Crohn's disease: There are now several reasonably robust studies of energy expenditure in adults with CD. The results are not fully concordant. Measured resting energy expenditure per kilogram in adult patients has been found similar to [62] or a little higher than [63,64] in healthy controls, remaining the case with correction for fat-free mass [64]. However, other studies show an inverse correlation between resting energy expenditure and CD activity index, the energy expenditure falling with increasing severity of inflammation [65,66]. Although total energy expenditure has been said to be normal and unaffected by CD activity [67], this now seems less likely given the modest or absent increase in resting energy expenditure and a typical reduction in physical activity at times of illness.

Children: In children with IBD, total energy expenditure appears to be lower than in healthy controls [68]. The probable reduction in resting energy expenditure seen in adults with CD seems more prominent in children and adolescents [68] and does not appear greatly influenced by levels of disease activity [69].

Energy prescription: The use of indirect calorimetry to measure resting energy expenditure is recommended for all difficult cases, but this must be supplemented by a concomitant assessment of physical activity to judge the likely total energy expenditure when determining the energy prescription.

Do patients with IBD have altered protein requirements?

Recommendation 7.

Protein requirements are increased in active IBD, and intake should be increased (to 1.2–1.5 g/kg/d in adults) relative to that recommended in the general population.

Grade of recommendation GPP – Strong consensus 96% agreement.

Recommendation 8.

The protein requirements in remission are generally not elevated and provision should be similar (about 1 g/kg/d in adults) to that recommended for the general population.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary for 7 and 8.

A significant percentage of all patients with IBD develop a reduction in lean mass, and patients with CD are more prone to it. An increase in obesity over time is a new reality and sarcopenic obesity has become a challenge [70–72]. This may occur due to chronically poor or unbalanced dietary intake, increased rates of protein turnover, and gut loss of nutrients during phases of active disease with consequent malabsorption or from the effect of disease treatments [73,74]. Corticosteroids increase the net loss of protein in children [75] and adults [76] with CD. In contrast, the administration of elemental or polymeric feed as treatment of CD or as adjunctive nutrition support results in the reduction of proteolysis and acquisition of lean tissue in children and adults [77–80].

The postsurgical situation in CD can become an issue because of several reasons leading to different types of intestinal failure [81,82]. Monitoring of anthropometry or bioelectrical impedance analysis provides insight into which patients develop relative deficits in lean mass and therefore would benefit from nutritional supplementation [83].

There is no high-quality evidence that the daily protein needs of patients with IBD differ from those of healthy controls, but as discussed elsewhere, poor appetite and restricted dietary intake are commonplace [84]. In patients receiving steroids and/or with dietary restrictions or gut rest, enteral nutrition (EN) may provide beneficial effects on protein turnover without deleterious consequences on disease activity. There is no good evidence that the daily protein needs of patients with IBD in remission differ from those of healthy controls. The provision of 1 g protein for each kilogram of body weight is therefore reasonable. However, in active inflammation, the proteolytic, catabolic response justifies an increase in provision to 1.2–1.5 g/kg body weight [85,86].

Do patients with IBD have an altered micronutrient requirement?

Recommendation 9.

Patients with IBD should be checked for micronutrient deficiencies regularly, including in the remission phase, and specific deficits should be appropriately corrected.

Grade of recommendation GPP – Strong consensus 95% agreement.

Commentary.

Patients with IBD are vulnerable to micronutrient deficits due to gut loss from diarrhea, malabsorption, intestinal failure, and inadequate dietary intake from anorexia accompanying disease activity. Therefore, they should be checked for micronutrient deficiencies regularly, at least once per year, on a clinical level as well by laboratory measurements, when appropriate and available. When interpreting blood results of micronutrients and trace elements it is important to consider that many serum values, or markers of status, are positive or negative acute phase reactants. The reliability of the plasma micronutrient levels measurement in the presence of systemic inflammation remains questionable [87]. Serum levels rise or fall, as part of the inflammatory response, for example, ferritin, and copper increase but folate, selenium, and zinc decrease in inflammation [88,89]. In light of this, some authors have examined micronutrient status in patients in clinical disease remission and found deficits in a variety of micronutrients [90]. Furthermore, deficits may be present even in apparently well-nourished individuals [91]. A daily multivitamin supplement may correct most deficiencies but is no guarantee of adequacy, even over the long term; iron, zinc, and vitamin D are likely to require specific replacement regimens [92]. Cacoub et al. suggested a common definition of iron deficiency for patients with chronic inflammatory conditions to provide better monitoring and therapeutic approach [93]. Santucci et al. noted that 37% of patients with zinc proven deficiency remained deficient and 15% had developed a new zinc deficiency despite supplementation [92]. Some of the macronutrients like zinc are suggested as a potential predictor of the disease course [90]. Poor compliance, particularly in adolescents, is common with multivitamin supplements and patient education about the rationale behind their use is important [94]. The micronutrient plasma concentrations improved during EN therapy, but carotenoid concentrations decreased significantly [95]. These observations highlight the need for routine monitoring (perhaps annually) to screen for micronutrient deficiency despite limitations [96]. At times when nutrition support is offered then multivitamin and micronutrient supplements should also be offered to ensure an appropriately balanced nutritional intake and avoid the risk of refeeding syndrome [97]. Recent research has focused on vitamin D; it and its receptor may have some immunomodulatory properties, which further highlights the need for specific attention to micronutrient status in patients with IBD [98].

Is iron supplementation needed in IBD?

Recommendation 10.

Iron supplementation should be recommended in all patients with IBD when iron deficiency anemia is present. The goal of iron supplementation is to correct anemia and normalize iron stores.

Grade of recommendation B – Strong consensus 96% agreement.

Recommendation 11.

Oral iron should be considered as first-line treatment in patients with iron deficiency or mild anemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron.

Grade of recommendation B – Strong consensus 91% agreement.

Recommendation 12.

Intravenous iron should be considered as first-line treatment in patients with clinically active IBD, those with previous intolerance to oral iron, those with hemoglobin below 100 g/L, and patients who need erythropoiesis-stimulating agents.

Grade of recommendation B – Strong consensus 96% agreement.

Commentary for 10 to 12.

Anemia is considered the most frequent extraintestinal manifestation of IBD, usually complicating the course both in UC and CD. All patients with IBD regardless of their age should be assessed for low ferritin levels, reduced transferrin saturation, and the presence of anemia [99]. The major forms of anemia in IBD are iron deficiency anemia, anemia of chronic disease, and anemia of mixed origin [ECCO Anemia Statement 1A] [99]. Diagnostic criteria for iron deficiency depend on the level of inflammation. For laboratory screening, complete blood count, serum ferritin, and C-reactive protein should be used [ECCO Anemia Statement 1B]. For patients

in remission or with mild disease, measurements should be performed every six to 12 months. In outpatients with active disease such measurements should be performed at least every three months [ECCO Anemia Statement 1B]. In patients without clinical, endoscopic, or biochemical evidence of active disease, serum ferritin <30 μg/L is an appropriate criterion for the diagnosis of iron deficiency anemia. In the presence of inflammation, a serum ferritin up to 100 μg/L may still be consistent with iron deficiency [ECCO Anemia Statement 1D]. In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for anemia of chronic disease are a serum ferritin >100 μg/L and transferrin saturation <20%. If the serum ferritin level is between 30 and 100 μg/L, a combination of true iron deficiency and anemia of chronic disease is likely [ECCO Anemia Statement 1E].

Iron supplementation is recommended in all patients with IBD, whatever their age when iron-deficiency anemia is present [ECCO Anemia Statement 2A], [100]. Quality of life improves with the correction of anemia, and this improvement is independent of clinical activity [101]. The European Crohn's and Colitis Organization (ECCO) guidelines [99] conclude that "intravenous iron is more effective, show a faster response, and is better tolerated than oral iron" and state that "intravenous iron should be considered as first-line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with hemoglobin below 100 g/L, and in patients who need erythropoiesis-stimulating agents; while oral iron may be used in patients with mild anemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron [99]. The estimation of iron need is usually based on baseline hemoglobin and body weight (Table 4) [102].

After successful treatment of iron deficiency anemia with intravenous iron, re-treatment with intravenous iron should be initiated as soon as serum ferritin drops below 100 μg/L or hemoglobin below 120 or 130 g/L according to gender [ECCO Anemia Statement 3E].

What is the role of dietitians and nurses for patients with IBD?

Recommendation 13.

All patients with IBD should undergo individual counseling by a dietitian as part of the multidisciplinary approach to improve nutritional therapy and avoid malnutrition and nutrition-related disorders.

Grade of recommendation GPP – Strong consensus 95% agreement.

Commentary.

There are very limited original data in this area, but there are several papers and guidelines that include statements indicating that the input of a dietitian is likely to be helpful in IBD management in adults and children. A multidisciplinary team that includes a dietitian should provide individualized dietary recommendations for each IBD patient while taking into consideration all of the patients' clinical aspects [103]. Nutritional deficiencies are more likely to develop in patients with CD affecting the small bowel than in those with isolated colonic disease or UC, but the latter groups can be affected also [104]. Nutritional screening and long-term monitoring have been adopted as a mandatory component of gastrointestinal management in many European countries, and it is further recommended that all patients with IBD have access to a dietitian with special expertise in IBD [84]. Nevertheless, self-induced elimination diets may be detrimental for patients in remission, therefore dietitian guidance should be advised [105].

Table 4
Simple scheme for estimation of total iron need [96].

Hemoglobin g/L	Body weight <70 kg	Body weight ≥70 kg
100-120 (women)	1000 mg	1500 mg
100-130 (men)	1000 mg	1500 mg
70–100	1500 mg	2000 mg

Recommendation 14.

As part of a multidisciplinary IBD team, nurses play a key role. This should include contributions to nutritional screening and dietary management.

Grade of recommendation GPP –Strong consensus 100% agreement.

Commentary.

There is only sparse evidence for the nurses' role concerning nutrition in IBD. However, the multidisciplinary approach is highlighted in several consensus statements and guidelines [83,105–107]. Nurses often have the primary contact with patients and will therefore naturally assess symptoms such as pain, fatigue, or unintentional weight loss. They could all be linked to nutritional problems. Nurses can explore the symptoms and refer to others in the multidisciplinary team if needed. Nurses will also often focus on adherence to treatment and/or nutrition plans [108]. It is evident that patients with IBD increasingly use alternative and complementary therapies (including nutritional components) for which appropriate evidence is lacking [109]. Nurses will be in a position to identify this and qualify the evidence, if possible. Furthermore, nurses will often see patients in special situations that need nutritional attention. These could be patients with stomas, patients who plan to travel, patients who are pregnant, elderly patients, patients with co-morbidity, or patients who will undergo surgery [106].

5. Dietetic recommendations in active disease

Should patients with IBD with active disease adhere to a specific diet?

Recommendation 15.

There is no "IBD diet" that can be generally recommended to promote remission in patients with IBD with active disease.

Grade of recommendation GPP – Strong consensus 91% agreement.

Commentary.

Diet studies in IBD aiming to induce remission, are mainly performed with EN or elemental diets. One small study compared a diet with ordinary foods (CD-TREAT), replicated from and comparable with exclusive EN in healthy adults, demonstrated similar microbiome changes and decreases gut inflammation and still needs to be studied in patients with active CD [110].

(Pooled) RCT data regarding the effects of experimental diets such as specific carbohydrate, paleolithic, gluten-free, low fermentable oligo-, di- and monosaccharides and polyols (FODMAP), anti-inflammatory diet, carrageenan-free diet, milk-free diet, low or high red meat diet, vegetarian diet and n-3 PUFA enriched diets on intestinal inflammation or on inducing remission are still lacking or give uncertain results at this time. This is also confirmed in the recently published Cochrane review, including 18 RCTs of which six in patients with active CD and one in patients with active UC [111]. A meta-analysis on predefined diets in IBD (10 out of 31 studies) shows a possible trial efficacy in IBD treatment [112]. No single firm conclusion can be drawn regarding the benefits of any dietary intervention in UC as well as in CD, possibly also due to the high heterogeneity of the data and the observed diets.

Therefore, no "oral IBD diet" can be generally recommended to promote remission in patients with IBD with active disease. This recommendation does not preclude the needs of all patients with IBD to receive an individual (nutritional) approach based on their specific personal situation, preferably with the active input of a dedicated dietitian or nutritionist as part of the multidisciplinary approach. However, particular diets can be recommended for IBD subgroups (see recommendations 16 and 17).

Recommendation 16.

CD exclusion diet (plus partial EN) should be considered as an alternative to exclusive EN in pediatric patients with mild to moderate CD to achieve remission.

Grade of recommendation B – Strong consensus 100% agreement.

Recommendation 17.

In adult patients, a CD exclusion diet can be considered with or without EN in mild to moderate active CD.

Grade of recommendation 0 – Strong consensus 95% agreement.

Commentary for 16 and 17.

For many years, there was insufficient evidence (based on only a few uncontrolled studies) to make firm recommendations for exclusion diets as induction therapy in IBD. However, in the past five years, the Crohn's Disease Exclusion Diet (CD exclusion diet; exclusion diet plus partial EN) has been launched based on studies with positive results in pediatric patients with CD. In a 12-week prospective RCT with 78 patients with mild to moderate CD, the CD exclusion diet appeared as effective in inducing rapid clinical response (week 3) as exclusive EN but better tolerated [113,114]. Studies in (young) adults are scarce and are expected [115].

For decades, exclusive EN has been the first-line treatment in pediatric patients with luminal CD. The reintroduction of whole foods after six weeks of treatment can be accompanied by the recurrence of inflammation and gastrointestinal symptoms. CD exclusion diet can be a long-term (nutritional) strategy since it combines (specific) whole foods during therapy combined with partial EN. Data on long-term effectiveness and possible risk of nutritional deficiencies or eating behavior disturbances due to long-term use of exclusion diets are not (yet) available.

Several studies, including an RCT in 96 adult patients, investigated a targeted exclusion diet on serum immunoglobulin (Ig)-G4 antibody titers. Although symptoms improved, no effect was seen on inflammation markers [116]. This lack of evidence is also mentioned in the latest Cochrane review [111]. However, more recent studies not yet included in the Cochrane review have been published in the meantime.

CD exclusion diet with or without partial EN was effective for induction and maintenance of remission in adults with mild-to-moderate biologic naive CD and might lead to endoscopic remission. These data suggest that a CD exclusion diet could be used for mild-to-moderate active CD and should be assessed in a powered RCT [117].

Are there subgroups of patients with CD with particular nutritional needs?

Recommendation 18.

CD can be accompanied by malabsorption or maldigestion, and dietary counseling may consider this.

Grade of recommendation 0 – Strong consensus 95% agreement.

Recommendation 19.

In patients with CD with intestinal strictures or stenosis in combination with obstructive symptoms, a diet with adapted texture, or exclusive EN via a tube ending distal to the obstruction (post-stenosis) can be recommended.

Grade of recommendation 0 – Strong consensus 91% agreement.

Commentary for 18 and 19.

Depending on the severity (degree of obstruction) and site of intestinal strictures, nutritional support may become necessary while the effects of treatment are awaited. Such treatment may be medical (with drugs) where the narrowing is mainly the result of inflammation, or mechanical (by balloon dilatation or surgery) when there is fibrotic scarring. In patients with radiologically identified but asymptomatic stenosis of the intestine, it is conventional to recommend a modified diet that is low in insoluble fiber, but there are no robust data to support this logical approach. When symptoms are present it may be necessary to adapt the diet to one of soft consistency, perhaps predominantly of nutritious fluids.

Intestinal fibrosis is a common feature of CD and may appear as a stricture, stenosis, or intestinal obstruction. Stenosing CD leads to a significantly impaired quality of life in affected patients and constitutes a challenging treatment situation. Food restructuring is higher in stricturing than in non-stricturing CD [118]. A prospective observational study in 59 adult (Chinese) patients with CD with inflammatory bowel strictures showed that 12 weeks of exclusive EN can effectively relieve inflammatory bowel strictures (81.4%) achieved symptomatic remission, 35 patients (53.8%) achieved radiologic remission, and 42 patients (64.6%) achieved clinical remission [119]. This is confirmed by Heerasing in 51 patients with CD requiring urgent surgery for structuring or penetrating complications, who received exclusive EN before surgery. In 25% of the patients, surgery was avoided and it was associated with inflammation reduction and incidence of postoperative complications [120].

Marafini did not find a positive therapeutic effect of a liquid diet in patients with CD with structuring disease concerning new subocclusive episodes [121]. Although it is common practice to recommend a modified diet with adapted consistency perhaps predominantly of nutritious fluids, at least in patients with radiologically identified stenosis of the (proximal) intestine and obstructive symptoms, or to feed distally by EN whenever this is possible, there are no robust data to support these logical approaches.

Recommendation 20.

Patients with IBD (adults and children) with active disease, under treatment with corticosteroids, or with suspected hypovitaminosis D, should be monitored for serum 25(OH) vitamin D status, and if required calcium/vitamin D supplementation should be prescribed for prevention of low bone mineral density. Osteopenia and osteoporosis should be managed according to current osteoporosis guidelines.

Grade of recommendation B – Strong consensus 96% agreement.

Commentary.

Osteoporosis is one of the most common extraintestinal complications in patients with IBD with a well-known role of calcium and vitamin D in the prevention of low bone mineral density. Its etiology is multifactorial and includes diet and a patient's nutritional status. Significant risk factors for low bone mineral density studied in adult IBD populations prove to be low serum vitamin D, male gender, Asian ethnicity, CD, low body mass index (BMI), dietary restrictions and avoiding dairy products, low calcium, and zinc intake, active disease as well as corticosteroid use, whereas no consensus on the role of age, or age at diagnosis was found [122–125]. In children and adolescents with IBD, risk factors associated with low bone mineral density are cumulative corticosteroid dose, height-for-age Z-score, and BMI Z-score [126].

Based on small observational recent studies, there are possible relations between increased bone mineral density in pediatric patients with CD after exclusive EN therapy (n = 18) [127] and with increased physical activity (n = 89) [128]. The positive effect of exclusive EN – partial EN diet on bone mineral density in IBD children was confirmed by the RCT of Lev-Tzion based on an increased serum C-Propeptide of Type I Procollagen (CICP) value, but not on dual-energy X-ray absorptiometry scans [129].

An RCT in 44 pediatric patients with IBD showed that 300,000 IU vitamin D once was as effective and safe compared to 50,000 IU vitamin D for six weeks in case of hypovitaminosis D [130]. Effective vitamin D supplementation in 55 pediatric patients with IBD was also reached with daily 2000 IU vitamin D supplementation during a median of 13.8 months. Besides this was positively associated with (trabecular) bone mineral density [131]. An RCT in adult IBD (65 UC and 59 CD) patients with hypovitaminosis D showed that vitamin D supplementation (150,000 IU/month during three months) is necessary and effective to treat hypovitaminosis D but (in combination with calcium) supplementation did not influence bone mineral density [132].

There is no overall consensus on the vitamin D status and necessary actions in children and adolescents with IBD. An RCT of 132 adult osteopenic patients with CD showed improved bone mineral density at the lumbar spine after two years of a once-weekly treatment course with risedronate 35 mg, concomitant with calcium and vitamin D supplementation [133]. An earlier RCT showed no significant benefit of calcium supplementation (1 g/day) alone on the bone mineral density at one year in corticosteroid-using patients with IBD with osteoporosis [134]. Evaluation for vitamin D deficiency is recommended in IBD and ensuring always an adequate supply of calcium and vitamin D, especially in steroid-treated patients with IBD. Limitation of corticosteroid use helps to prevent low bone mineral density.

Recommendation 21.

Patients with IBD with hyperoxaluria often also have fat malabsorption and these patients should be counseled regarding fat malabsorption.

Grade of recommendation GPP − Strong consensus 91% agreement.

Commentary.

Common causes of malabsorption in IBD are subgroups of patients with 1) intestinal insufficiency or intestinal failure after multiple intestinal resections or as a consequence of short bowel syndrome, 2) bile acid malabsorption after ileal resection or inflammation of the terminal ileum, 3) small intestinal bacterial overgrowth (SIBO), 4) disaccharide deficiency and/or 5) malabsorption due to other gastrointestinal disorders.

1) Chronic intestinal failure is a rare but most critical complication of CD which mandates a multidisciplinary therapeutic approach. In an adult (Danish) population (n = 78) of intestinal failure patients (parenteral nutrition (PN) dependent), 15% was caused by IBD [135]. In a study of 41 patients with CD and short bowel syndrome compared with 36 patients with CD without short bowel syndrome, it seemed that Montreal B1 behavior, IV steroids, and budesonide were predictors of development of short bowel syndrome [136] whereas in a Japanese study in 162 cases cumulative inflammation for the first time, in addition to the short residual small intestinal length and non-use of anti-tumor necrosis factor-α therapy were identified as potential risk factors [137].
2) Decreased reabsorption of conjugated bile acids leads to excess transmission to the colon, where deconjugation by bacteria occurs. Osmotic diarrhea and (in severe bile acid malabsorption) fat malabsorption might be a consequence [138]. If mild, bile acid diarrhea can be controlled by a sequestrant such as cholestyramine [139,140]. In a study cohort of 39 patients with CD who had undergone ileal resection, a response rate of 73% to bile acid sequestrants is reported [141]. In severe cases of bile acid malabsorption, however, steatorrhea may worsen as a result of cholestyramine treatment [142]. Skouras demonstrated a modest correlation between length of ileal resection and severity of bile acid malabsorption in patients with CD (n = 91) [143].
3) Current data on SIBO in patients with IBD are controversial. A systematic review with meta-analysis of 11 studies (with 1175 adult patients with IBD and 407 controls), showed that there is a substantial increase in the prevalence of SIBO in IBD with prior surgery and the presence of fibrostenosing disease as risk factors [144]. SIBO is reported to be present in on third of the patients with CD [145].
4) A lot of patients with IBD skip dairy products from their diets due to gastrointestinal complaints or symptoms suggestive of lactose intolerance. Data on the increased prevalence of lactose intolerance in IBD are controversial. A large retrospective cohort of hospital-admitted Korean patients with IBD (n = 598.129) demonstrated a 2.7 increased risk of lactose intolerance based on ICD-9 codes compared to controls [146]. Whereas a recently published observational study reported a same prevalence of lactose intolerance (lactase deficiency) in patients with IBD (n = 54) compared to controls (n = 69) [147]. Comparative data is published on fructose malabsorption; prevalence among patients with IBD is demonstrated to be equal to healthy controls. But the greater reported and experienced symptoms can be therapeutically relevant [148].
5) Ad Celiac disease is related to small intestinal villous atrophy and therefore related to (usually reversible and transient) malabsorption. A meta-analysis of 27 studies (including 41,482 patients with IBD) showed that celiac disease is a risk factor for IBD and to a lesser degree that patients with IBD have an increased risk of celiac disease [149]. This is confirmed in another systematic review with meta-analysis (including 65 studies) [150].

6. Medical nutrition therapy in active IBD

Is supportive medical nutrition therapy (oral nutritional supplements (ONS), EN, or PN) indicated in patients with IBD?

Recommendation 22.

ONS is the first step when medical nutrition is indicated in IBD, as supportive therapy in addition to normal food.

Grade of recommendation 0 − Strong consensus 92% agreement.

Commentary.

The decision on the optimal route of medical nutrition in IBD can be complex and involve several aspects, including the ability of the patient to eat, the absorptive capacity of the gastrointestinal tract, the nutritional and inflammatory status of the patient, and the therapeutic goals. ONS is the first step but generally is a minor supportive therapy used in addition to normal food [151]. By using ONS, a supplementary intake of up to 600 kcal/d can be achieved without compromising normal food intake in adults [152], and with well-reported observance [153] and acceptability [154]. The effect of EN in CD appears to be similar if the diet is drunk or applied via a tube.

Recommendation 23.

If oral feeding is not sufficient then EN can be considered as supportive therapy. EN using formulas or liquids usually take preference over PN unless it is completely contraindicated.

Grade of recommendation 0 − Strong consensus 96% agreement.

Commentary.

If oral feeding is not possible or insufficient, feeding the patient through a nasogastric or nasoenteric tube should be considered [155–157]. EN should also be considered in patients with a functional gastrointestinal tract but who are unable to swallow safely

[158]. In situations when the gut cannot absorb all nutritional needs, EN should nonetheless be attempted with supplementary PN [159,160].

Is primary medical nutritional therapy (EN or PN) indicated in active IBD?

Recommendation 24.

Exclusive EN is effective and can be recommended as the first line of treatment to induce remission in children and adolescents with mild active CD.

Grade of recommendation 0 – Strong consensus 100% agreement.

Commentary.

Primary nutritional therapy in the form of exclusive EN should be considered in patients with mild active CD. If the pediatric/adolescent patient has perianal fistulising disease or is at high risk of complications (extensive disease, significant growth retardation, deep ulcerations in the colon seen at endoscopy, severe osteoporosis, and stenosis or penetrating disease at diagnosis), current guidelines advise anti-tumor necrosis factor treatment as the first line of treatment [161]. In a recent RCT in new-onset moderate to severe pediatric CD, first-line infliximab was shown to be superior to exclusive EN (or corticosteroids), both as induction treatment and as maintenance treatment [162].

Old meta-analyses demonstrated that corticosteroids are better than exclusive EN in the induction of remission in adults. The argument in favor of exclusive EN is stronger in pediatric practice and will normally be the first choice in many centers. Firstly, this is because of the deleterious effects of undernutrition on growth. Secondly, since growth is so essential in children, this increases the possibility of avoiding the use of steroids or delaying their introduction, which is of paramount importance. Third, and most importantly, is the observed effect on induction of remission in pediatric studies demonstrating similar efficacy of steroids and exclusive EN [163], and that in some settings (i. e. concomitant immunomodulatory treatment) exclusive EN might even be superior to corticosteroids in children [164]. However, these studies suffer from methodological limitations. Recommendations in children are made only for exclusive EN as limited data suggest that partial EN may be less effective [138], though one RCT showed similar efficacy [165]. The data are weaker for adult practice, and most centers will continue to use steroids (or biologicals) as first-line therapy unless these agents are actively contraindicated. However, patient and disease characteristics also contribute to therapeutic management decisions and these may make EN therapy a first-line option also in selected cases of adults with acute CD [166]. EN is preferred because PN has not been shown to offer any advantage in CD and should be used only to improve nutritional status for surgery and when other modes of nutrition are not possible [167].

Exclusive EN is also effective in inducing remission in adults with mild active CD, However, the effects are inferior to drug treatment and therefore it is not recommended as the first line of treatment. This does not exclude the usage of exclusive EN in selected cases of adult patients with CD, e.g. those who do not tolerate drug treatment or who refuse it.

Recommendation 25.

Primary nutritional therapy (EN or PN) should not be recommended in adults or children with UC.

Grade of recommendation B – Strong consensus 92% agreement.

Commentary.

There may be a role for exclusive EN as adjunctive therapy in UC, augmenting corticosteroid responsiveness [168]. A Cochrane review concluded that there is insufficient evidence of the efficacy of nutritional therapy (symptoms-based diets, anti-inflammatory diet, a Carrageenan-free diet, milk-free diet) in active UC [111]. There are no prospective studies in children with UC, but the key mechanisms of the activity of exclusive EN (namely, changes in the intestinal microflora in CD) are likely also relevant to UC. Furthermore, the use of exclusive EN in pediatric patients with UC may add to better bone health [169]. See also recommendations 37 and 38.

Technical aspects of EN in IBD

Recommendation 26.

For EN in IBD, nasal tubes or percutaneous access can be used.

Grade of recommendation 0 – Strong consensus 96% agreement.

Recommendation 27.

Tube feeding in IBD should be preferentially administered via an enteral feeding pump, in particular, if EN is administered via a jejunal and not a gastric tube.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary for 26 and 27.

EN can be safely delivered by nasogastric tube, or percutaneous endoscopic gastrostomy [170–172]. Gastrostomy placement is safe in patients with CD and does not result in an increased incidence of peristomal disease or formation of prolonged gastrocutaneous fistulas after gastrostomy tube removal [173–176]. Continuous EN administered via an enteral feeding pump and increased slowly to the full prescribed volume appears to have lower complication rates than bolus delivery [170–172,177]. The most frequent complications of EN are mechanical (tube-related), then metabolic, and infectious, but these are not notably different from those seen in other chronic conditions [172,177]. Few patients with UC will need EN or PN other than during the most severe exacerbations and in the perioperative phase. EN is most appropriate and associated with significantly fewer complications than PN in acute UC. Bowel rest through PN does not alter the outcome, but there are no specific contraindications for the use of PN in UC. In CD, nutritional support is more often needed. There is no specific contraindication to the use of PN in patients with CD in comparison to other diseases, and a central or peripheral route may be selected according to its expected duration. There are not enough data to dictate the use of specific substrates in the composition of PN in CD. PN must however be adjusted to fulfill the needs of the individual patient. PN, especially at home, should be viewed as complementary non-exclusive nutrition, which can be tapered to a minimal level when body composition has been sufficiently restored.

Selection of formulations of EN in IBD

Recommendation 28.

Standard EN (polymeric diet with moderate fat content) should be employed for primary and supportive nutritional therapy in active IBD.

Grade of recommendation B – Consensus 90% agreement.

Recommendation 29.

Specific formulations or substrates (e.g. glutamine, n-3-fatty acids) should not be recommended in the use of EN or PN in patients with IBD.

Grade of recommendation B – Strong consensus 92% agreement.

Commentary for 28 and 29.

Several studies have compared the efficacies of different types (elemental, semi-elemental, oligomeric, or polymeric diets) of enteral formulas in the management of active CD. A Cochrane meta-analysis of ten trials showed no statistically significant difference

between patients treated with elemental (n = 188), and non-elemental diet (semi-elemental or polymeric diet; n = 146) [178]. A more recent Cochrane meta-analysis of 11 RCTs comparing elemental to non-elemental exclusive EN found similar clinical remission rates between the two groups [179]. Subgroup analysis between elemental, semi-elemental, and polymeric feeds, showed similar efficacy. Similarly, there was no difference in clinical remission rates between low-fat content (<20 g/1000 kcal) and high-fat content EN formulas. However, very low-fat content and very low long-chain triglycerides EN formulas were associated with higher clinical remission rates than those with higher content [180]. This recommendation does not contradict the usage of high medium-chain triglycerides (MCT) formula in selected patients with IBD, e.g. patients with ileal CD and bile salt malabsorption.

The protein composition did not appear to influence the therapeutic potential of EN. The present systematic inquiry reveals insufficient evidence to make firm recommendations [178,181]. It is therefore advised that standard feeds are employed if primary nutritional therapy is being employed.

The use of feeds supplemented with growth factors, ones with lower levels of emulsify-ing data, or oligomeric feeds, as alternatives to standard feeds, is not supported by reliable data. Equally, there is no evidence that any of these alternatives are inferior to the use of standard polymeric feeds [182].

Composition analysis of 61 EN formulations with evidence for efficacy in CD found many contained additives that are implicated in CD onset, including modified starches, carrageenan, carboxymethyl cellulose, and polysorbate 80 [183]. Clinical remission rates from RCTs in the latest Cochrane meta-analysis did not differ between studies utilizing formulations with such additives compared with studies that did not contain such additives [111].

There are not enough data to dictate the use of specific substrates in the composition of PN in CD. PN must however be adjusted to fulfill the needs of the individual patient. A recent systematic review of seven studies where glutamine was administered to the participants through oral (21–30 g or 0.5 g per kg body weight), enteral (7.87 g–8.3 g/100 g of the enteral formula), and/or parenteral (0.3 g/kg body weight) routes did not find any effect on disease course, anthropometric measurements, intestinal permeability and morphology, disease activity, intestinal symptoms, biochemical parameters, oxidative stress and inflammation markers in patients with IBD, regardless of the route of administration, either treated at a hospital or as outpatients [184]. No study of polymeric formulas readily allows assessment of the individual effects of an n-3-rich approach [185].

What is the indication for PN in IBD?

Recommendation 30.

PN shall be performed in IBD (i) when oral nutrition or EN is not sufficiently possible (e.g. when the gastrointestinal tract is dysfunctional or in patients with CD with short bowel), (ii) when there is an obstructed bowel where there is no possibility of placement of a feeding tube beyond the obstruction or where this has failed, or (iii) when other complications occur such as an anastomotic leak or a high output intestinal fistula.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary.

PN is indicated when there is an obstructed bowel where there is no possibility of placement of a feeding tube beyond the obstruction or where this has failed. It is required in patients with short bowel resulting in severe malabsorption of nutrients and/or fluid and electrolyte loss which cannot be managed enterally. PN is also indicated in surgical cases as above, and in any patient, who is intolerant of EN or in whom nutrition cannot be maintained by the enteral route [186]. However, it must be recognized that these patients in need of PN are those with the most complicated disease [187].

Are there specific recommendations for patients with IBD with an enterostoma?

Recommendation 31.

Patients with IBD with severe diarrhea or a high output jejunostomy or ileostomy should have fluid output and urine sodium monitored, and fluid input can be adapted accordingly (decrease hypotonic fluids and increase saline solutions, but also limit hypertonic fluids), with consideration of food intolerances that may enhance fluid output.

Grade of recommendation 0 – Strong consensus 100% agreement.

Recommendation 32.

Parenteral infusions (fluid and electrolytes) can be needed in the case of ongoing high output stomas.

Grade of recommendation 0 – Strong consensus 96% agreement.

Commentary for 31 and 32.

Patients with a high-output enterostomy or severe diarrhea are prone to dehydration and malnutrition, which may culminate in acute renal failure and wasting [188]. Ongoing and severe diarrhea or increased/high output stoma as well can result in intestinal insufficiency [189] with malabsorption, unintentional weight loss, malnutrition, nutritional deficiencies, and/or dehydration [190,191]. Malabsorption is an important contributing factor to malnutrition in IBD [192]. Multidisciplinary intestinal rehabilitation is the condicio sine qua non for successful management [188,193].

The retrospective study of Baker in 687 stoma patients [194], showed that early high output (within three weeks) from an ileostomy is common and although 49% resolved spontaneously, 51% needed ongoing medical treatment, usually because of a short small-bowel remnant. 71% of patients were treated with oral hypotonic fluid restriction, glucose-saline solution, and anti-diarrheal medication to wean from parenteral infusions and 8% had to continue parenteral or subcutaneous saline in the home setting.

Satisfactory home management with oral fluid restriction and monitoring of urine sodium content was demonstrated more than 35 years ago [195]. In a retrospective study of 16 adult patients with short bowel syndrome and high-output end-jejunostomy syndrome results demonstrate a potential benefit of thickening powder for the nutritional management of patients with short bowel syndrome type I. The ingredients of the powder were as follows: maltodextrin, xanthan gum, and guar gum [196].

In a study in 13 adult (ileal) increased/high output stoma patients, oral rehydration solutions supplemented with rice maltodextrins improved the sodium and potassium balance. The association of increased body weight with decreased serum renin concentrations suggests that a positive water balance also occurred [197]. In another study, three different saline and/or glucose solutions were tested in six patients with jejunostomies. Based on this small group, a sipped glucose electrolyte solution seemed to be the optimal mode of sodium replacement in patients with increased/high output stoma [198]. Santamaria et al. showed that early follow-up of patients with high output stoma after discharge resulted in a significant reduction in the rate of readmissions and allowed identification of a high percentage of patients with malnutrition [199].

No RCTs are available for nutritional treatment of IBD-related diarrhea or increased/high output stoma. Only case studies on the treatment of CD with increased/high output stoma have been

published, which show successful treatment with restriction of hypotonic fluids, sodium enriched diets, thickening powder, exclusive EN and/or parenteral sodium-containing infusions.

Which nutritional recommendations exist for subgroups of IBD?

Recommendation 33.

In patients with IBD, every effort should be made to avoid dehydration.

Grade of recommendation GPP – Strong consensus 91% agreement.

Commentary.

Among patients admitted to the hospital with IBD, most readmissions with venous thromboembolism occur within 60 days of discharge. The pathogenesis of venous thromboembolism in IBD is multifactorial and incompletely understood. Data suggest that it is not one particular mechanism that leads to hypercoagulability in IBD, but rather a complex interplay of systems. Dehydration could be one mechanism but there is no clinical study to support this. Studies are needed to evaluate the nutrition and hydration status such as specific mechanisms [200].

Although there are insufficient data to mandate routine prophylactic anticoagulation, this should be considered in all hospitalized patients with IBD and should be considered following the discharge from the hospital and after major surgery [201–205].

Recommendation 34.

Patients with CD and with a distal (low ileal or colonic) fistula and low output can usually receive all nutritional support **via the enteral route (generally as food).**

Grade of recommendation GPP– Strong consensus 100% agreement.

Recommendation 35.

Patients with CD and with a proximal fistula and/or a very high output should receive nutritional support **by partial or exclusive PN.**

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary for 34 and 35.

Patients with CD are prone to fistula formation between two intestinal sites or from the intestine to another organ (especially the skin, bladder, and vagina). Most occur postoperatively. The management of enterocutaneous fistulas in CD is a complex, great challenge with recurrence or further complications unless the nutritional state is optimized. It is demonstrated that in surgical patients, early nutritional support, independently of the route of administration, decreases the occurrence and severity of fistulas [166,206,207]. Malnutrition with BMI <20 kg/m^2 appears as an independent risk factor [208].

Treatment of intestinal fistulas is usually complex, depending on the location, scale, and nature of the symptoms, and warrants the input of a multidisciplinary team including a gastroenterologist, surgeon, and dietitian [207]. In patients with a distal (low ileal or colonic) fistula, it may be possible to provide all necessary nutritional support via the enteral route [104,209,210]. In the patient with a proximal fistula and/or a very high output it may be easier to manage the situation with a rested gut and full PN [211,212], decreasing the fluid and electrolyte requirements. In case of intestinal failure due to fistulas, a dietetic optimization can be proposed with adapted parenteral support. Parenteral support should distinguish fluid and energy/protein requirements. In a study including 48 patients with CD with enterocutaneous fistulas who were treated with short-peptide-based EN for three months, there was successful closure of enterocutaneous fistulas in 62.5% of patients. EN therapy can participate in the closure of enterocutaneous fistulas in a certain proportion of patients due to improvement in inflammatory conditions and nutrition status [206]. Surgical correction is more likely to be successful if the nutritional status has been optimized preoperatively [213].

Recommendation 36.

In patients with IBD in whom nutritional deprivation has extended over many days, standard precautions and interventions to prevent refeeding syndrome should be considered, particularly with respect to phosphate and thiamine.

Grade of recommendation 0– Strong consensus 92% agreement.

Commentary.

Refeeding syndrome should not be a problem in the well-managed patient with IBD but it is not unusual to encounter patients in whom nutritional deprivation has extended over many days and in whom this hot issue is pertinent. Standard precautions and interventions are mandatory in these high-risk patients, particularly in respect of phosphate and thiamine [214–216].

Recommendation 37.

EN appears safe and can be recommended as supportive therapy according to standard nutritional practice in patients with severe UC.

Grade of recommendation GPP– Strong consensus 100% agreement.

Recommendation 38.

PN may usually not be used in UC unless the patient cannot be fed effectively otherwise.

Grade of recommendation 0 – Strong consensus 95% agreement.

Commentary for 37 and 38.

EN has not been adequately evaluated in active UC. However, it appears safe and can be nutritionally adequate in patients with severe disease [217]. Its efficacy needs to be tested by additional studies in larger cohorts of patients. PN is recommended in malnourished patients with UC and in those with severe disease, when they are not able to tolerate EN, or cannot be fed effectively by either mouth or enteric tube [217–219]. A recent study showed that exclusive EN for seven days may augment corticosteroid responsiveness in patients with acute severe UC [168].

7. Surgical aspects of nutrition in IBD

Which nutritional strategies should be considered in the preoperative phase?

Recommendation 39.

It is recommended to assess the nutritional status before planned surgery. Dietetic interventions including nutritional therapy are indicated in patients with malnutrition and those at nutritional risk.

Grade of recommendation GPP– Strong consensus 100% agreement.

Commentary.

In a systematic review and meta-analysis, patients with CD were found to have lower energy intake than the reference value, especially in active disease. In particular, protein intake was significantly lower when compared to healthy controls [220]. Furthermore, 20–85% of patients with CD are malnourished and weight loss is common in the six months before surgery [221]. There is no clear evidence for the route of nutrition (oral, enteral, or parenteral) or the time frame prior to surgery. Preoperative nutrition supplementation is found to reduce postoperative complications in patients with CD. In particular, EN is superior when compared to the standard of care without nutrition support.

PN is not superior to the standard of care without nutrition [222]. Data comparing oral, enteral, or PN before planned surgery is sparse. A systematic review on exclusive EN before surgery found seven studies of medium or poor quality. Consequently, the review found the current evidence inconclusive [223]. A cohort study on patients with CD who underwent surgery also found that the use of EN support was inconclusive [224]. Prehabilitation before surgery, including nutrition assessment and possible interventions, is however recommended in the ESPEN Guideline: Clinical Nutrition in Surgery and the ECCO Guidelines on Surgical Treatment in CD: [82,107,225].

Recommendation 40.

Patients undergoing elective surgery may be treated according to an enhanced recovery (ERAS) protocol.

Grade of recommendation 0 – Strong consensus 96% agreement.

Recommendation 41.

Preoperative fasting from midnight should not be performed.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary to 40 and 41.

The recommendations have been adapted from the ESPEN Guideline: Clinical Nutrition in Surgery [107] in a slightly modified way since the principles apply equally to the IBD patient undergoing surgical intervention. Evidence of ERAS in patients with IBD is sparse [226]. It is however the opinion of the working group that the ERAS concept should be adopted to IBD patients. The subsequent guidance should be followed during the perioperative period. From a metabolic and nutritional point of view, the key aspects of perioperative care include.

- avoidance of long periods of preoperative fasting
- re-establishment of oral feeding as early as possible after surgery
- integration of nutrition into the overall management of the patient
- metabolic control e.g. of blood glucose
- reduction of factors exacerbating stress-related catabolism or impairing gastrointestinal function
- early mobilization to facilitate protein synthesis and muscle function.

Which nutritional strategies should be considered in the perioperative phase?

Recommendation 42.

In surgical patients, medical nutrition therapy (EN and/or PN as indicated) should be initiated without delay if the patient is malnourished at the time of surgery or if oral diet cannot be adequately recommenced within seven days after surgery.

Grade of recommendation GPP – Strong consensus 96% agreement.

Commentary.

This recommendation has been adapted from the ESPEN Guideline: Clinical Nutrition in Surgery [107] in a slightly modified way since the principles apply equally to the IBD patient undergoing surgical intervention. Nutritional support is indicated in patients with malnutrition and even in patients without significant malnutrition if it is anticipated that the patient will be unable to eat for more than five days perioperatively. It is also indicated in patients who cannot maintain oral intake above 50% of the recommended intake for more than seven days. In these situations, it is recommended to initiate nutritional support (preferably by the enteral route) without delay [107].

Recommendation 43.

Patients who do not meet their energy and/or protein needs from normal food should be encouraged to take ONS during the perioperative period.

Grade of recommendation GPP – Strong consensus 96% agreement.

Commentary.

Insufficient preoperative intake is an indication for dietary counseling or ONS because as Kuppinger et al. [227] showed for patients undergoing abdominal surgery, lower food intake before hospital admission is an independent risk factor for postoperative complications. Twenty-four trials on the use of ONS and EN have reported significant advantages from EN with particular regard to the reduction of infectious complications, length of hospital stay, and costs. In six RCTs postoperative and post-hospital administration of ONS have been investigated [228–232]. The available data do not show with certainty that routine administration improves outcomes, but they do show benefits in terms of nutritional status, rate of minor complications, well-being, and quality of life in patients who cannot meet their nutritional requirements at home from normal food (See ESPEN Guideline: Clinical Nutrition in Surgery [107]).

Recommendation 44.

If malnutrition is diagnosed, then IBD surgery should be delayed for 7–14 days whenever possible, and that time should be used for intensive medical nutrition (ONS, EN, and/or PN if indicated).

Grade of recommendation B – Strong consensus 95% agreement.

Commentary.

Undernutrition has a negative impact on the clinical course, the rate of postoperative complications, and mortality [233–238]. Therefore, patients with severe nutritional risk will benefit from nutritional therapy before major surgery even if surgery has to be delayed. “Severe” nutritional metabolic risk has been defined by the ESPEN working group as the presence of at least one of the following criteria [107].

- Weight loss >10–15% within six months
- BMI <18.5 kg/m^2
- NRS >5
- Serum albumin <30 g/L (with no evidence of hepatic or renal dysfunction)

A meta-analysis of five studies of 1111 patients showed a reduction in the rate of postoperative complications in the group receiving preoperative nutrition (20.0% - EN or total PN) compared with 61.3% in the group with standard care without nutrition therapy support (OR 0.26, 95% CI 0.07–0.99, $p < 0.001$) [222]. The recommendation is based on studies performed mostly on cancer patients, IBD individuals are different, and possibly they can wait longer in most cases. Because of the extrapolation from cancer to patients with IBD, a downgrade of the original grade of recommendation [107] from A to B seems to be justified. The time frame of 7–14 days is questionable, it might be longer in patients with IBD [239,240]. There are no controlled data for the duration of medical nutrition therapy before surgery – the recommendation of 7–14 days is in agreement with ESPEN Guideline: Clinical Nutrition in Surgery [107], which might be even longer in patients with IBD [239,240].

Recommendation 45.

If the energy and/or nutrient requirements cannot be met by oral and enteral intake alone (< 50% of the needs) for more than seven days, a combination of EN and PN is recommended.

Grade of recommendation GPP– Strong consensus 100% agreement.

Commentary.

As stated above, insufficient preoperative intake may affect complication rates. The controlled data for patients with IBD is of poor quality. The meta-analysis of Brennan et al. including five studies showed superiority of EN vs. PN therapy for patients with CD. Postoperative complications occurred in 21.9% of the group who received preoperative EN compared with 73.2% in the group that did not receive preoperative EN (OR 0.09, 95% CI 0.06–0.13, p < 0.001). Postoperative complications occurred in 15.0% of patients in the group who received preoperative total PN compared with 24.4% in the group who did not (OR = 0.65, 95% CI: 0.23–1.88, P = 0.43) [222]. The meta-analysis of Gordon–Dixon et al. including 7 retrospective studies with patients with CD undergoing resection showed fewer infections in patients with exclusive EN with a trend for fewer stoma formations. In another meta-analysis of 11 studies, EN has been shown to have efficacy in the treatment of CD [223]. As for the CD activity index or the rates of remission, no differences between EN and PN have been found. In comparison, polymeric vs. elemental formulas have shown better results regarding inflammation measured by C-reactive protein [241]. In a meta-analysis of 10 studies including a total of 557 individuals with IBD, 382 with CD, and 152 with UC, PN has shown to have efficacy for the treatment of IBD with special regard to the improvement of CD activity index and albumin serum level [242]. The guideline working group favors EN in the first line. Therefore, if the oral intake is inadequate, regardless of the intervention (oral food or ONS), EN should be initiated [107,243].

Recommendation 46.

PN shall be used as the only intervention only if EN is impossible (e.g. because of the absence of access, severe vomiting, or diarrhea) or contraindicated (e.g. because of intestinal obstructions or ileus, severe shock, intestinal ischemia).

Grade of recommendation A– Strong consensus 100% agreement.

Commentary.

The enteral route should always be preferred except when one or more of the following contraindications is present.

- Intestinal obstructions or ileus,
- Severe shock
- Intestinal ischemia
- High output fistula
- Severe intestinal hemorrhage

In those cases, PN may be needed for days or weeks until the function of the gastrointestinal tract returns. For further details, see the ESPEN guideline on Clinical Nutrition in Surgery [107].

Are particular nutritional strategies required in patients with CD during the perioperative phase?

Recommendation 47.

Surgical patients with CD should obtain early nutritional support**, because, independently of the route of administration, it decreases the risk of postoperative complications.**

Grade of recommendation B– Strong consensus 95% agreement.

Commentary.

The advantages of early EN within 24 h of surgery versus later commencement have been shown in two meta-analyses (one Cochrane systematic review) [244,245]. Early EN speeds up anastomotic healing as proven by Smeets et al. [246], which reduces postoperative complications' rate [247,248].

Recommendation 48.

In patients with CD with prolonged gastrointestinal failure (such as patients in whom resection has created a short bowel), PN is mandatory and life-saving at least in the early stages of intestinal failure, and therefore PN should be performed in such conditions.

Grade of recommendation GPP– Strong consensus 95% agreement.

Commentary.

See also ESPEN Guideline: Clinical Nutrition in Surgery [107]. Although EN has proven to be the most beneficial in almost all patient populations, it is relatively rare that it is sufficient in acute intestinal failure/enterocutaneous fistulas individuals because of the compromised integrity of the gastrointestinal tract. For type II (acute and chronic intestinal failure) patients, PN represents the only option regarding the delivery of nutrients [249,250], because they are not able to maintain the proper oral/enteral absorption of nutrients. Therefore, PN often represents the main option, alone or in association with EN (supplemental PN) [251].

Are particular nutritional strategies required in patients with UC during the perioperative phase?

Recommendation 49.

Patients with UC undergoing surgery should be provided with an individual nutritional strategy, which depends on the nutritional status and severity of the disease.

Grade of recommendation GPP– 100% agreement.

Commentary.

Patients undergoing surgery for UC are exposed to the risks of wound infection, intra-abdominal abscess, sepsis, bowel obstruction, and other postoperative complications [38]. Malnutrition is one of the significant risk factors for postoperative morbidity. Nutritional strategy for correction of nutritional status when possible is needed in the perioperative period. Nutrition strategies should always be tailored for each patient [38,252].

Which nutritional strategies should be considered in the postoperative phase?

Recommendation 50.

Normal food intake, ONS, or EN can be commenced early after surgery in most patients with IBD in the postoperative phase.

Grade of recommendation 0 – Strong consensus 100% agreement.

Recommendation 51.

In the early phase after proctocolectomy or colectomy, water and electrolytes should be administered according to individual needs to assure hemodynamic stability.

Grade of recommendation B– Strong consensus 95% agreement.

Commentary for 50 and 51.

As stated in the ESPEN Guideline: Clinical Nutrition in Surgery [107], early normal food or EN, including clear liquids on the first or second postoperative day, does not cause impairment of healing of anastomoses in the colon or rectum and leads to significantly shortened hospital length of stay. This has been emphasized by a Cochrane Systematic Review [236]. Meta-analyses [245,253,254] showed significant benefits concerning postoperative recovery and infection rate. Early postoperative nutrition is associated with significant reductions in total complications compared with traditional postoperative feeding practices and does not negatively affect outcomes such as mortality: anastomotic dehiscence, resumption of

bowel function, or hospital length of stay [254]. Avoiding intravenous water and electrolyte overload improves the healing of the anastomosis and reduces postoperative complications [255–258].

8. Microbiota modulation (probiotics, prebiotics, high fiber diets, etc.)

This section summarises the evidence and provides clinical recommendations for the use of microbiota-modulating treatments, i.e. probiotics, prebiotics, antibiotics, and fecal microbiota transplantation (FMT). CD, UC, and pouchitis are addressed separately. Where applicable, studies with active disease and remission are separated.

8.1. Probiotics in IBD

Probiotics are specific viable microorganisms that may confer health benefits [259,260]. They are regulated as food supplements that impact product quality control and safety evaluation [261–263].

Which probiotics can be recommended in CD/UC in active disease/remission?

Crohn's disease

Recommendation 52.

Probiotics should not be recommended for treatment of CD, neither for treatment of active disease nor for prevention of relapse in the remission phase or postoperative recurrence of disease.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary.

In CD, probiotic effects were investigated in 11 randomized trials [264–274]. Five studies with a total of 362 patients investigated postoperative endoscopic recurrence [265,267–269,272], and all five found probiotics non-superior to placebo in preventing recurrence. Four studies investigated patients with CD in remission [264,266,271,273]. While three found no effect of *Lactobacillus GG* [266], *Saccharomyces boulardii* [271], or a multistrain probiotic [273], one small study found a reduced clinical relapse rate with six months of use of *S. boulardii* compared with placebo [264]. Two studied patients with active disease, one not comparing outcome measures between treatment groups [270] and the other reporting reduced bloating and "feeling good score", but no clinical disease index or endoscopic data [274]. Four studies had high withdrawal rates, up to 70% [265,266,268,270], and two had poorly defined clinical outcome measures [273,274].

Ulcerative colitis

Recommendation 53.

In patients with UC, selected probiotics or probiotics-containing preparations can be used as an alternative to 5-aminosalicylic acid (5-ASA) standard therapy if 5-ASA is not tolerated for the treatment of mild or moderate active disease.

Grade of recommendation 0 – Consensus 85% agreement.

Commentary.

In UC, 20 controlled studies that investigated probiotic use and reported clinical outcomes were identified [273–292]. Of these, 12 included patients with mild-moderately active disease [276,278,280,281,283–285,287,289–292], and nine included patients in remission [273–275,277,279,282,286,288]. A Cochrane review of studies with probiotics to maintain remission in UC, published in 2011, concluded that insufficient evidence prevented conclusions regarding the therapeutic efficacy of probiotics in UC [293], however nine of the 20 studies have been published since the Cochrane review [273,274,285–291].

For patients with active disease, seven studies found probiotics such as bifidobacteria-fermented milk, synbiotics, and selected multistrain probiotics, to be superior to placebo [278,280,283,285,289,291,292], although two studies did not make a direct comparison between the active and the control group [278,285]. Most of these studies used multistrain probiotics [280,283,289,291,292]. Three studies found no difference between patients treated with probiotics and those treated with placebo [281,284,290], and one study has a very low completion rate with only 25 of 90 patients at regular termination [284]. One study found a probiotic non-inferior to 5-ASA treatment [276], and one study found the same probiotic inferior to placebo [287].

For patients in remission, one large study found a probiotic (E.coli Nissle strain 1917) non-inferior to 5-ASA [279], and one study found that the addition of a single-strain probiotic (bifidobacteria-fermented milk) led to more patients maintaining remission at 12 months [277]. Importantly, six studies found no effect of adding a probiotic compared with a placebo [273–275,282,286,288].

Pouchitis

Recommendation 54.

In pouchitis, multistrain probiotics can be considered to prevent pouchitis-

Grade of recommendation 0 – Strong consensus 95% agreement.

Commentary.

In pouchitis, limited evidence supports the effect of multistrain probiotics to prevent pouchitis, but data are weak and inconsistent and therefore insufficient to make strong clinical recommendations.

In pouchitis, six clinical controlled trials investigated the use of probiotics [294–299]. Three trials came from the same research group, reporting the use of a multistrain probiotic [294–296] and marked superiority over placebo in preventing the occurrence of pouchitis in patients with a newly formed pouch [295] and relapse in antibiotics-induced pouchitis remission [296]. Two studies investigated other probiotics and found no effect compared with placebo in patients with pouch dysfunction [298] or a newly formed pouch [299].

8.2. Prebiotics in IBD

Which prebiotics can be recommended in CD/UC in active disease/remission?

Prebiotics are fermentable carbohydrates with a wide variety of chemical structures that are administered for local or systemic health benefits. Hypotheses about the possibility of using prebiotics as a part of IBD therapy assume that supplementation with selected fiber fractions, including fermenting carbohydrates, aimed at the promotion of specific bacteria and/or the production of specific metabolites by specific bacteria, may cause the assumed beneficial effect for the host. Data on the use of prebiotics in patients with IBD are very limited. Most prebiotics used in studies of patients with IBD are classes of oligosaccharides and inulin.

Crohn's disease

Recommendation 55.

Prebiotic therapy should not be recommended for treatment in CD, neither in active disease nor for maintenance of remission.

Grade of recommendation B – Strong consensus 95% agreement.

Commentary.

Prebiotic therapy includes prebiotic supplements and high fiber diets. In a double-blind RCT, Benjamin et al. showed that the use of fructose-oligosaccharide was not associated with any health benefit for patients with CD [300]. Another team tried to

investigate the effects of synbiotic consumption on disease processes in patients with CD. The synbiotic comprised *Bifidobacterium longum* and a sachet containing inulin and oligofructose. Including 35 patients, the synbiotic group had reductions in CD activity index ($p = 0.020$) and histological scores ($p = 0.018$). There was little effect on mucosal IL-18, INF-g, and IL-1b; significant reductions occurred in tumor necrosis factor-α expression in synbiotic patients at three months ($p = 0.041$), although not at six months [270].

In patients with CD, fiber is more often relatively contraindicated because of the presence of strictures, and fiber in the form of the prebiotic fructooligosaccharide is apparently ineffective in CD [300]. In contrast to this, a loosely controlled study of wheat fiber supplementation found that the supplemented patients did better in respect of quality of life and had no apparent adverse events [301]. Another study of fiber supplementation also claims benefit, and this was through the uncontrolled use of an ovo-vegetarian diet with over 30 g of fiber for every 2000 kcal; maintenance of remission to one year was a remarkable 92% [302].

Taken together, there is no evidence that the use of prebiotics or synbiotics could beneficially modify the course of CD. The value of the studies conducted so far is limited, i.e. small numbers of the study groups, and their results are difficult to compare due to short duration and methodological differences.

Ulcerative colitis

Recommendation 56.

Prebiotic therapy cannot be recommended routinely for treatment in UC, neither for active disease nor for maintenance of remission.

Grade of recommendation 0 − Strong consensus 100% agreement.

Commentary.

Much of the recent literature relates to the effects of specific agents chosen as prebiotics and these are not considered here. It is recognized that many forms of fiber impact the gut microbiota and thus possibly the maintenance of remission in IBD. The evolving literature suggests that prebiotic fibers may be useful in the maintenance of remission in some patients with UC. Several small controlled studies have shown apparent benefits from the addition of fiber to the diet of patients with UC [303–305]. Given that the effects in maintaining remission were similar for germinated barley, ispaghula husk, and *Plantago ovata* seeds, it may be reasonable to conclude that this is a generic effect of increased dietary fiber intake.

In a recent cross-over study of 17 patients with UC in remission or with mild disease, participants were assigned randomly to two groups and received a low-fat high-fiber diet or an improved standard American diet (higher quantities of fruits, vegetables, and fiber than a typical standard American diet). All patients remained in remission throughout the study period and both diets (having more fiber than the typical standard diet) resulted in increased quality of life. The low-fat high-fiber diet decreased markers of inflammation and reduced intestinal dysbiosis in fecal samples [306].

Overall, as stated in the 2019 Cochrane review for dietary interventions for induction and maintenance of remission in IBD [111], none of the interventions, including fiber can be recommended for maintaining remission in IBD.

Several clinical trials have been conducted to treat UC with germinated barley foods, products which are mainly composed of dietary fiber and glutamine-rich protein. Germinated barley food may reduce clinical activity in patients with mild to moderate UC and appears to be an effective therapy for the maintenance of remission in these patients, but studies were small or only examined proxy variables for clinical effect. In a 2011 study of 41 patients with UC in remission, Faghfoori et al. found germinated barley food to reduce serum markers of proinflammatory cytokines, but without comparing it to placebo [307]. Similarly, Ishikawa examined the use of galactooligosaccharides for one year in 41 patients with UC and found reduced clinical activity, but without direct comparison to placebo [285]. Fructooligosaccharides were studied by Casellas et al. who compared mesalazine therapy in combination with oligofructose-enriched inulin and placebo in patients with mild to moderate UC [308]. Oral oligofructose-enriched inulin was well tolerated, and its supply resulted in a significantly earlier decrease in fecal calprotectin. Kamarli Altun and colleagues treated 40 patients with UC with a fructooligosaccharide-based synbiotic for eight weeks and found the synbiotic superior to no treatment, but a formal placebo treatment was not applied [291].

Pouchitis

Recommendation 57.

In pouchitis, no recommendations for the use of a prebiotic therapy can be made.

Grade of recommendation GPP− Strong consensus 95% agreement.

Commentary.

No RCTs were identified during a systematic literature search. Two narrative reviews speculate on the use of prebiotics in patients with pouchitis and summarise the rationale for conducting further clinical studies [309,310].

8.3. Antibiotics in IBD

Which antibiotics can be recommended in CD/UC in active disease/remission.

Antibiotics have been proposed to offer direct value as primary therapy for different aspects of IBD. These proposals are reviewed here. Although not directly related to nutrition, antibiotics, besides probiotics and prebiotic therapy, modulate the gut microbiota therefore might affect nutrition. There are many well-supported uses of antibiotics in the management of patients with IBD, including the treatment of its infectious complications including bacterial superinfection, perioperative prophylaxis of infection, and concurrent infections which may have been aggravated by IBD-related immunosuppression. These aspects are not considered further here.

Crohn's disease

Recommendation 58.

No antibiotic regimen can be generally recommended, neither for the management of active CD nor for maintenance of medically-induced remission.

Grade of recommendation 0− Strong consensus 84% agreement.

Commentary.

Treatment with single agents can be confidently advised against. Combinations comparable to those used in the treatment of mycobacterial infection are relatively toxic and of unproven value. Eighteen RCTs were considered; nine explored the effects of single agents, five examined combinations used in antituberculous therapy, and four looked at other combinations. The one pediatric RCT compared one antibiotic regimen with another and therefore could not be included here. Many of the studies were small and most were underpowered. No convincing statistically significant positive results were found.

Metronidazole was ineffective (or not different from 5-ASA therapy) as a single agent [311] and ineffective when combined

with ciprofloxacin or cotrimoxazole. Ciprofloxacin as a single agent was also ineffective [312], and it was ineffective when combined with doxycycline and hydroxychloroquine. Clarithromycin and clofazimine were also ineffective as single agents. There was a weak positive message from rifaximin, but only when given at 800 mg a day, with no advantage over placebo seen from either 400 mg or 1200 mg [313].

Antituberculous regimens (conventional and regimens for variant organisms) were mainly ineffective. Selby's study with clarithromycin, rifabutin, and clofazimine showed a better remission rate than placebo at 16 weeks (66% vs 50%; $p = 0.02$) but the effect was lost by 52 weeks despite continuing therapy [314]. The authors considered that this was non-specific and unrelated to a specific antimycobacterial effect. The only other positive result was that from Prantera's small study of clofazimine, ethambutol, dapsone, and rifampicin in steroid-dependent patients, in which there was a lower relapse rate at two months (3/19 vs. 11/17) [315]. In both trials, there were significant drug-related adverse events, and neither group of investigators has pursued this approach.

Most of the systematic reviews are out of date and the only ones considered current and relevant are those of the Cochrane Centres for antibiotics in general [316], and specifically for antituberculous therapy in maintenance of remission [317]. In the former, the authors conclude that, although antibiotics are probably safe, "moderate to high-quality evidence suggests that any benefit provided by antibiotics in active CD is likely to be modest and may not be clinically meaningful."

For maintenance of CD when remission has been achieved medically, only one RCT considers this scenario and was negative.

Ulcerative colitis

Recommendation 59.

No antibiotic regimen can be recommended in general in UC, neither for active disease including acute severe disease nor for maintenance of remission.

Grade of recommendation 0 − Consensus 89% agreement.

Commentary.

The papers fall into several distinct groups and most of the studies are inadequately powered for any definitive conclusions.

With regards to active disease, it may reasonably be concluded that single-agent antibiotic therapy is of very limited value. Only one paper with a single agent, namely tobramycin and published in 1990 [318], shows benefit in obtaining remission or clinical response. In this study of 84 patients with active disease, there was an objective benefit at one week in 74% of those receiving treatment compared to 43% of the controls. This was statistically significant but the benefit was probably short-lived and no other study has replicated this good result.

In acute disease of mild to moderate severity, amoxiclav [319], ciprofloxacin [320], rifaximin [321], and vancomycin [322], have all failed to show useful effects. Ciprofloxacin was also inferior to placebo in the relevant arms of a study where probiotics were also explored [287]. Neither metronidazole [323] nor ciprofloxacin [324] was beneficial as adjuncts in acute severe colitis.

Combinations of multiple antibiotics have shown more promise in mild to moderately severe active disease. Following the hypothesis that specific co-infection with *Fusobacterium varium* was important in some exacerbations of UC and therefore a key to effective antibiotic therapy, a pilot study was conducted comparing antibiotics to placebo in 20 patients in whom this infection could be shown [325,326]. The antibiotic combination - amoxicillin, tetracycline, and metronidazole - appeared to be of clinical benefit, but the small numbers involved and lack of statistical support make these papers (which describe the same study) difficult to interpret. The subsequent paper from the same group probably describes a different group of 26 patients in which the combination of amoxicillin, tetracycline, and metronidazole was given for two weeks. This indicated lasting benefit concerning clinical scores at three months ($p < 0.05$) [327]. The same 2-weeks combination of amoxicillin 1.5 g/d, tetracycline 1.5 g/d, and metronidazole 750 mg/d also generated a benefit that was still apparent at three months in a more powerful study (again from the same Japanese group) [328]. In this study of 210 patients there was a statistically better clinical response rate (49% vs 21%; $p < 0.0001$), and better endoscopic scores ($p < 0.002$), but no difference in remission rate at three months (19.0% vs 15.8%).

There has also been attention given to antibiotic combinations as adjunctive therapy in acute severe colitis and here too the results are ambiguous. The combination of tobramycin and metronidazole was ineffective [329]. The use of ceftriaxone in combination with metronidazole appeared ineffective based on the response on day 3 in a study of 50 patients with acute severe colitis (28% vs 24%; n. s.) [330]. There was less need for surgery in the controls than in those receiving the antibiotics, but the study was compromised by its very unbalanced randomization which allocated much more seriously ill patients to the antibiotic group. A similar study was conducted on a pediatric population with severe colitis ($n = 28$) who were randomized to a four-drug regimen with amoxicillin, vancomycin, metronidazole, and either doxycycline or ciprofloxacin or to placebo [331]. There was no difference in the need for salvage surgery between the groups, but the objective assessment of disease activity on scoring on day 5 was significantly better in those receiving antibiotics.

It seems that only two groups have formally evaluated the role of antibiotics in maintaining remission. In Lobo's paper of 1993, an initial possible benefit from tobramycin was short-lived and cannot be recommended for general use especially given the potential for toxicity from this drug [332]. Maintenance ciprofloxacin (1–1.5 g daily) was given for six months in a placebo-controlled trial ($n = 83$) [333], and clinical relapse to six months was significantly less frequent in the actively treated group (21% vs 44%; $p = 0.02$). However, the endoscopic and histological findings were advantageous only at three months, also suggesting only a short-term benefit.

All of the above studies compared the antibiotic(s) with placebo, and in most cases, conventional therapy with steroids and/or a mesalazine drug was continued alongside. There are two small studies in which antibiotics were compared with sulfasalazine. Gilat et al. compared metronidazole to sulfasalazine in 46 patients with non-severe UC [334]: the sulfasalazine was clearly superior with a response rate of 68% (vs. 26%; $p < 0.01$). The same group looked at the same comparison in the maintenance of remission over 12 months in 40 patients who had already been in remission for one to 11 months. In this study metronidazole, 600 mg/d was numerically slightly superior and the benefit just reached statistical significance at 12 months [335]. Other systematic reviews unsurprisingly conclude very cautiously [336–339]. The first (part of a pair of 2011 papers from the same group) considered that the data were sufficient to justify further trials, but not to give any positive recommendations [336]. The second paper in which they made a pooled analysis of antibiotic therapies was able to show a statistically significant effect in inducing remission in UC but considered the quality of evidence to be very low, and concluded that this approach could not be recommended as no particular class of drug could be advised for clinical use [337,340]. It considered only one of the three remission studies and made no recommendation there. Colombel and his colleagues were positively disposed towards the use of antibiotics in acute UC but gave no firm positive recommendation [338]. The most recent (2021) of the reviews available judged 12 RCTs and considered that antibiotic therapy had statistically significant efficacy in inducing remission (RR = 0.77; 95% CI 0.60–0.98; $p = 0.03$) with this

benefit extending to 12 months (RR = 0.83; 95% CI 0.73–0.94; p = 0.003) [339]. Nonetheless, they shared the uncertainties of the earlier authors and concluded that "more high-quality clinical trials are needed before clinical recommendations for antibiotic therapy in UC management are made".

Pouchitis

Recommendation 60.

Ciprofloxacin (first choice) and metronidazole can be used as initial therapy in acute pouchitis.

Grade of recommendation 0 − Consensus 90% agreement.

Recommendation 61.

No antibiotic regimen can currently be recommended for the prevention or the management of chronic resistant pouchitis.

Grade of recommendation 0 − Strong consensus 100% agreement.

Commentary for 60 and 61.

Original papers that describe the use of antibiotics in pouchitis fall into three distinct groups. All studies were inadequately powered for definitive conclusions.

In acute pouchitis, although antibiotics have been [341] and remain [342] the mainstay of therapy for episodes of acute pouchitis in patients who have had an ileoanal pouch created following surgery for UC, there are only three related RCTs. Most observational and uncontrolled studies have used metronidazole or ciprofloxacin and there is clinical confidence in their efficacy. A comparison of the two antibiotics in 2001 [343] used 1 g of ciprofloxacin and 20 mg/kg metronidazole in 16 patients. In both small groups, there was a statistically significant reduction in the pouchitis activity score and the numerical advantage lay with ciprofloxacin (10.1–3.3 compared to 9.7–5.8) which also had fewer side effects. The authors were overconfident in their claims (such as including an implausible p-value of 0.0002), but it is reasonable to conclude in favor of ciprofloxacin. A comparison of oral metronidazole with budesonide enemas in another small study (n = 26) showed no obvious difference (50% vs. 58%) in their clinical efficacy, and again there were more side effects with the metronidazole [344]. It was reasonably pointed out that some patients will prefer oral therapy. The third RCT was a pilot study of rifaximin 1.2 g in comparison to placebo in 18 patients [345]. The remission rate from the drug at four weeks was numerically but not statistically superior, and there does not appear to have been any attempt to conduct a more definitive study.

Patients with chronically active resistant pouchitis have been subject to only a single controlled trial in which 13 patients were randomized to metronidazole 1.2 g or placebo [346]. There was a clinical benefit in terms of bowel frequency which reached statistical significance despite the tiny numbers, but there were no clear differences in other symptoms, C-reactive protein, or endoscopic or histological assessment.

Co-infection with cytomegalovirus or *Clostridium difficile* may be responsible for difficulties in pouchitis management and should be specifically sought and treated appropriately.

For the prevention of pouchitis, the largest RCT in the pouchitis literature is a comparison of tinidazole 500 mg with placebo in the prevention of pouchitis which was only published in abstract form [347]. Amongst 38 patients randomized, the active agent was associated with a possible benefit at 12 months, with a relative risk of remaining free of pouchitis of 1.38 (81% vs 58%; n. s.). Because this study was only been described in abstract form, its veracity must be questioned.

Other systematic reviews unsurprisingly conclude cautiously [341,342,348–352]. The most recent of the Cochrane reviews allows consideration of uncontrolled data and favors antibiotic use in acute pouchitis [342]. In addition to ciprofloxacin and metronidazole, it identifies other antibiotics such as amoxicillin/co-amoxiclav, erythromycin, and tetracycline as also of potential value. The 2017 review of chronic pouchitis, on similar criteria, also supports the use of antibiotics, and in this context ciprofloxacin, rifaximin, and tinidazole are added to the list [352].

8.4. Fecal microbiota transplantation in IBD

FMT is the transfer of minimally processed feces from a healthy donor to a patient [353]. Treatment is carried out following standards for tissues and cells [354–356]. The use is effective in patients with recurrent *Clostridioides difficile* infection [357] and established in most countries [358]. FMT is considered for several experimental indications, including IBD.

Statement 1.

At present no recommendation can be made for or against FMT in IBD.

Strong consensus 100% agreement.

Commentary.

There is insufficient evidence to recommend FMT to treat IBD outside clinical trials. However, there are more data on UC compared to CD.

In CD, one study investigated the use of FMT to prevent relapse [359]. In 17 randomized patients with steroid-induced remission, a colonoscopic FMT or sham was conducted, and steroid-free remission week 10 was a secondary outcome measure, achieved in 88% vs. 44% of patients (p = 0.13).

In UC, seven controlled trials [360–366] investigated FMT provided via the upper or lower route with either single or multiple applications of fresh, cryopreserved, or lyophilized feces from single or multiple donors. Five of seven studies found FMT superior to placebo, mostly reporting clinical steroid-free remission rates in week 8. Long-term follow-ups indicate high relapse rates with a need for repeated treatments.

In pouchitis, two placebo-controlled studies investigated FMT in patients with chronic or antibiotics-dependant pouchitis [367,368]. A Finnish study included 26 patients for colonoscopic FMT or sham (autologous FMT) [368], and relapse rates week 52 were similar, i.e. 9/13 vs 8/13 (p = 0.18). In a pilot study that included six patients before premature termination [367], four patients who received oral encapsulated FMT and two patients receiving placebo all relapsed during 16 weeks of follow-up, and open-label extension FMT failed to prevent further relapses in five of six patients.

9. Dietetic and other recommendations specific for the remission phase

Which nutritional recommendations should be given in the remission phase of IBD?

Recommendation 62.

Patients should follow the principles of healthy dietary patterns and avoid individual nutritional triggers. If particular clinical problems are still present during the remission phase, the diet should be adjusted accordingly.

Grade of recommendation GPP − Strong consensus 100% agreement.

Commentary.

In general, no specific diet has proven to be effective in the maintenance of remission. None of the alternative diets or semi-exclusive diets seem effective in obtaining remission. However, individual food intolerances are frequently seen in patients with

IBD, lactose and dairy products, spices, herbs, fried, gas-generating, and fiber-rich products are often poorly tolerated [369–372]. Furthermore, there is evidence demonstrating that the low FODMAP diet has a favorable impact on gastrointestinal symptoms in patients with CD [373].

Patients with CD typically select a diet low in fiber and vegetables, and often one which is hypocaloric and associated with multiple micronutrient deficiencies [374]. Acquired lactase deficiency is particularly prevalent in patients with proximal CD and will warrant a lactose-restricted diet. Specific exclusion diets have been considered to have good effects by their protagonists, but for best results, it is proposed that the diets should be customized to avoid the patients' individual food intolerances. This strategy then makes it difficult to generalize. Limited controlled data support the elimination of lactose, dairy products in general, spices, herbs, fried foods, and gas-generating and fiber-rich products, but only when they are poorly tolerated. Their removal is then probably helpful in prolonging remission [375,376]. Other studies of reasonable quality have also included dietary manipulations, but alongside the use of partial EN; these studies are addressed in later sections. The use of an exclusive EN regimen is an extreme form of dietary exclusion for long-term adherence.

EN has been thought to have a role in preventing relapse in children with inactive [178,377–379] and the effect has also been observed in a Japanese study of adult CD patients [380–382]. Previous Cochrane evaluation considered that ongoing EN may help the maintenance of remission and reduce the use of corticosteroids in CD [383], but a recent Cochrane review stated that no firm conclusions on the efficacy and safety of EN therapy in quiescent CD can be drawn [384]. No recommendation is therefore made.

Recommendation 63.

Supplementation with n-3 fatty acids shall not be advised to supporthe maintenance of remission in patients with IBD.

Grade of recommendation A – Strong consensus 100% agreement.

Commentary.

Systematic reviews have concluded that supplementing the diet with n-3 fats is ineffective in the maintenance of remission of patients with UC [385,386]. This is therefore not advised. The above data were obtained in adults. It appears reasonable to extrapolate the conclusions into pediatric practice. A systematic review and meta-analysis from 2020 concluded that supplementation with PUFAs has little or no effect on the prevention or treatment of IBD [387]. This is in accord with the latest Cochrane review from 2014 [388] that has concluded that n-3 fatty acids are probably ineffective for maintenance of remission in CD.

Recommendation 64.

When more than 20 cm of the distal ileum, whether or not in combination with the ileocecal valve, is resected, or when vitamin B12 deficiency is documented, vitamin B12 should be administered to patients with CD.

Grade of recommendation B – Strong consensus 100% agreement.

Commentary.

A recent systematic review has assessed the literature for prevalence, risk factors, evaluation, and management of vitamin B12 deficiency in IBD [389]. Unresected UC does not predispose to low B12 levels or B12 deficiency. The prevalence of B12 deficiency in CD ranges from 5.6 to 38%. Resection of more than 30 cm of the distal ileum, whether or not in combination with the ileocecal valve, will put the patient at risk for B12 deficiency. Resection of less than 20 cm does not normally cause deficiency [390]. The ileal CD is not inevitably associated with vitamin B12 deficiency [391,392], but it is difficult to rule out its responsibility when more than 30–60 cm are involved [389]. Patients with CD with ileal involvement and/or resection and/or clinical deficiency features should be screened yearly for vitamin B12 deficiency [389].

Patients with a clinical deficiency should receive 1000 μg of vitamin B12 by intramuscular injection every other day for a week and then every month for life [393]. Patients with more than 20 cm of ileum resected should receive 1000 μg of vitamin B12 prophylactically also every month and indefinitely [393]. Oral therapy may be as effective but is poorly explored in CD. A retrospective open-label non-randomized study of 36 patients with CD has shown the oral route (1200 μg/d for 33 patients, 2400 μg/d for three patients) to be effective in treating vitamin B12 deficiency [394]. For now, parenteral supplementation remains the reference, but oral supplementation may become standard in the coming years.

Recommendation 65.

Selected patients with IBD, e. g. those treated with sulphasalazine and methotrexate should be supplemented prophylactically with vitamin B9/folic acid.

Grade of recommendation B – Strong consensus 95% agreement.

Commentary.

There are several causes of folate deficiency in IBD: low intake, malabsorption, excess folate utilization due to mucosal inflammation, and medications [395], while a high level of folate has been identified as reducing the risk of IBD [396]. A combination of adverse factors may be responsible for the deficiency of this vitamin. Drugs are responsible for folate deficiency mostly by inhibition of dihydrofolate reductase, an enzyme that catalyzes the reduction of dihydrofolic acid to tetrahydrofolic acid (methotrexate) [397] or via folate malabsorption (sulphasalazine) [398]. Azathioprine and 6-mercaptopurine also induce macrocytosis but through myelosuppressive activity.

A systematic review and meta-analysis of 10 studies reporting on 4517 patients found an overall protective effect for folic acid supplementation on the development of colorectal cancer (pooled HR = 0.58; 95% CI 0.37–0.80) [399]. An Italian study compared one month of supplementation with 15 mg of either folic or folinic acid in 30 IBD patients treated with sulphasalazine [400]. Both were able to restore the body stores of folate, but folinic acid was more efficient. The ECCO-ESPGHAN guidelines on the medical management of pediatric CD advise oral administration of folate in patients on methotrexate, 5 mg once weekly 24–72 h after the methotrexate, or 1 mg daily for five days per week [161]. This panel recommends the same practice in adults.

Recommendation 66.

ONS or EN can be recommended in patients with CD in remission if malnutrition cannot be treated sufficiently by dietary counseling.

Grade of recommendation GPP – Strong consensus 95% agreement.

Commentary.

The study with the lowest risk of bias compared supplemental (50%) EN with a regular diet in 51 adult patients with CD [401]. Patients in each arm of the study were on similar medications (5-ASA or azathioprine). The study showed that in the EN group, nine of 26 patients (34%) had a relapse during a mean follow-up of 11.9 months, as compared with 16 of 25 patients (64%) in the non-EN group (HR = 0.40; 95%CI 0.16–0.98; $p < 0.01$). The study of maintenance EN as an adjuvant to infliximab therapy has yielded conflicting results, with one negative [381] and two positive [402,403] studies published so far. A meta-analysis published by Nguyen et al. showed that a combination of

infliximab and EN therapy induces and maintains clinical remission more efficiently than infliximab monotherapy in patients with CD [404].

Elemental formulas have been the most studied. A systematic review was unable to show any significant difference in remission rate between elemental and polymeric formulas [405]. However, it found a lower adherence rate for elemental EN compared to an unrestricted diet. The European organizations for IBD and for pediatric gastroenterology and nutrition, ECCO and ESPGHAN, have advised on the possible use of partial maintenance EN in patients with very mild disease or low risk of relapse, preferring polymeric feeds, with elemental feeds being advised only in the case of allergy to cow's milk proteins [406].

Recommendation 67.

Neither EN nor PN can be recommended as primary therapy for maintaining remission in IBD.

Grade of recommendation GPP − Strong consensus 100% agreement.

Commentary.

Nutritional support has not been assessed as maintenance therapy in UC, and neither has PN in CD. A recent Cochrane review from 2019, evaluating the role of EN in the maintenance of remission, identified four RCTs in adult patients and concluded that no firm conclusions regarding the efficacy and safety of EN in quiescent CD can be drawn [384]. Also in 2019, Canadian pediatric guidelines suggested that for luminal CD in remission, if partial EN is used, it should be combined with other medications to maintain clinical remission [407].

In a systematic review from 2020, not including patients with active disease, nineteen studies assessing the use of partial EN for maintaining remission in CD were included, consisting of eight intervention trials (four RCTs) and 11 cohort trials [376]. Twelve studies recruited adults (n = 1076) and seven recruited children (n = 392). When maintenance EN consisted of more than 35% of the energy requirements, there was a significant reduction in the 1-year clinical relapse rate. The use of maintenance EN was associated with improved endoscopic indices and increased height and weight Z-scores in children. In another systematic review and meta-analysis from 2020, looking at studies with clinical relapse as the primary outcome, eight studies with 429 patients were identified [408]. The rate of clinical relapse at 0.5–2 years was significantly lower in patients receiving partial EN (420–1800 kcal/d) than in those not receiving nutrition therapy (RR 0.67, 95% CI 0.54–0.82, $p < 0.01$). Overall, as none of the studies evaluated partial EN as primary therapy, EN or PN can not be recommended as the primary therapy for maintaining remission in IBD.

What are the indications for physical activity in IBD during remission?

Recommendation 68.

In all patients with IBD, endurance training should be encouraged. In patients with IBD with decreased muscle mass and/or muscle performance, appropriate physical activity (mainly resistance training) should be recommended.

Grade of recommendation GPP− Strong consensus 100% agreement.

Commentary.

The systematic review of 19 body composition studies reporting on 926 patients with IBD revealed a low fat-free mass in 28% of patients with CD and 13% of patients with UC [409]. Low muscle mass, strength, and performance have been reported in adult IBD cohorts [410,411], and similar findings have also been made in children [412]. Sarcopenia was reported in 12% of patients with IBD with a mean age of 31 years, associated with osteopenia [410].

In a German study, 30 patients, aged 41 ± 14 years, with mild to moderate IBD were randomized to either supervised moderate-intensity running thrice a week for ten weeks or to a control group with no exercise. Health-related quality of life, reported as Inflammatory Bowel Disease Questionnaire (IBDQ) total score, improved by 19% in the intervention group and 8% in the control group, with significant differences for the IBDQ social sub-scale that was significantly improved in the intervention group compared with controls ($p = 0.023$) [413].

The reference treatment for sarcopenia, along with maintaining an adequate protein intake, is resistance training. This is what is advised in age-related sarcopenia [414]. However, this hasn't been assessed in patients with IBD. Still, the panel recommends prescribing resistance training (weight-bearing exercises) in patients with IBD with sarcopenia or features of sarcopenia (reduced muscle mass, strength, and/or performance).

Next to the positive effect on sarcopenia, an exercise intervention can be assumed to be safe and beneficial for the patient's overall health, and IBD-specific physical and psycho-social symptoms [415,416].

Are there special dietetic recommendations for patients with IBD with obesity?

Recommendation 69.

Patients with IBD and obesity should be advised to reduce weight only in phases of stable remission and then according to current obesity guidelines.

Grade of recommendation GPP − Strong consensus 100% agreement.

Commentary.

In a US study of 382,637 patients with IBD schedulded for surgery (using the Nationwide Inpatient Sample), patients with obesity had an increased rates of postoperative wound complications (OR 1.35, $p = 0.01$), infections (OR 1.16, $p = 0.02$), pulmonary complications (OR 1.21, $p = 0.02$), and shock (OR 1.30, $p = 0.02$) [417]. No difference in the risk of cardiovascular complications (OR 1.09, $p = 0.52$), perforations (OR 1.04, $p = 0.71$), venous thromboembolism (OR 1.18, $p = 0.40$) or death (OR 0.73, $p = 0.07$) was observed between surgeries in IBD patients with and without obesity [418].

Although there is growing evidence, that obesity adversely affects IBD-related medical and surgical treatment [418], there is, however, no association between obesity with increased health care utilization or IBD-related surgery. No controlled intervention study has addressed the treatment of obesity in patients with IBD. Studies from other autoimmune diseases (like psoriasis) suggest that weight reduction might improve the efficacy of anti-inflammatory therapies [419]. However, the high prevalence of both micronutrient deficiencies and sarcopenia, here indicating sarcopenic obesity, indicates that the patient on a restrictive diet is at risk of further deficiencies and muscle mass loss, especially in catabolic states such as those associated with IBD flares. Therefore, the panel recommends against low-calorie diets in patients with active disease and recommends endurance training as the first step in any effort to lose weight.

Are there special dietetic recommendations for pregnant and breastfeeding patients with IBD?

Recommendation 70.

In patients with IBD who are pregnant, iron status and folate levels should be monitored regularly and in the case of deficiencies, iron and/or vitamin B9/folic acid should be additionally supplemented.

Grade of recommendation GPP – Strong consensus 100% agreement.

Recommendation 71.

In patients with IBD who are breastfeeding, nutritional status should be monitored regularly and in case of deficiencies, they should be supplemented.

Grade of recommendation GPP – Strong consensus 100% agreement.

Commentary for 70 and 71.

The consequences of anemia and those of neural tube defects [420], along with the frequent deficiencies in patients with IBD warrant regular screening for iron and folate deficiencies, respectively, during pregnancy, along with nutritional follow-up.

As part of preconception care, it is well established that the neural tube defects hazard can be prevented with periconceptional folic acid supplementation [421]. This is supported by a Cochrane review showing a risk reduction of RR 0.31 (95% CI 0.17–0.58). Oral folic acid supplementation of 300–400 μg/d should be mandatory in IBD, too. The consequences of anemia and those of neural tube defects [420], along with the frequent deficiencies in patients with IBD warrant additional regular screening for iron and folate deficiencies, respectively, during pregnancy, along with nutritional follow-up.

There is little information available that is specific to the situation of the woman with IBD who is considering breastfeeding. However, there is no evidence of harm from the use of any nutritional intervention that is thought otherwise appropriate as part of the management of the new mother.

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Disclaimer

This guideline has been developed with reasonable care and with the best of knowledge available to the authors at the time of preparation. They are intended to assist healthcare professionals and allied healthcare professionals as an educational tool to provide information that may support them in providing care to patients. Patients or other community members using this guideline shall do so only after consultation with a health professional and shall not mistake this guideline as professional medical advice. This guideline must not substitute seeking professional medical and health advice from a health professional.

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Conflict of interest

The expert members of the working group were accredited by the ESPEN Guidelines Group, the ESPEN Education and Clinical Practice Committee, and the ESPEN executive. All expert members have declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE). If potential conflicts were indicated, they were reviewed by the ESPEN guideline officers and, in cases of doubts, by the ESPEN executive. None of the expert panel had to be excluded from the working group or from co-authorship because of serious conflicts. The conflict-of-interest forms are stored at the ESPEN guideline office and can be reviewed with legitimate interest upon request to the ESPEN executive.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.12.004.

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