Clinical Nutrition 39 (2020) 632–653

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease

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ARTICLE INFO

Article history:
Received 28 October 2019
Accepted 1 November 2019

Keywords:
Crohn's disease
Ulcerative colitis
Enteral nutrition
Parenteral nutrition
Inflammatory bowel disease
Nutritional therapy

SUMMARY

The present guideline is the first of a new series of "practical guidelines" based on more detailed scientific guidelines produced by ESPEN during the last few years. The guidelines have been shortened and now include flow charts that connect the individual recommendations to logical care pathways and allow rapid navigation through the guideline. The purpose of the present practical guideline is to provide an easy-to-use tool to guide nutritional support and primary nutritional therapy in inflammatory bowel disease (IBD). The guideline is aimed at professionals working in clinical practice, either in hospitals or in outpatient medicine, and treating patients with IBD. In 40 recommendations, 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. As in adults, malnutrition is prevalent in paediatric IBD, mainly in active disease and more in CD than in UC. 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.

2. Methodology

The present practical guideline consists of 40 recommendations and is based on the ESPEN Guideline: Clinical Nutrition in inflammatory bowel disease [1]. The original guideline was shortened by restricting the commentaries to the gathered evidence and literature on which the recommendations are based on. The

Abbreviations: CD, Crohn's disease; EN, enteral nutrition; IBD, inflammatory bowel disease; ONS, oral nutritional supplements; PN, parenteral nutrition; UC, ulcerative colitis.

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https://doi.org/10.1016/j.clnu.2019.11.002
0261-5614/

recommendations were not changed (except "artificial nutrition" was replaced by "medical nutrition" and language was adapted to American English), but the presentation of the content was transformed into a graphical presentation consisting of decision-making flow charts wherever possible. The original guideline was developed according to the standard operating procedure (SOP) for ESPEN guidelines [2]. This SOP is oriented on the methodology of the Scottish Intercollegiate Guidelines Network (SIGN). Literature was searched and graded into 1–4 according to evidence, and recommendations were created and graded into four classes (A/B/0/GPP). All recommendations were not only based on evidence, but also underwent a consensus process, which resulted in a percentage of agreement (%). Whenever possible, representatives from different professions (physicians, dieticians, nurses, others) as well as patient representatives were involved. The guideline process was funded exclusively by the ESPEN society. The guideline shortage and dissemination was funded in part by the UEG society, and also by the ESPEN society. For further details on methodology, see the full version of the ESPEN guideline [1] and the ESPEN SOP [2].

The ESPEN practical guideline "Clinical Nutrition in inflammatory bowel disease" has been structured according to a flow chart covering all nutritional aspects of IBD (Fig. 1).

3. Results

3.1. *Prevention of IBD* (*Fig. 2*)

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 CD or UC and is therefore recommended.

Grade of recommendation 0 – strong consensus (90% agreement).

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" [3]. 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 IBD patients (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 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 [4]: 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 [5], 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 [6]: 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 towards lower risk of UC (HR 0.72). In contrast, 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 [7]. At recruitment, dietary intakes of DHA 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).

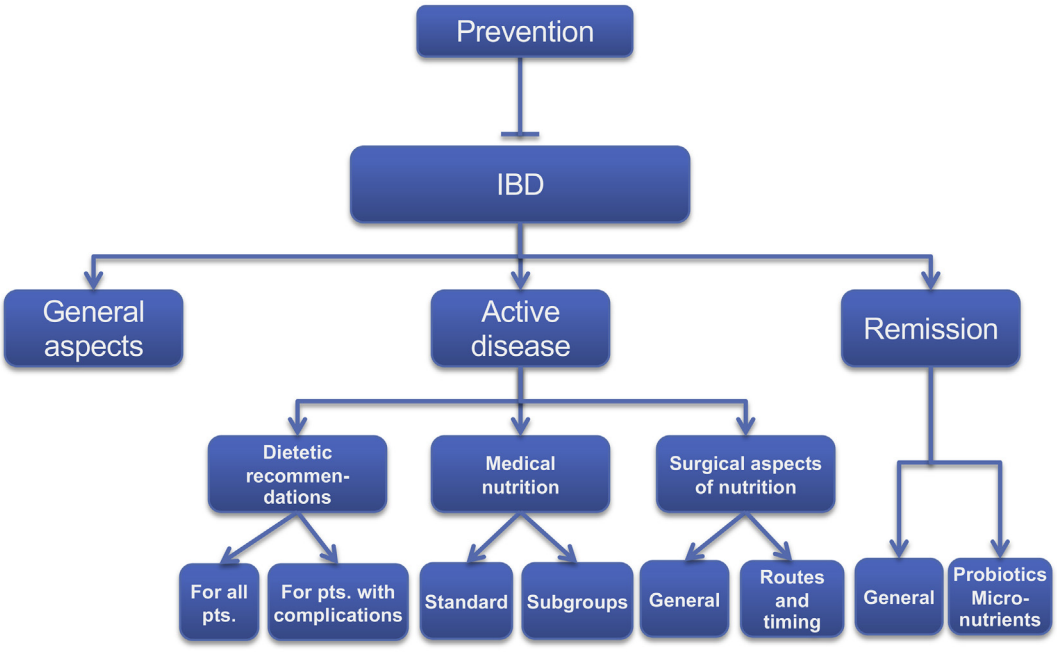

Fig. 1. Structure of the ESPEN Practical guideline "Clinical Nutrition in inflammatory bowel disease (IBD)".

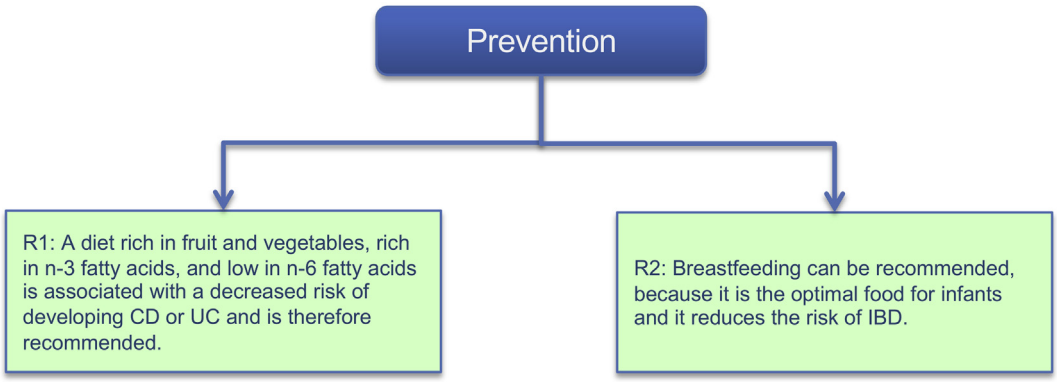

Fig. 2. Prevention of inflammatory bowel disease (IBD; Crohn's disease, CD; ulcerative colitis, UC).

Recommendation 2

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

Grade of recommendation B – strong consensus (93% agreement).

Systematic reviews from 2004 to 2009 concluded strongly in favor of breastfeeding [8,9] 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 [10]. 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) [11]. Two further publications confirmed this relationship, one from the US and another from Asia-Pacific [12,13]. Breastfeeding for around six months or longer is desirable in all infants [14].

3.2. *General aspects* (Fig. 3)

Recommendation 3A

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 (96% agreement).

Recommendation 3B

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

Grade of recommendation GPP – strong consensus (96% agreement).

Adults with IBD are at increased risk of malnutrition, with deficits more common in patients with CD than UC [15]. Obese patients may have covert deficits in lean mass which may be unmasked by tools such as skinfold thickness measurement. Patients with active IBD, particularly those whose disease is poorly responsive to medical therapy, are at highest risk of poor nutrition. In adults, risk of malnutrition can be assessed with validated screening tools [16].

Malnourished patients with IBD are more likely to be hospitalized following emergency department attendance [17] and are more likely to be admitted to hospital due to infection [18]. In hospitalized patients, malnutrition is an independent risk factor for venous thromboembolism [19], non-elective surgery [20], longer admission [15,20] and increased mortality [15].

Malnutrition in children: Malnutrition in childhood CD is common at diagnosis and may persist despite disease treatment [21]. Children with UC are also at risk of poor nutrition, but nutritional deficits may not be immediately obvious on assessment of just height and weight [22]. Although a variety of screening tools exists, the tools have poor ability to discern different levels of nutrition risk for children with IBD [23]. Poor nutrition in childhood IBD contributes to disrupted pubertal development and impaired growth velocity which may lead to short stature in adulthood. Of particularly importance in pediatric IBD is growth failure, which is the result of a combination of inflammation and chronic malnutrition [24].

Recommendation 4

In general, the energy requirements of patients with IBD are similar to those of the healthy population; provision should be in line with this.

Grade of recommendation GPP – strong consensus (93% agreement).

For clarity this question can be formulated in two ways; firstly, do patients with IBD have an altered energy requirement compared to healthy individuals, and secondly do energy requirements vary with disease activity.

There are relatively few studies examining energy expenditure in patients with UC and all studies are of only small numbers of patients. There may be an increase in metabolic activity at times of acute severe UC compared to remission in adults [25,26] which is understandable considering that systemic disturbance (fever and tachycardia) is common. However, an increase in resting energy expenditure is likely to be offset by reduction of physical activity. Significant reduction in dietary intake is common in acute UC and may result in negative energy balance [27].

One single study has measured total energy expenditure in adults with CD and recorded normal values [28]. Measured resting

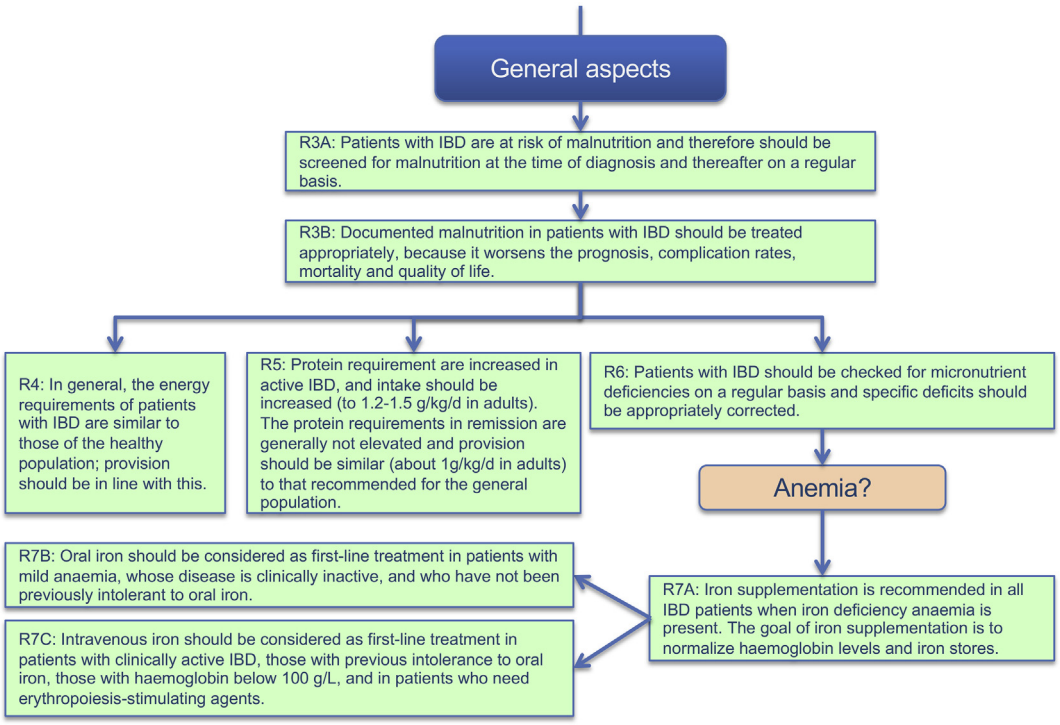

Fig. 3. General aspects of nutritional care in IBD (energy and protein requirement, iron supplementation). For abbreviations see Fig. 2.

energy expenditure per kilogram in adult patients has been found to be higher than [29] or the same as [30] that measured in healthy controls. However, this could be due to inadequate consideration of body size and the relative proportions of tissues of differing metabolic activity. No consistent association between CD activity and resting energy expenditure in adults has been demonstrated. In children with CD, measured resting energy expenditure has not been demonstrated to be significantly different. Measurement of resting energy expenditure by indirect calorimetry could be used in troublesome cases.

Recommendation 5A

Protein requirement 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 5B

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 (96% agreement).

Patients with IBD develop a relative reduction in lean mass and increase in obesity over time. This may occur due to chronically poor dietary intake, increased rates of protein turnover and gut loss of nutrients during phases of active disease or from the effect of disease treatments. Corticosteroids increase net loss of protein in children [31] and adults [32] with CD. In contrast administration of elemental or polymeric feed as treatment of CD or as adjunctive nutrition support results in reduction of proteolysis and acquisition of lean tissue in children and adults [33–35].

Monitoring of anthropometry provides insight into which patients develop relative deficits in lean mass and therefore would benefit from nutritional supplementation. There is no good evidence that the daily protein needs of IBD patients differ from those of healthy controls, but as discussed elsewhere poor appetite and restricted dietary intake is commonplace. In patients receiving steroids and 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 IBD patients in remission differ from those of healthy controls. 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 bodyweight [36,37].

Recommendation 6

Patients with IBD should be checked for micronutrient deficiencies on a regular basis and specific deficits should be appropriately corrected.

Grade of recommendation GPP – strong consensus (100% agreement).

Patients with IBD are vulnerable to micronutrient deficits due to gut loss from diarrhea and inadequate dietary intake from anorexia accompanying disease activity. At times when nutrition support is offered then multivitamin and micronutrient supplements should also be offered to ensure an appropriately balanced nutritional intake.

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. 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 [38]. In light of this, some authors have examined micronutrient status in patients in clinical disease remission and found deficits of a variety of micronutrients [39,40]. Furthermore, deficits may be present even in apparently well-nourished individuals [41]. These observations highlight the need for routine monitoring (perhaps annually) to screen for deficiency. 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 [42]. Poor compliance, particularly in adolescents, is common with multivitamin supplements and patient education about the rationale behind their use is important [43].

Consequences of deranged micronutrient status include anemia, impaired linear growth and poor bone health. 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 (Recommendation 11).

Recommendation 7A

Iron supplementation is recommended in all IBD patients when iron deficiency anemia is present. The goal of iron supplementation is to normalize hemoglobin levels and iron stores.

Grade of recommendation A – strong consensus (100% agreement).

Recommendation 7B

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

Grade of recommendation A – strong consensus (100% agreement).

Recommendation 7C

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 in patients who need erythropoiesis-stimulating agents.

Grade of recommendation A – strong consensus (93% agreement).

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 the presence of anemia [44]. The major forms of anemia in IBD are iron deficiency anemia, anemia of chronic disease and anemia of mixed origin [ECCO Anemia Statement 1A] [44]. 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 mild disease, measurements should be performed every six to twelve 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 IBD patients, whatever their age, when iron-deficiency anemia is present [ECCO Anemia Statement 2A]. Quality of life improves with correction of anemia, and this improvement is independent of clinical activity [45]. The European Crohn's and Colitis Organization (ECCO) guidelines [44] conclude that "IV iron is more effective, shows a faster response, and is better tolerated than oral iron" and state that "IV 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 [44]. The estimation of iron need is usually based on baseline hemoglobin and body weight (Table 1) [46].

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 12 or 13 g/dL according to gender [ECCO Anemia Statement 3E].

3.3. *Dietetic recommendations in active disease* (Figs. 4 and 5)

Recommendation 8

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

Grade of recommendation GPP – strong consensus (96% agreement).

RCT data regarding the effects of experimental diets such as specific carbohydrate, paleolithic, gluten-free, low fermentable oligo-, di- and monosaccharides and polyols (FODMAP), or ω-3 PUFA enriched diets on intestinal inflammation or on inducing remission are still lacking at this time. An adequately powered RCT of fructo-oligosaccharides showed no clinical benefit in patients with active CD [47]. See also Recommendation 31. Therefore, no "oral IBD diet" can be generally recommended to promote remission in IBD patients with active disease. This recommendation does not prelude the needs of all IBD patients to receive an individual (nutritional) approach based on their specific personal situation,

Table 1
Simple scheme for estimation of total iron need [46].

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

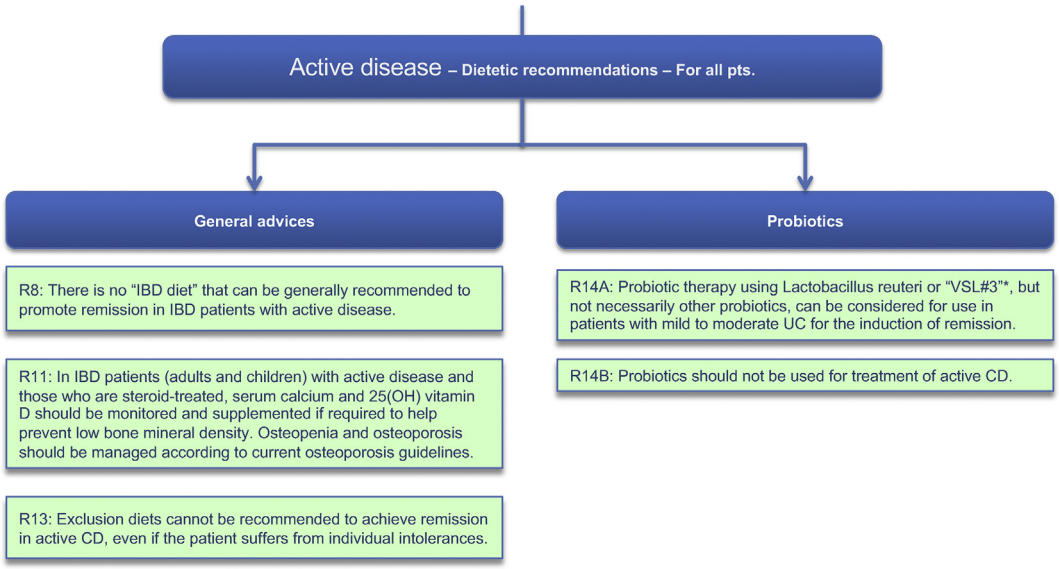

Fig. 4. Dietetic recommendations in active disease, part 1 (dietetic advice, probiotics). For abbreviations see Fig. 2. *The recommendations which recommend "VSL#3", refer only to the probiotic formulation used in the cited literature. Effective January 2016, that formulation is no more available under the same brand VSL#3.

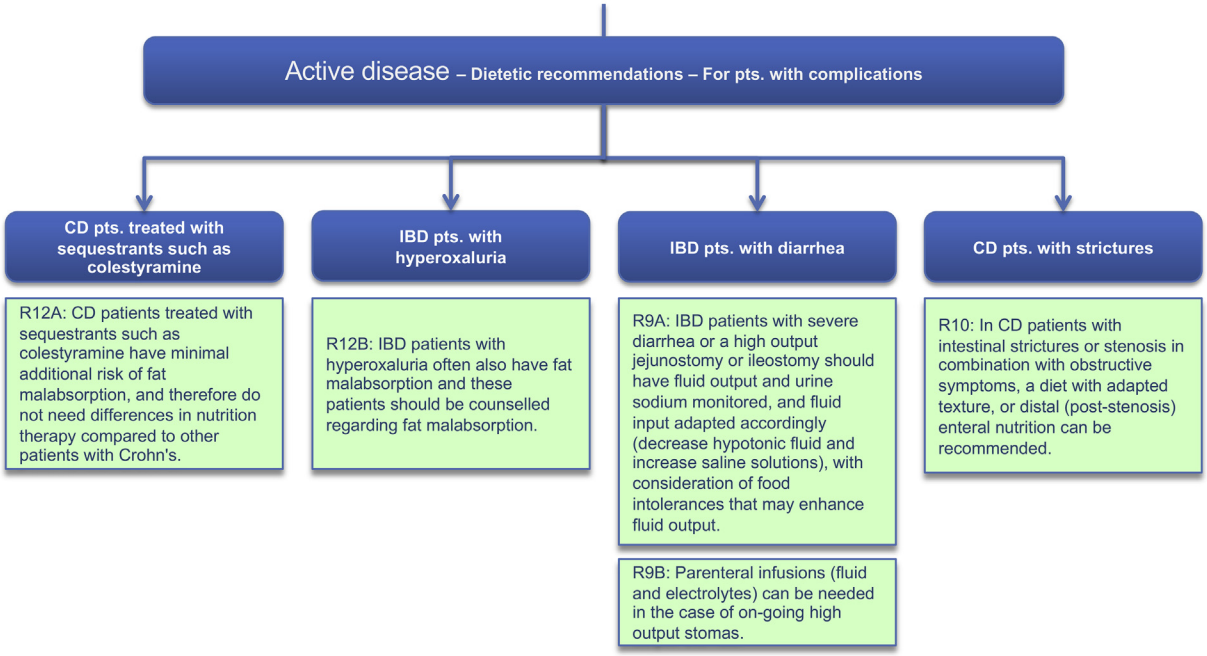

Fig. 5. Dietetic recommendations in active disease, part 2 (for patients with complications). For abbreviations see Fig. 2.

preferably with the active input of a dedicated dietician or nutritionist as part of the multidisciplinary approach.

Recommendation 9A

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

Grade of recommendation 0 – strong consensus (93% agreement).

Recommendation 9B

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

Grade of recommendation 0 – strong consensus (96% agreement).

Ongoing and severe diarrhea or increased/high output stoma can result in intestinal insufficiency [48] with malabsorption, unintentional weight loss, malnutrition, nutritional deficiencies and/or dehydration. Malabsorption is an important contributing factor to malnutrition in IBD [49]. The retrospective study of Baker in 687 stoma patients [50], 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% 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 home-setting. Satisfactory home management with oral fluid restriction and monitoring of urine sodium content was demonstrated more than 35 years ago [51]. In a study in 13 adult (ileal) increased/high output stoma patients, oral rehydration solutions containing rice maltodextrins supplementation 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 [52]. 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 [53]. No RCTs are available on nutritional treatment of IBD related diarrhea or increased/high output stoma. Only case studies on treatment of CD with increased/high output stoma have been published, which show successful treatment with restriction of hypotonic fluids, sodium enriched diets, exclusive enteral nutrition and/or parenteral sodium-containing infusions.

Recommendation 10

In CD patients with intestinal strictures or stenosis in combination with obstructive symptoms, a diet with adapted texture, or distal (post-stenosis) EN can be recommended.

Grade of recommendation GPP – strong consensus (95% agreement).

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 which is low in insoluble fiber, but there are no robust data to support this apparently 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. A recent Chinese prospective observational study in 59 adult CD patients with inflammatory bowel strictures showed that twelve weeks 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 [54]. 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 apparently logical approaches.

Recommendation 11

In IBD patients (adults and children) with active disease and those who are steroid-treated, serum calcium and 25(OH) vitamin D should be monitored and supplemented if required to help prevent low bone mineral density. Osteopenia and osteoporosis should be managed according to current osteoporosis guidelines.

Grade of recommendation B – strong consensus (96% agreement).

Significant risk factors for low bone mineral density studied in adult IBD populations (n = 116 and n = 205) prove to be low serum vitamin D, male gender, Asian ethnicity, CD, low BMI and corticosteroid use, whereas no consensus on role of age, or age at diagnosis was found [55,56]. 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 [57].

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 CD patients showed improved bone mineral density at lumbar spine after two years of once weekly treatment course with risedronate 35 mg, concomitant with calcium and vitamin D supplementation [58]. 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 IBD patients with osteoporosis [59]. Evaluation for vitamin D deficiency is recommended in IBD and ensuring always an adequate supply of calcium and vitamin D, especially in steroid-treated IBD patients. Limitation of corticosteroid use helps to prevent low bone mineral density.

Recommendation 12A

CD patients treated with sequestrants such as cholestyramine have minimal additional risk of fat malabsorption, and therefore do not need differences in nutrition therapy compared to other patients with CD.

Grade of recommendation GPP – consensus (86% agreement).

Recommendation 12B

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

Grade of recommendation GPP – consensus (88% agreement).

The common causes of bile acid malabsorption in CD are ileal resection and inflammation of the terminal ileum. Decreased reabsorption of conjugated gall 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 [60]. If mild, bile acid diarrhea can be controlled by a sequestrant such as cholestyramine [61,62]. In a double-blind cross-over study in 14 CD patients who

had undergone ileal resection, no negative effect of cholestyramine treatment on jejunal fat absorption was reported. In severe cases of bile acid malabsorption however, steatorrhea may worsen as a result of cholestyramine treatment [63].

Enteric (secondary) hyperoxaluria (with increased risk of kidney stones) occurs in severe small bowel CD associated with fat malabsorption and a consecutive elevation of intestinal oxalate absorption. Enteric hyperoxaluria may occur after ileal resection. Presence of the colon is an important factor, as oxalate remains available for colonic absorption because of concomitant fat malabsorption and its binding of calcium [64]. Urinary oxalate excretion correlates with fat excretion, as was shown in one study in CD patients undergoing intestinal resection. Increasing the dietary fat intake in these patients further increased urinary oxalate excretion [65]. Significantly lower mean values of urinary oxalate excretion were found in pediatric than in adult CD patients [66]. A reason for this may be the shorter history of CD, which usually also implies fewer bowel resections. This implies that a diet low in fat and oxalate and high in calcium should be recommended in patients with hyperoxaluria. Restriction of dietary oxalate (teas and fruits mainly) seems warranted only in those with recurring urinary tract stones.

Recommendation 13

Exclusion diets cannot be recommended to achieve remission in active CD, even if the patient suffers from individual intolerances.

Grade of recommendation GPP – strong consensus (96% agreement).

The systematic inquiry revealed insufficient evidence to make firm recommendations for exclusion diets as induction therapy. Exclusion diets have been described to alleviate symptoms [67], but only few uncontrolled studies report induction of remission [68,69].

In an RCT, longer maintenance of remission (after successful induction of remission using elemental formula) was seen in patients using a stepwise dietary introduction program excluding foods that worsened symptoms, compared to patients receiving corticosteroids on a tapering schedule while eating a normal diet [70]. Similar results on maintenance of remission were reported in an open label study by the same group using a personal food exclusion diet [71]. Another study reported maintenance of clinical remission using an IgG4 guided exclusion diet in adult CD patients [72].

Exclusion diets are labor-intensive for staff, and complex, challenging and often unpleasant for patients. The systematic enquiry revealed no evidence that exclusion diets are hazardous when applied under medical supervision. Evidence was not forthcoming to indicate that they contribute to nutritional deficiencies. Nonetheless it is good practice to monitor carefully for deficiencies that might be predicted from any particular set of exclusions.

Recommendation 14A

Probiotic therapy using Lactobacillus reuteri or "VSL#3"*, but not necessarily other probiotics, can be considered for use in patients with mild to moderate UC for the induction of remission.

Grade of recommendation 0 – strong consensus (92% agreement).

Recommendation 14B

Probiotics should not be used for treatment of active CD.

Grade of recommendation B – strong consensus (95% agreement).

Two clinical trials in pediatric UC patients show a moderate effect of rectal enemas containing *Lactobacillus reuteri* in mild distal UC [73] and of an oral preparation of the formulation previously known as VSL#3 in active UC [74]. The systematic enquiry indicated that probiotics were, in general, ineffective in active CD.

*The recommendations which recommend "VSL#3", refer only to the probiotic formulation used in the cited literature. Effective January 2016, that formulation is no more available under the same brand VSL#3.

3.4. ***Medical nutrition in active IBD*** *(Figs. 6 and 7)*

Recommendation 15A

Oral Nutrition Supplements (ONS) are the first step when medical nutrition is indicated in IBD, but generally are a minor supportive therapy used in addition to normal food.

Grade of recommendation 0 – strong consensus (92% agreement).

Recommendation 15B

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

Grade of recommendation A – strong consensus (100% agreement).

Recommendation 15C

PN is indicated in IBD (i) when oral nutrition or EN is not sufficiently possible, (e.g. when the GI tract is dysfunctional or in CD patients 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 B – strong consensus (96% agreement).

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 GI tract, the nutritional status of the patient, and the therapeutic goals. Oral Nutrition Supplements (ONS) are the first step but generally are a minor supportive therapy used in addition to normal food. By using ONS, a supplementary intake of up to 600 kcal/day can be achieved without compromising normal food intake in adults. If oral feeding

is not possible, feeding the patient through a nasogastric or nasoenteric tube should be considered. EN should be considered in patients with a functional gastrointestinal tract but who are unable to swallow safely [75,76]. In situations when the gut cannot absorb all nutritional needs, EN should nonetheless be attempted with supplementary PN [41,77,78]. 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 [79]. However, it must be recognized that these patients in need of PN are those with the most complicated disease [80].

Recommendation 16

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

Grade of recommendation B – strong consensus (92% agreement).

Primary nutritional therapy in the form of exclusive EN should be considered in all patients with acute active CD. This is a first choice in patients at high risk from alternative therapy such as steroids. Old meta-analyses demonstrated that corticosteroids are better than exclusive EN in 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 [81], and that in some settings (i. e. cconcomitant immunomodulatory treatment) exclusive EN might even be superior to corticosteroids in children [82]. 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 [60], though one RCT showed similar efficacy [83]. 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 contra-indicated. 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 [84]. 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 [85].

Recommendation 17A

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

Grade of recommendation B – strong consensus (96% agreement).

Recommendation 17B

EN in CD should be administered via an enteral feeding pump.

Grade of recommendation B – strong consensus (92% agreement).

EN can be safely delivered by nasogastric tube, or percutaneous endoscopic gastrostomy [86–88]. 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 [86–89]. 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 [88,89].

Few patients with UC will need EN or PN other than during the most severe exacerbations and in the peri-operative phase. EN is most appropriate and associated with significantly fewer complications than PN in acute UC. Bowel rest through intravenous nutrition does not alter the outcome, but nonetheless, 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 fulfil 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.

Recommendation 18A

Standard EN (polymeric, moderate fat content, no particular supplements) can be employed for primary and supportive nutritional therapy in active IBD.

Grade of recommendation 0 – strong consensus (96% agreement).

Recommendation 18B

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

Grade of recommendation B – strong consensus (96% agreement).

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) [90]. The protein composition did not appear to influence the therapeutic potential of EN. The present systematic enquiry reveals insufficient evidence to make firm recommendations [90,91]. It is

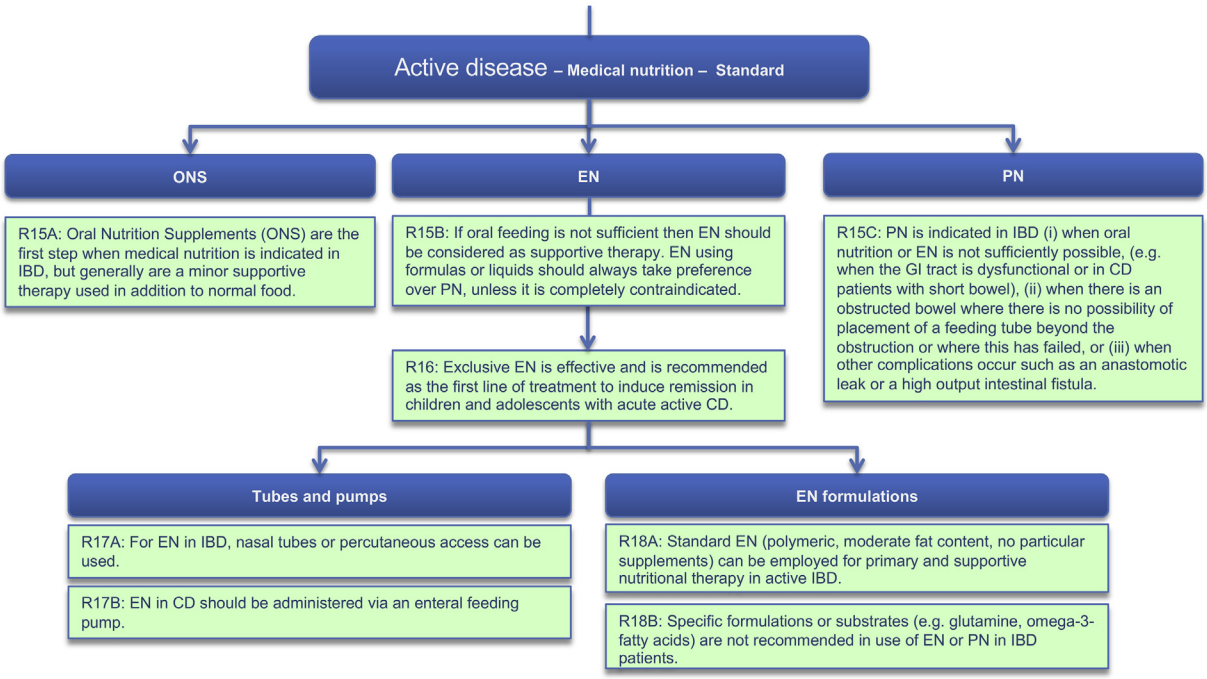

Fig. 6. Medical nutrition in active disease, part 1 (oral nutrition supplements, ONS; enteral nutrition, EN; parenteral nutrition, PN). For abbreviations see Fig. 2.

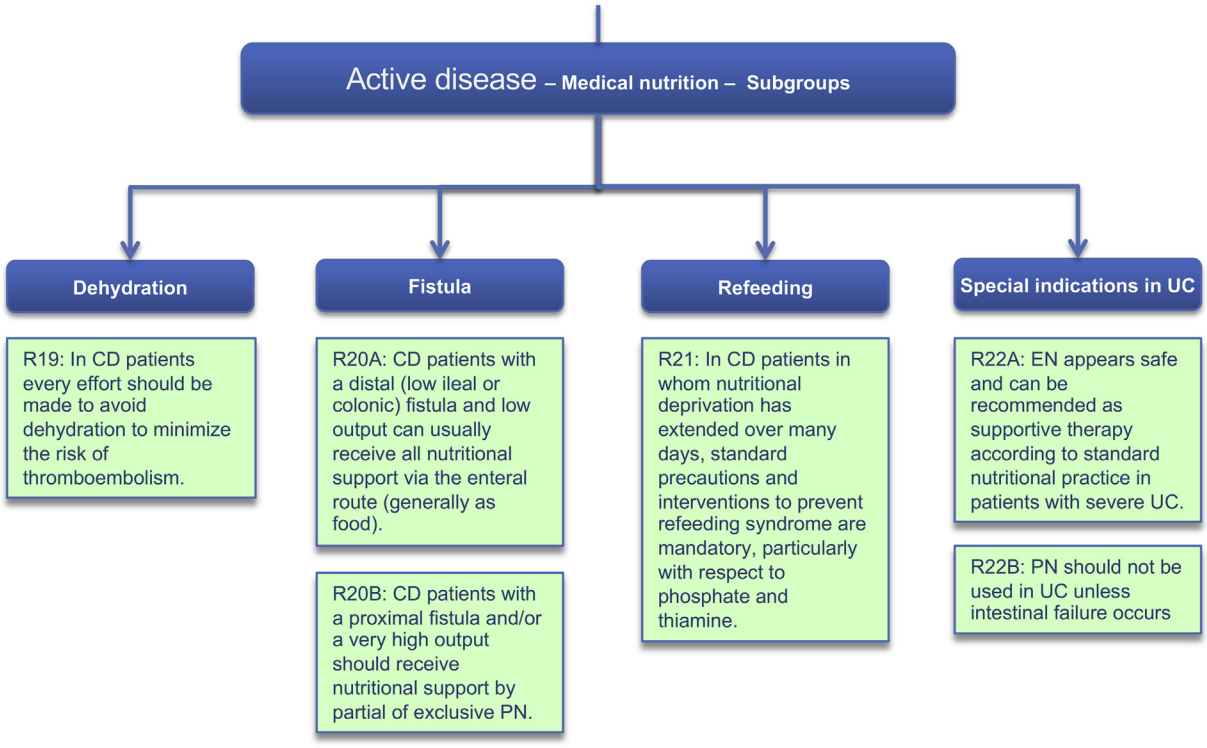

Fig. 7. Medical nutrition in active disease, part 2 (dehydration, fistulae refeeding etc.). For abbreviations see Fig. 2.

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 emulsifying 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 is inferior to the use of standard polymeric feeds [92].

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 fulfil the needs of the individual patient.

Recommendation 19

In CD patients every effort should be made to avoid dehydration to minimize the risk of thromboembolism.

Grade of recommendation GPP – strong consensus (100% agreement).

Although there are insufficient data to mandate routine anticoagulation, this should be considered in all IBD patients and especially those on PN, with every effort made to avoid dehydration [93–97].

Recommendation 20A

CD patients 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 0 – strong consensus (100% agreement).

Recommendation 20B

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

Grade of recommendation B – strong consensus (96% agreement).

Patients with CD are prone to fistulae formation between two intestinal sites or from intestine to another organ (especially skin, bladder and vagina). Most occur post-operatively. It is demonstrated that in surgical patients, early nutritional support, independently of the route of administration, decreases the occurrence and severity of fistulae [84,98,99]. Malnutrition with BMI <20 appears as an independent risk factor [100].

Treatment of intestinal fistulae is usually complex, depending on the location, scale and the nature of the symptoms, and warrants the input of a multidisciplinary team including gastroenterologist, surgeon and dietician [99]. In patients with a distal (low ileal or colonic) fistula it may be possible to provide all necessary nutritional support via the enteral route [101–103]. In the patient with a proximal fistula and/or a very high output it may be preferable to manage the situation with a rested gut and full PN [104,105], but even then, the psychological benefit of eating may warrant its inclusion in the nutritional regimen despite minimal expectations of useful nutrient absorption [102]. Surgical correction is more likely to be successful if nutritional status has been optimized pre-operatively [106].

Recommendation 21

In CD patients in whom nutritional deprivation has extended over many days, standard precautions and interventions to prevent refeeding syndrome are mandatory, particularly with respect to phosphate and thiamine.

Grade of recommendation B – strong consensus (100% agreement).

Refeeding syndrome should not be a problem in the well-managed patient with IBD but nonetheless 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 [107–109].

Recommendation 22A

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 22B

PN should not be used in UC unless intestinal failure occurs.

Grade of recommendation 0 – consensus (88% agreement).

EN has not been adequately evaluated in active UC. However, it appears safe and can be nutritionally adequate in patients with severe disease [110]. 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, only when they not able to tolerate EN, or cannot be fed effectively by either mouth or enteric tube [110–112].

3.5. ***Surgical aspects of nutrition in IBD*** *(Figs. 8 and 9)*

Recommendation 23A

In most elective surgery cases, pre-operative fasting from midnight should not be performed – instead, an enhanced recovery (ERAS) protocol can be used.

Grade of recommendation B, see ESPEN Surgery guideline [113] – strong consensus (100% agreement).

ESPEN has produced guidance on nutrition in the surgical patient [113] and most of the principles apply equally to the IBD patient undergoing surgical intervention. 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 pre-operative 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 impair GI function

- early mobilization to facilitate protein synthesis and muscle function.

Recommendation 23B

In emergency surgery patients, medical nutrition (EN, PN) should be initiated if the patient is malnourished at the time of surgery or if oral diet cannot be recommenced within 7 days after surgery.

Grade of recommendation B, see ESPEN Surgery guideline [113] – *consensus (88% agreement).*

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 seven days perioperatively. It is also indicated in patients who cannot maintain oral intake above 60–75% of recommended intake for more than ten days. In these situations, it is recommended to initiate nutritional support (preferably by the enteral route) without delay.

Recommendation 24A

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

Grade of recommendation B – strong consensus (100% agreement).

Insufficient preoperative intake is an indication for dietary counseling or ONS, because as Kuppinger et al. [114] 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 has been investigated [115–119]. The available data do not show with certainty that routine administration improves outcome, but they do show benefit 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.

Recommendation 24B

Patients who do not meet their energy and/or protein needs from normal food plus ONS should receive EN during the perioperative period.

Grade of recommendation B – strong consensus (100% agreement).

As stated above, insufficient preoperative intake affects complication rates. Therefore, if the oral intake is inadequate, regardless of the intervention (oral food or ONS), EN should be initiated [113]. Postoperatively, EN should be continued/started as many studies have shown the benefits and feasibility of feeding via a tube either inserted distal to the anastomosis, e. g. needle catheter jejunostomy, or inserted via the nose with its tip passed distally at the time of operation (nasojejunal tube) [120–125].

Recommendation 24C

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.

Grade of recommendation A, see ESPEN Surgery guideline [113] – *strong consensus (96% agreement).*

Undernutrition has a negative impact on the clinical course, the rate of postoperative complications and on mortality [126–131]. Therefore, patients with severe nutritional risk will benefit from nutritional therapy prior to major surgery even if surgery has to be delayed. “Severe” nutritional risk has been defined by an ESPEN working group (2006) as the presence of at least one of the following criteria:

- Weight loss > 10–15% within six months
- BMI < 18.5 kg/m2
- Serum albumin <30 g/l (with no evidence of hepatic or renal dysfunction)

Recommendation 25A

EN should always be preferred over the parenteral route, but combinations of EN and PN should be considered in patients in whom there is an indication for nutritional support and in whom >60% of energy needs cannot be met via the enteral route.

Grade of recommendation A, see ESPEN Surgery Guideline [113] – *strong consensus (100% agreement).*

Recommendation 25B

PN in the perioperative period in IBD patients should be usually used as supplementary to EN.

Grade of recommendation B – strong consensus (96% agreement).

Recommendation 25C

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

Grade of recommendation A – strong consensus (96% agreement).

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

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

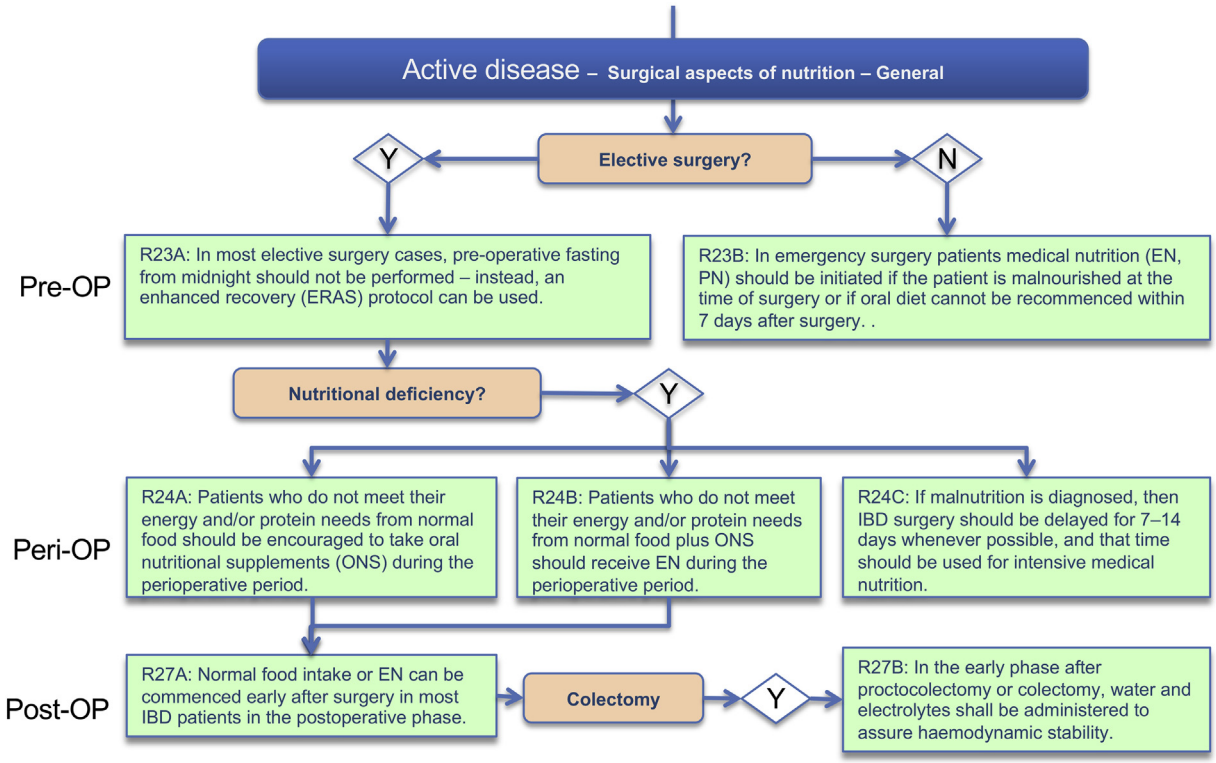

Fig. 8. Surgical aspects of nutrition in active disease (general recommendations). For abbreviations see Fig. 2.

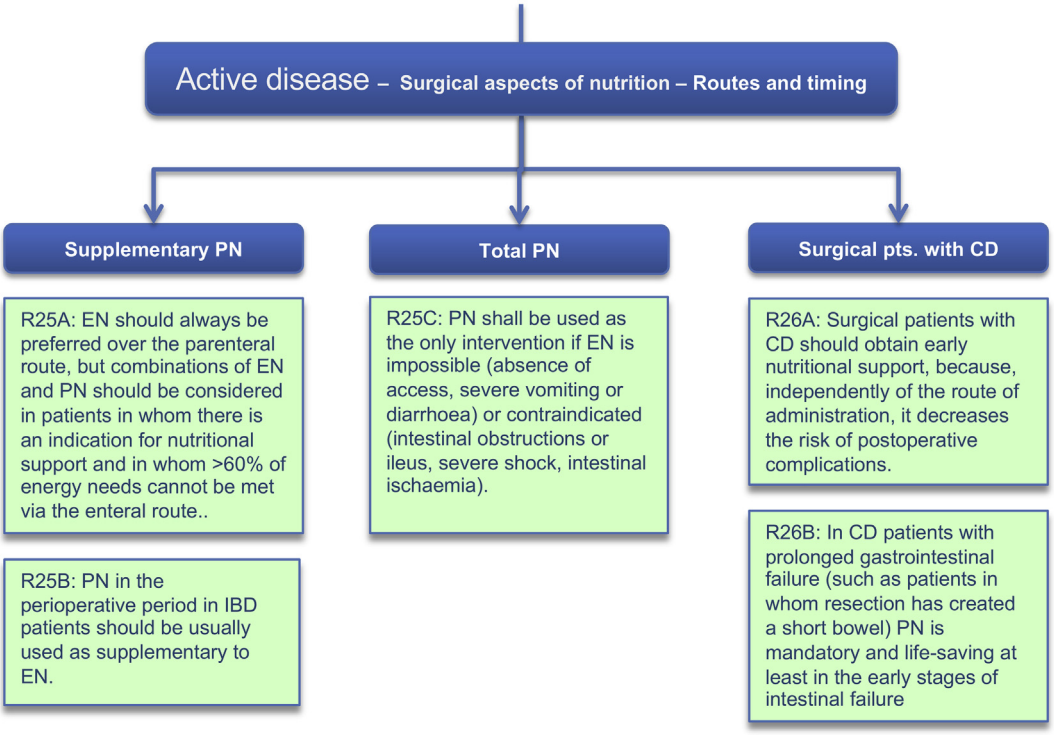

Fig. 9. Surgical aspects of nutrition in active disease (routes and timing). For abbreviations see Fig. 2.

In those cases, PN may be needed for a period of days or weeks until the function of gastrointestinal tract returns. For further details, see the ESPEN guideline on Clinical Nutrition in Surgery [113].

Recommendation 26A

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 (100% agreement).

The advantages of early EN within 24 h of surgery versus later commencement have been shown in two meta-analyses (one Cochrane systematic review) [132,133].

Recommendation 26B

In CD patients 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.

Grade of recommendation B, see ESPEN surgery guideline – strong consensus (92% agreement).

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 fistulae individuals because of the compromised integrity of the gastrointestinal tract. Therefore, PN often represents the main option, alone or in association with EN (supplemental PN) [72].

Recommendation 27A

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

Grade of recommendation 0, see ESPEN surgery guideline – strong consensus (100% agreement).

Recommendation 27B

In the early phase after proctocolectomy or colectomy, water and electrolytes shall be administered to assure hemodynamic stability.

Grade of recommendation A, see ESPEN surgery guideline – strong consensus (96% agreement).

As stated in the Surgical Guidelines [113], 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 [129]. Recent meta-analyses [133–135] showed significant benefits with regard to 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 outcome such as mortality: anastomotic dehiscence, resumption of bowel function, or hospital length of stay [135].

3.6. *Dietetic recommendations during remission* (*Figs. 10 and 11*)

Recommendation 28

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

Grade of recommendation GPP – strong consensus (100% agreement).

There are very limited original data in this area, but at least nine papers include statements indicating that the input of a dietician is likely to be helpful in IBD management in adults and children; the evidence base is poor. Nutritional deficiencies are self-evidently more likely in patients with CD affecting the small bowel than in those with isolated colonic disease or UC, but the latter groups can be afflicted also [102]. Nutritional screening has been adopted as a mandatory component of gastrointestinal management in many European countries, and it is further recommended that all IBD patients have access to a dietician with a special expertise in IBD.

Recommendation 29

No specific diet needs to be followed during remission phases of IBD.

Grade of recommendation 0 – strong consensus (96% agreement).

In general, no specific diet needs to be followed during remission phases. None of the alternative diets or semi-exclusive diets seems effective in obtaining remission. However, individual food intolerances are frequently seen in IBD patients, lactose and dairy products, spices, herbs, fried, gas-generating and fiber rich products are often poorly tolerated [136–139].

Patients with CD typically select a diet low in fiber and vegetables, and often one which is hypocaloric and associated with multiple micronutrient deficiencies [40]. 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 and there are no recent trials of exclusion diets. Limited controlled data support the elimination of lactose, dairy products in general, spices, herbs, fried foods, gas-generating and fiber-rich products, but only when they are poorly tolerated. Their removal is then probably helpful in prolonging remission [140]. Other studies of reasonable quality have also included dietary manipulations, but alongside the use of nutritional supplements; these studies are addressed in later sections. The use of an exclusive EN regimen is clearly an extreme form of dietary exclusion.

EN has been thought to have a role in preventing relapse in children with inactive CD [77,90,141,142] and the effect has also been observed in a Japanese study of adult CD patient [143–145]. Esaki et al. [146] considered from their trial of 145 patients with CD (mostly induced into remission with total PN) that, under maintenance with elemental/polymeric nutrition, the risk of recurrence

was lower in those with small bowel rather than large bowel involvement. However, the present systematic enquiry has indicated that overall the use of elemental EN is ineffective in maintaining remission in CD. This is therefore due for a verdict of not recommended. The panel considers this a controversial conclusion, especially in view of a previous Cochrane evaluation which considered that ongoing EN may help maintenance of remission and reduce use of corticosteroids in CD [86,146]. No recommendation is therefore made.

Recommendation 30

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

Grade of recommendation B – strong consensus (100% agreement).

Systematic reviews have reached the conclusion that supplementing the diet with n-3 fats is ineffective in the maintenance of remission of patients with UC [147,148]. This is therefore not advised. The above data were obtained in adults. It appears reasonable to extrapolate the conclusions into pediatric practice. The latest Cochrane review [149] has concluded that n-3 fatty acids are probably ineffective for maintenance of remission in CD.

Recommendation 31

Non-specific high fiber diets should not normally be recommended for maintenance of remission in IBD.

Grade of recommendation 0 – strong consensus (96% agreement).

Much of the recent literature relates to the effects of specific agents chosen as prebiotics and these are not considered here, but it is recognized that many forms of fiber will have an important effect on the gut microbiota and thus possibly on the maintenance of remission in IBD. It is generally agreed that dietary fiber is unwise in patients known to have intestinal stricturing (GPP), but the evolving literature suggests that prebiotic fibers may be useful in maintenance of remission in some patients with UC. Several small controlled studies have shown apparent benefit from the addition of fiber to the diet of patients with UC [150–152]. 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.

Fiber is more often relatively contra-indicated in CD because of the presence of strictures, and fiber in the form of the prebiotic fructo-oligosaccharide is apparently ineffective in CD [47]. However, in a loosely controlled study of wheat fiber supplementation the supplemented patients did better in respect of quality of life and had no apparent adverse events [153]. There is another recent study of fiber supplementation that 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% [154]. See also recommendation 8.

Recommendation 32A

Probiotic therapy should be considered for the maintenance of remission in UC.

Grade of recommendation B – strong consensus (96% agreement).

Recommendation 32B

Probiotic therapy should not be used for maintenance of remission in CD.

Grade of recommendation 0 – strong consensus (100% agreement).

The *Escherichia coli Nissle* 1917 strain and the multispecies formulation previously known as VSL#3 have benefit, supported by meta-analysis [155] in the maintenance of remission in patients – including children - with mild to moderate UC, in comparison to 5-aminosalicylate compounds [74,156,157]. Other probiotic preparations have been studied but although they have usually been well tolerated with trends toward benefit, significant effectiveness has not been demonstrated [158,159]. A cautionary note exists for *Lactobacillus rhamnosus* GG; case reports in both children and adults describe bacteremia with the administered probiotic in patients with acute severe UC [160,161].

Probiotics are probably ineffective in preventing disease recurrence for patients with CD [157]. Although some positive claims are made no unequivocal benefit can be discerned [162–167]. Probiotics are not currently recommended.

The recommendations which recommend “VSL#3”, refer only to the probiotic formulation used in the cited literature. Effective January 2016, that formulation is no more available under the same brand VSL#3.

Recommendation 33A

Colectomized patients with a pouch and pouchitis should be treated with a probiotic mixture (“VSL#3”*), if antibiotic treatment has failed.

Grade of recommendation B – strong consensus (96% agreement).

Recommendation 33B

The probiotic mixture “VSL#3”* may be used for primary and secondary prevention of pouchitis in patients with UC who have undergone colectomy and pouch-anal anastomosis.

Grade of recommendation B – strong consensus (100% agreement).

Antibiotics (ciprofloxacin, metronidazole) are the treatment of reference of acute pouchitis [168]. Two double-blind placebo-controlled trials performed in adults showed effectiveness of the formulation previously known as VSL#3 containing 450 billion colony forming units of eight lactic acid bacteria: *B. breve, B. longum, B.*

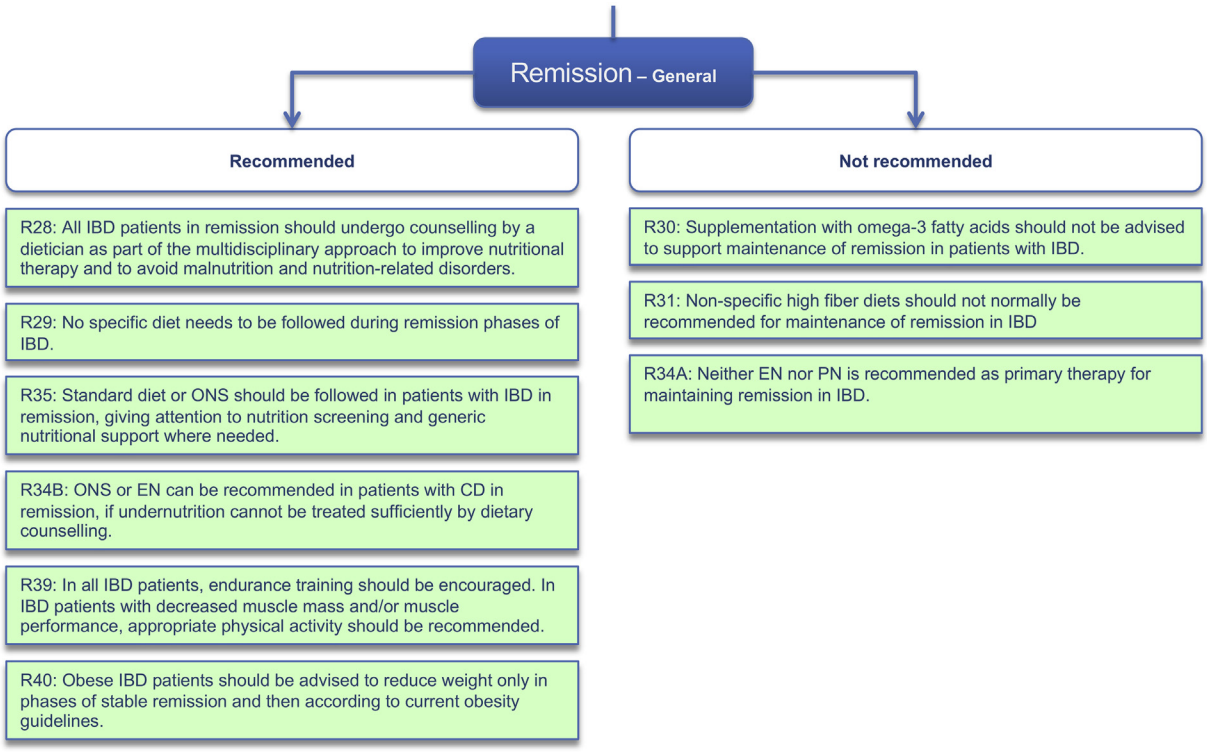

Fig. 10. Clinical nutrition during remission (general recommendations). For abbreviations see Fig. 2.

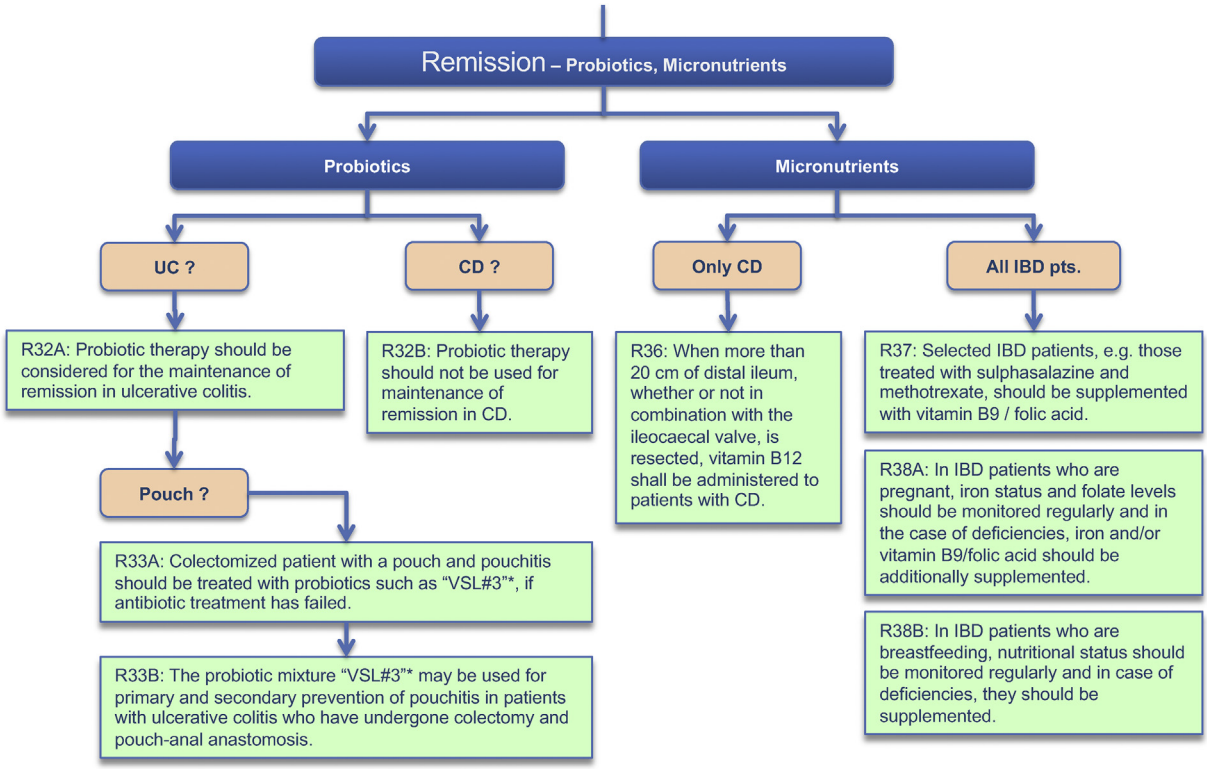

Fig. 11. Clinical nutrition during remission (probiotics, micronutrients). For abbreviations see Fig. 2. *The recommendations which recommend "VSL#3", refer only to the probiotic formulation used in the cited literature. Effective January 2016, that formulation is no more available under the same brand VSL#3.

infantis, L. acidophilus, L. casei, L. delbrueckii, L. plantarum and Streptococcus salivarius subsp. *Thermophilus*) in maintaining remission in patients with chronic pouchitis [169,170]. A pooled analysis of these two studies (76 participants) suggests that this bacteriotherapy may be more effective than placebo for maintenance of remission. Eighty-five per cent (34/40) of verum patients maintained remission at nine to twelve months compared to 3% (1/36) of placebo patients (RR 20.24). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (35 events) [171]. In another study [168] effects of this bacteriotherapy were evaluated as an adjunctive to a standard therapy. The decrease in UC disease activity index (UCDAI) scores of 50% or more was higher in the verum group than in the placebo group (63.1 vs. 40.8; per protocol $P = 0.010$). Remission was higher in the verum group than in the placebo group (47.7% vs. 32.4%; $P = 0.069$).

Prevention of pouchitis: The results of a small study (40 participants) suggest that the bacteriotherapy may be more effective than placebo for prevention of pouchitis [172]. Ninety per cent (18/20) of verum patients had no episode of acute pouchitis during the twelve-month study compared to 60% (12/20) of placebo patients (RR 1.50). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (30 events). In contrast, *L. rhamnosus* strain GG was not effective in preventing relapses [173]. Other guidelines suggest the use of the formulation previously known as VSL#3 both for maintenance of antibiotic-induced remission and for prevention of pouchitis in adults [174] and in pediatric UC [175].

*The recommendations which recommend "VSL#3", refer only to the probiotic formulation used in the cited literature. Effective January 2016, that formulation is no more available under the same brand VSL#3.

Recommendation 34A

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

Grade of recommendation GPP – strong consensus (100% agreement).

Recommendation 34B

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

Grade of recommendation GPP – strong consensus (100% agreement).

Nutritional support has not been assessed as a maintenance therapy in UC, neither has PN in CD. A recent systematic review of twelve RCTs and non-randomized cohort studies [176] (1169 patients, including 95 children), most of good quality, showed that maintenance EN was as or more effective than the comparator (standard diet, 5-ASA or azathioprine) in preventing CD relapses over periods of six months to four years. The study with the lowest risk of bias compared supplemental (50%) EN with a regular diet in 51 adult CD patients [177]. 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 [144] and two positive [178,179] studies published so far.

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 [180]. 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 a low risk of relapse, preferring polymeric feeds, with elemental feeds being advised only in the case of allergy to cow's milk proteins [181].

Recommendation 35

Standard diet or ONS should be followed in patients with IBD in remission, giving attention to nutrition screening and generic nutritional support where needed.

Grade of recommendation: GPP – strong consensus (95% agreement).

Few dietary supplementations have been tested in maintenance of remission in IBD patients with clinical endpoints. An open label, parallel-group, multicenter, randomized clinical trial demonstrated in 105 UC patients in remission that plantago ovata seeds (10 g twice daily) were as efficient as mesalamine (500 mg thrice daily) in maintaining remission to one year [151]. A Cochrane systematic review has analyzed six studies (1039 patients) of n-3 fatty acid supplementation [149]: there was a marginal significant benefit of n-3 therapy on maintenance of remission.

Recommendation 36

When more than 20 cm of distal ileum, whether or not in combination with the ileo-cecal valve, is resected, vitamin B12 shall be administered to patients with CD.

Grade of recommendation A – strong consensus (100% agreement).

A recent systematic review has assessed the literature for prevalence, risk factors, evaluation and management of vitamin B12 deficiency in IBD [182]. 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 distal ileum, whether or not in combination with the ileo-cecal valve, will put the patient at risk for B12 deficiency. Resection of less than 20 cm does not normally cause deficiency [183]. Ileal CD is not inevitably associated with vitamin B12 deficiency [184,185], but it is difficult to rule out its responsibility when more than 30–60 cm are involved [182]. CD patients with ileal involvement and/or resection and/or clinical deficiency features should be screened yearly for vitamin B12 deficiency [182].

Patients with clinical deficiency should receive 1000 μg of vitamin B12 by intramuscular injection every other day for a week and then every month for life [186]. Patients with more than 20 cm of ileum resected should receive 1000 μg of vitamin B12 prophylactically also every month and indefinitely [186]. Oral therapy may be as effective but is poorly explored in CD. A retrospective open-label non-randomized study of 36 CD patients has showed the oral route (1200 μg per day for 33, 2400 μg per day for three) to be

effective in treating vitamin B12 deficiency [187]. For now, parenteral supplementation remains the reference, but oral supplementation may become standard in the coming years.

Recommendation 37

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

Grade of recommendation B – strong consensus (100% agreement).

There are several causes for folate deficiency in IBD: low intake, malabsorption, excess folate utilization due to mucosal inflammation and medications. A combination of these factors may be responsible for the deficiency of this vitamin. Drugs are most responsible for folate deficiency by inhibition of dihydrofolate reductase, an enzyme that catalyzes reduction of dihydrofolic acid to tetrahydrofolic acid (methotrexate) [188] or folate malabsorption (sulphasalazine) [189]. 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 colo-rectal cancer (pooled HR = 0.58; 95%CI 0.37–0.80) [190]. An Italian study compared one month of supplementation with 15 mg of either folic or folinic acid in 30 IBD patients treated with sulphasalazine [191]. 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 [181]. This panel recommends the same practice in adults.

Recommendation 38A

In IBD patients 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 (95% agreement).

Recommendation 38B

In IBD patients 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).

The consequences of anemia and those of neural tube defects [192], along with the frequent deficiencies in IBD patients warrant 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.

Recommendation 39

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

Grade of recommendation: GPP – strong consensus (95% agreement).

The systematic review of 19 body composition studies reporting on 926 IBD patients revealed a low fat-free mass in 28% of CD patients and in 13% of UC patients [193]. Low muscle mass, strength and performance have been reported in adult IBD cohorts [194,195], similar findings have also been made in children [196]. Sarcopenia was reported in 12% of IBD patients of mean age 31 years, associated with osteopenia [194].

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 IBDQ total score, improved by 19% in the intervention group and 8% in the control group, with significant differences for the IBDQ social subscale that was significantly improved in the intervention group compared with controls ($p = 0.023$) [197].

The reference treatment for sarcopenia, along with maintaining an adequate protein intake, is resistance training. This is what is advised in age-related sarcopenia [198]. However, this hasn't been assessed in IBD patients. Still, the panel recommends prescribing resistance training (weight-bearing exercises) in IBD patients with sarcopenia or features of sarcopenia (reduced muscle mass, strength and/or performance).

Recommendation 40

Obese IBD patients 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).

Overweight and obesity are nowadays the most frequent nutritional disorder in IBD patients. Their prevalence varies between countries, affecting 32.7% of 581 US adult IBD patients (30.3% in CD patients and 35.2 in UC patients) [199] and 17% of 100 Irish adult CD patients [200]. An US study of 1494 IBD patients (31.5% obese) found an association between obesity and its usual comorbidities, a poor quality of life and high C-reactive protein levels [201]. However, obesity was not associated with increased health care utilization or IBD-related surgery. No intervention study has addressed the treatment of obesity in IBD patients. 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.

Conflict of Interest

No conflict of interests.

Acknowledgement

The development of this guideline was supported by ESPEN and the UEG.

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