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ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease

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Based on

ESPEN guideline: Clinical Nutrition in inflammatory bowel disease

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

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.

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 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 (Figure 1).

Results

I. Prevention of IBD (Figure 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)

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" (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 2,609 IBD patients (1,269 with CD and 1,340 with UC), and over 4,000 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).

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)

Commentary

Systematic reviews from 2004 and 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).

II. General aspects (Figure 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)

Commentary for A/B

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)

Commentary

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 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 1g/kg/d in adults) to that recommended for the general population.

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

Commentary for A/B

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 1g 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 to 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)

Commentary

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).

<u>Recommendation 7A</u>

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)

<u>Recommendation 7B</u>

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)

<u>Recommendation 7C</u>

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)

Commentary for A/B/C

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).

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

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].

III. Dietetic recommendations in active disease (Figures 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)

Commentary

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 re-

mission 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, 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)

Commentary for A/B

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)

Commentary

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)

Commentary

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 counselled regarding fat malabsorption.

Grade of recommendation GPP – consensus (88 % agreement)

Commentary for A/B

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)

Commentary

The systematic enquiry 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)

Commentary for A/B

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 "VSL#3"

in active UC (74). The systematic enquiry indicated that probiotics were, in general, ineffective in active CD.

*"VSL#3" refers only to the probiotic product used in the cited literature and equivalent products independent from the present product labeling.

IV. Medical nutrition in active IBD (Figures 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)

Commentary for A/B/C

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)

Commentary

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)

Commentary for A/B

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.

<u>Recommendation 18A</u>

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)

<u>Recommendation 18B</u>

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)

Commentary for A/B

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 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 relia-

ble 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)

Commentary

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)

Commentary for A/B

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). Surgi-

cal 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)

Commentary

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)

Commentary for A/B

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).

V. Surgical aspects of nutrition in IBD (Figures 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)

Commentary

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.

<u>Recommendation 23B</u>

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)

Commentary

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.

<u>Recommendation 24A</u>

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)

Commentary

Insufficient preoperative intake is an indication for dietary counselling 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 ad-

vantages 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)

Commentary

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)

Commentary

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 < 30g/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)

Commentary for A/B/C

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

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)

Commentary

The advantages of early EN within 24 hours 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)

Commentary for A/B

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 27 B

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)

Commentary for A/B

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).

V. Dietetic recommendations during remission (Figures 10 and 11)

Recommendation 28

All IBD patients in remission should undergo counselling 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)

Commentary

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)

Commentary

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 ele-

mental/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)

Commentary

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)

Commentary

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)

Commentary for A/B

The *E. coli Nissle* 1917 strain and the multispecies formulation "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.

"VSL#3" refers only to the probiotic product used in the cited literature and equivalent products independent from the present product labeling.

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)

Commentary for A/B

Antibiotics (ciprofloxacin, metronidazole) are the treatment of reference of acute pouchitis (168). Two double-blind placebo-controlled trials performed in adults showed effectiveness of a particular probiotic mixture ("VSL#3" containing 450 billion colony forming units of eight lactic acid bacteria: *B. breve, B. longum, B. 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, *Lactobacillus rhamnosus* strain GG was not effective in preventing relapses (173). ECCO guidelines suggest the use of "VSL#3" both for maintenance of antibiotic-induced remission and for prevention of pouchitis in adults (174) and in pediatric UC (175).

"VSL#3" refers only to the probiotic product used in the cited literature and equivalent products independent from the present product labeling.

<u>Recommendation 34A</u>

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

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

<u>Recommendation 34B</u>

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

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

Commentary for A/B

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 azathi-

oprine) 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 formulae (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).

<u>Recommendation 35</u>

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)

Commentary

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.

<u>Recommendation 36:</u>

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)

Commentary

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. Re-

section 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)

Commentary

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 colorectal 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 hours 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)

Commentary for A/B

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)

Commentary

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 sub-scale 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)

Commentary

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.

References

1. Forbes A, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, et al. ESPEN guideline: Clinical nutrition in inflammatory bowel disease. Clin Nutr. 2017;36:321-47.

2. Bischoff SC, Singer P, Koller M, Barazzoni R, Cederholm T, van Gossum A. Standard operating procedures for ESPEN guidelines and consensus papers. Clin Nutr. 2015;34:1043-51.

3. Hou JK, Abraham B, El-Serag H. Dietary Intake and Risk of Developing Inflammatory Bowel Disease: A Systematic Review of the Literature. Am J Gastroenterol 2011;106:563–73.

4. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Korzenik JR, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. Gastroenterology 2013;145:970-7.

5. Li F, Liu X, Wang W, Zhang D. Consumption of vegetables and fruit and the risk of inflammatory bowel disease: a meta-analysis. Eur J Gastroenterol Hepatol. 2015;27:623-30.

6. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Fuchs CS, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut 2014;63:776-84.

7. Tjonneland A, Overvad K, Bergmann MM, Nagel G, Linseisen J, Hallmans G, et al. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case-control study within a European prospective cohort study. Gut 2009;58:1606-11.

8. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. Am J Clin Nutr 2004; 80:1342-52.

9. Barclay AR, Russell RK, Wilson ML, Gilmour WH, Satsangi J, Wilson DC. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pediatr 2009;155: 421-6.

10. Gearry RB, Richardson AK, Frampton CM, Dodgshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. J Gastroenterol Hepatol 2010;25:325-33.

11. Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gamborg M, et al. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis. 2011;5:577-84.

12. Guo AY, Stevens BW, Wilson RG, Russell CN, Cohen MA, Sturgeon HC, et al. Early life environment and natural history of inflammatory bowel diseases. BMC Gastroenterol. 2014;14:216.

13. Ng SC, Tang W, Leong RW, Chen M, Ko Y, Studd C, et al. Asia-Pacific Crohn's and Colitis Epidemiology Study ACCESS Group. Environmental risk factors in inflammatory bowel disease: a population-based case-control study in Asia-Pacific. Gut. 2015;64:1063-71.

14. ESPGHAN Committee on Nutrition, Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, et al. Breast-feeding: A commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2009;49:112-25.

15. Nguyen GC, Munsell M, Harris ML. Nationwide prevalence and prognostic significance of clinically diagnosable protein-calorie malnutrition in hospitalized inflammatory bowel disease patients. Inflamm Bowel Dis 2008;14:1105-11.

16. Sandhu A, Mosli M, Yan B, Wu T, Gregor J, Chande N, et al. Self-Screening for Malnutrition Risk in Outpatient Inflammatory Bowel Disease Patients Using the Malnutrition Universal Screening Tool (MUST). JPEN. J Parenter Enteral Nutr 2016;40:507-10.

17. Gajendran M, Umapathy C, Loganathan P, Hashash JG, Koutroubakis IE, Binion DG. Analysis of hospital-based emergency department visits for inflammatory bowel disease in the USA. Dig Dis Sci 2016;61:389-99.

18. Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohns Colitis 2013;7:107-12.

19. Wallaert JB, De Martino RR, Marsicovetere PS, Goodney PP, Finlayson SR, Murray JJ, et al. Venous thromboembolism after surgery for inflammatory bowel disease: are there modifiable risk factors? Data from ACS NSQIP. Dis Colon Rectum 2012;55:1138-44.

20. Ananthakrishnan AN, McGinley EL, Binion DG, Saeian K. A novel risk score to stratify severity of Crohn's disease hospitalizations. Am J Gastroenterol 2010;105:1799-807.

21. Vasseur F, Gower-Rousseau C, Vernier-Massouille G, Dupas JL, Merle V, Merlin B, et al. Nutritional Status and Growth in Pediatric Crohn's Disease: A Population-Based Study. Am J Gastroenterol. 2010;105:1893-900.

22. Hill RJ, Davies PS. You look all right to me: compromised nutritional status in paediatric patients with ulcerative colitis. J Pediatr Gastroenterol Nutr 2013;56:385-9.

23. Wiskin AE, Owens DR, Cornelius VR, Wootton SA, Beattie RM. Paediatric nutrition risk scores in clinical practice: children with inflammatory bowel disease. J Hum Nutr Diet 2012;25:319-22.

24. Heuschkel R, Salvestrini C, Beattie RM, Hildebrand H, Walters T, Griffiths A. Guidelines for the management of growth failure in childhood inflammatory bowel disease. Inflamm Bowel Dis 2008;14:839-49.

25. Inoue M, Sasaki M, Takaoka A, Kurihara M, Iwakawa H, Bamba S, et al. Changes in energy metabolism after induction therapy in patients with severe or moderate ulcerative colitis. J Clin Biochem Nutr 2015;56:215-9.

26. Sasaki M, Johtatsu T, Kurihara M, Iwakawa H, Tanaka T, Bamba S, et al. Energy expenditure in Japanese patients with severe or moderate ulcerative colitis. J Clin Biochem Nutr 2010;47:32-6.

27. Klein S, Meyers S, O'Sullivan P, Barton D, Leleiko N, Janowitz HD. The metabolic impact of active ulcerative colitis. Energy expenditure and nitrogen balance. J Clin Gastroenterol 1988;10:34-40.

28. Stokes MA, Hill GL. Total energy expenditure in patients with Crohn's disease: measurement by the combined body scan technique. JPEN J Parenter Enteral Nutr 1993;17:3-7.

29. Capristo E, Addolorato G, Mingrone G, Greco AV, Gasbarrini G. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. Am J Gastroenterol. 1998;93:2411-9.

30. Zoli G, Katelaris PH, Garrow J, Gasbarrini G, Farthing MJ. Increased energy expenditure in growing adolescents with Crohn's disease. Dig Dis Sci 1996;41:1754-9.

31. Steiner SJ, Noe JD, Denne SC. Corticosteroids increase protein breakdown and loss in newly diagnosed pediatric Crohn disease. Pediatric research 2011;70:484-8.

32. O'Keefe SJ, Ogden J, Rund J, Potter P. Steroids and bowel rest versus elemental diet in the treatment of patients with Crohn's disease: the effects on protein metabolism and immune function. JPEN. Journal of parenteral and enteral nutrition 1989;13:455-60.

33. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46-54.

34. Hannon TS, Dimeglio LA, Pfefferkorn MD, Denne SC. Acute effects of enteral nutrition on protein turnover in adolescents with Crohn disease. Ped Res 2007;61:356-60.

35. Royall D, Jeejeebhoy KN, Baker JP, Allard JP, Habal FM, Cunnane SC, et al. Comparison of amino acid v peptide based enteral diets in active Crohn's disease: clinical and nutritional outcome. Gut 1994;35:783-7.

36. Griffiths RD, Hinds CJ, Little RA. Manipulating the metabolic response to injury. Br Med Bull 1999;55:181-95.

37. Royall D, Greenberg GR, Allard JP, Baker JP, Jeejeebhoy KN. Total enteral nutrition support improves body composition of patients with active Crohn's disease. JPEN J Parenter Enteral Nutr 1995;19:95-9.

38. Gerasimidis K, Edwards C, Stefanowicz F, Galloway P, McGrogan P, Duncan A, et al. Micronutrient status in children with IBD: true deficiencies or epiphenomenon of the systemic inflammatory response. J Pediatr Gastroenterol Nutr 2013;56:e50-1.

39. Filippi J, Al-Jaouni R, Wiroth JB, Hébuterne X, Schneider SM. Nutritional deficiencies in patients with Crohn's disease in remission. Inflamm Bowel Dis. 2006;12:185-91.

40. Geerling BJ, Badart-Smook A, Stockbrügger RW, Brummer RJ. Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. Am J Clin Nutr.1998;67:919-26.

41. Vagianos K, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. JPEN. Jour Jarenter Enteral NUtr. 2007;31:311-9.

42. Santucci NR, Alkhouri RH, Baker RD, Baker SS. Vitamin and zinc status pretreatment and post-treatment in patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2014;59:455-7.

43. Greenley RN, Stephens KA, Nguyen EU, Kunz JH, Janas L, Goday P, et al. Vitamin and mineral supplement adherence in pediatric inflammatory bowel disease. J Pediatr Psychol 2013;38:883-92.

44. Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, et al. European Crohn's and Colitis Organisation [ECCO]. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015;9:211-22.

45. Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in haemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis 2006;12:123–30.

46. Evstatiev R, Marteau P, Iqbal T, Khalif IL, Stein J, Bokemeyer B, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. Gastroenterology 2011;141:846–53, e1–2.

47. Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut. 2011;60:923-9.

48. Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, et al. Home Artificial Nutrition & Chronic Intestinal Failure; Acute Intestinal Failure Special Interest Groups of ESPEN. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171-80.

49. Hart JW, Bremner AR, Wootton SA, Beattie RM. Measured versus predicted energy expenditure in children with inactive Crohn's disease. Clinical Nutrition 2005;24:1047-55.

50. Baker ML, Williams RN, Nightingale JM. Causes and management of a high-output stoma. Colorectal Dis. 2011;13:191-7.

51. Grischkan D, Steiger E, Fazio V. Maintenance of home hyperalimentation in patients with high-output jejunostomies. Arch Surg. 1979;114:838-41.

52. Pironi L, Guidetti C, Incasa E, Poggioli G, Paganelli F, Merli C, et al. Oral rehydration solution containing rice maltodextrins in patients with total colectomy and high intestinal output. Int J Clin Pharmacol Res. 2000;20:55-60.

53. Nightingale JM, Lennard-Jones JE, Walker ER, Farthing MJ. Oral salt supplements to compensate for jejunostomy losses: comparison of sodium chloride capsules, glucose electrolyte solution, and glucose polymer electrolyte solution. Gut. 1992;33:759-61.

54. Hu D, Ren J, Wang G, Li G, Liu S, Yan D, et al. Exclusive enteral nutritional therapy can relieve inflammatory bowel stricture in Crohn's disease. J Clin Gastroenterol. 2014;48:790-5.

55. Abraham BP, Prasad P, Malaty HM Vitamin D deficiency and corticosteroid use are risk factors for low bone mineral density in inflammatory bowel disease patients. Dig Dis Sci 2014;59:1878-84.

56. Bakker SF, Dik VK, Witte BI, Lips P, Roos JC, Van Bodegraven AA. Increase in bone mineral density in strictly treated Crohn's disease patients with concomitant calcium and vitamin D supplementation. J Crohns Colitis. 2013;7:377-84.

57. Lopes LH, Sdepanian VL, Szejnfeld VL, de Morais MB, Fagundes-Neto U. Risk factors for low bone mineral density in children and adolescents with inflammatory bowel disease. Dig Dis Sci. 2008;53:2746-53.

58. van Bodegraven AA, Bravenboer N, Witte BI, Dijkstra G, van der Woude CJ, Stokkers PC, et al. Dutch Initiative on Crohn and Colitis (ICC). Treatment of bone loss in osteopenic patients with Crohn's disease: a double-blind, randomised trial of oral risedronate 35 mg once weekly or placebo, concomitant with calcium and vitamin D supplementation. Gut. 2014;63:1424-30.

59. Bernstein CN, Seeger LL, Anton PA, Artinian L, Geffrey S, Goodman W, et al. A randomized, placebo-controlled trial of calcium supplementation for decreased bone density in corticosteroid-using patients with inflammatory bowel disease: a pilot study. Aliment Pharmacol Ther. 1996;10:777-86.

60. Hebuterne X, Filippi J, Al-Jaouni R, Schneider S. Nutritional consequences and nutrition therapy in Crohn's disease. Gastroenterol Clin Biol 2009;33 Suppl 3:S235-44.

61. Jacobsen O, Højgaard L, Hylander Møller E, Wielandt TO, Thale M, et al. Effect of enterocoated cholestyramine on bowel habit after ileal resection: a double blind crossover study. Br Med J (Clin Res Ed). 1985;290:1315-8.

62. Little KH, Schiller LR, Bilhartz LE, Fordtran JS. Treatment of severe steatorrhea with ox bile in an ileectomy patient with residual colon. Dig Dis Sci. 1992;37:929-33.

63. Westergaard H. Bile Acid malabsorption. Curr Treat Options Gastroenterol. 2007;10:28-33.

64. Hylander E, Jarnum S, Jensen HJ, Thale M. Enteric hyperoxaluria: dependence on small intestinal resection, colectomy, and steatorrhoea in chronic inflammatory bowel disease. Scand J Gastroenterol. 1978;13:577-88.

65. Andersson H, Filipsson S, Hultén L. Urinary oxalate excretion related to ileocolic surgery in patients with Crohn's disease. Scand J Gastroenterol. 1978;13:465-9.

66. Hueppelshaeuser R, von Unruh GE, Habbig S, Beck BB, Buderus S, Hesse A, et al. Enteric hyperoxaluria, recurrent urolithiasis, and systemic oxalosis in patients with Crohn's disease. Pediatr Nephrol. 2012;27:1103-9.

67. Charlebois A, Rosenfeld G, Bressler B. The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. Crit Rev Food Sci Nutr. 2016;56:1370-8

68. Sigall-Boneh R, Pfeffer-Gik T, Segal I, Zangen T, Boaz M, Levine A. Partial enteral nutrition with a Crohn's disease exclusion diet is effective for induction of remission in children and young adults with Crohn's disease. Inflamm Bowel Dis. 2014; 20:1353-60.

69. Rajendran N, Kumar D. Food-specific IgG4-guided exclusion diets improve symptoms in Crohn's disease: a pilot study. Colorectal Dis. 2011;13:1009-13.

70. Riordan AM, Hunter JO, Cowan RE, Crampton JR, Davidson AR, Dickinson RJ, et al. Treatment of active Crohn's disease by exclusion diet: East Anglian multicentre controlled trial. Lancet. 1993; 342:1131-4.

71. Jones VA. Comparison of total parenteral nutrition and elemental diet in induction of remission of Crohn's disease. Long-term maintenance of remission by personalized food exclusion diets. Dig Dis Sci. 1987;32:100S-107S.

72. Slonim AE, Grovit M, Bulone L. Effect of exclusion diet with nutraceutical therapy in juvenile Crohn's disease. J Am Coll Nutr. 2009; 28:277-85.

73. Oliva S, Di Nardo G, Ferrari F, Mallardo S, Rossi P, Patrizi G, et al. Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis. Aliment Pharmacol Ther. 2012;35:327-34.

74. Miele E, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. Am J Gastroenterol 2009;104:437-43.

75. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004;53 Suppl 5:V1-16.

76. Valentini L, Schaper L, Buning C, Hengstermann S, Koernicke T, Tillinger W, et al. Malnutrition and impaired muscle strength in patients with Crohn's disease and ulcerative colitis in remission. Nutrition 2008;24:694-702.

77. Sakamoto N, Kono S, Wakai K, Fukuda Y, Satomi M, Shimoyama T, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis 2005;11:154-63.

78. Van Limbergen J, Haskett J, Griffiths AM, Critch J, Huynh H, Ahmed N, et al. Toward enteral nutrition for the treatment of pediatric Crohn disease in Canada: A workshop to identify barriers and enablers. Can J Gastroenterol Hepatol 2015;29:351-6.

79. Nguyen GC, Laveist TA, Brant SR. The utilization of parenteral nutrition during the in-patient management of inflammatory bowel disease in the United States: a national survey. Aliment Pharmacol Ther 2007;26:1499-507.

80. Nguyen DL, Parekh N, Bechtold ML, Jamal MM. National trends and in-hospital outcomes of adult patients with inflammatory bowel disease receiving parenteral nutrition support. JPEN J Parenter Enteral Nutr. 2016;40:412-6.

81. Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment Pharmacol Ther 2007;26:795-806.

82. Grover Z, Lewindon P. Two-Year Outcomes After Exclusive Enteral Nutrition Induction Are Superior to Corticosteroids in Pediatric Crohn's Disease Treated Early with Thiopurines. Dig Dis Sci 2015;60:3069-74.

83. Grogan JL, Casson DH, Terry A, Burdge GC, El-Matary W, Dalzell AM. Enteral feeding therapy for newly diagnosed pediatric Crohn's disease: a double-blind randomized controlled trial with two years follow-up. Inflamm Bowel Dis. 2012;18:246-253.

84. Li G, Ren J, Wang G, Hu D, Gu G, Liu S, et al. Preoperative exclusive enteral nutrition reduces the postoperative septic complications of fistulizing Crohn's disease. Eur J Clin Nutr. 2014;68:441-6.

85. Smith MA, Smith T, Trebble T. Nutritional management of adults with inflammatory bowel disease: practical lessons from the available evidence. Frontline Gastroenterology 2012;3:172-79.

86. Lochs H, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Shulz T, et al. ESPEN Guidelines on Enteral Nutrition: Gastroenterology. Clin Nutr 2006; 25, 260-274.

87. Fuchssteiner H, Nigl K, Mayer A, Kristensen B, Platzer R, Brunner B, et al. Nutrition and IBD: consensus of the Austrian working group of IBD (inflammatory bowel diseases) of the OGGH. Z Gastroenterol 2014;52:376–386.

88. August D, Teitelbaum D, Albina J, Bothe A, Guenter P, Heitkemper M, et al. ASPEN Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients; JPEN, 2002;26:1SA-138SA.

89. Matsui T, Sakurai T, Yao T. Nutritional therapy for Crohn's disease in Japan. J Gastroenterol. 2005;40 Suppl 16:25-31.

90. Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2007:CD005984.

91. Nakahigashi M, Yamamoto T, Sacco R, Hanai H, Kobayashi F. Enteral nutrition for maintaining remission in patients with quiescent Crohn's disease: current status and future perspectives. Int J Colorectal Dis. 2016;31:1-7.

92. Yamamoto T, Shiraki M, Nakahigashi M, Umegae S, Matsumoto K. Enteral nutrition to suppress postoperative Crohn's disease recurrence: a five-year prospective cohort study. Int J Colorectal Dis. 2013;28:335-40.

93. Giannotta M, Tapete G, Emmi G, Silvestri E, Milla M. Thrombosis in inflammatory bowel diseases: what's the link? Thromb J 2015; 13:14.

94. Zezos P, Kouklakis G, Saibil F. Inflammatory Bowel Disease and thromboembolism. World J Gastroenterol 2014;20:13863-78

95. Bhakta A, Tafen M, Ahmed M, Ata A, Abraham C, Bruce D, et al. Risk of catheter-associated deep venous thrombosis in inflammatory bowel disease. Dis Colon Rectum. 2014;57:1379-83.

96. Ha C, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. Am J Gastroenterol. 2009;104:1445-51.

97. Papay P, Miehsler W, Tilg H, Petritsch W, Reinisch W, Mayer A, et al. Clinical presentation of venous thromboembolism in inflammatory bowel disease. J Crohns Colitis. 2013;7:723-9.

98. Yan D, Ren J, Wang G, Liu S, Li J. Predictors of response to enteral nutrition in abdominal enterocutaneous fistula patients with Crohn's disease. Eur J Clin Nutr. 2014;68:959-63.

99. Visschers RG, Olde Damink SW, Winkens B, Soeters P, van Gemert WG. Treatment strategies in 135 consecutive patients with enterocutaneous fistulas. World J Surg. 2008;32:445-453.

100. Llop JM, Cobo S, Padulles A, Farran L, Jodar R, Badia MB. Nutritional support and risk factors of appearance of enterocutaneous fistulas. Nutr Hosp 2012;27:213-8.

101. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohn Colitis 2010;4:28–62.

102. Forbes A, Goldesgeyme E, Paulon E. Nutrition in inflammatory bowel disease. J Parent Ent Nutr 2011;35:571-80.

103. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011;60:571-607.

104. Uchino M, Ikeuchi H, Matsuoka H, Matsumoto T, Takesue Y, Tomita N. Clinical features and management of duodenal fistula in patients with Crohn's disease. Hepatogastroenterology. 2012;59:171-4.

105. Triantafillidis JK, Papalois AE. The role of total parenteral nutrition in inflammatory bowel disease: current aspects. Scand J Gastroenterol. 2014;49:3-14.

106. Ravindran P, Ansari N, Young CJ, Solomon MJ. Definitive surgical closure of enterocutaneous fistula: outcome and factors predictive of increased postoperative morbidity. Colorectal Dis. 2014;16:209-18.

107. Akobeng AK, Thomas AG. Refeeding syndrome following exclusive enteral nutritional treatment in Crohn disease. J Pediatr Gastroenterol Nutr. 2010 51:364-6.

108. Hernando A, Bretón I, Marín-Jimenez I, Menchén L. Refeeding syndrome in a patient with Crohn's disease. J Clin Gastroenterol. 2008;42:430-1.

109. Krznaric Z, Vranesic Bender D, Ljubas Keleric D, Brinar M. Wernicke's encephalopathy during parenteral nutrition in a Crohn's disease patient. Nutrition. 2011 27:503-4

110. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohn Colitis 2012;6:991–1030

111. Salinas H, Dursun A, Konstantinidis I, Nguyen D, Shellito P, Hodin R, et al. Does preoperative total parenteral nutrition in patients with ulcerative colitis produce better outcomes? Int J Colorectal Dis. 2012;27:1479-83.

112. Schwartz E. Perioperative parenteral nutrition in adults with inflammatory bowel disease: a review of the literature. Nutr Clin Pract. 2016;31:159-70.

113. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clin Nutr 2017;36:623-650

114. Kuppinger D, Hartl WH, Bertok M, Hoffmann JM, Cederbaum J, Küchenhoff H, et al. Nutritional screening for risk prediction in patients scheduled for abdominal operations. Br J Surg 2012;99:728-737.

115. Beattie AH, Prach AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut 2000;46:813-818

116. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ. Oral dietary supplements in pre- and postoperative surgical patients: a prospective and randomized clinical trial. Nutrition 2000;16:723-728.

117. Espaulella J, Guyer H, Diaz-Escriu F, Mellado-Navas JA, Castells M, Pladevall M. Nutritional supplementation of elderly hip fracture patients. A randomized, double-blind, placebo-controlled trial. Age Ageing 2000; 29:425-431.

118. Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. Br J Surg 2004;91:983-990.

119. Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev 2012; 11:CD008879.

120. Braga M, Gianotti L, Gentilini O, Liotta S, Di Carlo V. Feeding the gut early after digestive surgery: results of a nine-year experience. Clin Nutr 2002;21:59-65.

121. Daly JM, Bonau R, Stofberg P, Bloch A, Jeevanandam M, Morse M. Immediate postoperative jejunostomy feeding. Clinical and metabolic results in a prospective trial. Am J Surg 1987;153:198-206.

122. Delany HM, Carnevale N, Garvey JW, Moss GM. Postoperative nutritional support using needle catheter feeding jejunostomy. Ann Surg 1977;186:165-170.

123. Gabor S, Renner H, Matzi V, Ratzenhofer B, Lindenmann J, Sankin O, et al. Early enteral feeding compared with parenteral nutrition after oesophageal or oesophagogastric resection and reconstruction. Br J Nutr 2005;93:509-513

124. Gupta V. Benefits versus risks: a prospective audit. Feeding jejunostomy during esophagectomy. World J Surg 2009;33:1432-1438

125. Kemen M, Senkal M, Homann HH, Mumme A, Dauphin AK, Baier J, et al. Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact. Crit Care Med 1995; 23:652-659.

126. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. Summary of a conference sponsored by the National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. Am J Clin Nutr 1997; 66:683-706.

127. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med 1991;325:525-532.

128. Bozzetti F, Gavazzi C, Miceli R, Rossi N, Mariani L, Cozzaglio L, et al. Perioperative total parenteral nutrition in malnourished, gastrointestinal cancer patients: a randomized, clinical trial. JPEN J Parenter Enteral Nutr 2000;24:7-14.

129. Shukla HS, Rao RR, Banu N, Gupta RM, Yadav RC. Enteral hyperalimentation in malnourished surgical patients. Indian J Med Res 1984;80:339-346.

130. Von Meyenfeldt MF, Meijerink WJ, Rouflart MM, Builmaassen MT, Soeters PB. Perioperative nutritional support: a randomised clinical trial. Clin Nutr 1992;11:180-186.

131. Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW. Total parenteral nutrition in the surgical patient: a meta-analysis. Can J Surg 2001;44:102-111.

132. Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. Cochrane Database Syst Rev 2006 :CD004080.

133. Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. J Gastrointest Surg 2009; 13:569-575

134. Mazaki T, Ebisawa K. Enteral versus parenteral nutrition after gastrointestinal surgery: a systematic review and meta-analysis of randomized controlled trials in the English literature. J Gastrointest Surg 2008; 12:739-755

135. Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. JPEN J Parenter Enteral Nutr 2011;35:473-487.

136. Cohen AB, Lee D, Long MD, Kappelman MD, Martin CF, Sandler RS, et al. Dietary patterns and self-reported associations of diet with symptoms of inflammatory bowel disease. Dig Dis Sci 2013;58:1322-8.

137. Zvirbliene A, Kiudelis G, Zalinkevicius R, Kupcinskas L. [Dietary characteristics of patients with inflammatory bowel diseases]. Medicina (Kaunas) 2006;42:895-9.

138. Banos Madrid R, Salama Benerroch H, Moran Sanchez S, Gallardo Sanchez F, Albadalejo Merono A, et al. Lactose malabsorption in patients with inflammatory bowel disease without activity: would it be necessary to exclude lactose products in the diet of all patients? Anales de Medicina Interna 2004;21:212-14.

139. Triggs CM, Munday K, Hu R, Fraser AG, Gearry RB, Barclay ML, et al. Dietary factors in chronic inflammation: food tolerances and intolerances of a New Zealand Caucasian Crohn's disease population. Mutat Res 2010;690:123-38.

140. Jones VA, Dickinson RJ, Workman E, Wilson AJ, Freeman AH, Hunter JO. Crohn's disease: maintenance of remission by diet. Lancet. 1985;2:177-80.

141. Turner D, Zlotkin SH, Shah PS, Griffiths AM. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009:CD006320.

142. Cashman KD, Shanahan F. Is nutrition an aetiological factor for inflammatory bowel disease? Eur J Gastroenterol Hepatol 2003;15:607-13.

143. Tanaka T, Takahama K, Kimura T, Mizuno T, Nagasaka M, Iwata K, et al. Effect of concurrent elemental diet on infliximab treatment for Crohn's disease. J Gastroenterol Hepatol 2006;21:1143-9.

144. Yamamoto T, Nakahigashi M, Umegae S, Matsumoto K. Prospective clinical trial: enteral nutrition during maintenance infliximab in Crohn's disease. J Gastroenterol 2010;45:24-9.

145. Maconi G, Ardizzone S, Cucino C, Bezzio C, Russo AG, Bianchi Porro G. Pre-illness changes in dietary habits and diet as a risk factor for inflammatory bowel disease: a case-control study. World J Gastroenterol 2010;16:4297-304.

146. Esaki M, Matsumoto T, Hizawa K, Nakamura S, Jo Y, Mibu R, et al. Preventive effect of nutritional therapy against postoperative recurrence of Crohn disease, with reference to findings determined by intra-operative enteroscopy. Scand J Gastroenterol 2005; 40:1431-7.

147. Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38:1156-71.

148. Cabré E, Mañosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases - a systematic review. Br J Nutr. 2012;107 Suppl 2:S240-52.

149. Lev-Tzion R, Griffiths AM, Leder O, Turner D. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2014;2:CD006320.

150. Hallert C, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. Scand J Gastroenterol. 1991;26:747-50.

151. Fernández-Bañares F, Hinojosa J, Sánchez-Lombraña JL, Navarro E, Martínez-Salmerón JF, García-Pugés A, et al. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). Am J Gastroenterol. 1999;94:427-33.

152. Hanai H, Kanauchi O, Mitsuyama K, Andoh A, Takeuchi K, Takayuki I, et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. Int J Mol Med. 2004;13:643-7.

153. Brotherton CS, Taylor AG, Bourguignon C, Anderson JG. A high-fiber diet may improve bowel function and health-related quality of life in patients with Crohn disease. Gastroenterol Nurs. 2014;37:206-16.

154. Chiba M, Tsuji T, Nakane K, Komatsu M. High amount of dietary fiber not harmful but favorable for Crohn disease. Perm J. 2015;19:58-61.

155. Fujiya M, Ueno N, Kohgo Y. Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: a meta-analysis of randomized controlled trials. Clin J Gastroenterol 2014;7:1-13.

156. Kruis W, Fric P, Pokrotnieks J, Lukas M, Fixa B, Kascak M, et al. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut 2004;53:1617-23.

157. Floch MH, Walker WA, Sanders ME, Nieuwdorp M, Kim AS, Brenner DA, et al. Recommendations for Probiotic Use--2015 Update: Proceedings and Consensus Opinion. J Clin Gastroenterol 2015;49 Suppl 1:S69-73.

158. Ishikawa H, Matsumoto S, Ohashi Y, Imaoka A, Setoyama H, Umesaki Y, et al. Beneficial effects of probiotic bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: a randomized controlled study. Digestion 2011;84:128-33.

159. Yoshimatsu Y, Yamada A, Furukawa R, Sono K, Osamura A, Nakamura K, et al. Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. World J Gastroenterol 2015;21:5985-94.

160. Meini S, Laureano R, Fani L, Tascini C, Galano A, Antonelli A, et al. Breakthrough Lactobacillus rhamnosus GG bacteremia associated with probiotic use in an adult patient with severe active ulcerative colitis: case report and review of the literature. Infection 2015;43:777-81.

161. Vahabnezhad E, Mochon AB, Wozniak LJ, Ziring DA. Lactobacillus bacteremia associated with probiotic use in a pediatric patient with ulcerative colitis. J Clin Gastroenterol 2013;47:437-9.

162. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut 2002;51:405-9.

163. Schultz M, Sartor RB. Probiotics and inflammatory bowel diseases. Am J Gastroenterol 2000;95:S19-21.

164. Guslandi M, Giollo P, Testoni PA. A pilot trial of Saccharomyces boulardii in ulcerative colitis. Eur J Gastroenterol Hepatol 2003;15:697-8.

165. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2006:CD004826.

166. Campieri M, Rizzello F, Venturi A, Poggioli G, Ugolini F, Helwig U. Combination of antibiotic and probiotic treatment is efficacious in prophylaxis of post operative recurrence of Crohn's disease: a randomized controlled study vs mesalazine. Gastroenterology 2000;118:A4179.

167. Garcia Vilela E, De Lourdes De Abreu Ferrari M, Oswaldo Da Gama Torres H, Guerra Pinto A, et al. Influence of Saccharomyces boulardii on the intestinal permeability of patients with Crohn's disease in remission. Scand J Gastroenterol 2008;43:842-8.

168. Singh S, Stroud AM, Holubar SD, Sandborn WJ, Pardi DS. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Cochrane Database Syst Rev. 2015;11:CD001176.

169. Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut 2004;53:108–14.

170. Gionchetti P, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119:305-9.

171. Tursi A, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 2010;105:2218-27.

172. Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology. 2003;124:1202-9.

173. Kuisma J, Mentula S, Kahri A, Kahri A, Saxelin M, Farkkila M. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. Aliment Pharmacol Ther 2003;17:509-515.

174. Biancone L, Michetti P, Travis S, Escher JC, Moser G, Forbes A, et al. European evidence-based Consensus in the management of ulcerative colitis: special situations. J Crohns Colitis 2008;2:63-92.

175. Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. European Crohn's and Colitis Organization; European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012;55:340-61.

176. El-Matary W, Otley A, Critch J, Abou-Setta AM. Enteral Feeding Therapy for Maintaining Remission in Crohn's Disease: A Systematic Review. JPEN J Parenter Enteral Nutr. 2015;41:550-561.

177. Takagi S, Utsunomiya K, Kuriyama S, Yokoyama H, Takahashi S, Iwabuchi M, et al. Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: A random-ized-controlled trial. Aliment Pharmacol Ther 2006; 24: 1333-40

178. Hirai F, Ishihara H, Yada S, Esaki M, Ohwan T, Nozaki R, et al. Effectiveness of concomitant enteral nutrition therapy and infliximab for maintenance treatment of Crohn's disease in adults. Dig Dis Sci. 2013;58:1329-34.

179. Sazuka S, Katsuno T, Nakagawa T, Saito M, Saito K, Matsumura T, et al. Concomitant use of enteral nutrition therapy is associated with sustained response to infliximab in patients with Crohn's disease. Eur J Clin Nutr. 2012 Nov;66:1219-23.

180. Tsertsvadze A, Gurung T, Court R, Clarke A, Sutcliffe P. Clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in Crohn's disease: a systematic review and meta-analysis. Health Technol Assess. 2015;19:1-138.

181. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014;8:1179-207.

182. Battat R, Kopylov U, Szilagyi A, Saxena A, Rosenblatt DS, Warner M, et al. Vitamin B12 deficiency in inflammatory bowel disease: prevalence, risk factors, evaluation, and management. Inflamm Bowel Dis. 2014;20:1120-8.

183. Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. Nutrition. 2006;22:1210-3.

184. Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B(12) deficiency in patients with Crohn's disease. Inflamm Bowel Dis. 2008;14:217-23.

185. Yakut M, Ustün Y, Kabaçam G, Soykan I. Serum vitamin B12 and folate status in patients with inflammatory bowel diseases. Eur J Intern Med. 2010;21:320-3.

186. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013;368:149–160.

187. Plener I, Ferguson C, Kashkooli S, Saibil F. Oral B12 replacement in Crohn's disease - is B12 by injection obsolete? Aliment Pharmacol Ther. 2014;40:1365-6.

188. Hornung N, Ellingsen T, Stengaard-Pedersen K, Poulsen JH. Folate, homocysteine, and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the effect of low dose folic acid supplement. J Rheumatol 2004;31:2374–81.

189. Halsted CH, Gandhi G, Tamura R. Sulphasalazine inhibits the absorption of folates in ulcerative colitis. N Engl J Med 1981;305:1513–7.

190. Burr NE, Hull MA, Subramanian V. Folic Acid Supplementation May Reduce Colorectal Cancer Risk in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. J Clin Gastroenterol. 2017;51:247-253.

191. Pironi L, Cornia GL, Ursitti MA, Dallasta MA, Miniero R, Fasano F, et al. Evaluation of oral administration of folic and folinic acid to prevent folate deficiency in patients with inflammatory bowel disease treated with salicylazosulfapyridine. Int J Clin Pharmacol Res. 1988;8:143-8.

192. Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA. 2001;285:2981–6.

193. Bryant RV, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;38:213-25.

194. Bryant RV, Ooi S, Schultz CG, Goess C, Grafton R, Hughes J, et al. Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41:895-906.

195. Wiroth JB, Filippi J, Schneider SM, Al-Jaouni R, Horvais N, Gavarry O, et al. Muscle performance in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2005;11:296-303.

196. Werkstetter KJ, Ullrich J, Schatz SB, Prell C, Koletzko B, Koletzko S. Lean body mass, physical activity and quality of life in paediatric patients with inflammatory bowel disease and in healthy controls. J Crohns Colitis. 2012;6:665-73.

197. Klare P, Nigg J, Nold J, Haller B, Krug AB, Mair S, et al. The impact of a ten-week physical exercise program on health-related quality of life in patients with inflammatory bowel disease: a prospective randomized controlled trial. Digestion. 2015;91:239-47.

198. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014;43:748-59.

199. Flores A, Burstein E, Cipher DJ, Feagins LA. Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. Dig Dis Sci. 2015;60:2436-45.

200. Nic Suibhne T, Raftery TC, McMahon O, Walsh C, O'Morain C, O'Sullivan M. High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. J Crohns Colitis. 2013;7:e241-8.

201. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, Hashash JG, Dudekula A, Regueiro M, et al. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015;21:2857-63.

Figure 1

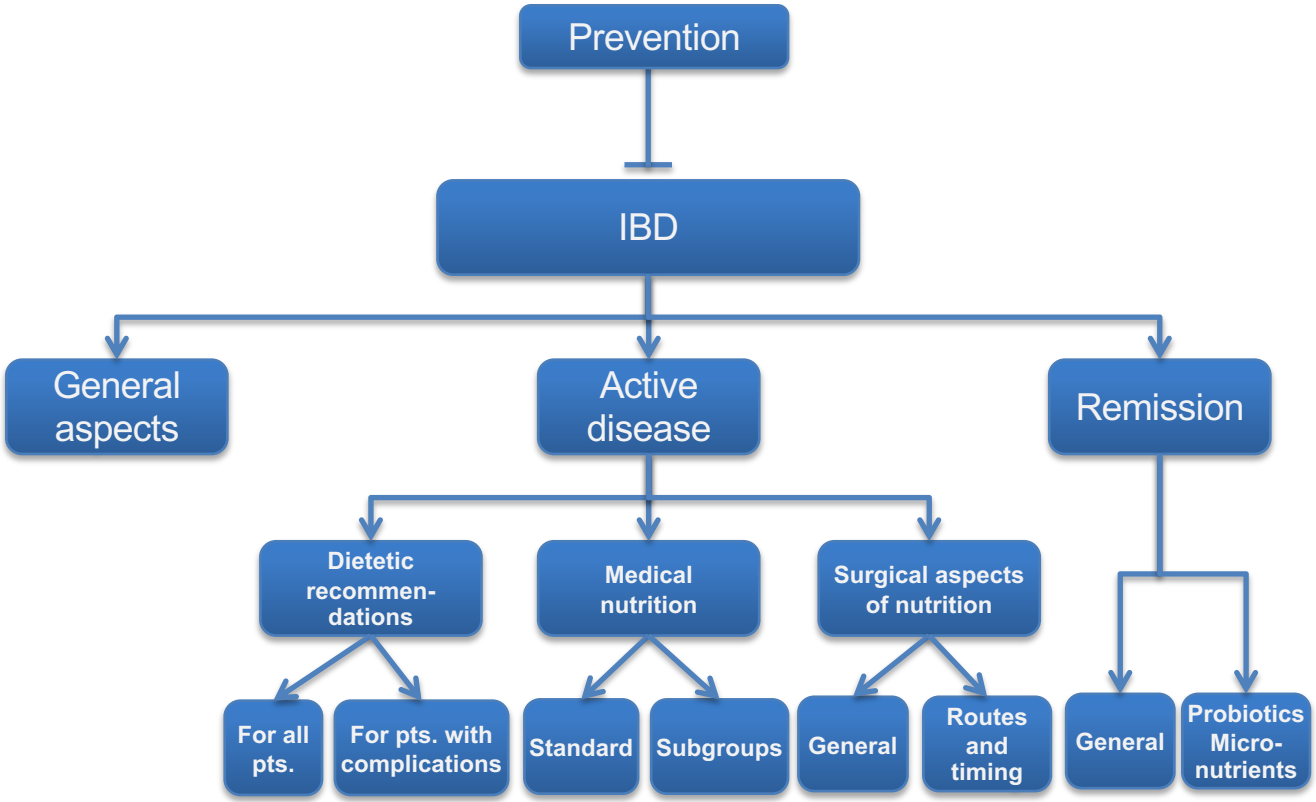

Prevention
IBD
General aspects
Active disease
Remission
Dietetic recommen-dations
Medical nutrition
Surgical aspects of nutrition
For all pts.
For pts. with complications
Standard
Subgroups
General
Routes and timing
General
Probiotics Micro-nutrients

Figure 2

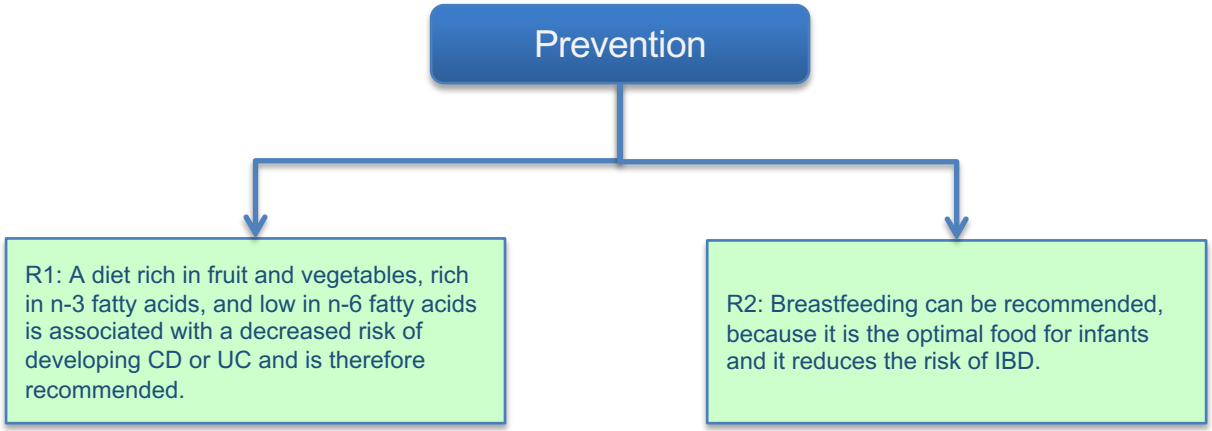

Prevention
R1: A diet rich in fruit and vegetables, rich in n-3 fatty acids, and low in n-6 fatty acids is associated with a decreased risk of developing CD or UC and is therefore recommended.
R2: Breastfeeding can be recommended, because it is the optimal food for infants and it reduces the risk of IBD.

Figure 3

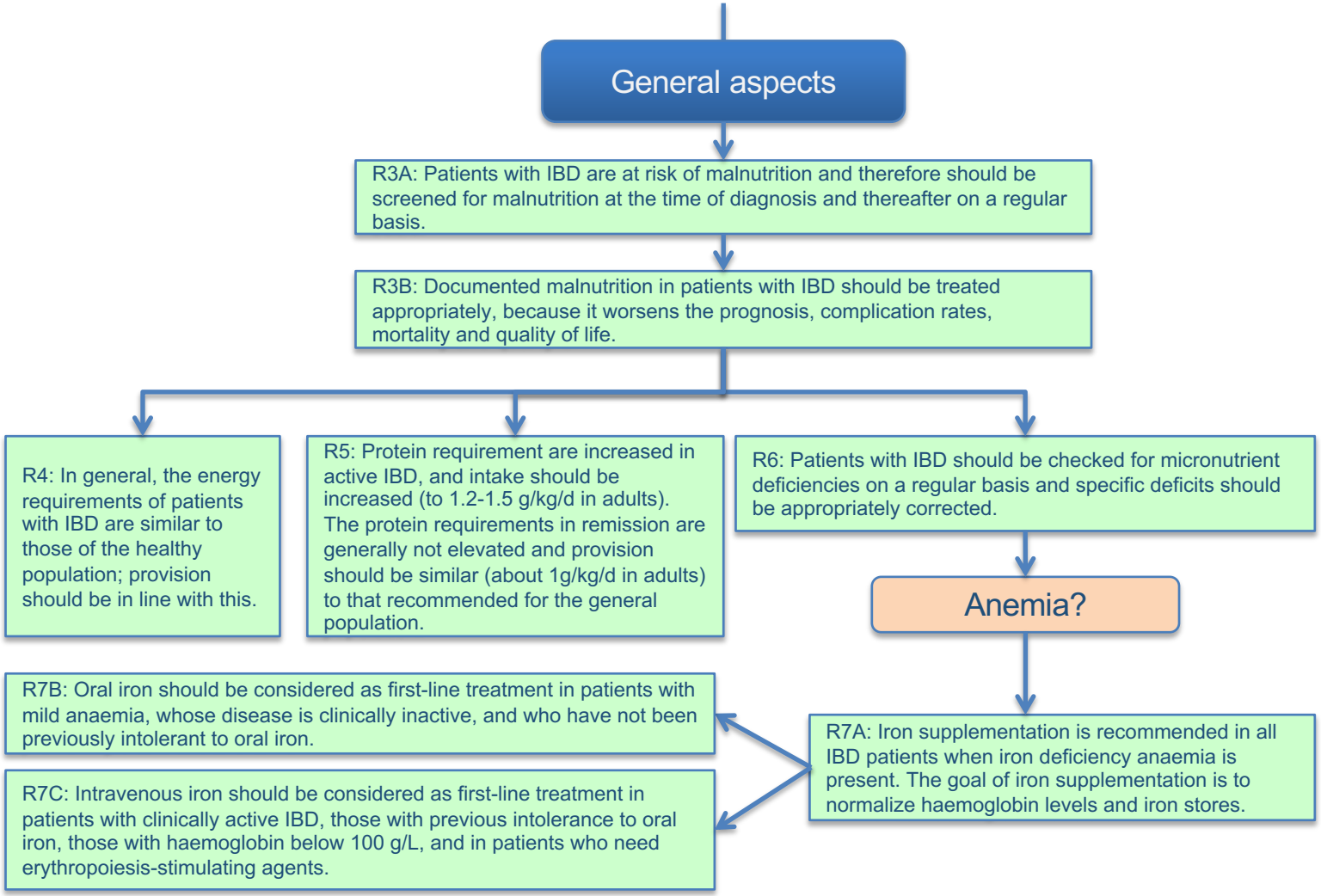

General aspects
R3A: Patients with IBD are at risk of malnutrition and therefore should be screened for malnutrition at the time of diagnosis and thereafter on a regular basis.
R3B: Documented malnutrition in patients with IBD should be treated appropriately, because it worsens the prognosis, complication rates, mortality and quality of life.
R4: In general, the energy requirements of patients with IBD are similar to those of the healthy population; provision should be in line with this.
R5: Protein requirement are increased in active IBD, and intake should be increased (to 1.2-1.5 g/kg/d in adults). The protein requirements in remission are generally not elevated and provision should be similar (about 1g/kg/d in adults) to that recommended for the general population.
R6: Patients with IBD should be checked for micronutrient deficiencies on a regular basis and specific deficits should be appropriately corrected.
Anemia?
R7A: Iron supplementation is recommended in all IBD patients when iron deficiency anaemia is present. The goal of iron supplementation is to normalize haemoglobin levels and iron stores.
R7B: Oral iron should be considered as first-line treatment in patients with mild anaemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron.
R7C: Intravenous iron should be considered as first-line treatment in patients with clinically active IBD, those with previous intolerance to oral iron, those with haemoglobin below 100 g/L, and in patients who need erythropoiesis-stimulating agents.

Figure 4

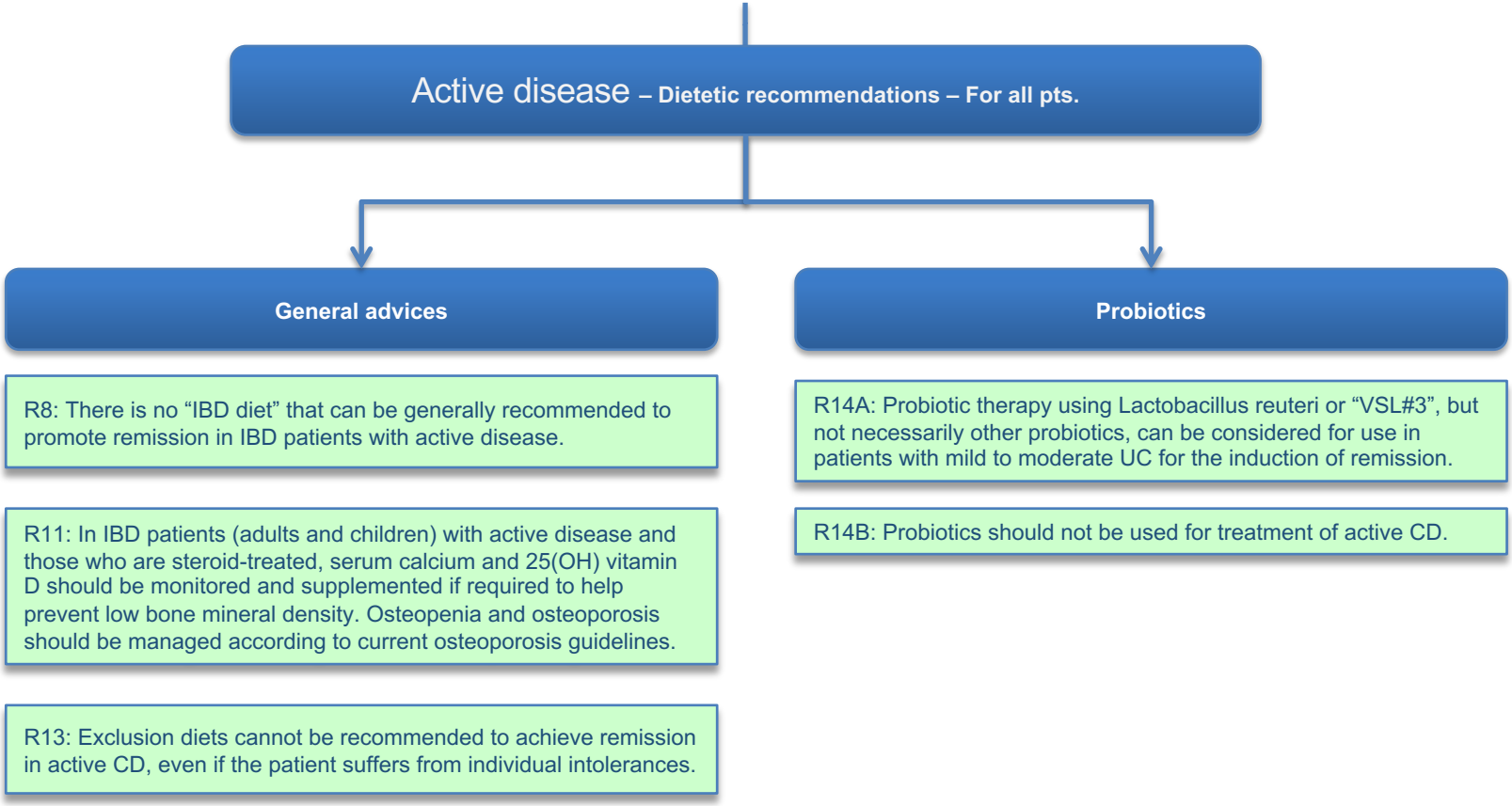

Active disease – Dietetic recommendations – For all pts.
General advices
Probiotics
R8: There is no “IBD diet” that can be generally recommended to promote remission in IBD patients with active disease.
R11: In IBD patients (adults and children) with active disease and those who are steroid-treated, 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.
R13: Exclusion diets cannot be recommended to achieve remission in active CD, even if the patient suffers from individual intolerances.
R14A: 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.
R14B: Probiotics should not be used for treatment of active CD.

Figure 5

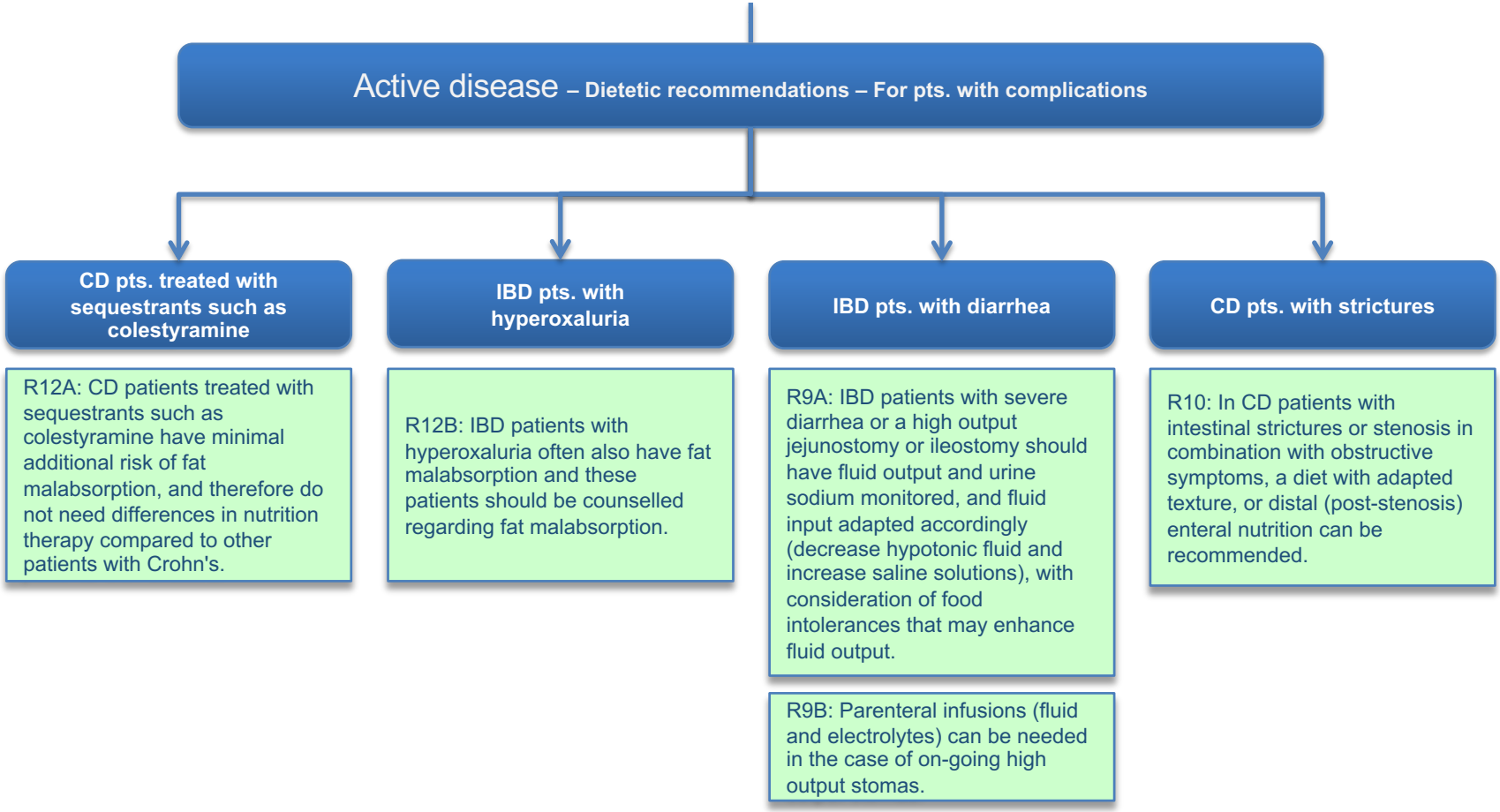

Active disease – Dietetic recommendations – For pts. with complications
CD pts. treated with sequestrants such as colestyramine
IBD pts. with hyperoxaluria
IBD pts. with diarrhea
CD pts. with strictures
R12A: CD patients treated with sequestrants such as colestyramine have minimal additional risk of fat malabsorption, and therefore do not need differences in nutrition therapy compared to other patients with Crohn's.
R12B: IBD patients with hyperoxaluria often also have fat malabsorption and these patients should be counselled regarding fat malabsorption.
R9A: 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.
R9B: Parenteral infusions (fluid and electrolytes) can be needed in the case of on-going high output stomas.
R10: In CD patients with intestinal strictures or stenosis in combination with obstructive symptoms, a diet with adapted texture, or distal (post-stenosis) enteral nutrition can be recommended.

Figure 6

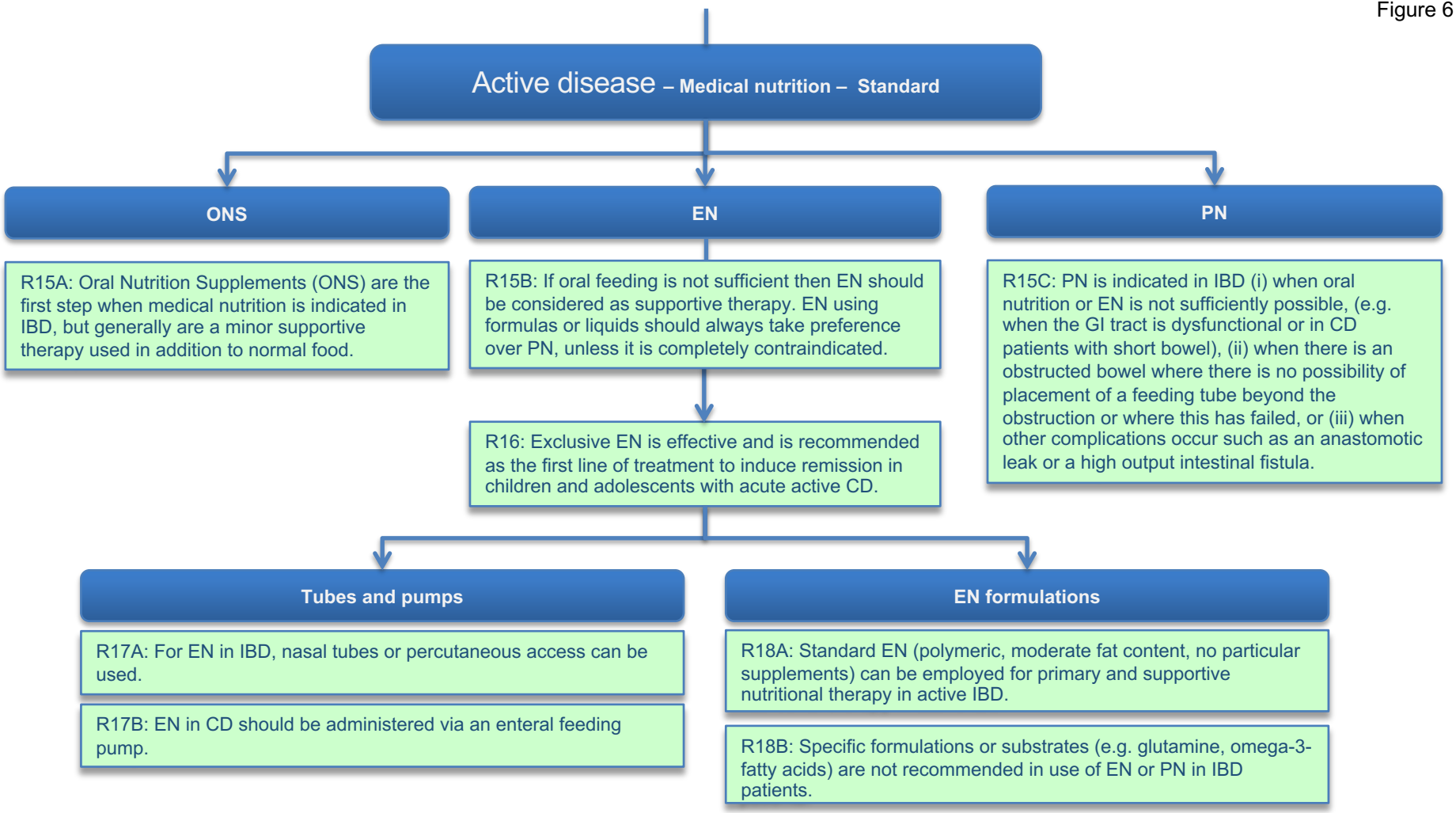

Active disease – Medical nutrition – Standard
ONS
EN
PN
R15A: Oral Nutrition Supplements (ONS) are the first step when medical nutrition is indicated in IBD, but generally are a minor supportive therapy used in addition to normal food.
R15B: If oral feeding is not sufficient then EN should be considered as supportive therapy. EN using formulas or liquids should always take preference over PN, unless it is completely contraindicated.
R15C: 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.
R16: Exclusive EN is effective and is recommended as the first line of treatment to induce remission in children and adolescents with acute active CD.
Tubes and pumps
EN formulations
R17A: For EN in IBD, nasal tubes or percutaneous access can be used.
R17B: EN in CD should be administered via an enteral feeding pump.
R18A: Standard EN (polymeric, moderate fat content, no particular supplements) can be employed for primary and supportive nutritional therapy in active IBD.
R18B: Specific formulations or substrates (e.g. glutamine, omega-3-fatty acids) are not recommended in use of EN or PN in IBD patients.

Figure 7

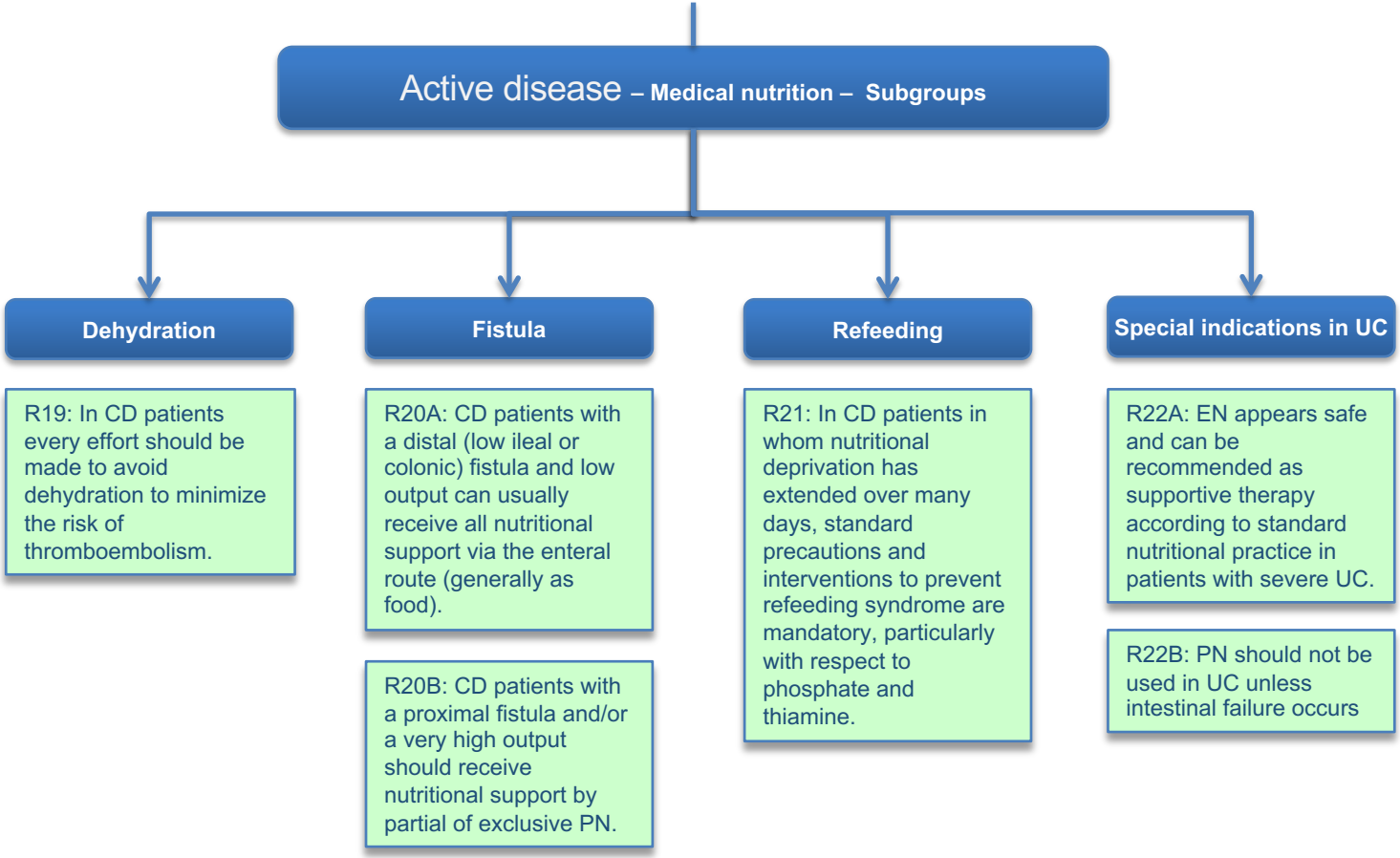
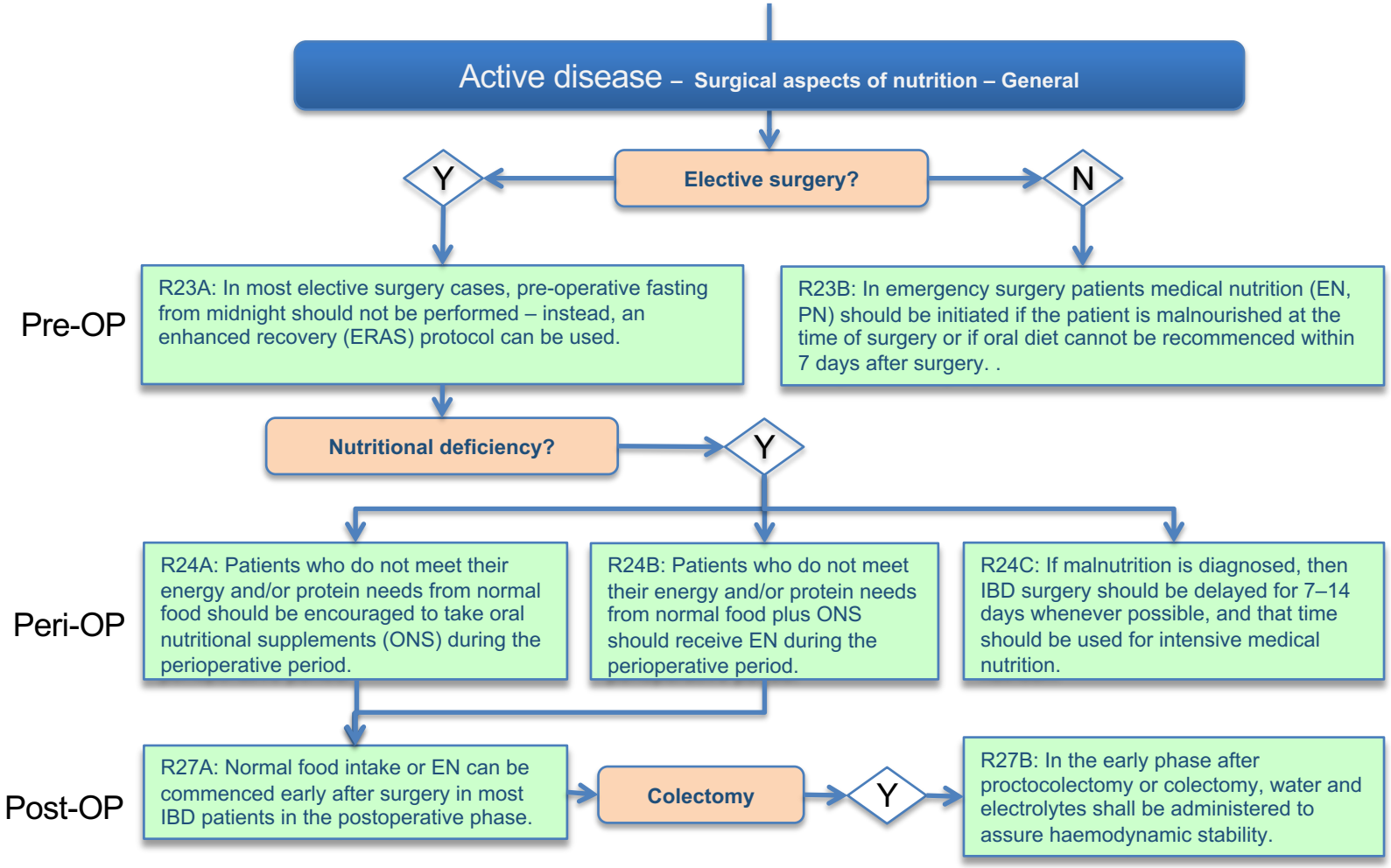

Active disease – Medical nutrition – Subgroups
Dehydration
R19: In CD patients every effort should be made to avoid dehydration to minimize the risk of thromboembolism.
Fistula
R20A: CD patients with a distal (low ileal or colonic) fistula and low output can usually receive all nutritional support via the enteral route (generally as food).
R20B: CD patients with a proximal fistula and/or a very high output should receive nutritional support by partial of exclusive PN.
Refeeding
R21: 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.
Special indications in UC
R22A: EN appears safe and can be recommended as supportive therapy according to standard nutritional practice in patients with severe UC.
R22B: PN should not be used in UC unless intestinal failure occurs

Figure 8


Active disease – Surgical aspects of nutrition – General
Elective surgery?
Y
N
Pre-OP
R23A: In most elective surgery cases, pre-operative fasting from midnight should not be performed – instead, an enhanced recovery (ERAS) protocol can be used.
R23B: 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. .
Nutritional deficiency?
Y
Peri-OP
R24A: 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.
R24B: Patients who do not meet their energy and/or protein needs from normal food plus ONS should receive EN during the perioperative period.
R24C: 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.
Post-OP
R27A: Normal food intake or EN can be commenced early after surgery in most IBD patients in the postoperative phase.
Colectomy
Y
R27B: In the early phase after proctocolectomy or colectomy, water and electrolytes shall be administered to assure haemodynamic stability.

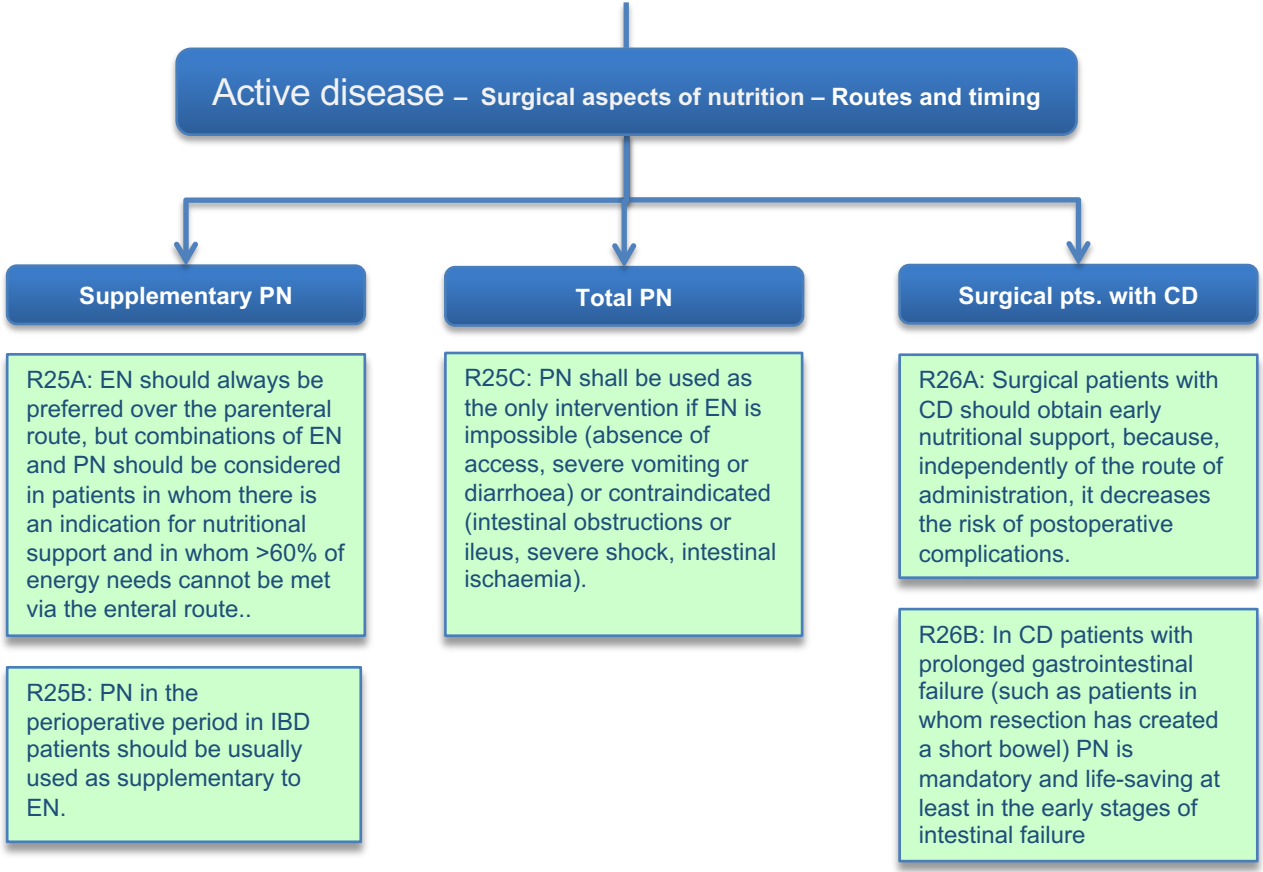

Active disease – Surgical aspects of nutrition – Routes and timing
Supplementary PN
Total PN
Surgical pts. with CD
R25A: EN should always be preferred over the parenteral route, but combinations of EN and PN should be considered in patients in whom there is an indication for nutritional support and in whom >60% of energy needs cannot be met via the enteral route..
R25B: PN in the perioperative period in IBD patients should be usually used as supplementary to EN.
R25C: PN shall be used as the only intervention if EN is impossible (absence of access, severe vomiting or diarrhoea) or contraindicated (intestinal obstructions or ileus, severe shock, intestinal ischaemia).
R26A: Surgical patients with CD should obtain early nutritional support, because, independently of the route of administration, it decreases the risk of postoperative complications.
R26B: 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

Figure 10

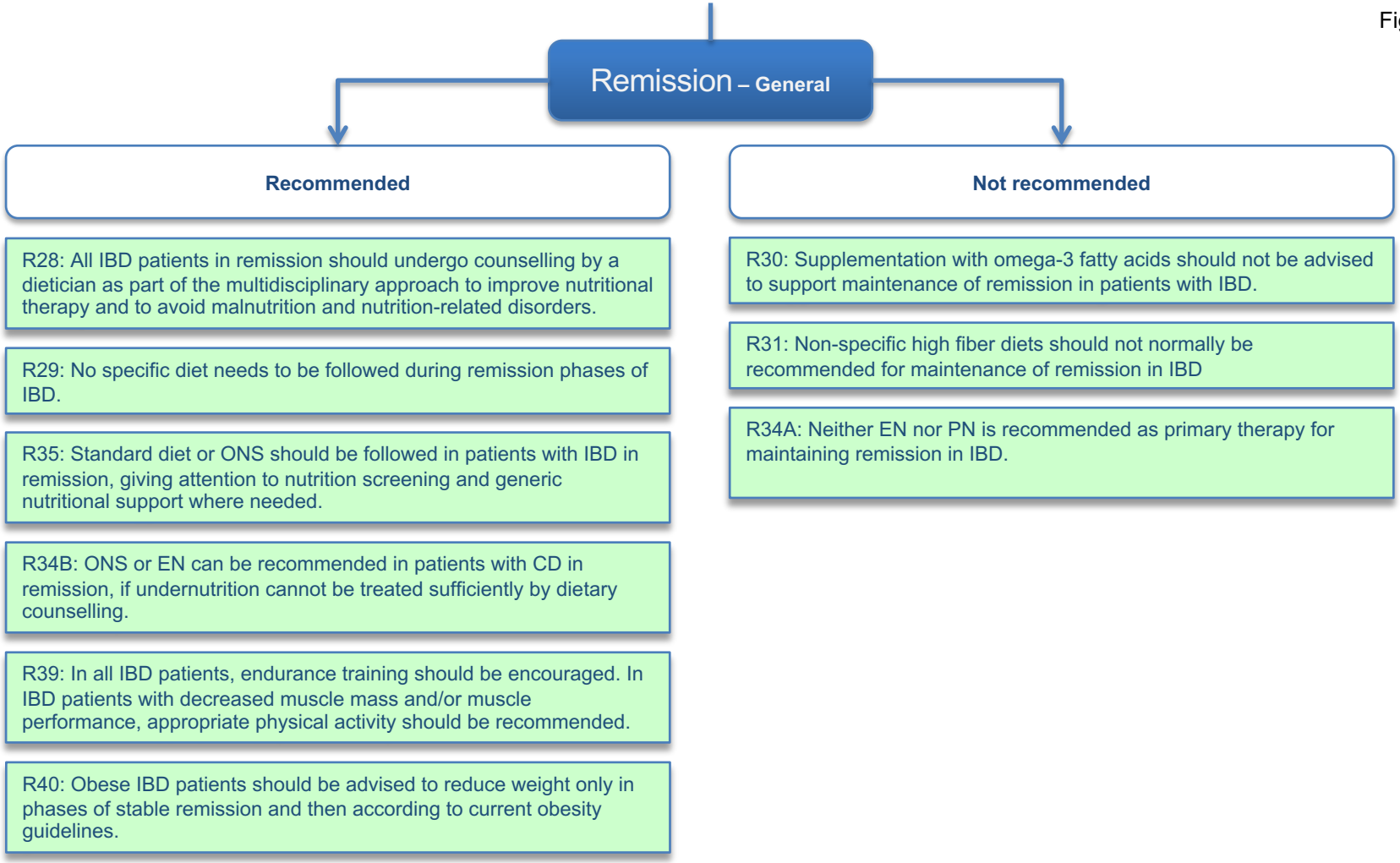
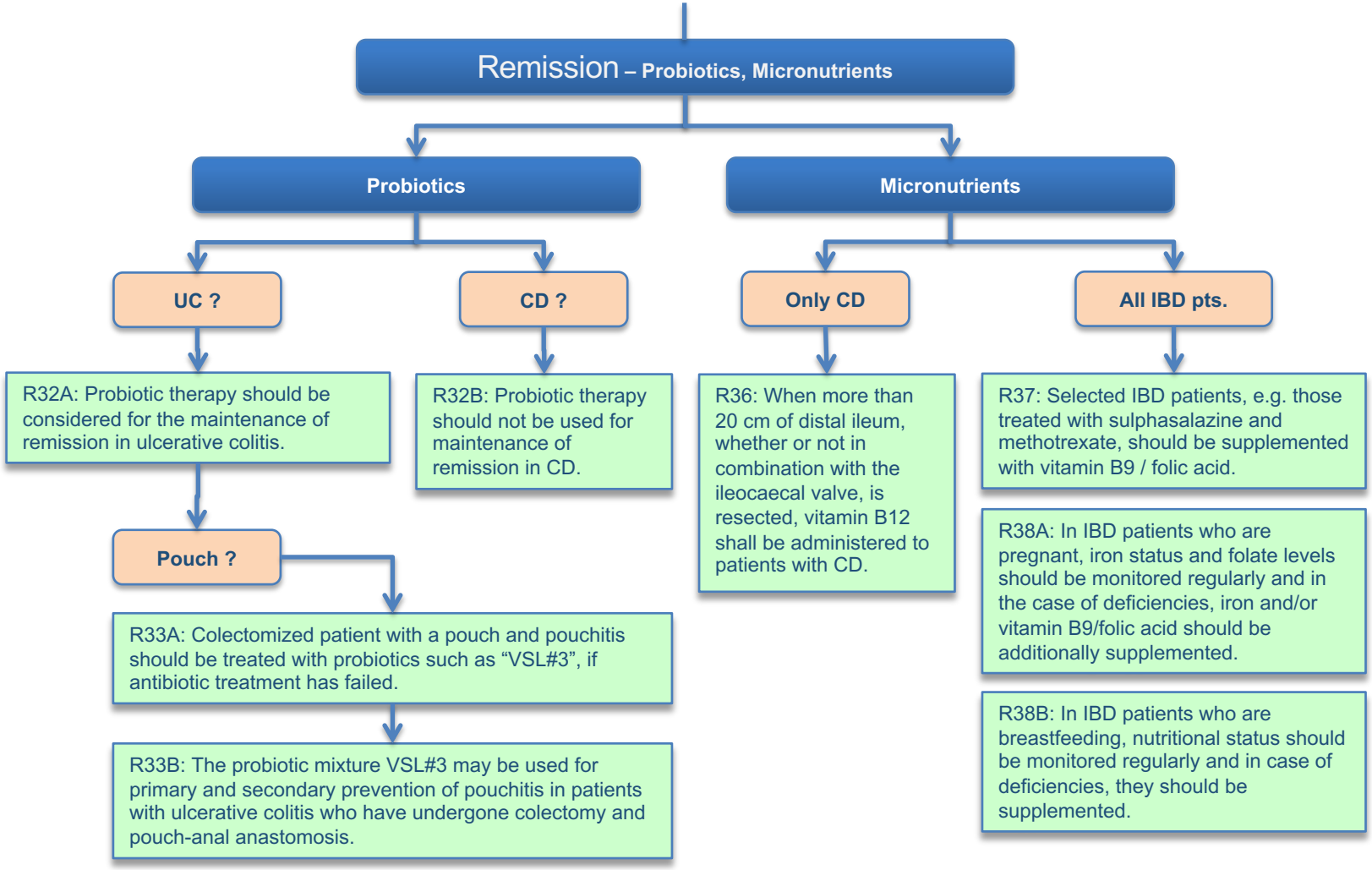

Remission – General
Recommended
R28: All IBD patients in remission should undergo counselling by a dietician as part of the multidisciplinary approach to improve nutritional therapy and to avoid malnutrition and nutrition-related disorders.
R29: No specific diet needs to be followed during remission phases of IBD.
R35: Standard diet or ONS should be followed in patients with IBD in remission, giving attention to nutrition screening and generic nutritional support where needed.
R34B: ONS or EN can be recommended in patients with CD in remission, if undernutrition cannot be treated sufficiently by dietary counselling.
R39: 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.
R40: Obese IBD patients should be advised to reduce weight only in phases of stable remission and then according to current obesity guidelines.
Not recommended
R30: Supplementation with omega-3 fatty acids should not be advised to support maintenance of remission in patients with IBD.
R31: Non-specific high fiber diets should not normally be recommended for maintenance of remission in IBD
R34A: Neither EN nor PN is recommended as primary therapy for maintaining remission in IBD.

Figure 11


Remission – Probiotics, Micronutrients
Probiotics
Micronutrients
UC ?
CD ?
Only CD
All IBD pts.
R32A: Probiotic therapy should be considered for the maintenance of remission in ulcerative colitis.
R32B: Probiotic therapy should not be used for maintenance of remission in CD.
R36: When more than 20 cm of distal ileum, whether or not in combination with the ileocaecal valve, is resected, vitamin B12 shall be administered to patients with CD.
R37: Selected IBD patients, e.g. those treated with sulphasalazine and methotrexate, should be supplemented with vitamin B9 / folic acid.
Pouch ?
R33A: Colectomized patient with a pouch and pouchitis should be treated with probiotics such as “VSL#3”, if antibiotic treatment has failed.
R33B: The probiotic mixture VSL#3 may be used for primary and secondary prevention of pouchitis in patients with ulcerative colitis who have undergone colectomy and pouch-anal anastomosis.
R38A: 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.
R38B: In IBD patients who are breastfeeding, nutritional status should be monitored regularly and in case of deficiencies, they should be supplemented.