



ESPEN guideline: Clinical nutrition in inflammatory bowel disease



Alastair Forbes^{a,*}, Johanna Escher^b, Xavier Hébuterne^c, Stanisław Kłęk^d,
Zeljko Krznaric^e, Stéphane Schneider^c, Raanan Shamir^f, Kalina Stardelova^g,
Nicolette Wierdsma^h, Anthony E. Wiskinⁱ, Stephan C. Bischoff^j

^a Norwich Medical School, University of East Anglia, Bob Champion Building, James Watson Road, Norwich, NR4 7UQ, United Kingdom

^b Erasmus Medical Center – Sophia Children's Hospital, Office Sp-3460, Wytemaweg 80, 3015 CN, Rotterdam, The Netherlands

^c Gastroentérologie et Nutrition Clinique, CHU de Nice, Université Côte d'Azur, Nice, France

^d General and Oncology Surgery Unit, Stanley Dudrick's Memorial Hospital, 15 Tyniecka Street, 32-050, Skawina, Krakau, Poland

^e Clinical Hospital Centre Zagreb, University of Zagreb, Kispaticeva 12, 10000, Zagreb, Croatia

^f Tel-Aviv University, Schneider Children's Medical Center of Israel, 14 Kaplan St., Petach-Tikva, 49202, Israel

^g University Clinic for Gastroenterohepatology, Clinical Centre "Mother Therese", Mother Therese Str No 18, Skopje, Republic of Macedonia

^h VU University Medical Center, Department of Nutrition and Dietetics, De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands

ⁱ Paediatric Gastroenterology & Nutrition Unit, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, BS2 8BJ, United Kingdom

^j Institut für Ernährungsmedizin (180) Universität Hohenheim, Fruwirthstr. 12, 70593 Stuttgart, Germany

ARTICLE INFO

Article history:

Received 21 December 2016

Accepted 28 December 2016

Keywords:

Crohn's disease

Ulcerative colitis

Enteral nutrition

Parenteral nutrition

Inflammatory bowel disease

Nutritional therapy

SUMMARY

Introduction: The ESPEN guideline presents a multidisciplinary focus on clinical nutrition in inflammatory bowel disease (IBD).

Methodology: The guideline is based on extensive systematic review of the literature, but relies on expert opinion when objective data were lacking or inconclusive. The conclusions and 64 recommendations have been subject to full peer review and a Delphi process in which uniformly positive responses (agree or strongly agree) were required.

Results: IBD is increasingly common and potential dietary factors in its aetiology are briefly reviewed. Malnutrition is highly prevalent in IBD – especially in Crohn's disease. Increased energy and protein requirements are observed in some patients. The management of malnutrition in IBD is considered within the general context of support for malnourished patients. Treatment of iron deficiency (parenterally if necessary) is strongly recommended. Routine provision of a special diet in IBD is not however supported. Parenteral nutrition is indicated only when enteral nutrition has failed or is impossible. The recommended perioperative management of patients with IBD undergoing surgery accords with general ESPEN guidance for patients having abdominal surgery. Probiotics may be helpful in UC but not Crohn's disease. Primary therapy using nutrition to treat IBD is not supported in ulcerative colitis, but is moderately well supported in Crohn's disease, especially in children where the adverse consequences of steroid therapy are proportionally greater. However, exclusion diets are generally not recommended and there is little evidence to support any particular formula feed when nutritional regimens are constructed. **Conclusions:** Available objective data to guide nutritional support and primary nutritional therapy in IBD are presented as 64 recommendations, of which 9 are very strong recommendations (grade A), 22 are strong recommendations (grade B) and 12 are based only on sparse evidence (grade 0); 21 recommendations are good practice points (GPP).

© 2017 European Society for Clinical Nutrition and Metabolism. Published by Elsevier Ltd. All rights reserved.

* Corresponding author.

E-mail addresses: alastair.forbes@uea.ac.uk (A. Forbes), j.escher@erasmusmc.nl (J. Escher), hebuterne.x@chu-nice.fr (X. Hébuterne), klek@poczta.onet.pl (S. Kłęk), zeljko.krznaric1@zg.t-com.hr (Z. Krznaric), stephane.schneider@unice.fr (S. Schneider), shamirraanan@gmail.com (R. Shamir), kalina.stardelova@gmail.com (K. Stardelova), N.Wierdsma@vumc.nl (N. Wierdsma), a.wiskin@nhs.net (A.E. Wiskin), bischoff.stephan@uni-hohenheim.de (S.C. Bischoff).

1. Introduction

Inflammatory bowel disease (IBD), predominantly ulcerative colitis (UC) and Crohn's disease (CD), is now common in the entire developed world. A systematic review conducted in 2012 demonstrated a range of prevalence rates for UC from 0.6 to 505 per 100,000, and for CD the estimates range from 0.6 to 322 per 100,000 [1,2]. IBD affects children as well as adults, with 15–20% of patients being diagnosed during childhood [3]. A study from Scotland suggests that as much as 50% of IBD may now present during childhood and adolescence [4].

The involvement of the gastrointestinal tract has encouraged the investigation of the relationship between nutrition and IBD, both for ways to prevent IBD and to support IBD treatment. 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 [5]. As in adults, malnutrition is prevalent in paediatric IBD, mainly in active disease and more in CD than in UC.

In both UC and CD malnutrition may be the result of reduced oral intake, increased nutrient requirements, increased gastrointestinal losses of nutrients, and occasionally from drug–nutrient interactions [5]. The severity of malnutrition in IBD is influenced by the activity, duration and extent of the disease, and particularly to the magnitude of the inflammatory response which drives catabolism and is anorexic. Patients with CD remain at risk even when their disease appears quiescent, whereas patients with UC generally develop problems only when the disease is active [6]. Although patients with IBD thus constitute a high-risk population for malnutrition, the principles of screening for malnutrition, with its subsequent assessment and management, are in common with those for other chronic conditions.

Nutritional care is clearly important in the treatment of patients with IBD and includes prevention of the treatment of malnutrition and micronutrient deficiencies, prevention of osteoporosis, and, in children promotion of optimal growth and development [7–11].

2. Methodology

The present ESPEN guideline for Clinical Nutrition in IBD began with updated methodology dating from 2011, which has since (2015) been replaced by new standard operating procedures for ESPEN guidelines and consensus papers [12]. These new and more rigorous methodologies for ESPEN guidelines both have a focus on disease rather than the historical technique-based approach (enteral vs parenteral). The multidisciplinary, multinational approach remains, but the guidelines are more structured and depend on systematic review, relying on expert opinion only when the systematic approach is not possible or yields inconclusive results. In the specific case of guidelines for Clinical Nutrition in IBD there were previous ESPEN guidelines for enteral and parenteral nutrition in gastrointestinal disease [13,14].

For the present guideline an expert writing panel was sought, both to retain some of the key contributors from 2006 and 2009 (by mutual consent) and to introduce new faces. An intended fully integrated approach for joint guidelines with the European Crohn's and Colitis Organisation (ECCO) and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) was explored, but although there were positive discussions practical obstacles prevented this. The following guidelines are therefore informed by discussion with representatives from ECCO and ESPGHAN, but are not joint guidelines and form the recommendations of ESPEN alone. The expert panel was accredited by the ESPEN Guidelines Group, by the ESPEN Education and Clinical

Practice Committee, and by the ESPEN Executive. All members of the working group had declared their individual conflicts of interest according to the rules of the International Committee of Medical Journal Editors (ICMJE).

Following the previous methodology, the expert panel created a series of clinical questions for adult and paediatric practice, presented according to the PICO formulation, which stands for Population, Intervention, Comparison and Outcome. PICO questions accordingly include short but exact definitions of the population of interest, the intervention, comparators, and outcome. It was anticipated that the data would not permit satisfactory analyses in all cases and that for some questions data would be differently robust for adult and child patients. It was nonetheless felt appropriate to try to present the data for all age groups in a comparable format. The interpretation of the data from the literature was to be based on the panel's decision as to the outcomes that matter most to patients, and not necessarily the outcomes presented in the original studies. It was recognised from the outset that some aspects of nutrition in IBD would not be susceptible to fruitful systematic review, and it was initially intended that the guidelines would be constructed in two parts: a first section with the elements which would necessarily be opinion-based, and a second section considering those elements susceptible to systematic review. The Cochrane team of Prof Leonard Leibovici in Israel was commissioned by ESPEN to conduct the systematic review according to questions devised by the expert panel for this second section. The Cochrane Centre assessed 1299 papers in the systematic review. The data were almost uniformly poor or absent, with studies which were typically small and underpowered. Few strong recommendations were possible and a major need for new and better research was identified. Only three Grade A recommendations were possible, and two of these were negative. Grade B evidence supported four further recommendations, but most of the questions for which clinical answers were sought remain unanswered (Table 1).

Faced with the poor, but not entirely unexpected, outcome of the systematic review, the design and methodology of the present guideline were modified substantially according to the current ESPEN methodology [12]. In conjunction with the ESPEN Guidelines Group the expert panel expanded the PICO-style questions to include the areas intentionally omitted from the original commission to the Cochrane Centre, and reformulated those originally selected so as to permit a more comprehensive framework to enable constructive and practical recommendations. A final list of 40 PICO-style questions was created, which ultimately generated 64 recommendations.

The time interval inherent in this process meant that it was necessary to redraft the commentaries intended to accompany the questions and recommendations, and in some cases to create these *de novo*. The opportunity was taken to perform an additional literature search based on PubMed terms relevant to each question (Appendix A). This process obviously falls short of a second systematic review, but its results are felt by the ESPEN Guidelines Group to represent sufficiently high levels of robustness and authority in combination with the earlier analysis. The combined

Table 1
Recommendations from the systematic review.

Grade A	Omega-3 supplementation in maintenance of UC not supported High fibre diet in maintenance of Crohn's not supported Treatment of iron deficiency anaemia in IBD is valuable (oral or iv)
Grade B	Probiotics are ineffective in maintenance of CD Elemental diet is ineffective in inducing remission in CD in adults Probiotics are effective in maintenance of UC Probiotics are effective in inducing remission in acute UC

result of these approaches means that the guidelines now form a single Results section based around 40 questions, and there is no longer a distinction between areas with and without expectations of strong objective data.

The recommendations were graded according to the Scottish Intercollegiate Guidelines Network (SIGN) grading system (Table 2). Grading is based on the systematic determination of the level of evidence for the literature, on which the recommendation is based. In total, 36 references have been graded as listed in the evidence table (Appendix B)

All recommendations were drafted by the working group were made available to interested ESPEN members via an internet platform for comments and online voting (DELPHI round, March/April 2016). Five voting options (agree, rather agree, indecisive, rather disagree, disagree) and the possibility to place individual comments were offered. A total of 29 experts participated in the Delphi process prior to the final consensus conference on April 18th, 2016. If the recommendations received more than 75% agreement in the DELPHI, they were usually finalized without further discussion. All other recommendations were revised by the working group and the revised versions underwent a second voting round during the final consensus conference. The voting results are indicated for each recommendation according to the current ESPEN classification (Table 3).

3. Results

1. Nutrition in aetiology and its potential to prevent inflammatory bowel disease

Can diet affect the incidence of IBD?

Recommendation 1:

A diet rich in fruit and vegetables, rich in n-3 fatty acids, and low in n-6 fatty acids is associated with a decreased risk of developing Crohn's disease or ulcerative colitis and is therefore recommended.

Grade of recommendation 0 – Strong consensus (90% agreement)

Commentary:

The rising incidence of IBD in Western countries has generally predated that in developing nations, supporting the hypothesis that 'Westernization' of our lifestyle has led to the increased incidence of IBD. Smoking, antibiotic use, and diet are potentially reversible risk factors for IBD. Multiple dietary components may impact on

Table 2
Grades of recommendations.

Grade	Level of evidence	Explanation
A	1++ or 1+	At least one metaanalysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	2++ or 2+	A body of evidence including studies rated as 2++, directly applicable to the target population; or a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
O	3 or 4	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2++ or 2+
GPP		Good practice points. Recommended best practice based on the clinical experience of the guideline development group

Table 3
Classification of the strength of consensus.

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

the resident flora, generating dysbiosis diminishing or damaging the mucus layer, may increase intestinal permeability or increase the ability of pathological microbiota to adhere to epithelial cells or translocate across the epithelial barrier. For example, in a recent study it has been shown that western diet induces changes in the composition of gut microbiota, alters host homeostasis and promotes an unfavourable gut colonisation in genetically susceptible mice [15].

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 and al. published the first systematic review entitled "Dietary Intake and Risk of Developing IBD" [16]. They used guideline-recommended methodology to evaluate the association between pre-illness intake of nutrients (fats, carbohydrates, protein) and food groups (fruits, vegetables, meats) and the risk of subsequent IBD diagnosis. Nineteen studies were included, encompassing 2609 IBD patients (1269 with CD and 1340 with UC), and over 4000 controls. The main results of this systemic review are the following:

- There is an increased risk of developing UC with high intake of total fat, PUFAs, omega-6 fatty acids, and meats,
- There is an increased risk of CD with high intake of PUFAs, omega-6 fatty acids, saturated fats, and meat.
- There is a decreased risk of CD, but not UC, with high intake of dietary fibre and fruits. A consistent association was shown between high dietary fibre and decreased risk of CD, with the protective effect observed to be statistically significant in those consuming more than 22.1 g/d. The review also observed that a high intake of fruit is associated with a 73–80% decreased risk of CD. This association was confounded by dietary fibre intake and the fact that a diet high in fruits may conversely be low in fats and meats.
- There is no consistent association between total carbohydrate intake and IBD risk, even in studies reporting intake greater than double the recommended daily intake.

Some important studies from established prospective cohorts [the Investigation into Cancer and Nutrition (EPIC) cohort and the Nurses' Health Study I and II cohorts], have been recently published and bring additional and important new insights.

Fibre, fruit and vegetables: In a large prospective cohort study including 170,776 female registered nurses followed over 26 years, 269 incident cases of CD and 338 cases of UC were identified [17]. Compared to women with the lowest energy-adjusted fibre intake, intake of fibre in the highest quintile (median 24 g per day) was associated with a significant reduction in risk of CD [hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.39–0.90] but not UC. Interestingly, this association seemed specific for fibre from fruits in particular, and only to a lesser degree from vegetables and cruciferous vegetables. No association was identified between intake of fibre from other sources such as cereals, whole grains, or legumes. This association was also slightly stronger with respect to small bowel as opposed to colonic CD.

In a recent meta-analysis including a total of 14 case–control studies [18], consumption of vegetables was negatively associated with the risk of UC (OR = 0.71, 95% CI 0.58–0.88, n = 9 studies), but

not with CD (OR = 0.66, 95% CI 0.40–1.09, $n = 8$ studies). Higher consumption of fruit was negatively associated with the risk of UC (OR = 0.69, 95% CI 0.49–0.96, $n = 8$ studies) and CD (OR = 0.57, 95% CI 0.44–0.74, $n = 10$ studies). On subgroup analysis the intake of vegetables was negatively associated with the risk of CD in studies carried out in Europe (OR = 0.36, 95% CI 0.23–0.57), but not in Asia (OR = 1.00, 95% CI 0.50–2.03).

Dietary fat: Among the 170,805 women enrolled in the Nurses' Health Study the effect of energy-adjusted cumulative average total fat intake, as well as specific types of fat and fatty acids, on the risk of CD and UC was examined using Cox proportional hazards models adjusting for potential confounders [19]. Cumulative energy-adjusted intake of total fat, saturated fats, unsaturated fats, $n-6$ and $n-3$ polyunsaturated fatty acids (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 (Hazard ratio (HR) 0.72; 95% CI 0.51–1.01). 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, 95% CI 0.94–1.92).

In the EPIC study, 229,702 participants were recruited from nine European centres between 1991 and 1998 [20]. 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 (odds ratio (OR): 2.49; 95% CI: 1.23 to 5.07, $p = 0.01$) with a significant trend across quartiles (OR 1.32 per quartile increase (95% CI: 1.04 to 1.66; $p = 0.02$ for trend). In another nested case–control analysis of the EPIC study [21], each participant who developed incident CD ($n = 79$) was matched with four controls. All higher quintiles of DHA intake were inversely associated with development of CD; the highest quintile had the greatest effect size (OR 0.07; 95% CI 0.02–0.81). The OR trend across quintiles of DHA was 0.54 (95% CI 0.30–0.99). Including BMI in the multivariate analysis, due to its correlation with dietary fat showed similar associations. There were no associations with the other dietary fatty acids studied.

Looked at from an alternative perspective in nearly 200 children with a new diagnosis of CD, Costea et al. again concluded that a high omega-6:omega-3 ratio in the diet predisposes to the condition (odds ratio of up to 3), but that this is the case only for those with specific polymorphisms of the CYP4F3 and FADS2 genes [22]. The two genes code for a leukotriene B4 inhibitor and for enzymes in PUFA metabolism respectively and further support an interaction between nature and nurture in IBD.

It is also possible (and of relevance to nutrition when it is used therapeutically) that it is not only the fats themselves that are important, but additional agents employed to keep them in forms that are aesthetically acceptable. The emulsifiers used in commercially prepared foods may be implicated in this regard, with at least one (polysorbate 80) having a proposed specific mechanism as it increases bacterial translocation across the intestinal epithelium [23].

Vitamin D: Khalili et al., using the Nurses' Health Study cohort, demonstrated a lower risk for both CD (HR 0.48, 95% CI 0.30–0.77) and UC (HR 0.62, 95% CI 0.42–0.90) in women who were residing in southern latitudes at age 30, compared to those residing in northern latitudes [24]. In a prospective cohort study of 72,719 women (age, 40–73 y) enrolled in the Nurses' Health Study, women completed an assessment of diet and lifestyle, from which a 25-hydroxy vitamin D [25(OH)D] prediction score was developed and validated against directly measured levels of plasma 25(OH)D [25]. During 1,492,811 person-years of follow-up 122 incident cases of CD and 123 new cases of UC were documented. The median predicted 25(OH)D level was 22.3 ng/mL in the lowest, and 32.2 ng/

mL in the highest quartiles. Compared with the lowest quartile for vitamin D levels, the multivariate-adjusted HR for CD was 0.54 (95% CI: 0.30–0.99) in the highest quartile for vitamin D, and 0.65 (95% CI, 0.34–1.25) for UC. Compared with women with a predicted 25(OH)D level less than 20 ng/mL, the multivariate-adjusted HR for UC was 0.38 (95% CI, 0.15–0.97) and a non-significant 0.57 for CD (95% CI, 0.19–1.70) for women with a predicted 25(OH)D level greater than 30 ng/mL. There was a significant inverse association between dietary and supplementary vitamin D and UC, and a non-significant reduction in CD risk.

Zinc: There has been limited examination of the role of micronutrients in IBD pathogenesis. Dietary zinc is promising as a risk factor and may influence risk of IBD through effects on autophagy, innate and adaptive immune response and maintenance of the intestinal barrier. In a recent study concerning zinc intake and incidence of IBD, data from 170,776 women from the Nurses Health Study I and Nurses Health (using semi-quantitative food questionnaire) were presented. There were 269 incident cases of CD and 338 of UC [26]. Zinc intake ranged from a median of 9 mg/day in the lowest quintile to 27 mg/day in the highest quintile. Compared to women with the lowest quintile of intake, the multivariate hazard ratios (HR) for CD were 0.92 (95% CI, 0.65–1.29) for the second quintile of intake, 0.60 (95% CI, 0.40–0.89) for the third quintile, 0.57 (95% CI, 0.38–0.86) for the fourth quintile, and 0.74 (95% CI, 0.50–1.10) for the highest quintile (p for trend = 0.003). Compared to individuals with intake of zinc less than the recommended daily allowance (8 mg/day), those with an intake of 8–16 mg/day (HR 0.69, 0.44–1.08) and >16 mg/day (HR 0.52, 0.32–0.86) had a reduced risk of CD. The association was stronger for dietary zinc (HR 0.63, 95% CI: 0.43–0.93), comparing extreme quintiles, than for zinc intake from supplements. In conclusion, in two large prospective cohorts of women, intake of zinc was inversely associated with risk of CD but not UC.

Dietary pattern: Within the prospective EPIC programme, a nested matched case–control study was performed among 366,351 participants with IBD data, which included 256 incident cases of UC and 117 of CD, and 4 matched controls per case [27]. Dietary intake was recorded at baseline from validated food frequency questionnaires. Incidence rate ratios for the development of UC and CD were calculated for quintiles of the Mediterranean diet score, and *a posteriori* dietary patterns were produced from factor analysis. No dietary pattern was associated with either UC or CD. Specifically there were no associations with a Mediterranean diet and either condition. However, when excluding cases occurring within the first 2 years after dietary assessment, there was a positive association between a “high sugar and soft drinks” pattern and UC risk (incidence rate ratios for the 5th versus the 1st quintile: 1.68 (1.00–2.82). When considering the foods most associated with the pattern, high consumers of sugar and soft drinks were at higher UC risk only if they had low vegetable intakes.

Other micronutrients, microparticles and the unintentional inclusion of trace metals in the diet, such as by the swallowing of toothpaste, have been explored and there are no robust data to indicate important effects on IBD pathogenesis (reviewed by Andersen et al. [28]).

In conclusion, the external environment offers particular promise as a modifiable risk factor for both incident disease and for outcomes in those with established disease [29]. Many concordant results suggest that a diet rich in fruits and vegetables in $n-3$ fatty acids and low in $n-6$ fatty acids is associated with a decreased risk of developing CD or UC. Interesting new data suggest that a diet rich in vitamin D and zinc may also protect against CD but not UC. Rigorous randomized controlled trials examining the effect of dietary factors are required to establish or refute the role of these factors in achieving and maintaining disease remission.

Does breastfeeding protect against IBD?

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:

An early case control study conducted in 9 countries included 499 patients to investigate childhood factors predicting IBD yielded no significant differences between patients and controls in the frequency of breast feeding, cereal consumption, sugar added to milk in infancy, and other dietetic factors [30]. This finding was confirmed in a German study [31]. In contrast, an Italian study indicated that lack of breastfeeding is associated with an increased risk of UC (OR = 1.5; 95% CI: 1.1–2.1) and CD (OR = 1.9; 95% CI: 1.1–3.3) [32]. Systematic reviews from 2004 and 2009 concluded strongly in favour of breastfeeding [33,34] 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 [0.41–0.74], UC OR 0.71 [0.52–0.96]) with a duration–response effect [35]. Comparable data were reported from a Danish cohort study, in which breastfeeding for >6 months decreased the odds of IBD (OR, 0.50; 95% CI, 0.23–1.11) [36]. More recently still, 2 further publications confirmed this relationship, one from the US and another from Asia–Pacific. The US study was a single centre study in which the relation between breastfeeding and requirement for disease-related surgery in 333 CD and 270 UC patients was examined. Among those with CD, being breastfed was associated with reduced risk of CD-related surgery (34% vs. 55%), while none of the early life variables influenced disease phenotype or outcome in UC [37]. The Asia–Pacific study included 442 incident IBD cases from eight countries in Asia and Australia and 940 controls. In a multivariate model, being breastfed for >12 months decreased the odds for CD (aOR 0.10; 95% CI 0.04 to 0.30) and UC (aOR 0.16; 0.08 to 0.31) in Asians [38].

Breastfeeding for around six months is desirable in all infants [39]. Regarding longer periods of breastfeeding, current European recommendations suggest that breastfeeding is continued as long as mutually desired by both mother and infant [39]. In summary, the majority of the literature (and in particular the more recent publications) supports the importance of breastfeeding as a protective factor in early childhood regarding the development of IBD.

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

Recommendation 3 A:

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 3 B:

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:

Adults with IBD are at increased risk of malnutrition, with deficits more common in patients with CD than UC [40]. 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 [41].

Malnourished patients with IBD are more likely to be hospitalised following emergency department attendance [42] and are more likely to be admitted to hospital due to infection [43]. In hospitalised patients malnutrition is an independent risk factor for venous thromboembolism [44], non-elective surgery [45], longer admission [40,45] and increased mortality [40].

Pragmatically optimising nutrition status may improve outcomes for patients with IBD therefore it is logical to screen for, and manage, undernutrition using an appropriately trained multidisciplinary team.

Malnutrition in children: Malnutrition in childhood Crohn's is common at diagnosis and may persist despite disease treatment [46]. 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 [47]. Although a variety of screening tools exists, the tools have poor ability to discern different levels of nutrition risk for children with IBD [48]. Poor nutrition in childhood IBD contributes to disrupted pubertal development and impaired growth velocity which may lead to short stature in adulthood.

Malnutrition plays a role in the pathogenesis of IBD, in its clinical presentation and in disease treatment and outcome. As in adults, the mechanisms involved include limited food intake, malabsorption of nutrients, and increased nutrient losses. With specific drugs (sulfasalazine, methotrexate, steroids) it can include interactions between these drugs and nutrients.

Of particular importance in paediatric IBD is growth failure, which is the result of a combination of inflammation and chronic malnutrition [49]. Growth failure is seen in 15–40% of children with IBD [49,50]. Both growth failure and delay of puberty are more common in Crohn's than in UC. Despite greater disease awareness, growth failure is still found to precede the diagnosis of Crohn's by many years in a high proportion of patients. This may have an adverse effect on the final height of these patients, who commonly fail to reach their final predicted height: short stature (final height below 5th percentile) is present in up to 30% of Crohn's patients [51].

Iron deficiency is particularly common in paediatric IBD, while other deficiencies include folic acid, zinc, magnesium, calcium, vitamins A, B12, D, E, and K [52]. A detailed discussion of nutritional assessment is beyond the scope of these guidelines, however, a careful account of nutrition intake, anthropometric measurements, including history of growth with plotting of previous measurements of weight and height and assessment of growth rate are essential. Laboratory work up to identify and treat nutrient deficiencies is also essential.

Do patients with IBD have altered energy requirements?

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. It is also worth noting that an individual patient's daily energy requirement includes their resting energy expenditure (REE), which includes the energy cost of depositing tissue/growth, energy expended in physical activity, and dietary

induced thermogenesis. An important consideration highlighted in paediatric data is how to adjust for differences in energy expenditure attributable to body size: patients with greater mass have greater REE. This effect may not be fully negated by expressing REE per unit of mass or lean mass, and alternative analyses have been proposed [53–55].

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 colitis compared to remission in adults [56,57] which is understandable considering that systemic disturbance (fever and tachycardia) is common. However, an increase in REE is likely to be offset by reduction of physical activity. Significant reduction in dietary intake is common in acute colitis and may result in negative energy balance [58]. Inconsistent results about changes in resting energy expenditure are found for milder disease activity and for children.

One single study has measured total energy expenditure in adults with CD and recorded normal values [59]. Comparison between other studies of resting energy is hampered by differing presentation of data. However, measured REE has consistently been found to be similar to predictive equations based on weight in adults [60,61] or children [62–65]. Measured REE/kg in adult patients has been found to be higher than [66] or the same as [67] 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. REE does not appear to be raised in patients with weight loss, but decreased nutrient intake and malabsorption has been shown in these patients [68,69]. No consistent association between CD activity and REE in adults has been demonstrated. In children with Crohn's, measured REE has not been demonstrated to be significantly different in children before and after infliximab (anti-TNF) [70–72] and no consistent association has been found between REE/kg FFM and markers of disease activity [73].

In summary, patients with IBD do not have an increased energy expenditure as a direct result of their disease and predictive equations are suitable for estimating requirements. Dietary intake may be inadequate to meet even normal requirements particularly during periods of disease activity which may lead to weight loss. Measurement of REE by indirect calorimetry could be used in troublesome cases.

Do patients with IBD have altered protein requirements?

Recommendation 5 A:

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

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

Recommendation 5 B:

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

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

Commentary:

Patients with IBD develop a relative reduction in lean mass and increase in adiposity 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 [74] and adults [75] with Crohn's. In contrast administration of elemental or polymeric feed as treatment of Crohn's or as adjunctive nutrition support results in reduction of proteolysis and acquisition of lean tissue in children and adults [1,76,77]. In children with active CD one study examined the reduction in protein turnover resulting from treatment with Infliximab and demonstrated improved protein metabolism in patients receiving parenteral nutrition both before and after infliximab treatment [72].

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 tube feeding may provide beneficial effects on protein turnover without deleterious consequences on disease activity.

There is no good evidence that the daily protein needs of IBD patients in remission differ from those of healthy controls. Provision of 1 g protein for each kilogram of body weight is therefore reasonable. However in active inflammation the proteolytic, catabolic response justifies an increase in provision to 1.2–1.5 g/kg bodyweight [78,79].

Do patients with IBD have an altered micronutrient requirement?

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 diarrhoea 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 [80]. In light of this some authors have examined micronutrient status in patients in clinical disease remission and found deficits of a variety of micronutrients [81,82]. Furthermore, deficits may be present even in apparently well nourished individuals [83]. 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 [84]. Poor compliance, particularly in adolescents, is common with multivitamin supplements and patient education about the rationale behind their use is important [85].

Consequences of deranged micronutrient status include anaemia, 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.

Is iron supplementation needed in IBD?

Recommendation 7 A:

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.

Grade of recommendation A – Strong consensus (100% agreement)

Recommendation 7 B:

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.

Grade of recommendation A – Strong consensus (100% agreement)

Recommendation 7 C:

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.

Grade of recommendation A – Strong consensus (93% agreement)

Commentary:

Anaemia is considered the most frequent extraintestinal manifestation of IBD, usually complicating the course both in UC and Crohn disease (CD). Prevalence rates of anaemia in IBD vary widely from 6 to 74% [86]. Anaemia is reported more frequently in hospitalized patients with IBD and occurs more frequently in CD than in UC [87]. In IBD patients anaemia increases, morbidity, rate of hospitalization, medical costs and deaths [86,88]. In the majority of cases, IBD-associated anaemia represents a combination of chronic iron deficiency and anaemia of chronic disease [86]. The currently used WHO definition of anaemia (Table 4) applies also to patients with IBD [89].

All patients with IBD regardless of their age should be assessed for the presence of anaemia [90]. The major forms of anaemia in IBD are iron deficiency anaemia (IDA), anaemia of chronic disease (ACD) and anaemia of mixed origin [ECCO Anaemia Statement 1A]. Diagnostic criteria for iron deficiency depend on the level of inflammation. For laboratory screening, complete blood count, serum ferritin, and C-reactive protein [CRP] should be used [ECCO Anaemia Statement 1B]. For patients in remission or mild disease, measurements should be performed every 6–12 months. In outpatients with active disease such measurements should be performed at least every 3 months [ECCO Anaemia 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 IDA. In the presence of inflammation, a serum ferritin up to 100 µg/L may still be consistent with iron deficiency [ECCO Anaemia Statement 1D]. In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for ACD 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 ACD is likely [ECCO Anaemia Statement 1E].

Iron supplementation is recommended in all IBD patients, whatever their age, when iron-deficiency anaemia is present [ECCO Anaemia Statement 2A]. Quality of life improves with correction of anaemia, and this improvement is independent of clinical activity [91]. The decision to supplement iron in patients without anaemia is more controversial and will depend on the patients' history, symptoms and individual preferences. Although there is evidence of benefit in treating iron deficiency without anaemia in other conditions such as chronic fatigue and heart failure, such evidence is not yet available in the context of IBD [90]. In a recent meta-analysis of randomized controlled trials comparing intravenous versus oral iron for the treatment on anaemia in IBD, five eligible studies, including 694 IBD patients, were identified [92]. IV iron demonstrated a higher efficacy in achieving a haemoglobin rise of ≥ 2.0 g/dL as compared to oral iron (OR: 1.57, 95% CI: 1.13, 2.18). Treatment discontinuation rates, due to adverse events or intolerance, were lower in the IV iron groups (OR: 0.27, 95% CI: 0.13, 0.59). Similarly, the occurrence of gastrointestinal adverse events was consistently lower in the IV iron groups. On the contrary, serious adverse events (SAEs) were more frequently reported among patients receiving IV iron preparations (OR: 4.57, 95% CI: 1.11, 18.8); however, the majority of the reported SAEs were judged as unrelated or unlikely to be related to the study medication. The recent European Crohn's and Colitis Organization (ECCO) guidelines [90] 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 haemoglobin below 100 g/L, and in patients who need erythropoiesis-stimulating agents; while oral iron may be used in patients with mild anaemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron [90]. The estimation of iron need is usually based on baseline haemoglobin and body weight (Table 5) [93].

Anaemia seems to recur frequently and fast after intravenous iron therapy [94]. After successful treatment of iron deficiency anaemia with intravenous iron, re-treatment with intravenous iron should be initiated as soon as serum ferritin drops below 100 µg/L or haemoglobin below 12 or 13 g/dL according to gender [ECCO Anaemia Statement 3E].

II. Dietetic recommendations in active disease

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

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:

Lately, there is interest in specific carbohydrate, paleolithic, gluten-free, low FODMAP, ω -3 PUFA enriched and other diets in

Table 4
Haemoglobin concentrations (in g/L) for diagnosis of anaemia, by population.

	Healthy	Mild anaemia	Moderate anaemia	Severe anaemia
Boys and girls (0.5–4 years)	≥ 110	100–109	70–99	<70
Boys and girls (5–11 years)	≥ 115	110–114	80–109	<80
Boys and girls (12–14 years)	≥ 110	110–119	80–109	<80
Non-pregnant women and girls (≥ 15 years)	≥ 120	110–119	80–109	<80
Pregnant women and girls (≥ 15 years)	≥ 120	100–109	70–99	<70
Men and boys (≥ 15 years)	≥ 130	110–129	80–109	<80

Table 5
Simple scheme for estimation of total iron need [93].

Haemoglobin 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

active IBD. However RCT data regarding the effects of experimental diets on intestinal inflammation or on inducing remission are still lacking at this time. An adequately powered RCT of fructo-oligosaccharides (FOS) showed no clinical benefit in patients with active CD [95]. Therefore, no “oral IBD diet” can be generally recommended to promote remission in IBD patients with active disease. This recommendation does not preclude 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. It is important that each IBD patient with active disease should undergo malnutrition screening and diet counselling in the case of malnutrition. It is recorded that approximately 75% of hospitalised CD patients suffer from malnutrition and 33% have a BMI <20 kg/m² [96]. Screening for nutritional deficiencies in chronic disease patients is warranted.

Enteral nutrition (EN), as an exclusive form of nutrition (EEN), has generated interest over 30 years as a treatment modality for active IBD since it is hypothesized to promote mucosal healing in the gastrointestinal tract by altering favourably the intestinal microbiota, reducing intestinal permeability, enhancing barrier defence and adaptation, and promoting a reduction of pro-inflammatory cytokines. In an open-label-trial in 37 CD children it was demonstrated that mucosa healing was significantly higher in the polymeric (74%; 95% CI 51%–89%) than the corticosteroid group (33%; 95% CI 16%–57%, $P < 0.05$) [97]. In these cases, polymeric EN seems more effective than elemental ones [98,99]. EN in a supplemental form as partial enteral nutrition (PEN) therapy induced remission in 47 children and young adults [100], whereas this effect was not found in a former RCT in 50 CD children [101]. Due to strong concerns over corticosteroid use and aiming for optimal growth in children, EN is often first-line therapy for paediatric patients with active CD [102]. Although EEN as primary therapy in adults with CD has also repeatedly been considered to be effective the data are not robust. Opposite results have appeared regarding the amount and nature of fat in the enteral formulae and on the question of polymeric versus elemental EN in RCTs of adults with active CD [103–105]. Meta-analyses do not support the use of EN as primary treatment for acute exacerbations of CD in adults [102,106]. Patchy clinical conviction and the data, which appear better than might be expected with placebo, ensure continuing controversy over its role in adults.

Is there specific dietetic advice for IBD patients with a stoma or severe diarrhoea?

Recommendation 9 A:

IBD patients with severe diarrhoea 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 9 B:

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:

In the case of extraordinary amount of faecal production, diarrhoea or increased/high output stoma (HOS), a systematic diagnostic approach is advised in which screening for clostridium, antibiotic associated diarrhoea, pouchitis in the case of IPAA, bile

acid diarrhoea/steatorrhoea after distal ileal resection, (distal) colonic inflammation, lactase deficiency in the case of proximal small intestinal inflammation, and coeliac disease should be incorporated. Depending on the underlying cause of diarrhoea in IBD, medication can be considered as well as a supportive diet regime in some cases (eg lactose restricted diet).

Ongoing and severe diarrhoea or HOS can result in intestinal insufficiency [107] with malabsorption, unintentional weight loss, malnutrition, nutritional deficiencies and/or dehydration. Malabsorption is an important contributing factor to malnutrition in IBD [64]. The retrospective study of Baker in 687 stoma patients [108], showed that early high output (within 3 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-diarrhoeal 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 [109]. In a study in 13 adult (ileal) HOS patients, oral rehydration solutions containing rice maltodextrins (R-ORS) 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 [110]. In another study, 3 different saline and/or glucose solutions were tested in 6 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 HOS [111]. No RCTs are available on nutritional treatment of IBD related diarrhoea or HOS. Only case studies on treatment of Crohn with HOS have been published, which show successful treatment with restriction of hypotonic fluids, sodium enriched diets, fully enteral nutrition and/or parenteral sodium-containing infusions.

What are the dietetic recommendations for CD patients with strictures?

Recommendation 10:

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.

Grade of recommendation GPP – Strong consensus (95% agreement)

Commentary:

Some patients with CD develop clinically significant intestinal strictures. Depending on their severity (degree of obstruction) and site, 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 fibre, 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. Different treatment approaches with potentially harmful side effects are frequently used: medical options (drugs) where the narrowing is mainly the result of inflammation, endoscopic (by balloon dilatation) or surgical approaches when there is fibrotic scarring. Depending on their

severity (degree of obstruction) and site, nutritional support may become necessary while the effects of treatment are awaited at least in case of (risk of) malnutrition.

A recent Chinese prospective observational study in 59 adult CD patients with inflammatory bowel strictures showed that 12-weeks exclusive enteral nutrition (EEN) 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 [112]. A small study of 7 patients showed no clinical effect of TPN on colonic strictures [113]. No RCTs are available on nutritional management in IBD strictures. Some case studies report on occasional effectiveness of TPN or semi-elementary enteral nutrition.

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 enteral nutrition whenever this is possible, there are no robust data to support these apparently logical approaches.

What are the dietetic recommendations for IBD patients with respect to bone mineral density (including those on steroid therapy)?

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:

Osteoporosis (low bone mineral density BMD) and fractures are frequently encountered in patients with CD. The prevalence of osteoporosis in paediatric patients with IBD is approximately the same as in adult patients. Osteoporosis may already be present before steroid treatment [114]. In order to prevent fractures, treatment with bone protecting drugs appears warranted early in the course of bone disease when bone loss is not yet prominent. Significant risk factors for low BMD 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 [115,116]. In children and adolescents with IBD risk factors associated with low BMD are cumulative corticosteroid dose, height-for-age Z-score, and BMI Z-score [117].

It should however be remembered also that prednisone treatment in CD can stimulate food intake, promoting an overall positive energy balance despite large faecal nutrient losses [118].

There is no overall consensus on the vitamin D status and necessary actions in children and adolescents with IBD. In Veit's study there is no difference in mean serum 25(OH)D concentration between children and adolescents with IBD and controls ($n = 58$ child vs $n = 116$ HC) [119]. Vitamin D deficiency is common (55%) among adult patients with active UC, particularly those requiring corticosteroids ($n = 34$) [120]. Vitamin D deficiency should be treated since low plasma 25(OH)D is associated with an increased risk of surgery and hospitalizations in both CD and UC, and normalization of 25(OH)D status is associated with a reduction in the risk of CD-related surgery ($n = 3217$ adults with IBD) [7]. Next, a higher plasma 25(OH)D is associated with reduced risk of *Clostridium difficile* infection in patients with IBD ($n = 3188$ adults with IBD) [8]. Vitamin D supplementation seemed effective in increasing serum 25(OH)D levels in 83 children with quiescent CD [121].

A RCT of 132 osteopenic CD patients, showed improved BMD at lumbar spine after 2 years of once weekly treatment course with risedronate 35 mg, concomitant with calcium and vitamin D supplementation [122]. An earlier RCT showed no significant benefit of calcium supplementation (1 g/day) alone on the BMD at 1 year in corticosteroid-using IBD patients with osteoporosis [123].

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 BMD.

Are there subgroups of patients with Crohn's disease who are at particular risk of fat malabsorption?

Recommendation 12 A:

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.

Grade of recommendation GPP – Consensus (86% agreement)

Recommendation 12 B:

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:

The common causes of bile acid malabsorption are ileal resection and inflammation of the terminal ileum, common in CD. Decreased reabsorption of conjugated gall bile acids leads to excess transmission to the colon, where deconjugation by bacteria occurs. Osmotic diarrhoea and (in severe bile acid malabsorption) fat malabsorption might be a consequence [96]. If mild, bile acid diarrhoea can be controlled by a sequestrant such as colestyramine [124,125]. In a double-blind cross-over study in 14 CD patients who had undergone ileal resection, no negative effect of colestyramine treatment on jejunal fat absorption was reported. In severe cases of bile acid malabsorption however, steatorrhoea may worsen as a result of colestyramine treatment [126].

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 [127]. 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 [128]. Significantly lower mean values of urinary oxalate excretion were found in paediatric than in adult Crohn's patients [129]. 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.

Are exclusion diets effective in achieving remission in active CD?

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 [130], but only few studies reports induction of remission [100,131]. In the open label study by Sigall-Boneh et al., 47 paediatric and adult CD patients received polymeric formula feed (50% of caloric intake) combined with an exclusion diet (no gluten, dairy products, gluten-free baked goods and breads, animal fat, processed meats, products containing emulsifiers, canned goods, and no packaged products). After 6 weeks, remission was obtained in 70% of children and 69% of adults [100]. Another uncontrolled study in only 6 paediatric patients with moderate-severe CD, using an elimination diet (free of dairy products, certain grains and carrageenan containing foods) together with nutraceuticals (consisting of fish peptides, bovine colostrum, boswellia serrata, curcumin and a multivitamin) as well as Lactobacillus GG, and also growth hormone (administered daily) showed induction of remission in all patients [131].

In a randomised controlled trial, longer maintenance of remission (after successful induction of remission using elemental formula) was seen in patients using a stepwise dietary introduction programme excluding foods that worsened symptoms, compared to patients receiving corticosteroids on a tapering schedule while eating a normal diet [132]. Similar results on maintenance of remission were reported in an open label study by the same group using a personal food exclusion diet [133]. Another study reported maintenance of clinical remission using a IgG4 guided exclusion diet in adult CD patients [134].

Exclusion diets are labour-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.

Is there evidence for a useful effect of probiotics in active IBD?

Recommendation 14 A:

Probiotic therapy using *Escherichia coli* Nissle 1917 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 14 B:

Probiotics should not be used for treatment of active CD.

Grade of recommendation B – Strong consensus (95% agreement)

Commentary:

Two clinical trials in paediatric UC patients show a moderate effect of rectal enemas containing *Lactobacillus reuteri* in mild distal colitis [135] and of an oral preparation of VSL#3 in active colitis [136]. There are no specific data confirming harm, but lack of efficacy and the possible enhanced risks of and from bacteraemia in acute severe colitis lead the panel to advise against their use.

The systematic enquiry indicated that probiotics were, in general, ineffective in active CD. Not a single RCT has been performed using probiotics as induction treatment in paediatric CD. As stated in the recent ECCO/ESPGHAN guidelines on paediatric CD, probiotics are also not recommended for maintenance of remission [137]. It is possible that probiotics other than those studied or optimised doses and periods of treatment might have more useful effects, but the panel recommended that they should not be used.

There are some positive data in respect of the use of Lactobacillus GG in maintenance in children with CD [138].

III. Artificial nutrition in active IBD

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

Recommendation 15 A:

Oral Nutrition Supplements (ONS) are the first step when artificial 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 15 B:

If oral feeding is not sufficient then tube feeding should be considered as supportive therapy. Enteral feeding using formulae or liquids should always take preference over parenteral feeding, unless it is completely contraindicated.

Grade of recommendation A – Strong consensus (100% agreement)

Recommendation 15 C:

PN is indicated in IBD (i) when oral or tube feeding 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:

The decision on the optimal route of artificial 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 (supportive care, treatment of malnutrition, induction of remission, maintenance of remission). The decision will also be influenced by the type of formula used in prior studies, and the dietary modulation of the intestinal immune response in IBD and its potential clinical implications.

Oral Nutrition Supplements (ONS) are the first step but generally are but 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. Enteral feeding using formulae or liquids should always take preference over parenteral feeding, unless it is completely contraindicated. If oral feeding is not possible, feeding the patient through a nasogastric or nasoenteric tube should be considered.

Enteral nutrition should be considered in patients with a functional gastrointestinal tract but who are unable to swallow safely [139,140]. In situations when the gut cannot absorb all nutritional needs, enteral nutrition should nonetheless be attempted with supplementary PN [83,141,142].

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 enteral nutrition or in whom nutrition cannot be maintained by the enteral route [143]. However, it must be

recognized that these patients in need of PN are those with the most complicated disease [144].

Is primary nutritional therapy (EN or PN) effective in active CD?

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:

There are strong clinical impressions supported by trials deemed to be of poor quality that primary nutritional therapy is effective in the induction of remission and that the remission rates are reproducibly better than might be expected from a placebo response. It is therefore recommended that primary nutritional therapy in the form of exclusive enteral nutrition (EEN) is considered in all patients with acute active CD and that 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 EEN in induction of remission in adults. The argument in favour of EEN is stronger in paediatric practice and will normally be the first choice in many centres. Firstly, this is because of the deleterious effects of undernutrition on growth [50]. Secondly, since growth is so essential in children, this increases the possibility of avoiding the use of steroids or delaying their introduction [145] which is of paramount importance. Third, and most importantly, is the observed effect on induction of remission in paediatric studies demonstrating similar efficacy of steroids and EEN [146], and that in some settings (i.e. concomitant immuno-modulatory treatment) EEN might even be superior to corticosteroids in children [147]. However, these studies suffer from major methodological limitations including lack of proper randomization and retrospective analysis. Furthermore, most of the data relate to mild to moderate disease activity.

Recommendations in children are made only for EEN as limited data suggest that partial enteral nutrition may be less effective than exclusive enteral nutrition [96], though one RCT showed similar efficacy [98].

Commentary:

The data are weaker for adult practice [148], and most centres 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 enteral nutritional therapy a first-line option also in selected cases of adults with acute CD [149].

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 [148].

When EN is indicated in IBD what special technical steps are needed?

Recommendation 17 A:

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

Grade of recommendation B – Strong consensus (96% agreement)

Recommendation 17 B:

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

Grade of recommendation B – Strong consensus (92% agreement)

Commentary:

There are few reliable data on special steps or complications peculiar to patients with IBD. Reference can be made to general guidelines for nutrition support in severely malnourished patients, in respect of both EN and PN. Some features specific to IBD can nonetheless be summarised.

Tube feeding can be safely delivered by nasogastric tube, or percutaneous endoscopic gastrostomy [13,150,151]. Continuous tube feeding administered via an enteral feeding pump and increased slowly to the full prescribed volume appears to have lower complication rates than bolus delivery [13,150–152]. 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 [152,153].

Few patients with UC will need artificial feeding other than during the most severe exacerbations and in the peri-operative phase. Enteral nutrition is most appropriate and associated with significantly fewer complications than parenteral nutrition in acute colitis. Bowel rest through intravenous nutrition does not alter the outcome, but nonetheless, there are no specific contraindications for the use of parenteral nutrition in UC.

In CD nutritional support is more often needed. Specific micronutrient deficiency states are relatively common in CD; these should be sought (perhaps annually) and corrected as appropriate – a need for supplementary iron (oral or intravenous) and for parenteral vitamin B12 being the most common.

There is no specific contraindication to the use of parenteral nutrition 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. This will reflect the extent of malabsorption, and enteric losses, and will influence the prescription of energy and amino acids, and especially of water, electrolytes and minerals. Each PN cycle (usually nocturnal) should be complete and adjusted according to progress (eg through the number of cycles per week). 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. The most frequent complications of PN in IBD are infectious (catheter sepsis), metabolic and mechanical. Specific attention should be paid to electrolyte supplementation (especially sodium and magnesium) in short bowel patients. Again, these risks and precautions are not notably different from those seen in other chronic conditions.

Is there any advantage to particular formulations (eg polymeric vs oligomeric, fat content, nutraceuticals)?

Recommendation 18 A:

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

Grade of recommendation 0 – Strong consensus (96% agreement)

Recommendation 18 B:

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

Grade of recommendation B – Strong consensus (96% agreement)

Commentary:

Several studies have compared the efficacies of different types (elemental, semi-elemental, oligomeric or polymeric diets) of enteral formulae 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; $n = 146$) [154]. The protein composition did not appear to influence the therapeutic potential of EN. The present systematic enquiry reveals insufficient evidence to make firm recommendations [154,155]. It is therefore advised that standard feeds are employed if primary nutritional therapy is being employed. There are hypothetical advantages from some amended formulations.

Comparing one form of enteral nutrition to another has not shown any difference in effectiveness for treating active CD, but a non-significant trend favouring low fat formulations has emerged [156–158]. Some centres may therefore wish to consider the use of feeds with lower fat content.

The use of feeds supplemented with growth factors, ones with lower levels of emulsifying data, or oligomeric feeds, as alternatives to standard feeds, is not supported by reliable data [155,159,160]. Equally there is no evidence that any of these alternatives is inferior to the use of standard polymeric feeds [102,161].

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. This will reflect the extent of malabsorption, and enteric losses, and will influence the prescription of energy and amino acids, and especially of water, electrolytes and minerals. Each PN cycle (usually nocturnal) should be complete and adjusted according to progress (eg through the number of cycles per week). 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 [14,162,163]. The most frequent complications of PN in IBD are infectious (catheter sepsis), metabolic and mechanical [164]. Specific attention should be paid to electrolyte supplementation (especially sodium and magnesium) in short bowel patients [14,163]. Again, these risks and precautions are not notably different from those seen in other chronic conditions.

What nutritional recommendations exist for CD patients at risk of thromboembolism?

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:

Patients with IBD are at increased risk of venous thromboembolism. Thrombosis is a specific feature of IBD that can be involved in both the occurrence of thromboembolic events and the pathogenesis of the disease itself [165,166]. The precise aetiology for the higher rates of thromboembolism in IBD and the specific association is as yet unknown, but multiple acquired and inherited factors are implicated. The impact of inflammation on coagulation has been confirmed by several experimental studies showing that inflammatory mechanisms shift the haemostatic balance to favour the activation of coagulation which, in turn, can also sustain inflammation promoting a vicious circle between chronic inflammation and thrombosis. 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 [165–169].

What nutritional recommendations exist for CD patients with fistulae?

Recommendation 20 A:

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 O – strong consensus (100% agreement)

Recommendation 20 B:

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

Grade of recommendation B – Strong consensus (96% agreement)

Commentary:

Patients with CD are prone to fistulae formation between 2 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 [149,170,171]. Malnutrition with BMI <20 appears as an independent risk factor that should be confirmed in further studies [172].

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 [171]. Treatment will often need to be surgical but some patients clearly benefit from drug treatment with immunomodulators or/and biologics [173,174]. Once a fistula is mature and there is no longer any possibility of a free communication with the peritoneal space, there ceases to be any contraindication to enteral nutrition. Indeed in the patient with a distal (low ileal or colonic) fistula it may be possible to provide all necessary nutritional support via the enteral route [173,175,176]. 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 [177,178], but even then the psychological benefit of eating may warrant its inclusion in the nutritional regimen despite minimal expectations of useful nutrient absorption [175]. Surgical correction is more likely to be successful if nutritional status has been optimised pre-operatively [179].

What are the nutritional recommendations for CD patients at risk for refeeding syndrome?

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 [180–182].

Are there special indications for artificial nutrition in UC?

Recommendation 22 A:

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 22 B:

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

Grade of recommendation O – Consensus (88% agreement)

Commentary:

The systematic enquiry demonstrated evidence in favour of the use of probiotics in induction of remission and in maintenance of UC – see elsewhere in this document.

Despite early indications that omega-3 fatty acid supplementation contributed beneficially in induction and maintenance the systematic enquiry documented an absence of effect from a diet supplemented by omega-3 fats in patients with UC in the maintenance of remission [183–188]. This is therefore not advised.

The above data were obtained in adults. It appears reasonable and safe to extrapolate the conclusions and suggested actions on omega-3 fats into paediatric practice.

Literature analysis otherwise yielded insufficient evidence to make firm recommendations. There are few aspects in which the presence of UC alters conventional management in any important way [189]. It is therefore advised that standard nutritional practice is followed in patients with UC, giving due attention to nutrition screening and to generic nutritional support where needed.

Enteral nutrition has not been adequately evaluated in active UC. However it appears safe and can be nutritionally adequate in patients with severe disease [189]. 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 enteral feeding, or cannot be fed effectively by either mouth or enteric tube [144,189–191].

IV. Surgical aspects of nutrition in IBD

ESPEN has produced guidance on nutrition in the surgical patient and most of the principles apply equally to the IBD patient undergoing surgical intervention. Briefly, the following guidance should be followed during the perioperative period.

How should nutritional support be performed in the preoperative phase?

Recommendation 23 A:

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 Surgery guidelines – Strong consensus (100% agreement)

Commentary:

It is inappropriate to replicate detailed analysis of ESPEN's Surgery Guidelines but brief comments are offered here to help in the specific case of patients having surgery for IBD.

Protocols for enhanced recovery after surgery (ERAS) aim to accelerate rehabilitation including a desirable reduction of length of hospital stay. Functional recovery is considered the most important target [192–196]. From a metabolic and nutritional point of view, therefore, 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 eg of blood glucose
- Reduction of factors which exacerbate stress related catabolism or impair GI function
- Early mobilisation to facilitate protein synthesis and muscle function.

Recommendation 23 B:

In emergency surgery patients artificial 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 Surgery guidelines – 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.

The influence of nutritional status on postoperative morbidity and mortality has been well documented in both retrospective [197–201] and prospective studies [202–209]. It is clear that inadequate oral intake for more than 14 days is associated with a higher mortality [210].

The general indications for nutritional support in surgery are in the prevention and treatment of undernutrition, ie the correction of undernutrition before surgery and the maintenance of nutritional status after surgery, when periods of prolonged fasting and/or severe catabolism are expected [ESPEN Guidelines for Surgery].

Which nutritional strategies need to be considered in the perioperative phase?

Recommendation 24 A:

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)

Recommendation 24 B:

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)

Recommendation 24 C:

If malnutrition is diagnosed, then IBD surgery should be delayed for 7–14 days whenever possible, and that time should be used for intensive artificial feeding.

Grade of recommendation A, see Surgery guideline – Strong consensus (96% agreement)

Commentary:

A: Insufficient preoperative intake is an indication for dietary counselling or ONS, because as Kuppinger et al. [211] 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 tube feeding (TF) have reported significant advantages from EN with particular regard to the reduction of infectious complications, length of hospital stay and costs.

In six randomised controlled trials postoperative and post-hospital administration of ONS has been investigated [212–216]. 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.

B: As stated above, insufficient preoperative intake affects complication rates. Therefore, if the oral intake is inadequate, regardless of the intervention (dietary counselling and/or ONS), tube feeding (TF) should be initiated (ESPEN Guidelines: Surgery). Postoperatively, TF should be continued/started as many studies have shown the benefits and feasibility of feeding via a tube either inserted distal to the anastomosis, eg needle catheter jejunostomy, or inserted via the nose with its tip passed distally at the time of operation (nasojejunal tube) [217–222].

C: Undernutrition has a negative impact on the clinical course, the rate of postoperative complications and on mortality [199,223–227]. 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 6 months
- BMI < 18.5 kg/m²
- Serum albumin <30 g/L (with no evidence of hepatic or renal dysfunction)

These parameters reflect undernutrition as well as disease-associated catabolism.

Enteral nutrition with either ONS or TF is always preferred in such situations. Only if the GI tract is dysfunctional should PN be used.

In the case of an emergency, such as a completely obstructing lesion, uncontrolled bleeding, toxic megacolon or an acute abdomen, surgery should not be postponed. In those cases EN or PN starts postoperatively.

When should parenteral nutrition be used in the perioperative phase?

Recommendation 25 A:

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 – Strong consensus (100% agreement)

Recommendation 25 B:

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 25 C:

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).

Grade of recommendation A – Strong consensus (96% agreement)

Commentary:

The enteral route should always be preferred except when one or more of the following contraindications exists [ESPEN Guidelines for Surgery 2016, manuscript in preparation]:

- Intestinal obstructions or ileus,
- Severe shock
- Intestinal ischaemia
- High output fistula
- Severe intestinal haemorrhage

In those cases parenteral nutrition may be needed for a period of days or weeks until the function of gastrointestinal tract returns.

As in other vulnerable surgical patients, nutritional support (by the enteral route if possible) should be instituted without delay even in patients without obvious undernutrition if it is anticipated that the patient will be unable to eat for more than 7 days perioperatively and in patients who cannot maintain oral intake above 60% of their recommended intake for more than 10 days.

The enteral route should always be preferred over parenteral nutrition, but combinations of enteral and parenteral nutrition (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.

Combined enteral/parenteral nutrition has not yet been evaluated in prospectively controlled clinical trials with patients undergoing elective surgery. The only studies available are those of Heyland et al. and Dhaliwal et al., which analysed the studies carried out on critically ill patients [228,229]. Unfortunately, those studies come from the same authors and contain those same patients to approximately 80%. Nonetheless, as inadequate oral intake for more than 14 days is associated with a higher mortality [210] the proper provision of nutrients must be ensured.

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

Recommendation 26 A:

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 enteral nutrition within 24 h of surgery versus later commencement have been shown in two meta-analyses (one Cochrane systematic review) [229,230].

Recommendation 26 B:

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 Surgery guidelines – Strong consensus (92% agreement)

Commentary:

Intestinal failure (IF) has been defined from reduction in gut function below the minimum necessary for the absorption of

macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth [107].

Although enteral nutrition has proven to be the most beneficial in almost all patient populations, it is relatively rare that it is sufficient in AIF/ECF individuals because of the compromised integrity of the gastrointestinal tract. Therefore, parenteral nutrition often represents the main option, alone or in association with EN (supplemental PN) [231].

Moreover, many authors have pointed out the possible advantages of PN when there is a limited tolerance of enteral nutrition due to intestinal dysfunction especially in the early postoperative phase, which is associated with a lower energy intake [232].

How should nutritional support be performed in the postoperative phase?

Recommendation 27 A:

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

Grade of recommendation 0, see 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 haemodynamic stability.

Grade of recommendation A, see Surgery guideline – Strong consensus (96% agreement)

Commentary:

As stated in the Surgical Guidelines, 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 [233–236] and leads to significantly shortened hospital length of stay [237]. This has been emphasized by a Cochrane Systematic Review [225]. Recent meta-analyses [230,238,239] 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 [239].

V. Dietetic recommendations during remission

What is the role of dietitians for IBD patients?

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 9 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 are not immune [175]. 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 specialist interest in IBD.

In gastrointestinal cancer studies it appears that the input of a dietician and specific dietary counselling is at least as valuable as nutrient supplement prescription [240] and a single incompletely controlled study in CD [241] supports the extrapolation of this finding to IBD practice. We therefore recommend specialist dietary counselling for all IBD patients in remission in order to improve any nutritional therapy offered and to help to avoid malnutrition and nutrition-related disorders.

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 fibre rich products are often poorly tolerated [242–245]. Acquired lactase deficiency (usually in patients with proximal Crohn's) will also warrant a lactose-restricted diet.

Are exclusion diets effective in maintaining remission 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:

There is now a substantial but mostly low quality literature which addresses diet in IBD.

Patients with CD typically select a diet low in fibre and vegetables, and often one which is hypocaloric and associated with multiple micronutrient deficiencies [82]. Acquired lactase deficiency is particularly prevalent in patients with proximal Crohn's 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 customised to avoid the patients' individual food intolerances. This strategy then makes it difficult to generalise 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 fibre-rich products, but only when they are poorly tolerated. Their removal is then probably helpful in prolonging remission [246]. 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 enteral nutritional regimen is clearly an extreme form of dietary exclusion.

Manipulation of the food in the diet has arguably been better studied in UC, but still in studies of relatively low quality. In UC there is a general and statistically significant tendency for patients in remission to eat less dietary fibre, fewer vegetables and more fat than control populations [247,248]. Cohort studies suggest that those who habitually consume more meat and alcohol have a higher relapse rate [249]. Elimination of cows' milk protein in unselected children with colitis is ineffective [250]. Conventional advice on healthy eating is therefore appropriate for patients with UC.

In summary, no specific diet needs to be routinely followed during remission phases of IBD. None of the alternative diets or semi-exclusive diets seems uniformly effective in maintaining remission. General advice on healthy eating can be given to patients with UC and Crohn's, probably aiming for a Mediterranean-style diet rich in fruit and vegetable fibre unless there are known strictures; even small amounts of red wine may be permitted [251]!

There is some evidence that enteral nutrition may reduce the relapse rate of patients with CD in remission but not sufficient to warrant a recommendation.

Enteral feeding has been thought to have a role in preventing relapse in children with inactive CD [141,154,156,252] but the effect has also been observed in a Japanese study of adult Crohn's patient [157,158,253]. Esaki et al. [254] considered from their trial of 145 patients with Crohn's (mostly induced into remission with TPN) that, under maintenance with elemental/polymeric nutrition, the risk of recurrence was lower in those with small bowel rather than large bowel involvement. However the present systematic enquiry has indicated that overall the use of elemental enteral feeding 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 [13,254]. No recommendation is therefore made.

Enteral nutrition may be used as an adjunct to other treatments. Tanaka et al. and Yamamoto et al. in their prospective studies showed that there appeared to be a higher rate of remission with infliximab in those patients receiving concurrent enteral nutrition, and that relapse rates were lower in those groups [157,158]. This conclusion could not be supported by the systematic review and should be considered unproven. No recommendation is therefore given.

Do omega-3 fatty acids prevent relapse in IBD?

Recommendation 30:

Supplementation with omega-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:

Once laboratory-based studies, case reports and informal reviews are excluded there are 19 papers for consideration. Strikingly there are more systematic reviews than original papers on the clinical effects of omega-3 fatty acids.

In UC in remission the actuarial relapse-free survival was significantly improved by n-3 fatty acids in the 2nd and 3rd months of a 2 year study, but the effect was then lost and the cumulative relapse rate at 2 years was not different from those taking placebo [187]. Similar negative results came from a 12 month study of a cocktail of gamma-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid, in which there were numerically more relapses in the actively treated group [188]. Systematic reviews have reached the conclusion that supplementing the diet with omega-3 fats is ineffective in the maintenance of remission of patients with UC [255,256]. This is therefore not advised.

The above data were obtained in adults. It appears reasonable to extrapolate the conclusions into paediatric practice.

In an early Italian double-blind, placebo-controlled study of fish-oil in the maintenance of remission in CD there was a statistically significant advantage to the actively treated group with sustained remission at 1 year of 59% against 26% in the controls [257]. No effect was however seen in a contemporary study performed in Germany in which the relapse rate was 70% in both groups [258]. EPIC-1 and EPIC-2, the most substantial studies to date compared 4 g/d of omega-3 free fatty acids to placebo for a year [259]. The relapse rates were 32% (EPIC-1) and 48% (EPIC-2) in patients who received omega-3 free fatty acids, and 36% and 49% respectively in those who received placebo; these differences were distant from statistical significance.

In children a 12 month study of eicosapentaenoic acid and docosahexaenoic acid used olive oil as a placebo [260]. There was a significant advantage in relapse rate in the fish oil-treated group,

but this has not been thought of sufficient weight to influence general paediatric practice [255,256].

The latest Cochrane review [261] has concluded that omega 3 fatty acids are probably ineffective for maintenance of remission in CD.

In summary, at present there is insufficient evidence to justify the prescription of omega-3 fatty acids in the remission phase of CD either in adults or children and this is accordingly not recommended.

Is there evidence for fibre in preventing relapse of active IBD?

Recommendation 31:

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

Grade of recommendation 0 – Strong consensus (96% agreement)

Commentary:

The use of a non-specific high fibre diet in CD was found to be ineffective. This is therefore not generally recommended. Much of the recent literature however relates to the effects of specific agents chosen as prebiotics and these are not considered here, but it is recognised that many forms of fibre 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 fibre is unwise in patients known to have intestinal structuring (GPP), but the evolving literature suggests that prebiotic fibres may be useful in maintenance of remission in some patients with UC.

Several small controlled studies have shown apparent benefit from the addition of fibre to the diet of patients with UC [262–264]. 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 fibre. The studies are not sufficiently robust to warrant general changes in practice, but increased amounts of fibre appear safe in UC and allow a consistent message about healthy eating to be delivered to patients (see section below).

Fibre is more often relatively contra-indicated in CD because of the presence of strictures, and fibre in the form of the prebiotic fructo-oligosaccharide is apparently ineffective in CD [95]. However, in a loosely controlled study of wheat fibre supplementation the supplemented patients did better in respect of quality of life and had no apparent adverse events [265]. There is another recent study of fibre supplementation that also claims benefit, and this was through the uncontrolled use of an ovo-vegetarian diet with over 30 g of fibre for every 2000 kcal. Maintenance of remission to 1 year was a remarkable 92% [266]. On balance, additional fibre will not be offered to patients with CD on this evidence, but it seems that vegetable fibre need not be discouraged in the majority of patients.

Is there evidence for probiotics in preventing relapse in IBD?

Recommendation 32 A:

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

Grade of recommendation B – Strong consensus (96% agreement)

Recommendation 32 B:

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

Grade of recommendation 0 – Strong consensus (100% agreement)

Commentary:

This question explores the role of probiotics to maintain remission and therefore prevent relapse in patients who have quiescent disease. See above (QUESTION 14) for the role of probiotics in inducing remission. There is considerable heterogeneity in probiotics studied which hinders analysis however some more frequently studied preparations have demonstrated consistent results.

E. coli Nissle 1917 and VSL#3 have benefit, supported by meta-analysis [267] in the maintenance of remission in patients – including children – with mild to moderate UC, in comparison to 5-aminosalicylate compounds [136,268,269]. Other probiotic preparations have been studied but although they have usually been well tolerated with trends toward benefit, significant effectiveness has not been demonstrated [270,271]. A cautionary note exists for *Lactobacillus rhamnosus* GG; case reports in both children and adults describe bacteraemia with the administered probiotic in patients with acute severe colitis [272,273].

Probiotics are probably ineffective in preventing disease recurrence for patients with CD [269]. Although some positive claims are made no unequivocal benefit can be discerned [274–279]. Probiotics are not currently recommended.

Which probiotic/nutritional concept should be followed in pouch patients?

Recommendation 33 A:

Colectomized patient with a pouch and pouchitis should be treated with probiotics such as VSL#3, if antibiotic treatment has failed.

Grade of recommendation B – Strong consensus (96% agreement)

Recommendation 33 B:

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.

Grade of recommendation B – Strong consensus (100% agreement)

Commentary:

Some patients with UC have their colon and rectum removed with construction of a pouch (made from a loop of small intestine) to serve in place of the rectum. This is known as ileal pouch-anal anastomosis (IPAA) surgery. Pouchitis is inflammation of the surgically constructed pouch. Symptoms of active pouchitis include diarrhoea, increased stool frequency, abdominal cramping, faecal urgency, tenesmus (feeling of constantly needing to pass stools), and incontinence. Pouchitis occurs in approximately 50% of patients following IPAA for chronic UC.

Food intolerance is a common, albeit mild, problem after ileal pouch-anal anastomosis [280]. Comparisons of the food consumption of patients without ($n = 23$) and with pouchitis ($n = 45$) showed that the former consumed twice as many fruit servings as the latter (3.6 ± 4.1 servings/d vs. 1.8 ± 1.7 servings/d, respectively, $P < 0.05$). In addition, the pouchitis patients consumed significantly fewer liposoluble antioxidants, such as cryptoxanthin and lycopene, and less vitamin A and vitamin C than the patients without pouchitis. Decreased consumption of antioxidants by patients with pouchitis may expose them to the effects of inflammatory and oxidative stress and contribute to the development of pouchitis [281]. Inflammation is a constant finding in the ileal reservoir of patients with an ileal pouch-anal anastomosis and is associated with decreased faecal concentrations of the short chain fatty acid butyrate, increased faecal pH, changes in faecal flora, and increased

concentrations of secondary bile acids. A study has evaluated the effect of enteral supplementation of inulin on inflammation of the ileal reservoir. Twenty patients received 24 g of inulin or placebo daily during three weeks in a randomized, double blind, crossover design. Stools were analysed after each test period for pH, short chain fatty acids, microflora, and bile acids. Inflammation was assessed endoscopically, histologically, and clinically. Compared with placebo, three weeks of dietary supplementation with 24 g of inulin increased butyrate concentrations, lowered pH, decreased numbers of *Bacteroides fragilis*, and diminished concentrations of secondary bile acids in faeces. This was endoscopically and histologically accompanied by a reduction of inflammation of the mucosa of the ileal reservoir [282].

Antibiotics (ciprofloxacin, metronidazole) are the treatment of reference of acute pouchitis [283]. As faecal stasis with immunologic reactivity seems to be important in the pathogenesis of pouchitis, several studies evaluated the effect of probiotics in chronic pouchitis and prevention of pouchitis [284].

Treatment of chronic pouchitis: Two double-blind placebo-controlled trials performed in adults showed effectiveness of the probiotic mixture VSL#3 (the probiotic mixture VSL#3™ contains 450 billion colony forming units of 8 lactic acid bacteria: *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus delbrueckii*, *Lactobacillus plantarum* and *Streptococcus salivarius* subsp. *thermophilus*) in maintaining remission in patients with chronic pouchitis [285,286]. A pooled analysis of these two studies (76 participants) suggests that VSL#3 may be more effective than placebo for maintenance of remission. Eighty-five per cent (34/40) of VSL#3 patients maintained remission at 9–12 months compared to 3% (1/36) of placebo patients (RR 20.24, 95% CI 4.28 to 95.81). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (35 events) [287]. In another study [283] effects of VSL#3 were evaluated as an adjunctive to a standard therapy. A total of 144 consecutive patients were randomly treated for 8 weeks with VSL#3 at a dose of 3600 billion CFU/day (71 patients) or with placebo (73 patients). The decrease in UC disease activity index (UCDAI) scores of 50% or more was higher in the VSL#3 group than in the placebo group (63.1 vs. 40.8; per protocol (PP) $P = 0.010$, confidence interval (CI): 95%: 0.51–0.74; intention to treat (ITT) $P = 0.031$, CI: 0.47–0.69). Remission was higher in the VSL#3 group than in the placebo group (47.7% vs. 32.4%; PP $P = 0.069$, CI: 0.36–0.60; ITT $P = 0.132$, CI: 0.33–0.56).

Prevention of pouchitis: The results of a small study (40 participants) suggest that VSL#3 may be more effective than placebo for prevention of pouchitis [288]. Ninety per cent (18/20) of VSL#3 patients had no episode of acute pouchitis during the 12 month study compared to 60% (12/20) of placebo patients (RR 1.50, 95% CI 1.02 to 2.21). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (30 events). In contrast, in a 3-month double blind, placebo-controlled trial *L. rhamnosus* strain GG (two gelatine capsules/day of $0.5\text{--}1 \times 10^{10}$ CFU/capsule) in patients with a previous history of pouchitis showed that this probiotic was not effective in preventing relapses [289].

ECCO guidelines suggest the use of VSL#3 both for maintenance of antibiotic-induced remission and for prevention of pouchitis in adults [290] and in paediatric UC [291].

Is artificial nutrition (ONS, EN, PN) effective in preventing relapse in IBD?

Recommendation 34 A:

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

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

Recommendation 34 B:

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:

Nutritional support hasn't been assessed as a maintenance therapy in UC, neither has PN in CD. A recent systematic review of twelve randomized controlled trials and non-randomized cohort studies [292] (1169 patients, including 95 children), most of good quality, showed that maintenance EN was as or more effective than the comparator (standard diet, 5-ASA or azathioprine) in preventing CD relapses over periods of 6 months to 4 years. The study with the lowest risk of bias compared supplemental (50%) EN with a regular diet in 51 adult CD patients [159]. Patients in each arm of the study were on similar medications (5-ASA or azathioprine). The study showed that in the EN group, 9 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; $P < 0.01$). Hanai et al. [293] compared the effect of 6-mercaptopurine (6-MP), an elemental diet and no therapy in CD patients in remission. After 2 years, the clinical remission rates were 60, 47 and 27% for 6-MP, elemental diet and the control group, respectively. The remission rates in the 6-MP and elemental diet groups were significantly higher than in the control group, with no significant difference between the 6-MP and the elemental diet group. A study from the UK found that supplemental elemental nutrition may only be useful in children not commencing azathioprine [294]. Esaki et al. [160] considered from their trial of 145 patients with Crohn's (mostly induced into remission with TPN) that, under maintenance with elemental/polymeric nutrition, the risk of recurrence was lower in those with small bowel rather than large bowel involvement. Along with a lower risk of clinical relapse, studies have showed a negative effect of EN on endoscopic inflammation scores and levels of pro-inflammatory cytokine [295].

The study of maintenance EN as an adjuvant to infliximab therapy has yielded conflicting results, with one negative [158] and two positive [296,297] studies published so far.

Elemental formulae have been the most studied. A systematic review was unable to show any significant difference in remission rate between elemental and polymeric formulae [298]. However, it found a lower adherence rate for elemental EN compared to an unrestricted diet, as well as compared to a polymeric EN (RR = 0.68, 95% CI 0.50–0.92) [105]. A low palatability (when EN is taken orally rather than via a NG tube) and higher cost may be responsible.

The European organizations for IBD and for paediatric 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 [137].

Due to the heterogeneity of published studies (children vs. adults, elemental vs. polymeric, supplemental vs. exclusive, duration, outcome criteria), to the fact that most studies come from a single country (Japan), and especially to the fact that most studies pre-date new maintenance treatment modalities (dosage of azathioprine metabolites and circulating biologicals), the panel considers that EN should not be a first line maintenance therapy. However, EN/ONS can be of interest for nutritional reasons, in the frequent cases of malnutrition or risk of malnutrition in CD patients in remission.

Is there any advantage to particular formulations (eg. polymeric vs oligomeric, or regarding fat content or supplementation with nutraceuticals) in IBD patients in remission?

Recommendation 35:

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

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

Commentary:

Few dietary supplementations have been tested in maintenance of remission in IBD patients with clinical endpoints. An open label, parallel-group, multicentre, 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 1 year [263]. A Cochrane systematic review has analysed 6 studies (1039 patients) of omega-3 fatty acid supplementation [261]: there was a marginal significant benefit of n-3 therapy on maintenance of remission. Thirty-nine per cent of patients in the n-3 group had relapsed by 12 months compared to 47% of placebo patients (6 studies, 1039 patients; RR 0.77, 95% CI 0.61 to 0.98). However, when the two largest studies at low risk of bias were considered alone, the benefit was no longer statistically significant (2 studies, 738 patients; RR 0.88, 95% CI 0.74 to 1.05).

Elemental EN formulae have been the most studied in CD patients in remission. A systematic review was unable to show any significant difference in remission rate between elemental and polymeric formulae [298]. However, it found a lower adherence rate for elemental EN compared to an unrestricted diet, as well as compared to polymeric EN (RR = 0.68, 95% CI 0.50–0.92) [105]. Lower palatability (when EN is taken orally rather than via a NG tube) and higher cost to the patient may be responsible.

Overall, the panel did not find enough evidence to make firm recommendations over and above previous European recommendations [13,137]. It is therefore advised that standard practice is followed in patients with CD in remission.

What are the indications for vitamin B12 therapy in CD?

Recommendation 36:

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

Grade of recommendation A – Strong consensus (100% agreement)

Commentary:

Vitamin B12 (cobalamin) is selectively absorbed in the distal ileum, bound with gastric-derived intrinsic factor. A recent systematic review has assessed the literature for prevalence, risk factors, evaluation and management of vitamin B12 deficiency in IBD [299]. 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-caecal valve, will put the patient at risk for B12 deficiency. Resection of less than 20 cm does not normally cause deficiency [300].

Ileal CD is not inevitably associated with B12 deficiency [301,302], but it is difficult to rule out its responsibility when more than 30–60 cm are involved [299].

The diagnosis of biochemical B12 deficiency is based on the association between low serum cobalamin levels (<148 pM) and a functional biomarker such as homocysteine (>15 μM) or

methylmalonic acid (>270 µM). The diagnosis of clinical B12 deficiency further requires macrocytosis and/or neurological symptoms [299].

CD patients with ileal involvement and/or resection and/or clinical deficiency features should be screened yearly for B12 deficiency [299].

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 [303]. Patients with more than 20 cm of ileum resected should receive 1000 µg of vitamin B12 prophylactically also every month and indefinitely [303]. It is recognized that this is more frequently than the 3-monthly injections typically advised in the past, but appears necessary to be sure to prevent clinical manifestations of deficiency.

Oral therapy may be as effective, but is poorly explored in CD. A retrospective open-label non-randomized study of 36 CD patients has shown the oral route (1200 µg per day for 33, 2400 µg per day for 3) to be effective in treating vitamin B12 deficiency [304]. For now, parenteral supplementation remains the reference, but oral supplementation may become standard in the coming years.

What are the indications for oral vitamin B9/folic acid therapy in IBD?

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:

A 2-year prospective Spanish study of 180 consecutive CD patient and 70 UC patients found a prevalence of folate deficiency of 22.3% in CD patients, compared to 4.3% in UC [305]. In contrast, the systematic assessment of 37 children with newly-diagnosed IBD by teams in the USA did not show any folate deficiency compared to controls [306].

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. Distinction between North American and European populations may also be explained by the supplementation of wheat with folate in the USA in attempts to prevent neural tube defects in unborn children.

Drugs are responsible for folate deficiency by inhibition of dihydrofolate reductase, an enzyme that catalyses reduction of dihydrofolic acid to tetrahydrofolic acid (methotrexate) [307] or folate malabsorption (sulphasalazine) [308]. Azathioprine and 6-mercaptopurine also induce macrocytosis but through myelosuppressive activity.

A systematic review and meta-analysis of 10 studies reporting on 4517 patients found an overall protective effect for folic acid supplementation on the development of colo-rectal cancer (pooled HR = 0.58; 95% CI: 0.37–0.80) [309].

An Italian study compared 1 month of supplementation with 15 mg of either folic or folinic acid in 30 IBD patients treated with sulphasalazine [310]. 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 paediatric CD advise oral administration of folate in patients on methotrexate, 5 mg once weekly 24–72 h after the methotrexate, or 1 mg daily for 5 days per week [137].

This panel recommends the same practice in adults. Furthermore, in patients with active disease, the few who take sulphasalazine and those who develop macrocytosis should always be

tested for folate deficiency (serum and red blood cell concentrations).

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

Recommendation 38 A:

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 38 B:

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:

A US team collected national data from 4.21 million deliveries in 2005, including 2372 in CD patients and 1368 in UC patients [311]. Blood transfusions occurred more frequently in women with CD (aOR, 2.82; 95% CI, 1.51–5.26), whereas protein-calorie malnutrition occurred more frequently both in women with CD (aOR, 20.0; 95% CI, 8.8–45.4) and with UC (aOR, 60.8; 95% CI, 28.2–131.0). A further review has more recently been published which also underlines the increased risks of nutritional deficiencies during pregnancy in IBD patients [312].

The consequences of anaemia and those of neural tube defects [313], along with the frequent deficiencies in IBD patients warrant regular screening for iron and folate deficiencies, respectively, during pregnancy, along with nutritional follow-up. Given the prior contact with the patient and the likelihood that pregnancy will already have been discussed because of its impact on the IBD, the opportunity should already have been taken to advise preconception or very early post-conception supplementation with folate.

The panel agrees on the fact that any proven deficiency requires supplementation.

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. The most important element from the infant's point of view is that the milk donor is as healthy as possible [312]. No nutritional measures different from standard practice are therefore recommended.

What are the indications for physical activity in IBD?

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 (631 CD and 295 UC) revealed a low fat-free mass in 28% of CD patients and in 13% of UC patients [314]. Low muscle mass [315,316], strength [140,315,317] and performance [317] have been reported in adult IBD cohorts, but similar findings have also been made in children [318]. Sarcopenia was reported in 12% of 137 Australian IBD patients of mean age 31 years, associated with osteopenia [315].

A US survey among 250 IBD patients reported that 16.4% never exercised, 32.8% exercised 1–2 times per week, 23.6% exercised 3–4 times per week, and 18.0% exercised more than four times per week. Ninety-nine patients (44%) reported that their IBD limited their exercise for reasons including fatigue ($n = 81$), joint pain ($n = 37$), embarrassment ($n = 23$), and weakness ($n = 21$) [319].

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 10 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 (Δ IBDQ_{social} = 6.27 ± 5.46 vs. 1.87 ± 4.76 , $p = 0.023$) [320]. Other studies were conducted in patients with a quiescent or moderately active disease and mostly showed positive effects on quality of life, not on disease activity [321]. Therefore, the panel recommends endurance training (for a minimum of 30 min three times a week) in all IBD patients.

The reference treatment for sarcopenia, along with maintaining an adequate protein intake, is resistance training. This is what is advised in age-related sarcopenia [322]. 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).

Are there special dietetic recommendations for obese IBD patients?

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) [323] and 17% of 100 Irish adult CD patients [324]. A Polish retrospective study of 675 new paediatric IBD cases (368 CD, 307 UC) revealed higher BMI values in UC patients than in CD patients. The prevalence of overweight and obesity was significantly higher in UC than in CD patients (4.89% CI95 2.76–7.93 vs. 2.45% CI95 1.12–4.59 and 8.47% CI95 5.61–12.16 vs. 1.9% CI95 0.77–3.88, respectively) [325].

The 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 CRP levels [326]. 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 [81] and sarcopenia [316], 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.

4. Discussion

The review panel and the other discussants do not hide their collective disappointment in the results of the initial systematic

review. It has proved remarkably difficult to provide evidence-based and clinically useful conclusions. Best evidence is gained from methodologically sound, randomized controlled trials (RCTs). It is more difficult to do such a trial of a nutritional intervention - where blinding is very challenging and placebo controls are impossible - than with a new drug. It is also difficult to make unique alterations in the dietary regimen (reducing the proportion of one macronutrient will almost inevitably lead to an increase in another). The situation is further complicated by the rapid recent changes in the medical management of IBD which might negate nutritional conclusions based on their effects on patients managed in other respects in now-outdated fashion. Moreover the decision to perform an RCT may not follow the burden of disease, but be prompted by the evaluation of a new product or mechanistic concept. In nutrition this frequently leads to the situation that relevant trials for important, clinical questions are missing partly because no sponsor can be found.

One may interpret non-superiority as ineffectiveness, as was many times the conclusion of the initial systematic review (for example the conclusion that elemental diet was ineffective in inducing remission in CD). This has made it difficult to provide clinically relevant recommendations. An admittedly less rigorous approach permits the conclusion that there was no difference between the use of polymeric and elemental formulae in children [188]. This intervention (polymeric vs elemental) is amenable to blinding, and indeed a recent blinded, randomised, controlled trial concluded that there was no difference in the rate of induction of remission (93% with elemental and 79% with polymeric feeding) [98]. We feel that the correct conclusion here is that there is no major advantage in using a particular formula rather than (as the meta-analysis would have it) that the treatment is ineffective because there was no placebo arm.

It is acknowledged also that some of the recommendations are beyond the means of some countries in Europe and of most of those in the developing world. Average salaries below 250 euros per month do not permit what richer countries take for granted. Hence the financial aspects of applying artificial nutrition may become the sole responsibility of the patient and family. Furthermore it is common for there to be limited availability of nutritional products (for example because only one of the supply companies is active in a given region, or because a company chooses to restrict its offerings in a particular geographical zone). Typically the more patient-friendly preparations are most vulnerable to this sort of restrictive practice.

Even the most economical formulations of parenteral nutrition are still more than 40 euros per bag. While it may be possible on life or death grounds to obtain this in hospital it is not unusual for less-informed governmental bodies to obstruct this; it is common for home parenteral nutrition to be unobtainable.

Creative adaptation of the advice given here will therefore sometimes be necessary.

We have tried to address each of these difficult areas and hope our Guideline indicates clearly where the interpretations are ours and based on a less than secure evidence base.

Conflict of interest

No other conflicts of interest are declared.

Acknowledgements

The systematic review was commissioned and funded by the educational and guidelines budget of ESPEN. The Israeli Cochrane Centre had no other involvement in the creation of this final document. A single physical meeting of the authors together with

the ESPEN central guidelines group was also funded by ESPEN. The individually named authors all have affiliations to professional bodies active in nutrition and/or IBD, and all have contributed to educational meetings on the topic of the guidelines (sometimes with speaker fees).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.clnu.2016.12.027>.

References

- 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(1):46–54.
- Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus Jr EV, Tysk C, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. *Gut* 2013;62(4):630–49.
- Sawczenko A, Sandhu BK, Logan RF, Jenkins H, Taylor CJ, Mian S, et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet* 2001;357(9262):1093–4.
- Armitage E, Drummond HE, Wilson DC, Ghosh S. Increasing incidence of both juvenile-onset Crohn's disease and ulcerative colitis in Scotland. *Eur J Gastroenterol Hepatol* 2001;13(12):1439–47.
- Goh J, O'Morain CA. Review article: nutrition and adult inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;17(3):307–20.
- Han PD, Burke A, Baldassano RN, Rombeau JL, Lichtenstein GR. Nutrition and inflammatory bowel disease. *Gastroenterology Clin N Am* 1999;28(2):423–43.
- Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. *Inflamm Bowel Dis* 2013 Aug;19(9):1921–7.
- Ananthakrishnan AN, Cagan A, Gainer VS, Cheng SC, Cai T, Szolovits P, et al. Higher plasma vitamin D is associated with reduced risk of *Clostridium difficile* infection in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014 May;39(10):1136–42.
- Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. *World J Gastroenterol* 2009;15(21):2570–8.
- Lucendo AJ, De Rezende LC. Importance of nutrition in inflammatory bowel disease. *World J Gastroenterol* 2009;15(17):2081–8.
- Yamamoto T, Nakahigashi M, Sanjibadi AR. Review article: diet and inflammatory bowel disease—epidemiology and treatment. *Aliment Pharmacol Ther* 2009;30(2):99–112.
- 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.
- Lochs H, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Schütz T, et al. DGEM (German Society for Nutritional Medicine), ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN guidelines on enteral nutrition: gastroenterology. *Clin Nutr* 2006;25:260–74.
- Van Gossum A, Cabre E, Hébuterne X, Jeppesen P, Krznaric Z, Messing B, et al. ESPEN guidelines on parenteral nutrition: gastroenterology. *Clin Nutr* 2009;28:415–27.
- Martinez-Medina M, Denizot J, Dreux N, Robin F, Billard E, Bonnet R, et al. Western diet induces dysbiosis with increased *E coli* in CEABAC10 mice, alters host barrier function favouring AIEC colonisation. *Gut* 2014;63:116–22.
- 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.
- 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.
- 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.
- 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;6:6:776–84.
- 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.
- Chan SSM, Luben R, Olsen A, Tjonneland A, Kaaks R, Lindgren S, et al. Association between high dietary intake of the n-3 polyunsaturated fatty acid docosahexaenoic acid and reduced risk of Crohn's disease. *Aliment Pharmacol Ther* 2014;39:834–42.
- Costea I, Mack DR, Lemaitre RN, Israel D, Marcil V, Ahmad A, et al. Interactions between the dietary polyunsaturated fatty acid ratio and genetic factors determine susceptibility to pediatric Crohn's disease. *Gastroenterology* 2014;146:929–31.
- Roberts CL, Rushworth SL, Richman E, Rhodes JM. Hypothesis: increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. *J Crohns Colitis* 2013;7:338–41.
- Khalili H, Huang ES, Ananthakrishnan AN, Higuchi L, Richter JM, Fuchs CS, et al. Geographical variation and incidence of inflammatory bowel disease among US women. *Gut* 2012;61:1686–92.
- Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, et al. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. *Gastroenterology* 2012;142:482–9.
- Ananthakrishnan AN, Khalili H, Song M, Higuchi LM, Richter JM, Chan AT. Zinc intake and risk of Crohn's disease and ulcerative colitis: a prospective cohort study. *Int J Epidemiol* 2015;44:1995–2005.
- Racine A, Carbonnel F, Chan SS, Hart AR, Bueno-de-Mesquita HB, Oldenburg B, et al. Dietary patterns and risk of inflammatory bowel disease in Europe: results from the EPIC study. *Inflamm Bowel Dis* 2016;22:345–54.
- Andersen V, Olsen A, Carbonnel F, Tjonneland A, Vogel U. Diet and risk of inflammatory bowel disease. *Dig Liver Dis* 2012;44:185–94.
- Ananthakrishnan AN. Environmental risk factors for inflammatory bowel diseases: a review. *Dig Dis Sci* 2015;60:290–8.
- Gilat T, Hacoen D, Lilos P, Langman MJ. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. *Scand J Gastroenterol* 1987;22:1009–24.
- Sonntag B, Stolze B, Heinecke A, Luegering A, Heidemann J, Lebidz P, et al. Preterm birth but not mode of delivery is associated with an increased risk of developing inflammatory bowel disease later in life. *Inflamm Bowel Dis* 2007;13:1385–90.
- Corrao G, Tragnone A, Caprilli R, Trallori G, Papi C, Andreoli A, et al. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC). *Int J Epidemiol* 1998;27:397–404.
- 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.
- 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.
- Geary RB, Richardson AK, Frampton CM, Dogshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. *J Gastroenterol Hepatol* 2010;25:325–33.
- Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gomborg 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.
- 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.
- 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.
- 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.
- 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.
- 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). *J Parenter Enter Nutr* 2016 [E-pub ahead of print].
- 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.
- 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.
- 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.
- Ananthakrishnan AN, McGinley EL, Binion DG, Saecian K. A novel risk score to stratify severity of Crohn's disease hospitalizations. *Am J Gastroenterol* 2010;105:1799–807.
- 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;105:1893–990.
- 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.

- [48] 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.
- [49] 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.
- [50] Shamir R, Phillip M, Levine A. Growth retardation in pediatric Crohn's disease: pathogenesis and interventions. *Inflamm Bowel Dis* 2007;13:620–8.
- [51] Shamir R. Nutrition and growth in inflammatory bowel disease. *World Rev Nutr Diet* 2013;106:156–61.
- [52] Shamir R, Seidman E. Clinical dilemmas in inflammatory bowel disease, new challenges. 2nd ed. Wiley-Blackwell; 2011.
- [53] Hill RJ, Cleghorn GJ, Withers GD, Lewindon PJ, Ee LC, Connor F, et al. Resting energy expenditure in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007;45:342–6.
- [54] Kushner RF, Schoeller DA. Resting and total energy expenditure in patients with inflammatory bowel disease. *Am J Clin Nutr* 1991;53:161–5.
- [55] Wiskin AE, Wootton SA, Culliford DJ, Afzal NA, Jackson AA, Beattie RM. Impact of disease activity on resting energy expenditure in children with inflammatory bowel disease. *Clin Nutr* 2009;28:652–6.
- [56] 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.
- [57] 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.
- [58] 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.
- [59] Stokes MA, Hill GL. Total energy expenditure in patients with Crohn's disease: measurement by the combined body scan technique. *J Parenter Enter Nutr* 1993;17:3–7.
- [60] Chan AT, Fleming CR, O'Fallon WM, Huizenga KA. Estimated versus measured basal energy requirements in patients with Crohn's disease. *Gastroenterology* 1986;91:75–8.
- [61] Mingrone G, Greco AV, Benedetti G, Capristo E, Semeraro R, Zoli G, et al. Increased resting lipid oxidation in Crohn's disease. *Dig Dis Sci* 1996;41:72–6.
- [62] Arai K, Funayama R, Takahashi M, Sakai R, Shimizu H, Obayashi N, et al. Validation of predictive equations for resting energy expenditure in Japanese pediatric Crohn's disease patients: preliminary study. *Pediatr Int* 2015;57:290–4.
- [63] Cormier K, Mager D, Bannister L, Fortin M, Richards H, Jackson C, et al. Resting energy expenditure in the parenterally fed pediatric population with Crohn's disease. *J Parenter Enter Nutr* 2005;29:102–7.
- [64] Hart JW, Bremner AR, Wootton SA, Beattie RM. Measured versus predicted energy expenditure in children with inactive Crohn's disease. *Clin Nutr* 2005;24:1047–55.
- [65] Hill RJ, Lewindon PJ, Withers GD, Connor FL, Ee LC, Cleghorn GJ, et al. Ability of commonly used prediction equations to predict resting energy expenditure in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;17:1587–93.
- [66] 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.
- [67] 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.
- [68] Rigaud D, Angel LA, Cerf M, Carduner MJ, Melchior JC, Sautier C, et al. Mechanisms of decreased food intake during weight loss in adult Crohn's disease patients without obvious malabsorption. *Am J Clin Nutr* 1994;60:775–81.
- [69] Vaisman N, Dotan I, Halack A, Niv E. Malabsorption is a major contributor to underweight in Crohn's disease patients in remission. *Nutrition* 2006;22:855–9.
- [70] Diamanti A, Basso MS, Gambarara M, Papadatou B, Bracci F, Noto C, et al. Positive impact of blocking tumor necrosis factor alpha on the nutritional status in pediatric Crohn's disease patients. *Int J Colorectal Dis* 2009;24:19–25.
- [71] Steiner SJ, Pfefferkorn MD, Fitzgerald JF, Denne SC. Carbohydrate and lipid metabolism following infliximab therapy in pediatric Crohn's disease. *Pediatr Res* 2008;64:673–6.
- [72] Steiner SJ, Pfefferkorn MD, Fitzgerald JF, Denne SC. Protein and energy metabolism response to the initial dose of infliximab in children with Crohn's disease. *Inflamm Bowel Dis* 2007;13:737–44.
- [73] Wiskin AE, Wootton SA, Cornelius VR, Afzal NA, Elia M, Beattie RM. No relation between disease activity measured by multiple methods and REE in childhood Crohn disease. *J Pediatr Gastroenterol Nutr* 2012;54:271–6.
- [74] Steiner SJ, Noe JD, Denne SC. Corticosteroids increase protein breakdown and loss in newly diagnosed pediatric Crohn disease. *Pediatr Res* 2011;70:484–8.
- [75] 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. *J Parenter Enter Nutr* 1989;13:455–60.
- [76] 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.
- [77] 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.
- [78] Griffiths RD, Hinds CJ, Little RA. Manipulating the metabolic response to injury. *Br Med Bull* 1999;55:181–95.
- [79] Royall D, Greenberg GR, Allard JP, Baker JP, Jeejeebhoy KN. Total enteral nutrition support improves body composition of patients with active Crohn's disease. *J Parenter Enter Nutr* 1995;19:95–9.
- [80] 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.
- [81] 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.
- [82] 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.
- [83] Vagianos K, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. *J Parenter Enter Nutr* 2007;31:311–9.
- [84] Santucci NR, Alkhoury RH, Baker RD, Baker SS. Vitamin and zinc status pre-treatment and post-treatment in patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2014;59:455–7.
- [85] 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.
- [86] Reinisch W, Staun M, Bhandari S, Muñoz M. State of the iron: how to diagnose and efficiently treat iron deficiency anaemia in inflammatory bowel disease. *J Crohns Colitis* 2013;4:29–40.
- [87] Bergamaschi G, Di Sabatino SA, Albertini A, Ardizzone S, Biancheri P, Bonetti E, et al. Prevalence and pathogenesis of anemia in inflammatory bowel disease. Influence of anti-tumor necrosis factor-alpha treatment. *Haematologica* 2010;95:199–205.
- [88] Cucino C, Sonnenberg A. Cause of death in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2001;7:250–5.
- [89] Lopez A, Cacoub P, MacDougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2015;387:907–16.
- [90] 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.
- [91] 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.
- [92] Bonovas S, Fiorino G, Allocca M, Lytras T, Tsantes A, Peyrin-Biroulet L, et al. Intravenous versus oral iron for the treatment of anaemia in inflammatory bowel disease: a systematic review and meta-analysis of randomized controlled trials. *Med Baltim* 2016;95:e2308.
- [93] 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.
- [94] Kulnigg S, Teischinger L, Dejaco C, Waldhor T, Gasche C. Rapid recurrence of IBD-associated anemia and iron deficiency after intravenous iron sucrose and erythropoietin treatment. *Am J Gastroenterol* 2009;104:1460–7.
- [95] 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.
- [96] Hébuterne 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.
- [97] Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 2006;4(6):744–53.
- [98] 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;18:246–53.
- [99] Ludvigsson JF, Krantz M, Bodin L, Stenhammar L, Lindquist B. Elemental versus polymeric enteral nutrition in paediatric Crohn's disease: a multi-centre randomized controlled trial. *Acta Paediatr* 2004;93:327–35.
- [100] 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.
- [101] Johnson T, Macdonald S, Hill SM, Thomas A, Murphy MS. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomised controlled trial. *Gut* 2006;55:356–61.
- [102] Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;1:CD000542.
- [103] Sakurai T, Matsui T, Yao T, Takagi Y, Hirai F, Aoyagi K, et al. Short-term efficacy of enteral nutrition in the treatment of active Crohn's disease: a randomized, controlled trial comparing nutrient formulas. *J Parenter Enter Nutr* 2002;26:98–103.

- [104] Gassull MA, Fernández-Bañares F, Cabré E, Papo M, Gíaffier MH, Sánchez-Lombrana JL, et al. European Group on Enteral Nutrition in Crohn's Disease. Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomised multicentre European trial. *Gut* 2002 Aug;51:164–8.
- [105] Verma S, Brown S, Kirkwood B, Gíaffier MH. Polymeric versus elemental diet as primary treatment in active Crohn's disease: a randomized, double-blind trial. *Am J Gastroenterol* 2000;95:735–9.
- [106] Messori A, Trallori G, D'Albasio G, Milla M, Vannozzi G, Pacini F. Defined-formula diets versus steroids in the treatment of active Crohn's disease: a meta-analysis. *Scand J Gastroenterol* 1996;31:267–72.
- [107] 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.
- [108] Baker ML, Williams RN, Nightingale JM. Causes and management of a high-output stoma. *Colorectal Dis* 2011 Feb;13:191–7.
- [109] Grischkan D, Steiger E, Fazio V. Maintenance of home hyperalimentation in patients with high-output jejunosomies. *Arch Surg* 1979 Jul;114:838–41.
- [110] Pironi L, Guidetti C, Incasa E, Poggioni 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.
- [111] 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 Jun;33:759–61.
- [112] 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 Oct;48:790–5.
- [113] Fuchigami T, Ohgushi H, Imamura K, Yao T, Omae T, Watanabe H, et al. Effects of total parenteral nutrition on colonic lesions in Crohn's disease: radiographic and endoscopic study. *Gastroenterol Jpn* 1982;17:521–9.
- [114] Walther F, Fusch C, Radke M, Beckert S, Findeisen A. Osteoporosis in pediatric patients suffering from chronic inflammatory bowel disease with and without steroid treatment. *J Pediatr Gastroenterol Nutr* 2006;43:42–51.
- [115] 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.
- [116] 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.
- [117] Lopes LH, Sdepanian VL, Szejnfeld VL, de Moraes 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.
- [118] Mingrone G, Benedetti G, Capristo E, De Gaetano A, Greco AV, Tataranni PA, et al. Twenty-four-hour energy balance in Crohn disease patients: metabolic implications of steroid treatment. *Am J Clin Nutr* 1998;67:118–23.
- [119] Veit LE, Maranda L, Fong J, Nwosu BU. The vitamin D status in inflammatory bowel disease. *PLoS One* 2014;9(7). e101583.
- [120] Blanck S, Abera F. Vitamin D deficiency is associated with ulcerative colitis disease activity. *Dig Dis Sci* 2013;58:1698–702.
- [121] Wingate KE, Jacobson K, Isenman R, Carroll M, Barker C, Israel D, et al. 25-Hydroxyvitamin D concentrations in children with Crohn's disease supplemented with either 2000 or 400 IU daily for 6 months: a randomized controlled study. *J Pediatr* 2014;164:860–5.
- [122] 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, randomized trial of oral risedronate 35 mg once weekly or placebo, concomitant with calcium and vitamin D supplementation. *Gut* 2014;63:1424–30.
- [123] 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.
- [124] Jacobsen O, Højgaard L, Hylander Møller E, Wielandt TO, Thale M, Jarnum S, 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.
- [125] 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.
- [126] Westergaard H. Bile acid malabsorption. *Curr Treat Options Gastroenterol* 2007 Feb;10:28–33.
- [127] Hylander E, Jarnum S, Jensen HJ, Thale M. Enteric hyperoxaluria: dependence on small intestinal resection, colectomy, and steatorrhea in chronic inflammatory bowel disease. *Scand J Gastroenterol* 1978;13:577–88.
- [128] 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.
- [129] 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.
- [130] 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* 2015;10:1370–8.
- [131] 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.
- [132] 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(8880):1131–4.
- [133] 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(12 Suppl):100S–7S.
- [134] Slonim AE, Grovit M, Bulone L. Effect of exclusion diet with nutraceutical therapy in juvenile Crohn's disease. *J Am Coll Nutr* 2009 Jun;28:277–85.
- [135] 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.
- [136] 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.
- [137] Rummelle 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.
- [138] Bousvaros A, Guandalini S, Baldassano RN, Botelho C, Evans J, Ferry GD, et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflamm Bowel Dis* 2005;11:833–9.
- [139] Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53(Suppl 5):V1–16.
- [140] 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.
- [141] 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.
- [142] 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.
- [143] 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.
- [144] 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. *J Parenter Enter Nutr* 2016;40:412–6.
- [145] Knight C, El-Matary W, Spray C, Sandhu BK. Long-term outcome of nutritional therapy in paediatric Crohn's disease. *Clin Nutr* 2005;24:775–9.
- [146] 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.
- [147] 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.
- [148] Smith MA, Smith T, Trebble T. Nutritional management of adults with inflammatory bowel disease: practical lessons from the available evidence. *Frontline Gastroenterol* 2012;3:172–9.
- [149] 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.
- [150] 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;52:376–86.
- [151] 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. *J Parenter Enteral Nutr* 2002;1(26). Supp.
- [152] Matsui T, Sakurai T, Yao T. Nutritional therapy for Crohn's disease in Japan. *J Gastroenterol* 2005;40(Suppl 16):25–31.
- [153] McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patients. Society of Critical Care medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *J Parenter Enteral Nutr* 2009;33:277–316.
- [154] Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;(3):CD005984.
- [155] 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.
- [156] 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;(1):CD006320.
- [157] 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.

- [158] 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.
- [159] 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 randomized-controlled trial. *Aliment Pharmacol Ther* 2006;24:1333–1340.
- [160] Esaki M, Matsumoto T, Nakamura S, Yada S, Fujisawa K, Jo Y, et al. Factors affecting recurrence in patients with Crohn's disease under nutritional therapy. *Dis Colon Rectum* 2006;49:S68–74.
- [161] 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.
- [162] Massironi S, Rossi RE, Cavalcoli FA, Della Valle S, Fraquelli M, Conte D. Nutritional deficiencies in inflammatory bowel disease: therapeutic approaches. *Clin Nutr* 2013;32:904–10.
- [163] Kulick D, Deen D. Specialized nutrition support. *Am Fam Physician* 2011;83(2):173–83.
- [164] Ukleja A, Romano MM. Complications of parenteral nutrition. *Gastroenterol Clin N Am* 2007;36:23–46.
- [165] Giannotta M, Tapete G, Emmi G, Silvestri E, Milla M. Thrombosis in inflammatory bowel diseases: what's the link? *Thromb J* 2015;13:14.
- [166] Zegos P, Kouklakis G, Saibil F. IBD and thromboembolism. *World J Gastroenterol* 2014 Oct 14;20(38).
- [167] 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.
- [168] 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.
- [169] 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.
- [170] 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.
- [171] 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;32:445–53.
- [172] Llop JM, Cobo S, Padullas A, Farran L, Jodar R, Badia MB. Nutritional support and risk factors of appearance of enterocutaneous fistulas. *Nutr Hosp* 2012;27:213–8.
- [173] 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.
- [174] Wędrychowicz A, Zajac A, Tomasik P. Advances in nutritional therapy in inflammatory bowel diseases: review. *World J Gastroenterol* 2016;21(22):1045–66.
- [175] Forbes A, Goldesgeyde E, Paulon E. Nutrition in inflammatory bowel disease. *J Parent Ent Nutr* 2011;35:571–80.
- [176] 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.
- [177] 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* 2001;59:171–4.
- [178] Triantafyllidis JK, Papalois AE. The role of total parenteral nutrition in inflammatory bowel disease: current aspects. *Scand J Gastroenterol* 2014;49:3–14.
- [179] Ravindran P, Ansari N, Young CJ, Solomon MJ. Definitive surgical closure of enterocutaneous fistula: outcome and factors predictive of increased post-operative morbidity. *Colorectal Dis* 2014;16:209–18.
- [180] Akobeng AK, Thomas AG. Refeeding syndrome following exclusive enteral nutritional treatment in Crohn disease. *J Pediatr Gastroenterol Nutr* 2010;51:364–6.
- [181] Hernando A, Bretón I, Marín-Jimenez I, Menchén L. Refeeding syndrome in a patient with Crohn's disease. *J Clin Gastroenterol* 2008;4:430–1.
- [182] 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.
- [183] McCall TB, O'Leary D, Bloomfield J, O'Morain CA. Therapeutic potential of fish oil in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 1989;3:415–24.
- [184] Hawthorne AB, Daneshmend TK, Hawkey CJ, Belluzzi A, Everitt SJ, Holmes GK, et al. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. *Gut* 1992;33:922–8.
- [185] Stenson WF, Cort D, Rodgers J, Burakoff R, DeSchryver-Kecskemeti K, Gramlich TL, et al. Dietary supplementation with fish oil in ulcerative colitis. *Ann Intern Med* 1992;116:609–14.
- [186] Aslan A, Triadafilopoulos G. Fish oil fatty acid supplementation in active ulcerative colitis: a double-blind, placebo-controlled, crossover study. *Am J Gastroenterol* 1992;87:432–7.
- [187] Loeschke K, Ueberschaer B, Pietsch A, Gruber E, Ewe K, Wiebecke B, et al. n-3 fatty acids only delay early relapse of ulcerative colitis in remission. *Dig Dis Sci* 1996 Oct;41:2087–94.
- [188] Middleton SJ, Naylor S, Woolner J, Hunter JO. A double-blind, randomized, placebo-controlled trial of essential fatty acid supplementation in the maintenance of remission of ulcerative colitis. *Aliment Pharmacol Ther* 2002;16:1131–5.
- [189] 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.
- [190] 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.
- [191] Schwartz E. Perioperative parenteral nutrition in adults with inflammatory bowel disease: a review of the literature. *Nutr Clin Pract* 2015;31:159–70.
- [192] Aahlin EK, von Meyenfeldt M, Dejong CH, Ljungqvist O, Fearon KC, Lobo DN, et al. Functional recovery is considered the most important target: a survey of dedicated professionals. *Perioper Med Lond* 2014;30(3):5.
- [193] Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005;24:66–77.
- [194] Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J. Enhanced Recovery after Surgery Study Group. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg* 2011;146:571–7.
- [195] Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, et al. Enhanced Recovery After Surgery (ERAS) Group. Consensus review of optimal perioperative care in colorectal surgery: enhanced recovery after surgery (ERAS) group recommendations. *Arch Surg* 2009;144:961–9.
- [196] Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. *Crit Care Clin* 2010;26:527–47.
- [197] Engelman DT, Adams DH, Byrne JG, Aranki SF, Collins Jr JJ, Couper GS, et al. Impact of body mass index and albumin on morbidity and mortality after cardiac surgery. *J Thorac Cardiovasc Surg* 1999;118:866–73.
- [198] Kama NA, Coskun T, Yuksek YN, Yazgan A. Factors affecting post-operative mortality in malignant biliary tract obstruction. *Hepatogastroenterology* 1999;46:103–7.
- [199] 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.
- [200] Koval KJ, Maurer SG, Su ET, Aharonoff GB, Zuckerman JD. The effects of nutritional status on outcome after hip fracture. *J Orthop Trauma* 1999;13:164–9.
- [201] Takagi K, Yamamori H, Toyoda Y, Nakajima N, Tashiro T. Modulating effects of the feeding route on stress response and endotoxin translocation in severely stressed patients receiving thoracic esophagectomy. *Nutrition* 2000;16:355–60.
- [202] Dannhauser A, Van Zyl JM, Nel CJ. Preoperative nutritional status and prognostic nutritional index in patients with benign disease undergoing abdominal operations - Part I. *J Am Coll Nutr* 1995;14:80–90.
- [203] Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. *J Hum Nutr Diet* 2010;23:393–401.
- [204] Lavernia CJ, Sierra RJ, Baerga L. Nutritional parameters and short term outcome in arthroplasty. *J Am Coll Nutr* 1999;18:274–8.
- [205] Malone M. Longitudinal assessment of outcome, health status, and changes in lifestyle associated with long-term home parenteral and enteral nutrition. *J Parenter Enter Nutr* 2002;26:164–8.
- [206] Mazolewski P, Turner JF, Baker M, Kurtz T, Little AG. The impact of nutritional status on the outcome of lung volume reduction surgery: a prospective study. *Chest* 1999;116:693–6.
- [207] Pedersen NW, Pedersen D. Nutrition as a prognostic indicator in amputations. A prospective study of 47 cases. *Acta Orthop Scand* 1992;63:675–8.
- [208] Rey-Ferro M, Castano R, Orozco O, Serna A, Moreno A. Nutritional and immunologic evaluation of patients with gastric cancer before and after surgery. *Nutrition* 1997;13:878–81.
- [209] Fukuda Y, Yamamoto K, Hirao N, Nishikawa K, Maeda S, Haraguchi N, et al. Prevalence of malnutrition in gastric cancer patients undergoing gastrectomy. *Ann Surg Oncol* 2015;22:S778–85.
- [210] Sandstrom R, Drott C, Hyltander A, Arfvidsson B, Schersten T, Wickstrom I, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg* 1993;217:185–95.
- [211] 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;99:728–37.
- [212] 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;46:813–8.
- [213] 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;16:723–8.
- [214] Espauella 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;29:425–31.

- [215] 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;91:983–90.
- [216] Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. *Cochrane Database Syst Rev* 2012;11:CD008879.
- [217] 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.
- [218] 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.
- [219] Delany HM, Carnevale N, Garvey JW, Moss GM. Postoperative nutritional support using needle catheter feeding jejunostomy. *Ann Surg* 1977;186:165–70.
- [220] 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;93:509–13.
- [221] Gupta V. Benefits versus risks: a prospective audit. Feeding jejunostomy during esophagectomy. *World J Surg* 2009;33:1432–8.
- [222] 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;23:652–9.
- [223] Veterans Affairs. Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs total parenteral nutrition cooperative study group. *N Engl J Med* 1991;325:525–32.
- [224] 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. *J Parenter Enter Nutr* 2000;24:7–14.
- [225] Shukla HS, Rao RR, Banu N, Gupta RM, Yadav RC. Enteral hyperalimentation in malnourished surgical patients. *Indian J Med Res* 1984;80:339–46.
- [226] Von Meyenfeldt MF, Meijerink WJ, Rouffart MM, Builmaassen MT, Soeters PB. Perioperative nutritional support: a randomised clinical trial. *Clin Nutr* 1992;11:180–6.
- [227] 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;44:102–11.
- [228] Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *J Parenter Enter Nutr* 2003;27:355–73.
- [229] 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.
- [230] 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;13:569–75.
- [231] Klek S, Forbes A, Gabe S, Holst M, Wanten G, Irtun O, et al. Management of acute intestinal failure: a position paper from the European society for clinical nutrition and metabolism (ESPEN) special interest group. *Clin Nutr* 2016;35:1209–18.
- [232] Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. *Ann Surg* 1997;226:369–77.
- [233] Feo CV, Romanini B, Sortini D, Ragazzi R, Zamboni P, Pansini GC, et al. Early oral feeding after colorectal resection: a randomized controlled study. *ANZ J Surg* 2004;74:298–301.
- [234] Jeffery KM, Harkins B, Cresci GA, Martindale RG. The clear liquid diet is no longer a necessity in the routine postoperative management of surgical patients. *Am Surg* 1996;62:167–70.
- [235] Reissman P, Teoh TA, Cohen SM, Weiss EG, Noguera JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. *Ann Surg* 1995;222:73–7.
- [236] Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus “nil by mouth” after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *Br Med J* 2001;323:773–6.
- [237] Barlow R, Price P, Reid TD, Hunt S, Clark GW, Havard TJ, et al. Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. *Clin Nutr* 2011;30:560–6.
- [238] 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;12:739–55.
- [239] Osland E, Yunus RM, Khan S, Memon MA. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. *J Parenter Enter Nutr* 2011;35:473–87.
- [240] Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. *Am J Clin Nutr* 2012;96:1346–53.
- [241] Imes S, Pinchbeck B, Thomson AB. Diet counselling improves the clinical course of patients with Crohn's disease. *Digestion* 1988;39:7–19.
- [242] 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.
- [243] Zvirbliene A, Kiudelis G, Zalinkevicius R, Kupcinskas L. Dietary characteristics of patients with inflammatory bowel diseases. *Med Kaunas* 2006;42(11):895–9.
- [244] Banos Madrid R, Salama Benerroch H, Moran Sanchez S, Gallardo Sanchez F, Albadalejo Merono A, Mercader Martinez J. Lactose malabsorption in patients with inflammatory bowel disease without activity: would it be necessary to exclude lactose products in the diet of all patients? *An Med Interna* 2004;21:212–4.
- [245] 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.
- [246] Jones VA, Dickinson RJ, Workman E, Wilson AJ, Freeman AH, Hunter JO. Crohn's disease: maintenance of remission by diet. *Lancet* 1985;2(8448):177–80.
- [247] James SL, Christophersen CT, Bird AR, Conlon MA, Rosella O, Gibson PR, et al. Abnormal fibre usage in UC in remission. *Gut* 2015;64:562–70.
- [248] Walton M, Alauyte I. Do patients living with ulcerative colitis adhere to healthy eating guidelines? A cross-sectional study. *Br J Nutr* 2014;112:1628–35.
- [249] Jowett SL, Seal CJ, Pearce MS, Phillips E, Gregory W, Barton JR, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. *Gut* 2004;53:1479–84.
- [250] Strisciuglio C, Giannetti E, Martinelli M, Sciorio E, Staiano A, Miele E. Does cow's milk protein elimination diet have a role on induction and maintenance of remission in children with ulcerative colitis? *Acta Paediatr* 2013;102:e273–8.
- [251] Swanson GR, Tieu V, Shaikh M, Forsyth C, Keshavarzian A. Is moderate red wine consumption safe in inactive inflammatory bowel disease? *Digestion* 2011;84:238–44.
- [252] Cashman KD, Shanahan F. Is nutrition an aetiological factor for inflammatory bowel disease? *Eur J Gastroenterol Hepatol* 2003;15:607–13.
- [253] 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.
- [254] 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.
- [255] Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:1156–71.
- [256] 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.
- [257] Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N Engl J Med* 1996;334:1557–60.
- [258] Lorenz-Meyer H, Bauer P, Nicolay C, Schulz B, Purmann J, Fleig WE, et al. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Study Group Members (German Crohn's Disease Study Group). *Scand J Gastroenterol* 1996;31:778–85.
- [259] Feagan BG, Sandborn WJ, Mittmann U, Bar-Meir S, D'Haens G, Bradette M, et al. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC randomized controlled trials. *JAMA* 2008;299:1690–7.
- [260] Romano C, Cucchiara S, Barabino A, Annesse V, Sferlazzas C. Usefulness of omega-3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: a double-blind, randomized, placebo-controlled study. *World J Gastroenterol* 2005;11:7118–21.
- [261] 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;28:2.
- [262] Hallert C, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. *Scand J Gastroenterol* 1991;26:747–50.
- [263] Fernández-Bañares F, Hinojosa J, Sánchez-Lombrana JL, Navarro E, Martínez-Salmerón JF, García-Pugés A, et al. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalazine 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.
- [264] 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.
- [265] 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.
- [266] 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.
- [267] 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.

- [268] 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.
- [269] 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.
- [270] 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(2):128–33.
- [271] 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.
- [272] Meini S, Laureano R, Fani L, Tascini C, Galano A, Antonelli A, et al. Break-through *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.
- [273] 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.
- [274] Pranter C, Scribano ML, Falasco G, Andreoli A, Luzzi 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.
- [275] Schultz M, Sartor RB. Probiotics and inflammatory bowel diseases. *Am J Gastroenterol* 2000;95(1 Suppl):S19–21.
- [276] Guslandi M, Giollo P, Testoni PA. A pilot trial of *Saccharomyces boulardii* in ulcerative colitis. *Eur J Gastroenterol Hepatol* 2003;15:697–8.
- [277] Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2006;CD004826.
- [278] 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.
- [279] Garcia Vilela E, De Lourdes De Abreu Ferrari M, Oswaldo Da Gama Torres H, Guerra Pinto A, Carolina Carneiro Aguirre A, Paiva Martins F, 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.
- [280] Steenhagen E, de Roos NM, Bouwman CA, van Laarhoven CJ, van Staveren WA. Sources and severity of self-reported food intolerance after ileal pouch-anal anastomosis. *J Am Diet Assoc* 2006;106:1459–62.
- [281] Ianco O, Tulchinsky H, Lusthaus M, Ofer A, Santo E, Vaisman N, et al. Diet of patients after pouch surgery may affect pouch inflammation. *World J Gastroenterol* 2013;19:6458–64.
- [282] Welters CF, Heineman E, Thunnissen FB, van den Bogaard AE, Soeters PB, Baeten CG. Effect of dietary inulin supplementation on inflammation of pouch mucosa in patients with an ileal pouch-anal anastomosis. *Dis Colon Rectum* 2002;45:621–7.
- [283] 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.
- [284] Durchschein F, Petritsch W, Hammer HF. Diet therapy for inflammatory bowel diseases: the established and the new. *World J Gastroenterol* 2016;22:2179–94.
- [285] Mimura T, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot JC, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004;53:108–14.
- [286] 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.
- [287] 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.
- [288] 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.
- [289] Kuisma J, Mentula S, Jarvinen H, Kahri A, Saxelina M, Farkkila M. Effect of *Lactobacillus rhamnosus* GG on ileal pouch inflammation and microbial flora. *Aliment Pharmacol Ther* 2003;17:509–15.
- [290] 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.
- [291] 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.
- [292] El-Matary W, Otleay A, Critch J, Abou-Setta AM. Enteral feeding therapy for maintaining remission in Crohn's disease: a systematic review. *J Parenter Enter Nutr* 2015 Dec 8. pii: 0148607115621051.
- [293] Hanai H, Iida T, Takeuchi K, Arai H, Arai O, Abe J, et al. Nutritional therapy versus 6-mercaptopurine as maintenance therapy in patients with Crohn's disease. *Dig Liver Dis* 2012;44:649–54.
- [294] Duncan H, Buchanan E, Cardigan T, Garrick V, Curtis L, McGrogan P, et al. A retrospective study showing maintenance treatment options for paediatric CD in the first year following diagnosis after induction of remission with EEN: supplemental enteral nutrition is better than nothing! *BMC Gastroenterol* 2014;14:50.
- [295] Yamamoto T, Nakahigashi M, Saniabadi AR, Iwata T, Maruyama Y, Umegae S, et al. Impacts of long-term enteral nutrition on clinical and endoscopic disease activities and mucosal cytokines during remission in patients with Crohn's disease: a prospective study. *Inflamm Bowel Dis* 2007;13:1493–501.
- [296] 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.
- [297] 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;66:1219–23.
- [298] 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.
- [299] 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.
- [300] Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. *Nutrition* 2006;22:1210–3.
- [301] 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.
- [302] 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 Aug;21:320–3.
- [303] Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med* 2013;368:149–60.
- [304] 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.
- [305] Bermejo F, Algaba A, Guerra I, Chaparro M, De-La-Poza G, Valer P, et al. Should we monitor vitamin B12 and folate levels in Crohn's disease patients? *Scand J Gastroenterol* 2013;48:1272–7.
- [306] Heyman MB, Garnett EA, Shaikh N, Huen K, Jose FA, Harmatz P, et al. Folate concentrations in pediatric patients with newly diagnosed inflammatory bowel disease. *Am J Clin Nutr* 2009;89:545–50.
- [307] 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.
- [308] Halsted CH, Gandhi G, Tamura R. Sulphasalazine inhibits the absorption of folates in ulcerative colitis. *N Engl J Med* 1981;305:1513–7.
- [309] 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* 2016 [E-pub ahead of print].
- [310] 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.
- [311] Nguyen GC, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitalizations among women with inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol* 2009;7:329–34. R37.1.
- [312] Nguyen GC, Seow CH, Maxwell C, Huang V, Leung Y, Jones J, et al., for the IBD in Pregnancy Consensus Group. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology* 2016;150:734–57.
- [313] 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.
- [314] Bryant RV, Trott MJ, Bartholomewsz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:213–25.
- [315] 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.
- [316] Schneider SM, Al-Jaouni R, Filippi J, Wiroth JB, Zealandin G, Arab K, et al. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. *Inflamm Bowel Dis* 2008;14:1562–8.
- [317] 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.
- [318] 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.
- [319] DeFilippis EM, Tabani S, Warren RU, Christos PJ, Bosworth BP, Scherl EJ. Exercise and self-reported limitations in patients with inflammatory bowel disease. *Dig Dis Sci* 2016;61:215–20.
- [320] 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.
- [321] Narula N, Fedorak RN. Exercise and inflammatory bowel disease. *Can J Gastroenterol* 2008;22:497–504.
- [322] 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.
- [323] Flores A, Burstein E, CIPHER DJ, Feagins LA. Obesity in inflammatory bowel disease: a marker of less severe disease. *Dig Dis Sci* 2015;6:2436–45.
- [324] 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 Aug;7:e241–8.
- [325] Pituch-Zdanowska A, Banaszkiwicz A, Dziekiewicz M, Łazowska-Przeorek I, Gawrońska A, Kowalska-Duplaga K, et al. Overweight and obesity in children with newly diagnosed inflammatory bowel disease. *Adv Med Sci* 2016;61:28–31.
- [326] 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.