ESPEN Guideline: Clinical Nutrition in inflammatory bowel disease

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Abstract:

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).

Keywords: Crohn’s disease, ulcerative colitis, enteral nutrition, parenteral nutrition, inflammatory bowel disease, nutritional therapy

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 anorexigenic. Patients with CD remain at risk even when their disease appears quiescent, whereas patients with UC generally develop problems only when the disease is active (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).

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 (Bischoff et al., 2015). 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 (Lochs et al. 2006; Van Gossum et al. 2009).

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 sus-

ceptible 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 (Bischoff et al., 2015). 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 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 agree, 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).

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

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 poulation; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target poulation, 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

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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

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Results

I. 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 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 (12).

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” **(13)**. They used guideline-recommended methodology to evaluate the association between pre-illness intake of nutrients (fats, carbohydrates, protein) and food groups (fruits, vegetables, meats) and the risk of subsequent IBD diagnosis. Nineteen studies were included, encompassing 2,609 IBD patients (1,269 with CD and 1,340 with UC), and over 4,000 controls. The main results 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 **(14)**. Compared to women with the lowest energy-adjusted fibre intake, intake of fibre in the highest quintile (median 24 grams 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 **(15)**, 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 **(16)**. 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 con-

trast, 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 **(17)**. 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 (18), 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 (19). 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 (20).

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 (21). 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 (22). During 1,492,811 person-years of follow-up 122 incident cases of CD and 123 new cases of UC were documented. The median predict-

ed 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 (23). 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 8-16mg/day (HR 0.69, 0.44 - 1.08) and >16mg/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 (24). 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 5^{th} versus the 1^{st} 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 (25)).

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 (26). 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 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 (27). This finding was confirmed in a German study (28). 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) **(29)**. Systematic reviews from 2004 and 2009 concluded strongly in favour of breastfeeding (29a, 29b) 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 (30). 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) **(31)**. 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 (32). 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 **(33)**.

Breastfeeding for around six months is desirable in all infants (34). Regarding longer periods of breastfeeding, current European recommendations suggest that breastfeeding is continued as long as mutually desired by both mother and infant (34). 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 (35). 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 (36).

Malnourished patients with IBD are more likely to be hospitalised following emergency department attendance (37) and are more likely to be admitted to hospital due to infection (38).

In hospitalised patients malnutrition is an independent risk factor for venous thromboembolism (39), non-elective surgery (40), longer admission (35,40) and increased mortality (35).

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 (41). 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 (42). Although a variety of screening tools exists, the tools have poor ability to discern different levels of nutrition risk for children with IBD (43). 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 particularly importance in paediatric IBD is growth failure, which is the result of a combination of inflammation and chronic malnutrition (44). Growth failure is seen in 15-40% of children with IBD (44,45). 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 (46).

Iron deficiency is particularly common in paediatric IBD, while other deficiencies include folic acid, zinc, magnesium, calcium, vitamins A, B12, D, E, and K (47). 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 (48-50).

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 (51,52) 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 (53). 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 (54). 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 (55, 56) or children (57-60). Measured REE/kg in adult patients has been found to be higher than (61) or the same as (62) 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 (63,64). 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) (65-67) and no consistent association has been found between REE/kg FFM and markers of disease activity (68).

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

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

Recommendation 5 B:

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

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

Commentary:

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 (69) and adults (70) 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 (1,71,72). 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 (67).

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 1g protein for each kilogram of body weight is therefore reasonable. However in active inflammation the proteolytic, catabolic response justifies an increase in provision to 1.2 to 1.5 g/kg bodyweight (73,74).

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 (75) . In light of this some authors have examined micronutrient status in patients in clinical disease remission and found deficits of a variety of micronutrients (76,77). Furthermore, deficits may be present even in apparently well nourished individuals (78). 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 (79). Poor compliance, particularly in adolescents, is common with multivitamin supplements and patient education about the rationale behind their use is important (80).

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% (81). Anaemia is reported more frequently in hospitalized patients with IBD and occurs more frequently in CD than in UC (82). In IBD patients anaemia increases, morbidity, rate of hospitalization, medical costs and deaths (81,83). In the majority of cases, IBD-associated anaemia represents a combination of chronic iron deficiency and anaemia of chronic disease (81). The currently used WHO definition of anaemia (Table 4) applies also to patients with IBD (84).

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

All patients with IBD regardless of their age should be assessed for the presence of anaemia (85). 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 to 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 **(86)**. 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 (85). 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 **(87)**. 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 (85) 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 (85). The estimation of iron need is usually based on baseline haemoglobin and body weight (Table 5) (88).

Table 5: Simple scheme for estimation of total iron need (88)

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

Anaemia seems to recur frequently and fast after intravenous iron therapy (89). 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 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 (90). Therefore, no "oral IBD diet" can be generally recommended to promote remission in IBD patients with active disease. This recommendation does not prelude the needs of all IBD patients to receive an individual (nutritional) approach based on their specific personal situation, preferably with the active input of a dedicated dietician or nutritionist as part of the multidisciplinary approach. 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/m^2 (91). 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) (92). In these cases, polymeric EN seems more effective that elemental ones (**93**,94). EN in a supplemental form as partial enteral nutrition (PEN) therapy induced remission in 47 children and young adults (95), whereas this effect was not found in a former RCT in 50 CD children (96). 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 (97). 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 formulas and on the question of polymeric versus elemental EN in RCTs of adults with active CD (98-100). Meta-analyses do not support the use of EN as primary treatment for acute exacerbations of CD in adults (97,101). 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 (102) 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 (103), 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 (104). 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 (105). 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 (106). 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 (107). A small study of 7 patients showed no clinical effect of TPN on colonic strictures (108). 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 (109). 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 **(110,111)**. 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 **(112)**.

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 (113).

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) (114). Vitamin D deficiency is common (55%) among adult patients with active UC, particularly those requiring corticosteroids (n=34) (115). 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 (116).

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 **(117)**. 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 **(117)**.

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 (91). If mild, bile acid diarrhoea can be controlled by a sequestrant such as cholestyramine (119,120). 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 (121).

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 (122). 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 (123). Significantly lower mean values of urinary oxalate excretion were found in paediatric than in adult Crohn’s patients (124). 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 (125), but only few studies reports induction of remission (95,126). 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 (95). 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 (126).

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 (127). Similar results on maintenance of remission were reported in an open label study by the same group using a personal food exclusion diet (128). Another study reported maintenance of clinical remission using a IgG4 guided exclusion diet in adult CD patients (129).

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 E. 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 **(130)** and of an oral preparation of VSL#3 in active colitis **(131)**. 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 (132). 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 (133).

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 formulas 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 formulas 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 (134,**135**). In situations when the gut cannot absorb all nutritional needs, enteral nutrition should nonetheless be attempted with supplementary PN (78,136,**137**).

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 (138). However, it must be recognized that these patients in need of PN are those with the most complicated disease (139).

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 (45). Secondly, since growth is so essential in children, this increases the possibility of avoiding the use of steroids or delaying their introduction (140) 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 **(141)**, and that in some settings (i.e. concomitant immuno-modulatory treatment) EEN might even be superior to corticosteroids in children **(142)**. 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 **(93)**.

Commentary:

The data are weaker for adult practice (143), 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 **(144)**.

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 (143).

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 (145-147). 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 (145-148). 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 [148,149].

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 formulas in the management of active CD. A Cochrane meta-analysis of ten trials showed no statistically significant difference between patients treated with elemental (n=188), and non-elemental diet (semi-elemental or polymeric diet; n=146) **(150)**. The protein composition did not appear to influence the therapeutic potential of EN. The present systematic enquiry reveals insufficient evidence to make firm recommendations [**150**,151]. 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 [152-154). 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 (151,155,156). Equally there is no evidence that any of these alternatives is inferior to the use of standard polymeric feeds (97,**157**).

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 (158-160). The most frequent complications of PN in IBD are infectious (catheter sepsis), metabolic and mechanical (161). Specific attention should be paid to electrolyte supplementation (especially sodium and magnesium) in short bowel patients (159,160). 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 (162,163). 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 (162-166).

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 0 – 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 (144,**167**,**168**). Malnutrition with BMI <20 appears as an independent risk factor that should be confirmed in further studies (169).

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 **(168)**. Treatment will often need to be surgical but some patients clearly benefit from drug treatment with immunomodulators or/and biologics (170,171). 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 (170,172,173). 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 (174,175), but even then the psychological benefit of eating may warrant its inclusion in the nutritional regimen despite minimal expectations of useful nutrient absorption (172). Surgical correction is more likely to be successful if nutritional status has been optimised pre-operatively (176).

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 (**177**-179).

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 0 – 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 (180-185). 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 (186). 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 [186]. 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 [139,186-188).

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 (189-193). 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 (194-198) and prospective studies (199-206). It is clear that inadequate oral intake for more than 14 days is associated with a higher mortality (207).

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* (208) 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 (209-213). 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) (214-219).

C: Undernutrition has a negative impact on the clinical course, the rate of postoperative complications and on mortality (196,220-224). 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 < 30g/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 peri-operatively 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 (225,226). 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 (207) 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 hours of surgery versus later commencement have been shown in two meta-analyses (one Cochrane systematic review) (226,227).

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 (102).

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) (228).

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 (229).

How should nutritional support be performed in the postoperative phase?

Recommendation 27A:

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

Grade of recommendation 0, see 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 (230-233) and leads to significantly shortened hospital length of stay (234). This has been emphasized by a Cochrane Systematic Review (226). Recent meta-analyses (227,235,236) 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 (236).

V. Dietetic recommendations during remission

What is the role of dieticians 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 (172). 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 (237) and a single incompletely controlled study in CD (238) 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 (239-242). 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 (77). 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 **(243)**. 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 (244,245). Cohort studies suggest that those who habitually consume more meat and alcohol have a higher relapse rate (246). Elimination of cows' milk protein in unselected children with colitis is ineffective (247). 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 (248)!

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 (136,**150**,152,249) but the effect has also been observed in a Japanese study of adult Crohn's patient (153,154,250). Esaki *et al* (251) 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 (145,251). 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 (153,154). 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 (184). 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 (185). 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 **(252,253)**. 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 (254). No effect was however seen in a contemporary study performed in Germany in which the relapse rate was 70% in both groups (255). 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 (256). 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 (257). 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 **(252,253).**

The latest Cochrane review **(258)** 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 (259-261). 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 (90). 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 (262). 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 30g of fibre for every 2000kcal. Maintenance of remission to 1 year was a remarkable 92% (263). 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 **(264)** in the maintainance of remission in patients – including children - with mild to moderate UC, in comparison to 5-aminosalicylate compounds (131,265,266). Other probiotic preparations have been studied but although they have usually been well tolerated with trends toward benefit, significant effectiveness has not been demonstrated (267,268). 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 (269,270).

Probiotics are probably ineffective in preventing disease recurrence for patients with CD (266). Although some positive claims are made no unequivocal benefit can be discerned (271-276). 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 con-

structed 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 (277). 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 (278). 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 (279).

Antibiotics (ciprofloxacin, metronidazole) are the treatment of reference of acute pouchitis (**280**). 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 (281).

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: *B. breve, B. longum, B. infantis, L. acidophilus, L. casei, L. delbrueckii, L. plantarum and Streptococcus salivarius subsp. thermophilus*) in maintaining remission in patients with chronic pouchitis (282,283). 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 VLS#3

patients maintained remission at 9 to 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) **(280)**. In another study (284) 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 3,600 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 (285). 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 *Lactobacillus rhamnosus* strain GG (two gelatine capsules/day of 0.5-1 x 1010 CFU/capsule) in patients with a previous history of pouchitis showed that this probiotic was not effective in preventing relapses (286).

ECCO guidelines suggest the use of VSL#3 both for maintenance of antibiotic-induced remission and for prevention of pouchitis in adults (287) and in paediatric UC (288).

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 (289) (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 (155). 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 < .01). Hanai et al. (290) 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 (291). Esaki *et al* (156) 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 (292).

The study of maintenance EN as an adjuvant to infliximab therapy has yielded conflicting results, with one negative (154) and two positive (293,294) 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 (295). 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) (100). 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 (132).

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 nutriceuticals) 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 (260). A Cochrane systematic review has analysed 6 studies (1039 patients) of omega-3 fatty acid supplementation **(258)**: 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 (295). 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) (100). 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 (132,145). 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 **(296)**. 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 (296a).

Ileal CD is not inevitably associated with B12 deficiency (297,298), but it is difficult to rule out its responsibility when more than 30-60 cm are involved **(296)**.

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 **(296)**.

CD patients with ileal involvement and/or resection and/or clinical deficiency features should be screened yearly for B12 deficiency **(296)**.

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 (299). Patients with more than 20 cm of ileum resected should receive 1000 µg of vitamin B12 prophylactically also every month and indefinitely (299). 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 showed the oral route (1200 µg per day for 33, 2400 µg per day for 3) to be effective in treating vitamin B12 deficiency (300). 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 (301). 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 (302).

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) (303) or folate malabsorption (sulphasalazine) (304). 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) (305).

An Italian study compared 1 month of supplementation with 15 mg of either folic or folinic acid in 30 IBD patients treated with sulphasalazine **(306)**. 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 hours after the methotrexate, or 1 mg daily for 5 days per week (132).

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 (307). 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 (308).

The consequences of anaemia and those of neural tube defects (309), 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 (nugyen 2016). 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 (310). Low muscle mass (311,312), strength (135,311,313) and performance (313) have been reported in adult IBD cohorts, but similar findings have also been made in children (314). Sarcopenia was reported in 12% of 137 Australian IBD patients of mean age 31 years, associated with osteopenia (311).

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) (315).

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 (ΔIBDQsocial = 6.27 ± 5.46 vs. 1.87 ± 4.76, p = 0.023) (316). 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 (317). Therefore, the panel recommends endurance training (for a minimum of 30 minutes 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 (318). 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) (319) and 17% of 100 Irish adult CD patients (320). 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) (321)

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 (322). 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 (76) and sarcopenia (312), 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.

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 admitedly less rigorous approach permits the conclusion that there was no difference between the use of polymeric and elemental formulae in children (185). 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) **(93)**. 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.

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References

001 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.

002 Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV, Jr., Tysk C, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. Gut 2013;62(4):630-49.

003 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.

004 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.

005 Goh J, O'Morain CA. Review article: nutrition and adult inflammatory bowel disease. Aliment Pharmacol Ther 2003;17(3):307-20.

006 Han PD, Burke A, Baldassano RN, Rombeau JL, Lichtenstein GR. Nutrition and inflammatory bowel disease. Gastroenterology clinics of North America 1999;28(2):423-43.

007 Ananthakrishnan AN, Cagan A, Gainer VS, Cai T, Cheng SC, Savova G, Chen P, Szolovits P, Xia Z, De Jager PL, Shaw SY, Churchill S, Karlson EW, Kohane I, Plenge RM, Murphy SN, Liao KP. 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.

008 Ananthakrishnan AN, Cagan A, Gainer VS, Cheng SC, Cai T, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. 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.

009 Hartman C, Eliakim R, Shamir R. Nutritional status and nutritional therapy in inflammatory bowel diseases. World J Gastroenterol 2009;15(21):2570-8.

010 Lucendo AJ, De Rezende LC. Importance of nutrition in inflammatory bowel disease. World J Gastroenterol 2009;15(17):2081-8.

011 Yamamoto T, Nakahigashi M, Saniabadi 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 Dec;34(6):1043-51. doi: 10.1016/j.clnu.2015.07.008. Epub 2015 Jul 16.

Lochs H[1], Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Schütz T, van Gemert W, van Gossum A, Valentini L; DGEM (German Society for Nutritional Medicine), Lübke H, Bischoff S, Engelmann N, Thul P; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Gastroenterology. Clin Nutr. 2006 Apr;25(2):260-74. Epub 2006 May 15.

Van Gossum A[1], Cabre E, Hébuterne X, Jeppesen P, Krznaric Z, Messing B, Powell-Tuck J, Staun M, Nightingale J; ESPEN. ESPEN Guidelines on Parenteral Nutrition: gastroenterology. Clin Nutr. 2009 Aug;28(4):415-27. doi: 10.1016/j.clnu.2009.04.022. Epub 2009 Jun 9.

012 Martinez-Medina M, Denizot J, Dreux N, Robin F, Billard E, Bonnet R, Darfeuille-Michaud A, Barnich N. Western diet induces dysbiosis with increased E coli in CEABAC10 mice, alters host barrier function favouring AIEC colonisation. Gut. 2014;63:116-2

013 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.

014 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(5):970-7.

015 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.

016 Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Fuchs CS, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut 2014;63(5):776-84.

017 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(12):1606-11.

018 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(8):834-42.

019 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(4):929-31.

020 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(4):338-41.

021 Khalili H, Huang ES, Ananthakrishnan AN, Higuchi L, Richter JM, Fuchs CS, Chan AT. Geographical variation and incidence of inflammatory bowel disease among US women. Gut. 2012;61:1686-92.

022 Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, Richter JM, Fuchs CS, Chan AT. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology. 2012;142:482-9.

023 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 Nov 5. pii: dyv301.

024 Racine A, Carbonnel F, Chan SS, Hart AR, Bueno-de-Mesquita HB, Oldenburg B, van Schaik FD, Tjønneland A, Olsen A, Dahm CC, Key T, Luben R, Khaw KT, Riboli E, Grip O, Lindgren S, Hallmans G, Karling P, Clavel-Chapelon F, Bergman MM, Boeing H, Kaaks R, Katzke VA, Palli D, Masala G, Jantchou P, Boutron-Ruault MC. Dietary Patterns and Risk of Inflammatory Bowel Disease in Europe: Results from the EPIC Study. Inflamm Bowel Dis. 2016;22:345-54.

025 Andersen V, Olsen A, Carbonnel F, Tjonneland A, Vogel U. Diet and risk of inflammatory bowel disease. Dig Liver Dis 2012;44(3):185-94.

026 Ananthakrishnan AN.Environmental risk factors for inflammatory bowel diseases: a review. Dig Dis Sci. 2015 Feb;60(2):290-8.

027 Gilat T, Hacohen 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.

028 Sonntag B, Stolze B, Heinecke A, Luegering A, Heidemann J, Lebiedz P, Rijcken E, Kiesel L, Domschke W, Kucharzik T, Maaser C. 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 Nov;13(11):1385-90.

029 Corrao G, Tragnone A, Caprilli R, Trallori G, Papi C, Andreoli A, Di Paolo M, Riegler G, Rigo GP, Ferraù O, Mansi C, Ingrosso M, Valpiani D. 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 Jun;27(3):397-404.

029a 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.

029b 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.

030 Gearry RB, Richardson AK, Frampton CM, Dodgshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. J Gastroenterol Hepatol 2010;25(2):325-33.

031 Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gamborg M, Munkholm P. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis. 2011 Dec;5(6):577-84.

032 Guo AY, Stevens BW, Wilson RG, Russell CN, Cohen MA, Sturgeon HC, Thornton A, Giallourakis C, Khalili H, Nguyen DD, Sauk J, Yajnik V, Xavier RJ, Ananthakrishnan AN. Early life environment and natural history of inflammatory bowel diseases. BMC Gastroenterol. 2014 Dec 16;14:216.

033 Ng SC, Tang W, Leong RW, Chen M, Ko Y, Studd C, Niewiadomski O, Bell S, Kamm MA, de Silva HJ, Kasturiratne A, Senanayake YU, Ooi CJ, Ling KL, Ong D, Goh KL, Hilmi I, Ouyang Q, Wang YF, Hu P, Zhu Z, Zeng Z, Wu K, Wang X, Xia B, Li J, Pisespongsa P, Manatsathit S, Aniwan S, Simadibrata M, Abdullah M, Tsang SW, Wong TC, Hui AJ, Chow CM, Yu HH, Li MF, Ng KK, Ching J, Wu JC, Chan FK, Sung JJ; 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 Jul;64(7):1063-71.

034 ESPGHAN Committee on Nutrition, Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Michaelsen KF, Mihatsch W, Moreno LA, Puntis J, Shamir R, Szajewska H, Turck D, van Goudoever J. Breast-feeding: A commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2009 Jul;49(1):112-25.

035 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(8):1105-11.

036 Sandhu A, Mosli M, Yan B, Wu T, Gregor J, Chande N, et al. Self-Screening for Malnutrition Risk in Outpatient Inflammatory Bowel Disease Patients Using the Malnutrition Universal Screening Tool (MUST). JPEN. J Parenter Enteral Nutr 2015. ePub ahead of print.

037 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 Feb;61(2):389-99

038 Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. J Crohns Colitis 2013;7(2):107-12.

038a Schneider SM, Al-Jaouni R, Filippi J, Wiroth JB, Zeanandin G, Arab K, Hébuterne X. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2008 Nov;14(11):1562-8.

039 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(11):1138-44.

040 Ananthakrishnan AN, McGinley EL, Binion DG, Saeian K. A novel risk score to stratify severity of Crohn's disease hospitalizations. Am J Gastroenterol 2010;105(8):1799-807.

041 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. The American journal of gastroenterology 2010;105(8):1893-90.

042 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(4):385-9.

043 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.

044 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(6):839-49.

045 Shamir R, Phillip M, Levine A. Growth retardation in pediatric Crohn's disease: pathogenesis and interventions. Inflamm Bowel Dis 2007;13(5):620-8.

046 Shamir R. Nutrition and growth in inflammatory bowel disease. World Rev Nutr Diet 2013;106:156-61.

047 Shamir R, Seidman E. Clinical dilemmas in inflammatory bowel disease, new challenges. 2nd ed: Wiley-Blackwell, 2011.

048 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(3):342-6.

049 Kushner RF, Schoeller DA. Resting and total energy expenditure in patients with inflammatory bowel disease. Am J Clin Nutr 1991;53(1):161-5.

050 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(6):652-6.

051 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(3):215-9.

052 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(1):32-6.

053 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(1):34-40.

054 Stokes MA, Hill GL. Total energy expenditure in patients with Crohn's disease: measurement by the combined body scan technique. JPEN J Parenter Enteral Nutr 1993;17(1):3-7.

055 Chan AT, Fleming CR, O'Fallon WM, Huizenga KA. Estimated versus measured basal energy requirements in patients with Crohn's disease. Gastroenterology 1986;91(1):75-8.

056 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(1):72-6.

057 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(2):290-4.

058 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. JPEN: Journal of Parenteral & Enteral Nutrition 2005;29(2):102-7.

059 Hart JW, Bremner AR, Wootton SA, Beattie RM. Measured versus predicted energy expenditure in children with inactive Crohn's disease. Clinical Nutrition 2005;24(6):1047-55.

060 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(7):1587-93.

061 Capristo E, Addolorato G, Mingrone G, Greco AV, Gasbarrini G. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. The American journal of gastroenterology 1998;93(12):2411-9.

062 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(9):1754-9.

063 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(5):775-81.

064 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(9):855-59.

065 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(1):19-25.

066 Steiner SJ, Pfefferkorn MD, Fitzgerald JF, Denne SC. Carbohydrate and lipid metabolism following infliximab therapy in pediatric Crohn's disease. Pediatric research 2008;64(6):673-6.

067 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(6):737-44.

068 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(2):271-6.

069 Steiner SJ, Noe JD, Denne SC. Corticosteroids increase protein breakdown and loss in newly diagnosed pediatric Crohn disease. Pediatric research 2011;70(5):484-8.

070 O'Keefe SJ, Ogden J, Rund J, Potter P. Steroids and bowel rest versus elemental diet in the treatment of patients with Crohn's disease: the effects on protein metabolism and immune function. JPEN. Journal of parenteral and enteral nutrition 1989;13(5):455-60.

071 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(3):356-60.

072 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(6):783-7.

073 Griffiths RD, Hinds CJ, Little RA. Manipulating the metabolic response to injury. Br Med Bull 1999;55(1):181-95.

074 Royall D, Greenberg GR, Allard JP, Baker JP, Jeejeebhoy KN. Total enteral nutrition support improves body composition of patients with active Crohn's disease. JPEN J Parenter Enteral Nutr 1995;19(2):95-9.

075 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(6):e50-1.

076 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 Mar;12(3):185-91.

077 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 May;67(5):919-26.

078 Vagianos K, Bector S, McConnell J, Bernstein CN. Nutrition assessment of patients with inflammatory bowel disease. JPEN. Journal of parenteral and enteral nutrition 2007;31(4):311-9.

079 Santucci NR, Alkhouri RH, Baker RD, Baker SS. Vitamin and zinc status pretreatment and posttreatment in patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2014;59(4):455-7.

080 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(8):883-92.

081 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 Jul;7(6):429-40.

082 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(2):199–205.

083 Cucino C, Sonnenberg A. Cause of death in patients with inflammatory bowel disease. Inflamm Bowel Dis 2001;7:250–5.

084 Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2015 Aug 24. pii: S0140-6736(15)60865-0. doi: 10.1016/S0140-6736(15)60865-0. ePub ahead of print.

085 Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, Gomollon F, Iqbal T, Katsanos K, Koutroubakis I, Magro F, Savoye G, Stein J, Vavricka S. European Crohn’s and Colitis Organisation [ECCO]. European consensus on the diagnosis and man-

agement of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015;9:211-22.

086 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.

087 Bonovas S, Fiorino G, Allocca M, Lytras T, Tsantes A, Peyrin-Biroulet L, Danese S. Intravenous Versus Oral Iron for the Treatment of Anaemia in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2016;95:e2308.

088 Evstatiev R, Marteau P, Iqbal T, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. Gastroenterology 2011;141:846–53, e841–42.

089 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.

090 Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL, Kamm MA, Sanderson JD, Knight SC, Forbes A, Stagg AJ, Whelan K, Lindsay JO. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut. 2011 Jul;60(7):923-9.

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

092 Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, Russo PM, Cucchiara S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol. 2006 Jun;4(6):744-53.

093 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(2):246-253.

094 Ludvigsson JF, Krantz M, Bodin L, Stenhammar L, Lindquist B. Elemental versus polymeric enteral nutrition in paediatric Crohn’s disease: a multicentre randomized controlled trial. Acta Paediatr. 2004;93(3):327-335.

095 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(8):1353-60.

096 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(3):356-61.

097 Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn’s disease. Cochrane Database Syst Rev. 2007;1:CD000542.

098 Sakurai T, Matsui T, Yao T, Takagi Y, Hirai F, Aoyagi K, Okada M. Short-term efficacy of enteral nutrition in the treatment of active Crohn's disease: a randomized, controlled trial comparing nutrient formulas. JPEN. 2002 Mar-Apr;26(2):98-103.

099 Gassull MA, Fernández-Bañares F, Cabré E, Papo M, Giaffer MH, Sánchez-Lombraña JL, Richart C, Malchow H, González-Huix F, Esteve M; 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(2):164-8.

100 Verma S, Brown S, Kirkwood B, Giaffer MH. Polymeric versus elemental diet as primary treatment in active Crohn's disease: a randomized, double-blind trial. Am J Gastroenterol. 2000 Mar;95(3):735-9.

101 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 Mar;31(3):267-72.

102 Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, Forbes A, Gabe S, Gillanders L, Holst M, Jeppesen PB, Joly F, Kelly D, Klek S, Irtun Ø, Olde Damink SW, Panisic M, Rasmussen HH, Staun M, Szczepanek K, Van Gossum A, Wanten G, Schneider SM, Shaffer J; 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 Apr;34(2):171-80.

103 Baker ML, Williams RN, Nightingale JM. Causes and management of a high-output stoma. Colorectal Dis. 2011 Feb;13(2):191-7.

104 Grischkan D, Steiger E, Fazio V. Maintenance of home hyperalimentation in patients with high-output jejunostomies. Arch Surg. 1979 Jul;114(7):838-41.

105 Pironi L, Guidetti C, Incasa E, Poggioli G, Paganelli F, Merli C, Fumi L, Miglioli M. Oral rehydration solution containing rice maltodextrins in patients with total colectomy and high intestinal output. Int J Clin Pharmacol Res. 2000;20(3-4):55-60.

106 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(6):759-61.

107 Hu D, Ren J, Wang G, Li G, Liu S, Yan D, Gu G, Zhou B, Wu X, Chen J, Ding C, Wu Y, Wu Q, Liu N, Li J. Exclusive enteral nutritional therapy can relieve inflammatory bowel stricture in Crohn's disease. J Clin Gastroenterol. 2014 Oct;48(9):790-5.

108 Fuchigami T, Ohgushi H, Imamura K, Yao T, Omae T, Watanabe H, Nakano H. Effects of total parenteral nutrition on colonic lesions in Crohn's disease: radiographic and endoscopic study. Gastroenterol Jpn. 1982 Dec;17(6):521-9.

109 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 Jul;43(1):42-51.

110 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 Aug;59(8):1878-84.

111 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 Jun;7(5):377-84.

112 Lopes LH, Sdepanian VL, Szejnfeld VL, de Morais MB, Fagundes-Neto U. Risk factors for low bone mineral density in children and adolescents with inflammatory bowel disease.Dig Dis Sci. 2008 Oct;53(10):2746-53.

113 Mingrone G, Benedetti G, Capristo E, De Gaetano A, Greco AV, Tataranni PA, Gasbarrini G. Twenty-four-hour energy balance in Crohn disease patients: metabolic implications of steroid treatment. Am J Clin Nutr. 1998 Jan;67(1):118-23.

114 Veit LE, Maranda L, Fong J, Nwosu BU. The vitamin D status in inflammatory bowel disease.PLoS One. 2014 Jul 3;9(7):e101583. doi: 10.1371/journal.pone.0101583. eCollection 2014.

115 Blanck S, Aberra F. Vitamin D deficiency is associated with ulcerative colitis disease activity. Dig Dis Sci. 2013 Jun;58(6):1698-702.

116 Wingate KE, Jacobson K, Issenman R, Carroll M, Barker C, Israel D, Brill H, Weiler H, Barr SI, Li W, Lyon MR, Green TJ. 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 Apr;164(4):860-5.

117 van Bodegraven AA, Bravenboer N, Witte BI, Dijkstra G, van der Woude CJ, Stokkers PC, Russel MG, Oldenburg B, Pierik M, Roos JC, van Hogezand RA, Dik VK, Oostlander AE, Netelenbos JC, van de Langerijt L, Hommes DW, Lips P; Dutch Initiative on Crohn and Colitis (ICC). Treatment of bone loss in osteopenic patients with Crohn's disease: a double-blind, randomised trial of oral risedronate 35 mg once weekly or placebo, concomitant with calcium and vitamin D supplementation. Gut. 2014 Sep;63(9):1424-30.

118 Bernstein CN, Seeger LL, Anton PA, Artinian L, Geffrey S, Goodman W, Belin TR, Shanahan F. 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 Oct;10(5):777-86.

119 Jacobsen O, Højgaard L, Hylander Møller E, Wielandt TO, Thale M, Jarnum S, Krag E. Effect of enterocoated cholestyramine on bowel habit after ileal resection: a double blind crossover study. Br Med J (Clin Res Ed). 1985 May 4;290(6478):1315-8.

120 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 Jun;37(6):929-33.

121 Westergaard H. Bile Acid malabsorption. Curr Treat Options Gastroenterol. 2007 Feb;10(1):28-33.

122 Hylander E, Jarnum S, Jensen HJ, Thale M. Enteric hyperoxaluria: dependence on small intestinal resection, colectomy, and steatorrhoea in chronic inflammatory bowel disease. Scand J Gastroenterol. 1978;13(5):577-88.

123 Andersson H, Filipsson S, Hultén L. Urinary oxalate excretion related to ileocolic surgery in patients with Crohn's disease. Scand J Gastroenterol. 1978;13(4):465-9.

124 Hueppelshaeuser R, von Unruh GE, Habbig S, Beck BB, Buderus S, Hesse A, Hoppe B. Enteric hyperoxaluria, recurrent urolithiasis, and systemic oxalosis in patients with Crohn's disease. Pediatr Nephrol. 2012 Jul;27(7):1103-9.

125 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 Jan 8:0. (ePub ahead of print)

126 Rajendran N, Kumar D. Food-specific IgG4-guided exclusion diets improve symptoms in Crohn's disease: a pilot study. Colorectal Dis. 2011 Sep;13(9):1009-13.

127 Riordan AM, Hunter JO, Cowan RE, Crampton JR, Davidson AR, Dickinson RJ, Dronfield MW, Fellows IW, Hishon S, Kerrigan GN, et al. Treatment of active Crohn's disease by exclusion diet: East Anglian multicentre controlled trial. Lancet. 1993 Nov 6; 342(8880):1131-4.

128 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 Dec;32(12 Suppl):100S-107S.

129 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(3):277-85.

130 Oliva S, Di Nardo G, Ferrari F, Mallardo S, Rossi P, Patrizi G, Cucchiara S, Stronati L. Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis. Aliment Pharmacol Ther. 2012 Feb;35(3):327-34.

131 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(2):437-43.

132 Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis. 2014 Oct;8(10):1179-207.

133 Bousvaros A, Guandalini S, Baldassano RN, Botelho C, Evans J, Ferry GD, Goldin B, Hartigan L, Kugathasan S, Levy J, Murray KF, Oliva-Hemker M, Rosh JR, Tolia V, Zholudev A, Vanderhoof JA, Hibberd PL. 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 Sep;11(9):833-9.

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

135 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(7-8):694-702.

136 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(2):154-63.

137 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(7):351-6.

138 Nguyen GC, Laveist TA, Brant SR. The utilization of parenteral nutrition during the inpatient management of inflammatory bowel disease in the United States: a national survey. Aliment Pharmacol Ther 2007;26(11-12):1499-507.

139 Nguyen DL, Parekh N, Bechtold ML, Jamal MM. National trends and in-hospital outcomes of adult patients with inflammatory bowel disease receiving parenteral nutrition support. JPEN J Parenter Enteral Nutr. 2016 Mar;40(3):412-6.

140 Knight C, El-Matary W, Spray C, Sandhu BK. Long-term outcome of nutritional therapy in paediatric Crohn's disease. Clin Nutr 2005;24(5):775-9.

141 Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment Pharmacol Ther 2007;26(6):795-806.

142 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(10):3069-74.

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

144 Li G, Ren J, Wang G, Hu D, Gu G, Liu S, Ren H, Wu X, Li J. Preoperative exclusive enteral nutrition reduces the postoperative septic complications of fistulizing Crohn's disease. Eur J Clin Nutr. 2014 Apr;68(4):441-6.

145 Lochs H, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Shulz T, van Gemert W, van Gossum A, Valentini L, DGEM: Lubke H, Bischoff S, Engelman N, Thui P: ESPEN Guidelines on Enteral Nutrition: Gastroenterology. Clin Nutr 2006; 25, 260-274.

146 Fuchssteiner H, Nigl K, Mayer A, Kristensen B, Platzer R, Brunner B, Weiß I, Haas T, Benedikt M, Gröchenig HP, Eisenberger A, Hillebrand P, Reinisch W, Vogelsang H. Nutrition and IBD: consensus of the Austrian working group of IBD (inflammatory bowel diseases) of the OGGH. Z Gastroenterol 2014; 52 (4) 376–386.

147 August D, Teitelbaum D, Albina J, Bothe A, Guenter P, Heitkemper M, et al. ASPEN Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients; JPEN,Vol 1, No 26; Supp Jan- Feb 2002,

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

149 McClave SA, Martindale RG, Vanek VW 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), JPEN J Parent and Enteral Nutr. 2009;33(3); 277-316

150 Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2007(3):CD005984.

151 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 Jan;31(1):1-7.

152 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.

153 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(7):1143-9.

154 Yamamoto T, Nakahigashi M, Umegae S, Matsumoto K. Prospective clinical trial: enteral nutrition during maintenance infliximab in Crohn's disease. J Gastroenterol 2010;45(1):24-9.

155 Takagi S, Utsunomiya K, Kuriyama S, Yokoyama H,Takahashi S, Iwabuchi M, Takahashi H, Takahashi S, Kinouchi Y, Hiwatashi N, Funayama Y, Sasaki I, Tsuji I, ShimosegawaT. Effectiveness of an ‘half elemental diet’ as maintenance therapy for Crohn’s disease: A randomized-controlled trial. Aliment Pharmacol Ther 2006; 24: 1333-134012.

156 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. =R33.5

157 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 Mar;28(3):335-40.

158 Massironi S, Rossi RE, Cavalcoli FA, Della Valle S, Fraquelli M, Conte D Nutritional deficiencies in inflammatory bowel disease: therapeutic approaches. Clin Nutr. 2013 Dec;32(6):904-10.

159 Van Gossum A, Cabre E, Hebuterne X, Jeppsen P, Krznaric Z, Messing B, Powell-Tuck J, Staun M, Nightingale J: ESPEN Guidelines on Parenteral Nutrition: Gastroenterology, Clinical Ntrition 28 (2009),415-427 has been moved up the list and is now listed at about line 1846

160 Kulick D, Deen D. Specialized nutrition support. Am Fam Physician 2011;83(2):173-83.

161 Ukleja A, Romano MM. Complications of parenteral nutrition. Gastroenterol Clin N Am 2007;36:23–46.

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

163 Zezos P et al . IBD and thromboembolism. World J Gastroenterol 2014 October 14; 20(38): 13863-13878 ISSN 1007-9327

164 Bhakta A, Tafen M, Ahmed M, Ata A, Abraham C, Bruce D, Valerian BT, Lee EC. Risk of catheter-associated deep venous thrombosis in inflammatory bowel disease. Dis Colon Rectum. 2014 Dec;57(12):1379-83.

165 Ha C, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. Am J Gastroenterol. 2009 Jun;104(6):1445-51.

166 Papay P, Miehsler W, Tilg H, Petritsch W, Reinisch W, Mayer A, Haas T, Kaser A, Feichtenschlager T, Fuchssteiner H, Knoflach P, Vogelsang H, Platzer R,Tillinger W, Jaritz B, Schmid A, Blaha B, Dejaco C, Sobala A, Weltermann A, Eichinger S, Novacek G. Clinical presentation of venous thromboembolism in inflammatory bowel disease. J Crohns Colitis. 2013 Oct;7(9):723-9.

167 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 Aug;68(8):959-63.

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

169 Llop JM, Cobo S, Padulles A, Farran L, Jodar R, Badia MB. Nutritional support and risk factors of appearance of enterocutaneous fistulas. Nutr Hosp 2012;27(1):213-8.

170 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.

171 Wędrychowicz A, Zając A, Tomasik P. Advances in nutritional therapy in inflammatory bowel diseases: Review. World J Gastroenterol. 2016 Jan 21;22(3):1045-66.

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

173 Mowat C, Cole A, Windsor A, et al. . Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011;60:571-607.

174 Uchino M, Ikeuchi H, Matsuoka H, Matsumoto T, Takesue Y, Tomita N. Clinical features and management of duodenal fistula in patients with Crohn's disease. Hepatogastroenterology. 2012 Jan-Feb;59(113):171-4.

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

176 Ravindran P, Ansari N, Young CJ, Solomon MJ. Definitive surgical closure of enterocutaneous fistula: outcome and factors predictive of increased postoperative morbidity. Colorectal Dis. 2014 Mar;16(3):209-18.

177 Akobeng AK, Thomas AG. Refeeding syndrome following exclusive enteral nutritional treatment in Crohn disease. J Pediatr Gastroenterol Nutr. 2010 Sep;51(3):364-6.

178 Hernando A, Bretón I, Marín-Jimenez I, Menchén L. Refeeding syndrome in a patient with Crohn's disease. J Clin Gastroenterol. 2008 Apr;42(4):430-1.

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

180 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(5):415-24.

181 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(7):922-8.

182 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(8):609-14.

183 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(4):432-7.

184 Loeschke K, Ueberschaer B, Pietsch A, Gruber E, Ewe K, Wiebecke B, Heldwein W, Lorenz R. n-3 fatty acids only delay early relapse of ulcerative colitis in remission. Dig Dis Sci. 1996 Oct;41(10):2087-94.

185 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 Jun;16(6):1131-5.

186 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

187 Salinas H, Dursun A, Konstantinidis I, Nguyen D, Shellito P, Hodin R, Bordeianou L. Does preoperative total parenteral nutrition in patients with ulcerative colitis produce better outcomes? Int J Colorectal Dis. 2012 Nov;27(11):1479-83.

188 Schwartz E. Perioperative parenteral nutrition in adults with inflammatory bowel disease: a review of the literature. Nutr Clin Pract. 2015 ePub ahead of print

189 Aahlin EK, von Meyenfeldt M, Dejong CH, Ljungqvist O, Fearon KC, Lobo DN, Demartines N, Revhaug A, Wigmore SJ, Lassen K. Functional recovery is considered the most important target: a survey of dedicated professionals. Perioper Med (Lond). 2014 Jul 30;3:5.

190 Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, Nygren J, Hausel J, Soop M, Andersen J, Kehlet H. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr. 2005 Jun;24(3):466-77.

191 Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J; Enhanced Re-

covery After Surgery Study Group. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg. 2011 May;146(5):571-7.

192 Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, von Meyenfeldt MF, Fearon KC, Revhaug A, Norderval S, Ljungqvist O, Lobo DN, Dejong CH; 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 Oct;144(10):961-9.

193 Varadhan KK, Lobo DN, Ljungqvist O. Enhanced recovery after surgery: the future of improving surgical care. Crit Care Clin. 2010 Jul;26(3):527-47.

194 Engelman DT, Adams DH, Byrne JG, Aranki SF, Collins JJ,Jr, Couper GS, Allred EN, Cohn LH, Rizzo RJ. Impact of body mass index and albumin on morbidity and mortality after cardiac surgery. J Thorac Cardiovasc Surg 1999; 118:866-873

195 Kama NA, Coskun T, Yuksek YN, Yazgan A. Factors affecting post-operative mortality in malignant biliary tract obstruction. Hepatogastroenterology 1999; 46:103-107.

196 Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P. 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

197 Koval KJ, Maurer SG, Su ET, Aharonoff GB, Zuckerman JD. The effects of nutritional status on outcome after hip fracture. J Orthop Trauma 1999; 13:164-169

198 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; 16:355-360

199 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.

200 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.

201 Lavernia CJ, Sierra RJ, Baerga L. Nutritional parameters and short term outcome in arthroplasty. J Am Coll Nutr 1999;18:274-278

202 Malone M. Longitudinal assessment of outcome, health status, and changes in lifestyle associated with long-term home parenteral and enteral nutrition. JPEN J Parenter Enteral Nutr. 2002 May-Jun;26(3):164-8.

203 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; 116:693-696.

204 Pedersen NW, Pedersen D. Nutrition as a prognostic indicator in amputations. A prospective study of 47 cases. Acta Orthop Scand 1992; 63:675-678.

205 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;13:878-881

206 Fukuda Y, Yamamoto K, Hirao N, Nishikawa K, Maeda S, Haraguchi N, Miyake M, Hama N, Miyamoto A, Ikeda M, Nakamori S, Sekimoto M, FGujitani K, Tsujinaka T. Ann Surg Oncol 2015; Aug 19 epub ahead of print

207 Sandstrom R, Drott C, Hyltander A, Arfvidsson B, Schersten T, Wickstrom I, Lundholm K. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. Ann Surg 1993; 217:185-195

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

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

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

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

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

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

214 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

215 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.

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

217 Gabor S, Renner H, Matzi V, Ratzenhofer B, Lindenmann J, Sankin O, Pinter H, Maier A, Smolle J, Smolle-Juttner FM. Early enteral feeding compared with parenteral nutrition after oesophageal or oesophagogastric resection and reconstruction. Br J Nutr 2005; 93:509-513

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

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

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

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

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

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

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

225 Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr.2003;27(5):355–373.

226 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; (4):CD004080.

226a Dhaliwal R, Jurewitsch B, Harrietha D, Heyland DK. Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. Intensive Care Med.2004;30(8):1666–1671.

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

228 Klek S, Forbes A, Gabe S 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 (in print)

229 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; discussion 377-80

230 Feo CV, Romanini B, Sortini D, Ragazzi R, Zamboni P, Pansini GC, Liboni A. Early oral feeding after colorectal resection: a randomized controlled study. ANZ J Surg 2004; 74:298-301

231 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; 62:167-170.

232 Reissman P, Teoh TA, Cohen SM, Weiss EG, Nogueras JJ, Wexner SD. Is early oral feeding safe after elective colorectal surgery? A prospective randomized trial. Ann Surg 1995;222:73-77.

233 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; 323:773-776.

234 Barlow R, Price P, Reid TD, Hunt S, Clark GW, Havard TJ, Puntis MC, Lewis WG. Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. Clin Nutr 2011; 30:560-566

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

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

237 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 Dec;96(6):1346-53.

238 Imes S, Pinchbeck B, Thomson AB. Diet counselling improves the clinical course of patients with Crohn's disease. Digestion. 1988;39(1):7-19.

239 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(5):1322-8.

240 Zvirbliene A, Kiudelis G, Zalinkevicius R, Kupcinskas L. [Dietary characteristics of patients with inflammatory bowel diseases]. Medicina (Kaunas) 2006;42(11):895-9.

241 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? Anales de Medicina Interna 2004;21(5):212-14.

242 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(1-2):123-38.

243 Jones VA, Dickinson RJ, Workman E, Wilson AJ, Freeman AH, Hunter JO. Crohn's disease: maintenance of remission by diet. Lancet. 1985 Jul 27;2(8448):177-80.

244 James SL, Christophersen CT, Bird AR, Conlon MA, Rosella O, Gibson PR, Muir JG. Abnormal fibre usage in UC in remission. Gut. 2015 Apr;64(4):562-70.

245 Walton M, Alaunyte I. Do patients living with ulcerative colitis adhere to healthy eating guidelines? A cross-sectional study. Br J Nutr. 2014 Nov 28;112(10):1628-35).

246 Jowett SL, Seal CJ, Pearce MS, Phillips E, Gregory W, Barton JR, Welfare MR. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut. 2004 Oct;53(10):1479-84.

247 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 Jun;102(6):e273-8.

248 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.

249 Cashman KD, Shanahan F. Is nutrition an aetiological factor for inflammatory bowel disease? Eur J Gastroenterol Hepatol 2003;15(6):607-13.

250 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(34):4297-304.

251 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(12):1431-7.

252 Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013 Nov;38(10):1156-71.

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

254 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(24):1557-60.

255 Lorenz-Meyer H, Bauer P, Nicolay C, Schulz B, Purrmann J, Fleig WE, Scheurlen C, Koop I, Pudel V, Carr L. 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 Aug;31(8):778-85.

256 Feagan BG, Sandborn WJ, Mittmann U, Bar-Meir S, D'Haens G, Bradette M, Cohen A, Dallaire C, Ponich TP, McDonald JW, Hébuterne X, Paré P, Klvana P, Niv Y, Ardizzone S, Alexeeva O, Rostom A, Kiudelis G, Spleiss J, Gilgen D, Vandervoort MK, Wong CJ, Zou GY, Donner A, Rutgeerts P. Omega-3 free fatty acids for the maintenance of remission in Crohn disease: the EPIC Randomized Controlled Trials. JAMA. 2008 Apr 9;299(14):1690-7.

257 Romano C, Cucchiara S, Barabino A, Annese 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 Dec 7;11(45):7118-21.

258 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 Feb 28;2:CD006320.

259 Hallert C, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. Scand J Gastroenterol. 1991 Jul;26(7):747-50.

260 Fernández-Bañares F, Hinojosa J, Sánchez-Lombraña JL, Navarro E, Martínez-Salmerón JF, García-Pugés A, González-Huix F, Riera J, González-Lara V, Domínguez-Abascal F, Giné JJ, Moles J, Gomollón F, Gassull MA. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). Am J Gastroenterol. 1999 Feb;94(2):427-33. =R34.1

261 Hanai H, Kanauchi O, Mitsuyama K, Andoh A, Takeuchi K, Takayuki I, Araki Y, Fujiyama Y, Toyonaga A, Sata M, Kojima A, Fukuda M, Bamba T. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. Int J Mol Med. 2004 May;13(5):643-7

262 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 May-Jun;37(3):206-16.

263 Chiba M, Tsuji T, Nakane K, Komatsu M. High amount of dietary fiber not harmful but favorable for Crohn disease. Perm J. 2015 Winter;19(1):58-61.

264 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):1-13.

265 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(11):1617-23.

266 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.

267 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.

268 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(19):5985-94.

269 Meini S, Laureano R, Fani L, Tascini C, Galano A, Antonelli A, et al. Breakthrough Lactobacillus rhamnosus GG bacteremia associated with probiotic use in an adult patient with severe active ulcerative colitis: case report and review of the literature. Infection 2015;43(6):777-81.

270 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(5):437-9.

271 Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. Gut 2002;51(3):405-9.

272 Schultz M, Sartor RB. Probiotics and inflammatory bowel diseases. Am J Gastroenterol 2000;95(1 Suppl):S19-21.

273 Guslandi M, Giollo P, Testoni PA. A pilot trial of Saccharomyces boulardii in ulcerative colitis. Eur J Gastroenterol Hepatol 2003;15(6):697-8.

274 Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2006(4):CD004826.

275 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.

276 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(7):842-8.

277 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(9):1459-62.

278 Ianco O, Tulchinsky H, Lusthaus M, Ofer A, Santo E, Vaisman N, Dotan I. Diet of patients after pouch surgery may affect pouch inflammation. World J Gastroenterol. 2013;19:6458-64.

279 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.

280 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 Nov 23;11:CD001176. doi: 10.1002/14651858.CD001176.pub3.

281 Durchschein F, Petritsch W, Hammer HF. Diet therapy for inflammatory bowel diseases: The established and the new. World J Gastroenterol. 2016;22:2179-94.

282 Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3)

for maintaining remission in recurrent or refractory pouchitis. Gut 2004;53:108–14.

283 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(2):305-9.

284 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(10):2218-27.

285 Gionchetti P, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, Vitali B, Poggioli G, Miglioli M, Campieri M. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. Gastroenterology. 2003 May;124:1202-9.

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

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

288 Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, Dias JA, Bronsky J, Braegger CP, Cucchiara S, de Ridder L, Fagerberg UL, Hussey S, Hugot JP, Kolacek S, Kolho KL, Lionetti P, Paerregaard A, Potapov A, Rintala R, Serban DE, Staiano A, Sweeny B, Veerman G, Veres G, Wilson DC, Ruemmele FM; 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.

289 El-Matary W, Otley A, Critch J, Abou-Setta AM. Enteral Feeding Therapy for Maintaining Remission in Crohn's Disease: A Systematic Review. JPEN J Parenter Enteral Nutr. 2015 Dec 8. pii: 0148607115621051.

290 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(8):649-654.

291 Duncan H, Buchanan E, Cardigan T, Garrick V, Curtis L, McGrogan P, Barclay A, Russell RK. 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 Mar 20;14:50.

292 Yamamoto T, Nakahigashi M, Saniabadi AR, Iwata T, Maruyama Y, Umegae S, Matsumoto K. 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 Dec;13(12):1493-501.

293 Hirai F, Ishihara H, Yada S, Esaki M, Ohwan T, Nozaki R, Ashizuka S, Inatsu H, Ohi H, Aoyagi K, Mizuta Y, Matsumoto T, Matsui T. Effectiveness of concomitant enteral nutrition therapy and infliximab for maintenance treatment of Crohn's disease in adults. Dig Dis Sci. 2013 May;58(5):1329-34. R33.8

294 Sazuka S, Katsuno T, Nakagawa T, Saito M, Saito K, Matsumura T, Arai M, Sato T, Yokosuka O. Concomitant use of enteral nutrition therapy is associated with sustained response to infliximab in patients with Crohn's disease. Eur J Clin Nutr. 2012 Nov;66(11):1219-23. R33.9

295 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

2704 systematic review and meta-analysis. Health Technol Assess. 2015 Mar;19(26):1-138.
2705 R33.10

2706 296 Battat R, Kopylov U, Szilagyi A, Saxena A, Rosenblatt DS, Warner M, Bessissow T,
2707 Seidman E, Bitton A. Vitamin B12 deficiency in inflammatory bowel disease: prevalence, risk
2708 factors, evaluation, and management. Inflamm Bowel Dis. 2014 Jun;20(6):1120-8.

2709 296a Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with
2710 limited ileal resection. Nutrition. 2006 Nov-Dec;22(11-12):1210-3.

2711 297 Headstrom PD, Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B(12)
2712 deficiency in patients with Crohn's disease. Inflamm Bowel Dis. 2008 Feb;14(2):217-23.

2713 298 Yakut M, Ustün Y, Kabaçam G, Soykan I. Serum vitamin B12 and folate status in pa-
2714 tients with inflammatory bowel diseases. Eur J Intern Med. 2010 Aug;21(4):320-3.

2715 299 Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013;368:149–160.

2716 300 Plener I, Ferguson C, Kashkooli S, Saibil F. Oral B12 replacement in Crohn's disease -
2717 is B12 by injection obsolete? Aliment Pharmacol Ther. 2014 Dec;40(11-12):1365-6.

2718 301 Bermejo F, Algaba A, Guerra I, Chaparro M, De-La-Poza G, Valer P, Piqueras B, Ber-
2719 mejo A, García-Alonso J, Pérez MJ, Gisbert JP. Should we monitor vitamin B12 and folate
2720 levels in Crohn's disease patients? Scand J Gastroenterol. 2013 Nov;48(11):1272-7.

2721 302 Heyman MB, Garnett EA, Shaikh N, Huen K, Jose FA, Harmatz P, Winter HS, Baldas-
2722 sano RN, Cohen SA, Gold BD, Kirschner BS, Ferry GD, Stege E, Holland N. Folate concen-
2723 trations in pediatric patients with newly diagnosed inflammatory bowel disease. Am J Clin
2724 Nutr. 2009 Feb;89(2):545-50.

2725 303 Hornung N, Ellingsen T, Stengaard-Pedersen K, Poulsen JH. Folate, homocysteine,
2726 and cobalamin status in patients with rheumatoid arthritis treated with methotrexate, and the
2727 effect of low dose folic acid supplement. J Rheumatol 2004;31:2374–81.

2728 304 Halsted CH, Gandhi G, Tamura R. Sulphasalazine inhibits the absorption of folates in
2729 ulcerative colitis. N Engl J Med 1981;305:1513–7.

2730 305 Burr NE, Hull MA, Subramanian V. Folic Acid Supplementation May Reduce Colorectal
2731 Cancer Risk in Patients With Inflammatory Bowel Disease : A Systematic Review and Meta-
2732 Analysis. J Clin Gastroenterol. 2016 Feb 22. R36.5

2733 306 Pironi L, Cornia GL, Ursitti MA, Dallasta MA, Miniero R, Fasano F, Miglioli M, Barbara L.
2734 Evaluation of oral administration of folic and folinic acid to prevent folate deficiency in pa-
2735 tients with inflammatory bowel disease treated with salicylazosulfapyridine. Int J Clin Phar-
2736 macol Res. 1988;8(2):143-8.

2737 307 Nguyen GC, Boudreau H, Harris ML, Maxwell CV. Outcomes of obstetric hospitaliza-
2738 tions among women with inflammatory bowel disease in the United States. Clin Gastroenter-
2739 ol Hepatol. 2009 Mar;7(3):329-34. R37.1

2740 308 Nguyen GC, Seow CH, Maxwell C, Huang V, Leung Y, Jones J, et al for the IBD in
2741 Pregnancy Consensus Group. The Toronto consensus statements for the management of
2742 inflammatory bowel disease in pregnancy. Gastroenterology 2016; 150:734-57. R37.2

2743 309 Honein MA, Paulozzi LJ, Mathews TJ, et al. Impact of folic acid fortification of the US
2744 food supply on the occurrence of neural tube defects. JAMA. 2001;285:2981–2986.

2745 310 Bryant RV, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body compo-
2746 sition in adults with inflammatory bowel disease. Aliment Pharmacol Ther. 2013
2747 Aug;38(3):213-25. R38.1

311 Bryant RV, Ooi S, Schultz CG, Goess C, Grafton R, Hughes J, Lim A, Bartholomeusz FD, Andrews JM. Low muscle mass and sarcopenia: common and predictive of osteopenia in inflammatory bowel disease. Aliment Pharmacol Ther. 2015 May;41(9):895-906.

312 Schneider SM, Al-Jaouni R, Filippi J, Wiroth JB, Zeanandin G, Arab K, Hébuterne X. Sarcopenia is prevalent in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2008 Nov;14(11):1562-8.

313 Wiroth JB, Filippi J, Schneider SM, Al-Jaouni R, Horvais N, Gavarry O, Bermon S, Hébuterne X. Muscle performance in patients with Crohn's disease in clinical remission. Inflamm Bowel Dis. 2005 Mar;11(3):296-303.

314 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 Jul;6(6):665-73.

315 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 Jan;61(1):215-20.

316 Klare P, Nigg J, Nold J, Haller B, Krug AB, Mair S, Thoeringer CK, Christle JW, Schmid RM, Halle M, Huber W. 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(3):239-47.

317 Narula N, Fedorak RN. Exercise and inflammatory bowel disease. Can J Gastroenterol. 2008 May;22(5):497-504.

318 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 Nov;43(6):748-59.

319 Flores A, Burstein E, Cipher DJ, Feagins LA. Obesity in Inflammatory Bowel Disease: A Marker of Less Severe Disease. Dig Dis Sci. 2015 Aug;60(8):2436-45.

320 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(7):e241-8.

321 Pituch-Zdanowska A, Banaszkiewicz 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 Mar;61(1):28-31.

322 Seminerio JL, Koutroubakis IE, Ramos-Rivers C, Hashash JG, Dudekula A, Regueiro M, Baidoo L et al. Impact of Obesity on the Management and Clinical Course of Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015 Dec;21(12):2857-63.

Appendix A

PubMed search terms for the PICO questions (undertaken after the initial systematic review by the Cochrane Centre)

PICO 1

(Diet OR nutrition OR food) AND (Crohn OR colitis OR IBD) AND (Etiology OR incidence)

PICO 2

Breastfeeding AND (Crohn or colitis or IBD)

PICO 3

((((Crohn$) OR Ulcerative Colitis) OR Inflammatory Bowel Disease)) AND ((((nutritional consequences[Title/Abstract]) OR nutritional status[Title/Abstract]) OR nutrition assessment[Title/Abstract]) OR malnutrition[Title/Abstract]) - 680 hits 27 relevant

PICO 4

(energy expenditure[Title/Abstract]) AND (((Ulcerative Colitis) OR Crohn$) OR Inflammatory Bowel Disease) - 68 results, 34 relevant

PICO 5

(((body protein[Title/Abstract]) OR protein turnover[Title/Abstract]) OR protein requirement[Title/Abstract]) OR protein metabolism[Title/Abstract]) AND (((Ulcerative Colitis) OR Crohn$) OR Inflammatory Bowel Disease) - 47 hits, 13 relevant

PICO 6

(((((((micronutrient[Title/Abstract]) OR trace element[Title/Abstract]) OR mineral[Title/Abstract]) OR vitamin[Title/Abstract]) AND (((Ulcerative Colitis) OR Crohn$) OR Inflammatory Bowel Disease)) AND Humans[Mesh])) NOT review - 811 hits, 20 most relevant

PICO 7

(Iron OR ferrous OR anemia) and (Crohn OR colitis OR IBD)

PICO 8

((diet or exclusion diet or exclusive diet or restricted diet or experimental diet or nutrition support) and Active and (ibd or inflammatory bowel disease or Crohn or colitis) not review), 12 references

PICO 9

(IBD or Crohn or colitis) and (diarrhea or diarrhoea or stoma) and (nutrition or fluid or diet) 34 retrieved, 6 references pertinent

PICO 10

((diet or nutrition or enteral nutrition or fluid or total parenteral nutrition or TPN) and (stricture or stenos*) and (ibd or inflammatory bowel disease or Crohn) not review) 97 retrieved, 2 references used

PICO 11

((diet or nutrition or calcium or vitamin D) and (steroid or corticosteroid) and (IBD or inflammatory bowel disease or Crohn or colitis) not review) 942 retrieves, 12 references.

PICO 12

1) Crohn, malabsorption and colestyramine yielded 14 items, one of which was relevant to the topic.

2) Crohn, fat malabsorption and bile yielded 12 items, two of which were relevant, and one was useful as a review.

3) IBD, malabsorption, steatorrhoea and hyperoxaluria yielded 31 items, 3 of them were relevant.

PICO 13

Crohn and exclusion diet yielded 32 items, 6 of these were relevant.

PICO 14

1) Crohn, probiotics and pediatric, using a filter for randomised controlled trials yielded 1 result.
2) ulcerative colitis, probiotics and pediatric, using a filter for randomised controlled trials yielded 2 results, both relevant.

PICO 15

(Inflammatory bowel disease or Crohn Or ulcerative colitis) AND (Nutrition Supplements, OR enteral nutrition OR parenteral nutrition). This yielded 1752 papers. Papers retrieved by the previous systemic search done at the Tel-Aviv University were reviewed as well.

PICO 16

(enteral nutrition OR parenteral nutrition) and (inflammatory bowel disease or Crohn). This yielded 1634 papers. Papers retrieved by the previous search done at the Tel-Aviv University were reviewed as well.

PICO 17

(Crohn or colitis or IBD) AND (nutrition or enteral nutrition or TPN or nasogastric or gastrostomy) AND (therapy or treatment)

PICO 18

(Crohn or colitis or IBD) AND (nutrition or enteral nutrition or TPN or nasogastric or gastrostomy) AND (polymeric or oligomeric or peptide or elemental)

PICO 19

Crohn AND (Thrombosis or thrombotic or coagulation)

PICO 20

(Crohn or colitis or IBD) AND Fistula AND (Nutrition or malnutrition)

PICO 21

Crohn and refeeding syndrome

PICO 22

(Colitis or ulcerative colitis) AND (Artificial nutrition or PEG or enteral feed or parenteral feed or TPN)

PICO 23 to PICO 27

Source material taken from the ESPEN Guidelines for Nutrition in Surgery 2016

PICO 28 & 28a

("Dietician" OR "Nutritionist") AND ("Crohn" OR "Colitis" OR "IBD") generates 11 papers, only two of which present original data (which from this point of view were irrelevant in one case).

PICO 29

restricted to human data - ("Diet" AND "Remission") AND ("IBD" OR "Crohn" OR "colitis") yielded 327 citations. Excluding case reports, reviews and opinion pieces and papers concerned with treatment of active disease leaves 47 papers for consideration.

PICO 30

(Crohn OR colitis OR IBD) AND (fat OR lipid OR omega OR fish oil) AND (remission) AND (human) generated 286 citations.

PICO 31

(Crohn OR colitis OR IBD) AND (remission) AND (fiber) yielded 52 citations.

PICO 32 and 33

E.Coli Nissle 1917[Title] OR VSL#3[Title] OR probiotic[Title] AND (((Ulcerative Colitis) OR Crohn$) OR Inflammatory Bowel Disease). 265 results 30 relevant

PICO 34

(crohn OR ulcerative colitis OR ibd) AND (enteral nutrition or parenteral nutrition) AND (maintenance OR remission): 371 results retrieved, 20 relevant

PICO 35

((((("crohn") OR "ulcerative colitis") OR "ibd")) AND ((((((((("enteral nutrition formula" OR "enteral nutrition formulas" OR "enteral nutrition formulation" OR "enteral nutrition formulations" OR "enteral nutrition mixtures" OR "enteral nutrition products" OR "enteral nutrition regimen" OR "enteral nutrition regimens" OR "enteral nutrition supplement" OR "enteral nutrition supplementation" OR "enteral nutritional formula" OR "enteral nutritional formulae" OR "enteral nutritional formulas" OR "enteral nutritional products" OR "enteral nutritional solutions" OR "enteral nutritional supplementation" OR "enteral nutritional supplements" OR "enteral omega 3 fa" OR "enteral omega 3 fatty" OR "enteral omega 3 fatty acid" OR "enteral pharmaconutrition" OR "enteral probiotic supplementation" OR "enteral probiotics" OR "enteral probiotics administration" OR "enteral probiotics supplementation" OR "enteral product" OR "enteral products"))) OR (("parenteral nutrition additives" OR "parenteral nutrition admixture" OR "parenteral nutrition admixtures" OR "parenteral nutrition emulsion" OR "parenteral nutrition emulsions" OR "parenteral nutrition formula" OR "parenteral nutrition formulae" OR "parenteral nutrition formulas" OR "parenteral nutrition formulation" OR "parenteral nutrition formulations" OR "parenteral nutrition lipid emulsions" OR "parenteral nutrition mixture" OR "parenteral nutrition mixtures" OR "parenteral nutrition preparation" OR "parenteral nutrition prepa-

rations" OR "parenteral nutrition product"))) OR "oral nutritional supplements") OR "glutamine") OR fatty acids) OR "pharmaconutrition") OR (("immunonutrition" OR "immunonutrition formula"))) OR (("immune enhancing diet" OR "immune enhancing diets" OR "immune enhancing diets ieds" OR "immune enhancing effect" OR "immune enhancing effects" OR "immune enhancing enteral diet" OR "immune enhancing enteral diets" OR "immune enhancing feeds" OR "immune enhancing formula" OR "immune enhancing formulae" OR "immune enhancing formulas" OR "immune enhancing function" OR "immune enhancing functions" OR "immune enhancing ingredients" OR "immune enhancing nutrients" OR "immune enhancing nutrition" OR "immune enhancing oral formula" OR "immune enhancing oral formulas" OR "immune enhancing substrates"))) AND (maintenance OR remission) AND Humans AND Clinical trials: 45 results retrieved, 8 relevant

PICO 36

cobalamin deficiency OR B12 AND crohn: 157 results retrieved, 10 relevant

PICO 37

folate deficiency OR B9 AND (crohn OR ulcerative colitis OR IBD): 141 results retrieved, 16 relevant

PICO 38

pregnancy AND (crohn or IBD OR ulcerative colitis) AND nutrition): 60 results retrieved, 0 relevant

PICO 39

((((("crohn") OR "ulcerative colitis") OR "ibd")) AND (((((((("sarcopenia") OR "myopenia") OR "dynapenia") OR "muscle mass") OR "muscle strength") OR "muscle function") OR "muscle performance") OR "exercise"): 191 results retrieved, 30 relevant

PICO 40

("obesity/therapy") AND ((("crohn") OR "ulcerative colitis") OR "ibd"): 11 results retrieved, 0 relevant

Appendix B

Evidence table

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 C – strong consensus (90 % agreement)

1. 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. [13]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 2++	*Countries:* *Centres:* *Setting:* *Funding Sources:* Houston Veterans Affairs Health Services Research and Development Center of Excellence grant HFP90-020 and National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases Center Grant P30 DK56338 *Dropout rates:* *Study limitations:* -Given the heterogeneity among study design, nutrient cutoffs and study populations pooling of data from different studies was not possible -limitations of included studies , publications bias -no independent verifying of IBD diagnosis in the studies -possible occurrence of recall bias because of retrospective nature of the majority of stud-	*Total no. patients*: n = 2609 (18 case-control studies, 1 cohort-study) • Cases with Crohn's disease n=1,269 • cases with ulcerative colitis n=1340 *Inclusion criteria:* Fully published case-control and cohort studies of the association between pre-illness diet and IBD risk *Exclusion criteria:* studies investigating diet as therapy for IBD; ecological studies	We performed a systematic review using 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.

	ies - heterogeneity among studies in time from IBD diagnosis to diet-pattern ascertainment -different aged populations (may reflect different dietary patterns or subsets of IBD) - no exploration on the influence of diet on current disease activity		
Notes	Risk estimates were reported for highest level of intake, with daily-intake cutoffs included where data were available ***Author's Conclusion:*** High dietary intakes of total fats, PUFAs, omega-6 fatty acids, and meat were associated with an increased risk of CD and UC. High fiber and fruit intakes were associated with decreased CD risk, and high vegetable intake was associated with decreased UC risk.		
Outcome measures/results	dietary fats (total fat intake, saturated fat, monounsaturated fatty acids (MUFAs), total polyunsaturated fatty acids (PUFAs), omega-3 fatty acids, long-chain omega-3 fatty acids, and omega-6 fatty acids);carbohydrates (total carbohydrates, mono- and disaccharides,polysaccharides);proteins (total protein, animal protein, vegetable protein); food groups: fruits, vegetables, fiber, meat, fish, dairy, eggs	Nineteen studies were included, encompassing 2,609 IBD patients (1,269 Crohn's disease (CD) and 1,340 ulcerative colitis (UC) patients) and over 4,000 controls. Studies reported a positive association between high intake of saturated fats, monounsaturated fatty acids, total polyunsaturated fatty acids (PUFAs), total omega-3 fatty acids, omega-6 fatty acids, mono- and disaccharides, and meat and increased subsequent CD risk. Studies reported a negative association between dietary fiber and fruits and subsequent CD risk. High intakes of total fats, total PUFAs, omega-6 fatty acids, and meat were associated with an increased risk of UC. High vegetable intake was associated with a decreased risk of UC.	

2. 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(5):970-7. [14]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective study 2+	*Countries:* *Centres:* *Setting:* *Funding Sources:* Research Scholars Award of the American Gastroenterological Association (A.N.A), Crohn's and Colitis Foundation of America (H.K.), the Broad Medical Research Program of the Broad Foundation (A.T.C), and the National Institutes of Health *Dropout rates:* *Study limitations:* - results are limited to IBD with onset at older ages - cohort consisted entirely of women, mostly of Caucasian race, there are limited data to suggest a differential effect of environmental exposures on IBD risk based on race or sex - attenuation in the magnitude of association of total fiber with CD (lag of 4–8 years between the final time point of assessment of diet and the diagnosis of CD or UC) -limited number of cases across each quintile - observational study design (no exclusion of possible confounders)	*Total no. patients*: 170.776 (76.738 NHS I und 94.038 NHS II) • 269 cases of CD • 338 cases of UC *Inclusion criteria:* woman, who completed a detailed FFQ in 1984 in NSH I and in 1991 in NHS II *Exclusion criteria:* Women who were deceased prior to the first dietary questionnaire, had a diagnosis of cancer (except non-melanoma skin cancer) or were diagnosed with IBD prior to this baseline diet questionnaire	We performed this prospective trial to examine the association between long-term intake of dietary fiber and risk of incident CD and UC. Furthermore, we examined the impact of fiber intake from different sources to shed light on the specific mechanisms through which dietary fiber intake may modulate risk of disease. Therefore we collected and analyzed data from 170,776 women, followed over 26 y, who participated in the Nurses' Health Study, followed for 3,317,425 person-y. Dietary information was prospectively ascertained via administration of a validated semi-quantitative food frequency questionnaire every 4 y. Self-reported CD and UC were confirmed through review of medical records.
Notes	***Author's Conclusion:*** In conclusion, we demonstrate that high long-term intake of dietary fiber was associated with a reduction in risk of CD, particularly for fiber intake from fruits and potentially from overall vegetables and cruciferous vegetables. This association supports experimental findings suggesting the importance of dietary fiber in modulating the gut microbiome or as a source of aryl hydrocarbon receptor. Further studies exploring these potential mechanisms as well a potential role for dietary fiber in the prevention or treatment of CD merits further study.		
Outcome measures/results	*Primary outcome measure:* Intake of dietary fiber	We confirmed 269 incident cases of CD (incidence 8/100,000 person-y) and 338 cases of UC (incidence 10/100,000 person-y). Compared to the lowest quintile of energy-adjusted cumulative average intake of dietary fiber, intake of	

	Secondary outcome measures: total energy intake; fruit and vegetables consumption; Ascertainment/diagnosis date of CD and UC; cigarette smoking; menopausal status; use of oral contraceptives; post-menopausal hormone use; aspirin, non-steroidal anti-inflammatory drugs (NSADs); weight	the highest quintile (median of 24.3 g/day) was associated with a 40% reduction in risk of CD (multivariate HR for CD, 0.59; 95% confidence interval [CI], 0.39–0.90). This apparent reduction appeared to be greatest for fiber derived from fruits; fiber from cereals, whole grains, or legumes did not modify risk. In contrast, neither total intake of dietary fiber (multivariate HR, 0.82; 95% CI 0.58–1.17) nor intake of fiber from specific sources appeared to be significantly associated with risk of UC.

<table>
<tr><td colspan="4">3. 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. [15]</td></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>Meta-analysis
1-</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:
-results based on case-control studies were were prone to recall bias and interviewer Bias
-different adjustment of confounders in studies (may influence associations between intake of vegetables and fruit and the risk of IBD)
-different diet assessment methods and the retrospective among studies led to incomparability in the results to some extent
-limited number of studies in the subgroup analysis</td><td>Total no. patients: n = 2762 (14 case-control studies)
Cases of UC n = 1419
Cases of CD n = 1343
Inclusion criteria: observational studies published originally; topic of interest was consumption of vegetables and/or fruit; outcome was UC and/or CD; odds ratios (ORs) or relative risks with corresponding 95% confidence intervals (CIs) were reported or could be calculated from the data presented in articles; studies were reported in English or Chinese

Exclusion criteria:</td><td>We carried out a comprehensive meta-analysis by combining the results from all available observational studies to assess the risk of UC and CD for highest versus lowest consumption of vegetables and fruit separately and explore the potential between study heterogeneity and publication bias.</td></tr>
<tr><td>Notes</td><td colspan="3">Subgroup analysis was carried out by the continent (Asia and Europe) and the status (yes or no) of adjusting for smoking.
Author’s Conclusion:
This meta-analysis indicates that consumption of vegetables and fruit might be associated inversely with the risk of UC and CD, and the results need to be further confirmed.</td></tr>
<tr><td>Outcome measures/results</td><td>consumption of vegetables and/or fruit; occurrence of UC and/or CD</td><td colspan="2">A total of 14 case–control studies were included in this meta-analysis. On the basis of the highest versus the lowest analysis, consumption of vegetables was associated inversely with the risk of ulcerative colitis (UC) (OR =0.71, 95% CI 0.58–0.88, n= 9 studies), but not with Crohn’s disease (CD) (OR =0.66, 95% CI 0.40–1.09, n =8 studies). Higher consumption of fruit was associated inversely 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). For intake of vegetables and the risk of CD, subgroup analysis showed a significant association for 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). No significant publication bias was found for the analysis of intake of vegetables and the risk of UC, intake of fruit and the risk of UC, and intake of vegetables and the risk of CD.</td></tr>
</table>

4. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, de Silva P, Fuchs CS, et al. Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease. Gut 2014;63(5):776-84. [16]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective study and systematic review 2+	*Countries:* *Centres:* *Setting:* *Funding Sources:* Research Scholars Award of the American Gastroenterological Association (A.N.A.), Crohn's and Colitis Foundation of America (H.K.), the Broad Medical Research Program of the Broad Foundation (A.T.C), and the National Institutes of Health *Dropout rates :* *Study limitations:* -*cohort* consisted entirely of female health professionals, most of whom were Caucasian (limited data to support a differential effect of diet on risk of IBD according to gender, race, or profession) -observational study design and therefore unable to confirm causality	*Total no. patients*: n= 238386 (121,700 Nurses Health Study I; 116,686 Nurses Health Study II) • Cases of CD n= 269 • Cases of UC n= 338 *Inclusion criteria:* women who first completed a detailed dietary assessment *Exclusion criteria:* Women who were deceased prior to the first dietary questionnaire, reported a diagnosis of IBD prior to the baseline dietary assessment, or had a history of cancer (excluding non-melanoma skin cancer)	We conducted a prospective study of women enrolled in the Nurses' Health Study cohorts. Diet was prospectively ascertained every four years using a validated semi-quantitative food frequency questionnaire. Self-reported CD and UC were confirmed through medical record review. We examined 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 using Cox proportional hazards models adjusting for potential confounders. As well we performed a systematic review of the literature examining the association between overall dietary fat intake or intake of specific fatty acids and risk of CD and UC.
Notes	The systematic review included 15 studies. Covariates/base line characteristics associated with IBD were selected for inclusion in the multivariate model : Body mass index (BMI); Cigarette smoking (current, past, or never), oral contraceptive use (ever or never), post-menopausal hormone use (premenopausal, never, current, or past use); use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) ***Author's Conclusion:*** In conclusion, using two large prospective cohorts of women, we demonstrate that total fat, saturated or unsaturated fat, or individual PUFA did not influence risk of CD. However, our results suggest that women in the highest quintile of long-term dietary intake of long-chain n-3 PUFA may have a significantly reduced risk while those with high trans-saturated fat intake may have an increased risk of UC. Our findings		

	support experimental data demonstrating the importance of n-3 PUFA in modulating the production of inflammatory mediators such as prostaglandins and leukotrienes, maintenance of the intestinal barrier, regulation of the adaptive immune response, and immune cell adhesion and trafficking. Further studies are needed to confirm our results and explore the potential of modifying fatty acid intake in the prevention or treatment of UC.	
Outcome measures/results	total dietary fat; saturated fats (SFA), trans-unsaturated fat, poly-unsaturated fatty acids (PUFA), mono-unsaturated fats (MUFA), n-3 fatty acids; linoleic acid, eicosapentaenoic acid (EPA); docosahexaenoic acid (DHA)	Among 170,805 women, we confirmed 269 incident cases of CD (incidence 8/100,000 person-years) and 338 incident cases of UC (incidence 10/100,000 person-years) over 26 years and 3,317,338 person-years of follow-up. 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).

5. 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(12):1606-11. [17]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
a nested case–control study 2+/-	*Countries:* *Centres:* *Setting:* *Funding Sources:* The Sir Halley Stewart Trust, The National Association for Colitis and Crohn's Disease and The NHS Executive Eastern Region. EPIC-Norfolk is supported by Cancer Research UK and The Medical Research Council, UK. EPIC-Malmö is supported by The Swedish Cancer Society, The Swedish Research Council and The Region of Skane. EPIC-Denmark is supported by The Danish Cancer Society. EPIC-Heidelberg is supported by "Stiftung Landesbank Baden-Württemberg", the European Union and Deutsche Krebshilfe. EPIC-Potsdam is supported by the Federal Ministry of Research and Technology, the European Union and Deutsche Krebshilfe. EPIC-Florence is supported by the Associazione Italiana per la Ricerca contro il Cancro (AIRC-Milan) and Regione Toscana. *Dropout rates:* *Study limitations:* -data on smoking were only available at recruitment and not during subsequent follow-up -The generalisability of any cohort study, namely its external validity, needs to be considered -under-representation of younger women with ulcerative colitis - no detection of a negative association with cigarette smoking at recruitment, this may be because healthier volunteers are more likely to participate in a cohort study	*Total no. patients*: n = 203193 • incident cases of ulcerative colitis n= 126 *Inclusion criteria:* *Exclusion criteria:*	To investigate the effect of dietary linoleic acid intake and the risk of developing incident ulcerative colitis dietary data from participates (resident in the UK, Sweden, Denmark, Germany or Italy) of a prospective cohort study, the European Prospective Investigation into Cancer and Nutrition (EPIC), were available and analyzed. These participants were followed up for the diagnosis of ulcerative colitis. Each case was matched with four controls and the risk of disease calculated by quartile of intake of linoleic acid adjusted for gender, age, smoking, total energy intake and centre.

Notes	-Nutrient intake was calculated by multiplying the frequency of consumption of relevant foods by their fatty acid content as determined from national databases of food content. The dietary fatty acids which were calculated were: linoleic acid (n-6 PUFA), α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid (n-3 PUFAs) and oleic acid (an n-9 monounsaturated fatty acid). ***Author's Conclusion:*** The data support a role for dietary linoleic acid in the aetiology of ulcerative colitis. An estimated 30% of cases could be attributed to having dietary intakes higher than the lowest quartile of linoleic acid intake.	
Outcome measures/results	Intake of linoleic acid (n-6 PUFA), α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid (n-3 PUFAs) and oleic acid (an n-9 monounsaturated fatty acid); occurrence of ulcerative colitis	A total of 126 participants developed ulcerative colitis (47% women) after a median follow-up of 4.0 years (range, 1.7–11.3 years). The highest quartile of intake of linoleic acid was associated with an increased risk of ulcerative colitis (odds ratio (OR)=2.49, 95% confidence interval (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).

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)

<table>
<tr><td colspan="4">6. Corrao G, Tragnone A, Caprilli R, Trallori G, Papi C, Andreoli A, Di Paolo M, Riegler G, Rigo GP, Ferraù O, Mansi C, Ingrosso M, Valpiani D. 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 Jun;27(3):397-404. [29]</td></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>Case-control study
2-</td><td>Countries: Italy
Centres:
Setting:
Funding Sources:

Dropout rates: n= 39 (4,5%)

Study limitations:
- sources of bias (selection of the samples and confounding effects) might affect the validity of results</td><td>Total no. patients: n= 858
• cases of UC n= 594
• cases of CD n= 225
• cases of controls n= 819

Inclusion criteria:patients aged 18-65 years; patients in whom the first diagnosis of IBD had been made between I January 1989 and 31 December 1992

Exclusion criteria: cases diagnosed within the study areas but resident elsewhere; Patients with a diagnosis of IBD made prior to 1989;patients with infectious disease, from pneumology, gynaecology and obstetric departments and patients with gastrointestinal, metabolic, neoplastic and cardiovascular diseases</td><td>We carried out a matched case-control study by using data from a case-control study carried out in Italy 1989-1992. We estimated the odds ratios (OR) and the population attributable risks (AR) for inflammatory bowel diseases in relation to smoking, oral contraception and breastfeeding in infancy.</td></tr>
<tr><td>Notes</td><td colspan="3">Controls were randomly selected from the patients resident in the areas considered, who were either examined by or admitted to the same hospital as the cases and 1:1 matched to each case by gender and age at diagnosis (±3 years). Controls had acute diseases not related to smoking, oral contraceptive use or immunological disorders.
Author's Conclusion:
Taken together, the considered factors were responsible for a proportion of IBD ranging from 26% (CD females) to 36% (CD males). It is concluded that other environmental and genetic factors may be involved in the aetiology of IBD.</td></tr>
<tr><td>Outcome measures/results</td><td>anamnestic and lifestyle information, breastfeeding in infancy, smoking habits and use of oral contraceptives (OC)</td><td colspan="2">Compared with non-smokers, former smokers were at increased risk of UC (OR= 3.0; 95% confidence interval [CI] : 2.1^.3), whereas current smokers were at increased risk of CD (OR = 1.7; 95% CI: 1.1-2.6). Females who reported use of oral contraceptives for at least one month before onset of symptoms had a higher risk of CD (OR = 3.4; 95% CI : 1.0-11.9), whereas no significant risk was observed for UC. Lack of breastfeeding was associated with an increased risk of UC (OR = 1.5; 95% CI : 1.1-2.1) and CD (OR = 1.9; 95% CI</td></tr>
</table>

		: 1.1-3.3). Being a 'former smoker' was the factor with the highest attributable risk of UC both in males (AR '= 28%; 95% CI : 20-35 %) and in females (AR = 12%; 95% CI : 5-18%). Smoking was the factor with the highest attributable risk for CD in males (AR = 31%; 95% CI : 11-50%). Lack of breastfeeding accounted for the highest proportion of CD in females (AR = 11%; 95% CI : 1-22%). Oral contraceptive use accounted for 7% of cases of UC and for 11% of cases of CD.

7. Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gamborg M, Munkholm P. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis. 2011 Dec;5(6):577-84. [31]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Case-control study 2-	*Countries: Denmark* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:* -limited power to detect associations because of one-to-one match of cases and controls - orthopaedic controls may not be entirely comparable to the general population - combined results for IBD may not be appropriate, recognizing that CD and UC are different disease entities with suggested differences in aetiology - testing of a relatively large number of environmental factors may in some cases have resulted in falsely rejection of the null hypothesis -some questions regarding early lifetime factors may have been affected byrecall bias -no formal validation or forward/backward translation of the Adapted questionnaire	*Total no. patients*: n= 267 • cases with CD n= 123 • cases with UC n=144 *Inclusion criteria:* patients were diagnosed with IBD (CD, UC or indeterminate colitis) *Exclusion criteria:*	We performed a case-control trial to asses the influence of exposure to specific environmental factors on development of CD and UC. Patients diagnosed with Crohn's disease (CD) and with ulcerative colitis (UC) in Copenhagen (2003–2004) were matched 1:1 on age and gender to orthopaedic controls. Participants received a questionnaire with 87 questions concerning environmental factors prior to IBD/orthopaedic admission.
Notes	***Author's Conclusion:*** Among Danish patients with CD and UC belonging to an unselected cohort, disease occurrence was found to be associated both with well-known factors such as smoking and appendectomy, and with more debated factors including breastfeeding, tonsillectomy, childhood vaccinations, childhood infections, and dietary intake of fibres and sugar. *Highlights:* ► The aetiology of inflammatory bowel diseases remains uncertain. ► Smoking was positively associated with CD and negatively associated with UC. ► Low consumption of dietary fibres and high consumption of sugar increased the risk for IBD. ► Appendectomy decreased the risk for UC. Tonsillectomy decreased the risk for both UC and CD. ► Childhood infections and vaccinations may also play an aetiological role in IBD.		
Outcome measures/results	questionnaire with 87 questions concerning environmental factors: 1) markers of immunity and infections (breast feeding; appendectomy before age 20 and > 1 year prior to diagnosis; tonsillec-	Being breastfed > 6 months (OR, 0.50; 95% CI, 0.23–1.11) and undergoing tonsillectomy (OR, 0.49; 95% CI, 0.31–0.78) decreased the odds for IBD, whereas appendectomy decreased the odds for UC only (OR, 0.29; 95% CI, 0.12–0.71). Vaccination against pertussis (OR, 2.08; 95%	

	tomy before age 20 and > 1 year prior to diagnosis; childhood vaccinations against tuberculosis, pertussis, measles, rubella, diphtheria, tetanus, or polio; childhood infections including measles, pertussis, rubella, chickenpox, mumps, and scarlet fever; sanitary conditions before age 20 [access to running water at home]) 2) diet (daily, weekly or rarer consumption of fruit, vegetables, egg, bread, cereal, sugar, and coffee) 3) use of oral contraceptives 4) Smoking habits at diagnosis (classified as non-smoker, ex-smoker, or active smoker [defined as a daily consumption of tobacco for at least 6 months]).	CI, 1.07–4.03) and polio (OR, 2.38; 95% CI, 1.04–5.43) increased the odds for IBD, whereas measles infection increased the odds for UC (OR, 3.50; 95% CI, 1.15–10.6). Low consumption of fibres and high consumption of sugar were significantly associated with development of CD and UC. Smoking increased the risk for CD and protected against UC.

8. Ng SC, Tang W, Leong RW, Chen M, Ko Y, Studd C, Niewiadomski O, Bell S, Kamm MA, de Silva HJ, Kasturiratne A, Senanayake YU, Ooi CJ, Ling KL, Ong D, Goh KL, Hilmi I, Ouyang Q, Wang YF, Hu P, Zhu Z, Zeng Z, Wu K, Wang X, Xia B, Li J, Pisespongsa P, Manatsathit S, Aniwan S, Simadibrata M, Abdullah M, Tsang SW, Wong TC, Hui AJ, Chow CM, Yu HH, Li MF, Ng KK, Ching J, Wu JC, Chan FK, Sung JJ; 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 Jul;64(7):1063-71. [33]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Case-control study 2-	*Countries:* China, Hong Kong, Indonesia, Sri Lanka, Macau, Malaysia, Singapore, Thailand, Australia *Centres:* *Setting:* *Funding Sources:* Ferring Pharmaceuticals, Hong Kong, and Direct Grant Faculty of Medicine Chinese University of Hong Kong *Dropout rates:* *Study limitations:* -no randomly recruitment of controls - missing data - some questions (early lifetime factors) are likely to be subjected to recall bias -possible occurrence of false positive results due to chance arising from the evaluation of 87 questions -no conduction of the formal validation of the IOIBD questionnaire	*Total no. patients*: n= 442 • cases of CD n= 186 • cases of UC n= 256 • cases of controls n= 940 *Inclusion criteria:* diagnosis remained confirmed at 6-month follow-up *Exclusion criteria:*	This prospective population-based case-control study in Asia-Pacific examined risk factors prior to patients developing IBD. Therefore IBD cases diagnosed between 2011 and 2013 from eight countries in Asia and Australia and controls (frequency-matched by sex, age and geographical location) completed an environmental factor questionnaire at diagnosis. Unconditional logistic regression models were used to estimate adjusted ORs (aOR) and 95% CIs.
Notes	***Author's Conclusion:*** This first population-based study of IBD risk factors in Asia-Pacific supports the importance of childhood immunological, hygiene and dietary factors in the development of IBD, suggesting that markers of altered intestinal microbiota may modulate risk of IBD later in life.		
Outcome measures/results	questionnaire of 87 questions proposed to be environmental risk factors for CD and/or UC: (i) Childhood factors up to 20 years including breast feeding, appendectomy, tonsillectomy, eczema, vaccinations (tuberculosis, pertussis, measles, rubella, diphtheria, tetanus, polio), childhood infections (measles, pertussis, rubella, chickenpox,	In multivariate model, being breast fed >12 months (aOR 0.10; 95% CI 0.04 to 0.30), antibiotic use (aOR 0.19; 0.07 to 0.52), having dogs (aOR 0.54; 0.35 to 0.83), daily tea consumption (aOR 0.62; 0.43 to 0.91) and daily physical activity (aOR 0.58; 0.35 to 0.96) decreased the odds for CD in Asians. In UC, being breast fed >12 months (aOR 0.16; 0.08 to 0.31), antibiotic use (aOR 0.48; 0.27 to 0.87), daily tea (aOR 0.63; 0.46 to 0.86)	

	mumps, scarlet fever) and pet ownership (ii) food habits before diagnosis including daily, weekly or less frequent consumption of fruit, vegetables, egg, cereal, bread, cereal, coffee, tea, juice, sugar and fast food (iii) smoking habits (current smoker, non-smoker, ex-smoker); (iv) sanitary conditions such as the availability of inhouse water tap, hot water tap or flush toilet (v) others factors including daily physical activity, oral contra-ceptive pill and stressful events before diagnosis	or coffee consumption (aOR 0.51; 0.36 to 0.72), presence of hot water tap (aOR 0.65; 0.46 to 0.91) and flush toilet in childhood (aOR 0.71; 0.51 to 0.98) were protective for UC development whereas ex-smoking (aOR 2.02; 1.22 to 3.35) increased the risk of UC.

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)

9. 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. [86]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1-	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* n=30 (37,5%) *Study limitations:*	*Total no. patients*: n=80 • Intervention group n=21 • controls n=29 *Inclusion criteria:* Patients with IBD who had been anemic (Hb ≤ 11.5 g/dL in females and ≤13.0 g/dL in males) in the preceding 12 months; nonanemic patients with active IBD, who were deemed to be at risk for becoming anemic *Exclusion criteria:*	The present study examined the association between changes in hemoglobin (Hb) in a population of IBD patients and changes in quality of life (QOL) and cognitive function (CF) independent of change in disease activity (DA). Subsidiary aims were to assess whether the use of iron was associated with worsening DA. Iron replacement was given to 21 patients with low Hb. Intervention group (patients with anemia, iron-treated group) -Oral ferrous sulfate (200 mg t.d.s.)or intravenous iron sucrose (200-mg intravenous aliquots twice per week)

			Control group (patients without anemia) -no treatment
Notes	3-month review: All patients treated with iron were reviewed at 3 months with measurement of Iron ferritin level. Response to iron was defined as full (Hb rise of ≥2 g/dL), partial (Hb riseof 1–1.9 g/dL), or no response (Hb change of <1 g/dL). Patients with a full or partial response to oral iron were continued on this treatment. Patients with no response to oral iron were offered treatment with intravenous iron sucrose. Patients given intravenous iron sucrose with a <2 g/dL rise in Hb were offered further treatment with this medication. 6-month review: all enrolled patients were reviewed at 6 months with following measurements: blood count and ferritin, QOL and CF assessments. definitions to grade the Hb response to treatment: ≥2 g/dL was a significant response, 1 to 2 g/dL was a moderate response, 0.5 to 1.0 g/dL was a slight response, 20.5 to 0.5 g/dL was defined as no change, and a fall of >0.5 g/dL was defined as a decrease. ***Author's Conclusion:*** Treatment of IBD-associated anemia with iron may lead to improvement in patients' QOL.		
Outcome measures/ results	Quality of life (QOL), cognitive function (CF), disease activity (DA), Hb were recorded at baseline and at 6 months	The iron-treated group had lower Hb and higher DA scores compared with the non-iron-treated group at baseline. In a hierarchical regression model, changes in DA accounted for 13% (P=0.17) and changes in Hb accounted for 18% (P=0.005) of the variance in change in SF-36 and 12% (P=0.23) and 17% (P=0.009) in the Inflammatory Bowel Disease Questionnaire. In this pilot study, although no associations were identified between changes in Hb or DA and CF, increases in Hb improved QOL scores in IBD patients independent of changes in DA. We found no similar effect with CF, but again, the sample size was small. We found no evidence that iron therapy causes worsening of DA.	

10. Bonovas S, Fiorino G, Allocca M, Lytras T, Tsantes A, Peyrin-Biroulet L, Danese S. Intravenous Versus Oral Iron for the Treatment of Anaemia in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2016;95:e2308. [87]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Meta-anaylsis 1-	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:* -occurrence of risk of bias in all included trials(treatments were not evaluated in terms of cost;no distinction was made between different preparations of IV or oral iron) - quality of evidence in the performed review is moderate	*Total no. patients*: n=694 (within 5 RCTs) *Inclusion criteria:* randomized controlled trials (RCTs) with either a parallel or crossover design; adult patients with IBD; trials comparing IV versus oral iron supplementation against each other (ie, head-to-head trials) for correcting anemia (We accepted any definition of anemia used by study authors, provided that all male participants had <13.0 g/dL and all the female participants had <12.0 g/dL of hemoglobin (ie, all participants met the WHO criteria for anemia for adult males and nonpregnant females)) *Exclusion criteria:* observational studies; no investigation of patients with IBD; no reported (or provided insufficient data for) outcomes of interest; studies conducted in pediatric populations	We conducted a systematic review and meta-analysis to integrate evidence from randomized controlled trials having enrolled adults with IBD, and comparing IV versus oral iron (head-to-head) for correcting iron-deficiency anemia
Notes	***Author's Conclusion:*** In conclusion, synthesis of the existing randomized evidence supports that IV iron is more effective and better tolerated than oral iron supplementation for correcting anemia in adult patients with IBD.		
Outcome measures/results	*Primary outcome measure:* effect of treatments on the hemoglobin response (defined as the rate of patients who achieved an increase of at least 2.0 g/dL in hemoglobin concentration at the end of the follow-up) *Secondary outcome measures:* rates of discontinuation of the intervention due to adverse events or intolerance; occurrence of serious adverse events (SAEs) (defined as any untoward medical occurrence that results in death, requires hospital admission or prolongation of existing hospital stay, causes persistent or significant disability/ incapacity, or is life threatening);rates of gastrointestinal adverse events (nausea, vomiting, abdominal pain, diarrhea)	Five eligible studies, including 694 IBD patients, were identified. In meta-analysis, IV iron demonstrated a higher efficacy in achieving a hemoglobin 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. We found no evidence of publication bias, or between-study heterogeneity, across all analyses. Risk of bias was high across primary studies, because patients and personnel were not blinded to the intervention.	

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)

<table>
<tr><td colspan="4">11. 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 Aug;59(8):1878-84. [110]</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study details/limitations</td><td>Patient characteristics</td><td>Interventions</td></tr>
<tr><td>Prospective Study
2+</td><td>Countries:
Centres: Baylor Clinic IBD Center
Setting:
Funding Sources:

Dropout rates: n= 2 (1,2%)

Study limitations:</td><td>Total no. patients: n= 168 (cases with CD n= 105; cases with UC n= 61)
• patients with abnormal BMD n= 66
• patients with osteopenia n= 54
• patients with osteoporosis n= 14
•
Inclusion criteria:
Exclusion criteria:</td><td>We conducted a prospective cross-sectional study in adult IBD patients to investigate the role of vitamin D in low BMD while controlling for other risk factors in inflammatory bowel diseases (IBD) patients. Demographic data including age, gender, ethnicity, BMI, along with disease type and location, vitamin D levels, prior corticosteroid use, and anti-TNF use were recorded and evaluated with DEXA results.</td></tr>
<tr><td>Notes</td><td colspan="3">BMD: WHO classification of lumbar spine and hip T scores as osteopenia defined as <−1.0 or osteoporosis defined as <−2.5. Low BMD was defined by the presence of either osteopenia or osteoporosis
Vitamin D: vitamin D insufficiency defined as serum vitamin D 25-hydroxy levels between 20 and <30 ng/mL; vitamin D deficiency defined as serum vitamin D 25-hydroxy levels <20 ng/mL
Author’s Conclusion:
Low vitamin D, male gender, Asian ethnicity, CD, and corticosteroid use significantly increased the risk of having low BMD, while age and disease location did not affect BMD in our IBD population. It remains important to evaluate for vitamin D nutritional deficiency and limit corticosteroid use to help prevent low BMD in IBD patients.</td></tr>
<tr><td>Outcome measures/results</td><td>bone mineral density (BMD); vitamin D level; demographic data (age, gender, ethnicity), BMI, IBD type (CD, UC), disease location, medication use</td><td colspan="2">A total of 166 patients [105 Crohn’s disease (CD), 61 ulcerative colitis (UC)] qualified for the study. Low BMD was found in 40 %, twice as frequently in CD than in UC (p = 0.048). Higher prevalence of low BMD was associated with those of male gender (p = 0.05), Asian ethnicity (p = 0.02), and history of corticosteroid use (p = 0.001). Age, body mass index, or disease location did not increase the risk of low BMD. The overall prevalence of low vitamin D was 60 %, with insufficiency (25-hydroxy levels between 20 and 30 ng/mL) found in 37 % and deficiency (levels <20 ng/mL) found in 23 % of the patients. Vitamin D insufficient and deficient patients were two times (p = 0.049) and almost 3 times (p = 0.02) as likely to have low BMD, respectively.</td></tr>
</table>

<table>
<tr><td colspan="4">12. 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 Jun;7(5):377-84. [111]</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study details/limitations</td><td>Patient characteristics</td><td>Interventions</td></tr>
<tr><td>cohort study
2 -</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:
-retrospective, observational study and therefore associations may not reflect causality
- Sizeable bias in patient selection exists regarding BMD assessment at baseline and during follow-up
- Potentially, this was a population with a more complicated disease course (more prone to have detrimental metabolic bone disease so, treated by a stricter approach)</td><td>Total no. patients: n= 567
• CD patients with DXA scan n = 205
• CD patients without DXA n = 367

Inclusion criteria: documented Crohn’s disease (at least 5 years) by means of standard clinical, laboratory, endoscopic and histological features, age older than 18 years at first DXA, BMD measurement had to be performed in the period between January 1998 and January 2010 with a Hologic Delphi in our institute

Exclusion criteria: use of any bisphosphonate derivative at the moment of the first scan and/or during follow-up, documented osteomalacia due to vitamin D deficiency</td><td>We performed a cohort study to evaluate the natural course of bone density change in BMD over time when CD is actively and strictly treated whilst vitamin D and calcium were supplemented, and to investigate the influence of several clinical and medical factors on BMD in CD patients.
Therefore CD patients were enrolled when measurement of BMD by dual X-ray absorptiometry (DXA) was available. Follow-up DXA scan was performed in subjects with known risk factors besides Crohn indicative for low BMD. Treatment of CD patients was according to a protocol which is comparable to the current (inter)national guidelines. In osteopenic patients, supplemental vitamin D (800 IU) and Calcium (500–1000 mg) were prescribed.</td></tr>
<tr><td>Notes</td><td colspan="3">BMD assessments were indicated and performed when CD patients had known risk factors for decreased BMD, such as previous glucocorticosteroid use, low body mass index (BMI), postmenopausal status, short bowel syndrome, or clinically suspected insufficient dietary intake of calcium.
Author’s Conclusion:
Higher age, male sex, low BMI, and a higher age at diagnosis of CD were associated with low BMD. Follow-up of BMD in CD patients showed a contraintuitive small increase of BMD at lumbar spine and total hip in CD patients only using supplemental vitamin D and calcium next to strict treatment of CD.</td></tr>
<tr><td>Outcome measures/results</td><td colspan="2">age, sex, date of diagnosis of CD, duration of CD, age at first dual-energy X-ray absorptiometry (DXA), BMI (kg/m^2) during DXA measurement, cumulative glucocorticosteroid use, smoking history, surgical history</td><td>Mean BMD at baseline was 0.97 ± 0.16 gram/cm^2 in lumbar spine and 0.87 ± 0.12 gram/cm^2 in the total hip. At baseline, higher age and low Body Mass Index (BMI), were negatively correlated with BMD. Eighty-four patients underwent a second BMD assessment with a median interval period of 4 years (IQR 3–6). A mean annual increase of + 0.76% (95%CI: − 2.63%; + 3.87%) in lumbar spine and + 0.43% (95%CI: − 2.65% ; + 1.11%) in total hip was observed.</td></tr>
</table>

13. Lopes LH, Sdepanian VL, Szejnfeld VL, de Morais MB, Fagundes-Neto U. Risk factors for low bone mineral density in children and adolescents with inflammatory bowel disease.Dig Dis Sci. 2008 Oct;53(10):2746-53. [112]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
transversal study 2-	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:*	*Total no. patients*: n = 40 • Patients with ulcerative colitis n = 26 • Patients with Crohn's disease n = 14 *Inclusion criteria:* diagnosis of ulcerative colitis or Crohn's disease (diagnosis being based on clinical, endoscopic, and histological criteria); minimum age of 5 years, and maximum of 20 years old; informed consent by the patients and parents to participate in the study *Exclusion criteria:* patients with the following associated diseases: chronic rheumatism, nephropathy, endocrinopathy, primary or secondary immunodeficiency, malabsorption syndrome (except when related to the IBD); patients with other associated diseases whose treatment involved chronic use of corticosteroids	We performed this trial to evaluate bone mineral density of the lumbar spine in children and adolescents with inflammatory bowel disease, and to identify the clinical risk factors associated with low bone mineral density.
Notes	-Anthropometric indicators were expressed in terms of Z score, recommended by the World Health Organization. - Three-day food records using a self-completed questionnaire of total food and beverage intake at the time of bone densitometry measurements were used to measure calcium intake -calcium Intake was analyzed by the information of 25 patients (15 patients did not hand in the requested nutritional questionnaire) ***Author's Conclusion:*** The prevalence of low bone mineral density in children and adolescents with inflammatory bowel disease is considerably high and independent risk factors associated with bone mineral density are corticosteroid cumulative dose in milligrams, height-for-age Z-score, and BMI Z-score.		
Outcome measures/results	bone mineral density Z-score and age, height-for-age Z-score, BMI Z-score, cumulative corticosteroid dose in milligrams and in milligrams per kilogram, disease duration, number of disease relapses, calcium intake	Low bone mineral density (Z-score bellow −2) was observed in 25% of patients. Patients with Crohn's disease and ulcerative colitis had equivalent prevalence of low bone mineral density. Multiple linear regression models demonstrated that height-for-age Z-score, BMI Z-score, and cumulative corticosteroid dose in mg had independent effects on BMD, respectively, $\beta = 0.492$ ($P = 0.000$), $\beta = 0.460$ ($P = 0.001$), $\beta = –0.014$ ($P = 0.000$), and these effects remained significant after adjustments for disease duration, respectively, $\beta = 0.489$ ($P = 0.013$), $\beta = 0.467$ ($P = 0.001$), and $\beta = −0.005$ ($P = 0.015$). The model accounted for 54.6% of the variability of the BMD Z-score (adjusted $R^2 = 0.546$).	

14. van Bodegraven AA, Bravenboer N, Witte BI, Dijkstra G, van der Woude CJ, Stokkers PC, Russel MG, Oldenburg B, Pierik M, Roos JC, van Hogezand RA, Dik VK, Oostlander AE, Netelenbos JC, van de Langerijt L, Hommes DW, Lips P; Dutch Initiative on Crohn and Colitis (ICC). Treatment of bone loss in osteopenic patients with Crohn's disease: a double-blind, randomised trial of oral risedronate 35 mg once weekly or placebo, concomitant with calcium and vitamin D supplementation. Gut. 2014 Sep;63(9):1424-30. [117]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	*Countries:* *Centres:* *Setting:* *Funding Sources:* Alliance for Better Bone Health (Warner Chilcott, Rockaway, New Jersey, USA, formerly Procter & Gamble Pharmaceuticals, Cincinnati, Ohio, USA, and Sanofi-Aventis, Bridgewater, New Jersey, USA). *Dropout rates: n = 14 (10,6%)* *Study limitations:*	*Total no. patients*: n = 132 • Risedronate group n = 56 • Placebo group n = 62 *Inclusion criteria:* established quiescent CD by standard clinical, histological, endoscopic criteria and osteopenia; patients between 18 and 70 years; No glucocorticoid therapy (more than 7.5 mg prednisolone-equivalent daily) 3 months prior to screening or during the screening phase; No use of bisphosphonates for 12 months prior to study *Exclusion criteria:* patients with malabsorptive syndromes; patients with documented diseases with an impact on bone metabolism; medication specifically aimed to improve bone metabolism; Vitamin D deficiency (< serum 25-hydroxyvitamin D concentration 25 nmol/L); Pregnancy or wish to become pregnant	This double-blind, placebo-controlled randomised trial of risedronate with calcium and vitamin D supplementation was performed in osteopenic Crohn's disease patients. Patients were treated for 2 years with follow-up after 3 and after every 6 months. Disease characteristics and activity and bone turnover markers were assessed at all visits; dual x-ray absorptiometry was performed at baseline, 12 and 24 months; radiographs of the spine at baseline and 24 month. Intervention group - 35 mg risedronate (Actonel) once per; calcium and vitamin D (1000 mg and 800 IU, respectively, Calci-Chew D3) daily at night-time; Treatment was continued for 24 months. Placeo group -placebo; calcium and vitamin D (1000 mg and 800 IU, respectively, Calci-Chew D3) daily at night-time; Treatment was continued for 24 months.
Notes	***Author's Conclusion:*** A 24-month treatment course with risedronate 35 mg once weekly, concomitant with calcium and vitamin D supplementation, in osteopenic Crohn's disease patients improved bone density at lumbar spine.		
Outcome measures/results	Primary outcome measure: change in BMD and T-score at lumbar spine and/or total hip derived from DXA after 24	Of 132 consenting patients, 131 were randomised (67 placebo and 64 risedronate). Patient characteristics were similar in both groups, although the risedronate group was slightly heavier (body mass index 24.3 vs 23.0 kg/m^2). Bone mineral density at lumbar spine increased 0.04 g/cm^2 on average in the risedronate group versus 0.01 g/cm^2 in the placebo group (p=0.007). The mean increase in total hip bone mineral density was 0.03 versus 0.01 g/cm^2, respectively (p=0.071). Fracture prevalence and incidence were similar. Change of T-scores and concentrations of bone turnover markers were consistent with a beneficial effect of risedronate	

	months treatment with risedronate Secondary outcome measures: changes in markers of bone metabolism; number of vertebral fractures; CD activity and safety of drug administration were monitored by clinical scores (CDAI, CRP); routine clinical, haematological and biochemical parameters	when compared with placebo. The effect of risedronate was primarily demonstrated in the first 12 months of treatment. No serious unexpected suspected adverse events were observed.

Recommendation 14 A:

Probiotic therapy using E. 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)

<table>
<tr><td colspan="4">15. Oliva S, Di Nardo G, Ferrari F, Mallardo S, Rossi P, Patrizi G, Cucchiara S, Stronati L. Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis. Aliment Pharmacol Ther. 2012 Feb;35(3):327-34. [130]</td></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>RCT
1-</td><td>Countries:
Centres: Pediatric Gastroenterology and Liver Unit of the Sapienza University of Rome
Setting:
Funding Sources:
Dropout rates: n = 9 (22,5%)
Study limitations:</td><td>Total no. patients: n = 40
• Intervention group n = 16
• Placebo group n = 15

Inclusion criteria: patients with confirmed endoscopic and histological diagnosis of ulcerative proctitis/proctosigmoiditis with mild to moderate disease activity

Exclusion criteria: other causes of active proctitis or proctosigmoiditis such as infections, medical drugs and CD; patients who had received either oral or topical corticosteroids, topical aminosalicylates, antibiotics during the previous 12 weeks; immunomodulators during the previous 20 weeks</td><td>We performed this prospective randomised, placebo-controlled study to assess in children with active distal UC the effectiveness of Lactobacillus (L) reuteri ATCC 55730 enema on inflammation and cytokine expression of rectal mucosa.

Intervention group
-administration of an enema solution containing 10^{10} CFU of L. reuteri ATCC 55730 for 8 weeks in addition to chronic oral mesalazine at a dose ranging from 50 to 75 mg/kg/day during the last 12 weeks

Placebo group
- enema solution with placebo for 8 weeks in addition to oral mesalazine at a dose ranging from 50 to 75 mg/kg/day during the last 12 weeks</td></tr>
<tr><td>Notes</td><td colspan="3">Disease activity: Remission was defined as a final DAI score of <2.0 points; clinical response was defined as a reduction in the DAI of ≥2 points. Clinical relapse was defined as the occurrence or worsening of symptoms, accompanied by an increase in the DAI score to 4 and necessitating a change in therapy.
Author's Conclusion:
In children with active distal ulcerative colitis, rectal infusion of L. reuteri is effective in improving mucosal inflammation and changing mucosal expression levels of some cytokines involved in the mechanisms of inflammatory bowel disease.</td></tr>
<tr><td>Outcome measures/results</td><td>Primary outcome measure: variation in the disease activity as defined by Mayo DAI</td><td colspan="2">Thirty-one patients accomplished the trial (17 males, median age 13 year, range 7–18). Mayo score (including clinical and endoscopic features) decreased significantly in the L. reuteri group (3.2 ± 1.3 vs. 8.6 ± 0.8, P < 0.01) compared with placebo (7.1 ± 1.1 vs. 8.7 ± 0.7, NS); furthermore, histological score significantly</td></tr>
</table>

	secondary outcome measure: changes in the rectal histology; changes in the inflammatory cytokine mucosal expression	decrease only in the *L. reuteri* group (0.6 ± 0.5 vs. 4.5 ± 0.6, $P < 0.01$) (placebo: 2.9 ± 0.8 vs. 4.6 ± 0.6, NS). At the post-trial evaluation of cytokine mucosal expression levels, IL-10 significantly increased ($P < 0.01$) whereas IL-1β, TNFα and IL-8 significantly decreased ($P < 0.01$) only in the *L. reuteri* group.

16. 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(2):437-43. [131]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	*Countries: Italy* *Centres:* Department of Pediatrics of the University of Naples "Federico II" *Setting:* *Funding Sources:* *Dropout rates:n= 4 (12,1%)* *Study limitations:*	*Total no. patients*: n= 33 • Intervention group n= 14 • Placebo group n= 15 *Inclusion criteria: patients with* new diagnosis of UC, established on accepted historical, endoscopic, histologic, and/or radiologic criteria, which needed a steroid therapy to induce the remission of the disease *Exclusion criteria:* children who had received therapy inducing remission of UC; children who required outpatient antibiotic therapy and/or required surgery for complications related to UC; children with documented history of allergic reaction to *Lactobacillus* or other probiotic compound or with history of endocarditis, rheumatic valvular disease, congenital cardiac malformations, or cardiac surgery; and children who had received *Lactobacillus, Bifidobacterium, Enterococcus, Saccharomyces*, or any other probiotic bacterial supplement within the past 10 days	to assess the efficacy of VSL#3 on induction and maintenance of remission and to evaluate the safety and tolerability of the probiotic preparation therapy in children with active UC patients with newly diagnosed UC were randomized to receive either VSL#3 or an identical placebo in conjunction with concomitant steroid induction and mesalamine maintenance treatment. Children were prospectively evaluated at four time points: within 1 month, 2 months, 6 months, and 1 year after diagnosis or at the time of relapse Intervention group - Intake of VSL#3 (weight-based dose, range: 450–1,800 billion bacteria/day) containing viable lyophilized bacteria of four strains of *Lactobacillus* (*L. paracasei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*), three strains of *Bifidobacterium* (*B. longum*, *B. breve*, and *B. infantis* one strain of *Streptococcus salivarius* subsp. *thermophilus* (designated hereafter as *S. thermophilus*) associated to concomitant steroid induction treatment (oral methylprednisolon: 1 mg/kg/day, maximum 40 mg/day per 4 weeks) and oral mesalamine maintenance treatment (50 mg/kg/day) for 1 year or until relapse Placebo group - identical placebo associated to concomitant steroid induction treatment (oral methylprednisolon: 1 mg/kg/day, maximum 40 mg/day per 4 weeks) and oral mesalamine maintenance treatment (50 mg/kg/day) for 1 year or until relapse Children were prospectively evaluated at four time points: within 1 month, 2 months, 6 months, and 1 year after diagnosis or at the time of relapse. Lichtiger colitis activity index and a physician's global assessment were used to measure disease activity. At baseline, within 6 months and 12 months or at the time of

			relapse, all patients were assessed endoscopically and histologically.
Notes	Lichtiger colitis activity index (LCAI): Individual scores for each section of the test including symptoms, characteristics of stool, and physical examination were computed. A sustained drop in LCAI to ≤2 after steroid therapy was considered remission. Response was defined by a decrease in LCAI ≥3 points, but final score ≥3. Clinical relapse was defined as the occurrence or worsening of symptoms, accompanied by an increase in LCAI>3 points, sufficient to require treatment with corticosteroids, azathioprine/immunosuppressive agents, or surger ***Author's Conclusion:*** This is the first pediatric, randomized, placebo-controlled trial that suggests the efficacy and safety of a highly concentrated mixture of probiotic bacterial strains (VSL#3) in active UC and demonstrates its role in maintenance of remission.		
Outcome measures/results	questionnaires regarding disease activity (stool frequency, stool consistency, hematochezia, abdominal pain, extraintestinal manifestations of disease, and overall patient functioning); Lichtiger colitis activity index (LCAI), physician's global assessment; Laboratory data (blood count, albumin, erythrocyte sedimentation rate, and C-reactive protein); colonoscopy with mucosal biopsy and histological scores (at time of relapse)	All 29 patients responded to the inflammatory bowel disease (IBD) induction therapy. Remission was achieved in 13 patients (92.8%) treated with VSL#3 and IBD therapy and in 4 patients (36.4%) treated with placebo and IBD therapy (*P*<0.001). Overall, 3 of 14 (21.4%) patients treated with VSL#3 and IBD therapy and 11 of 15 (73.3%) patients treated with placebo and IBD therapy relapsed within 1 year of follow-up (*P*=0.014; RR=0.32; CI=0.025–0.773; NNT=2). All 3 patients treated with VSL#3 and 6 of 11 (54.5%) patients treated with placebo relapsed within 6 months of diagnosis. At 6 months, 12 months, or at time of relapse, endoscopic and histological scores were significantly lower in the VSL#3 group than in the placebo group (*P*<0.05). There were no biochemical or clinical adverse events related to VSL#3.	

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 formulas 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)

17. 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(7-8):694-702. [135]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Prospective controlled (Case-Cohort) Study 2+	*Countries: Germany, Austria, Italy* *Centres:* *Setting:* *Funding Sources:* Charité-Universitätsmedizin Berlin; Austrian Society of Clinical Nutrition (AKE) *Dropout rates:* *Study limitations:* - no information was availa-	*Total no. patients*: n= 144 • Patients with Crohn's disease n= 94 • Patients with ulcerative colitis n= 50 • Controls n= 61 *Inclusion criteria:* patients with IBD in clinical remission *Exclusion criteria:* evere concomitant diseases, pregnancy, ostomy, deliberate adherence to an extreme diet (e.g., macrobiotics, vegan), celiac disease,	We performed this prospective, controlled, and multicentric study to evaluate nutritional status, body composition, muscle strength, and quality of life in patients with inflammatory bowel disease in clinical remission. In addition, possible effects of gender, malnutrition, inflammation, and previous prednisolone therapy were investigated. Therefore we compared patients with IBD with quiescent disease with healthy controls and a pair-matched subgroup of well-nourished patients with no actual prednisolone intake by body mass index (BMI), sex,

	ble on physical activity	proctitis, or proctosigmoiditis in UC and extensive small bowel resections in CD. Actual maintenance medication was recorded in all patients	and age to healthy controls.
Notes	-Remission was defined as a Crohn's Disease Activity Index (CDAI) <150 or an Ulcerative Colitis Activity Index (CAI) <5 -IBD patients: Pair-matched analysis involved a subgroup of 47 well-nourished patients with IBD being in remission for at least 3 mo (41 female and 6 male, 30 with CD, 17 with UC). Well nourished was defined as an SGA grade A, a BMI within the normal range, and a serum albumin level >40 mg/L -Twenty-six patients took multivitamins and 15 patients were supplemented with intramuscular vitamin B12 ***Author's Conclusion:*** In CD and UC, selected micronutrient deficits and loss of BCM and muscle strength are frequent in remission and cannot be detected by standard malnutrition screening.		
Outcome measures/results	Nutritional status (subjective global assessment [SGA], body mass index, albumin, trace elements), body composition (bioelectrical impedance analysis, anthropometry); biochemical parameters (C-reactive protein (CRP), blood count, albumin, total protein, cholesterol, erythrocytes, ferritin, hemoglobin, magnesium, selenium, zinc, vitamin B12, and folate levels, (IL-6); food intake (food-frequency questionnaire); Handgrip strength; quality of life; fecal calprotectin	Most patients with inflammatory bowel disease (74%) were well nourished according to the SGA, body mass index, and serum albumin. However, body composition analysis demonstrated a decrease in body cell mass (BCM) in patients with CD (23.1 kg, 20.8–28.7, $P = 0.021$) and UC (22.6 kg, 21.0–28.0, $P = 0.041$) compared with controls (25.0 kg, 22.0–32.5). Handgrip strength correlated with BCM ($r = 0.703$, $P = 0.001$) and was decreased in patients with CD (32.8 kg, 26.0–41.1, $P = 0.005$) and UC (31.0 kg, 27.3–37.8, $P = 0.001$) compared with controls (36.0 kg, 31.0–52.0). The alterations were seen even in patients classified as well nourished. BCM was lower in patients with moderately increased serum C-reactive protein levels compared with patients with normal levels.	

<table>
<tr><td colspan="5">18. 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(7):351-6. [137]</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study details/limitations</td><td colspan="2">Patient characteristics</td><td>Interventions</td></tr>
<tr><td>workshop report/ commentary</td><td>Countries:
Centres:
Setting:
Funding Sources: Nestlé Health Science
Dropout rates:
Study limitations:</td><td colspan="2">Total no. patients: n=20
Inclusion criteria:
Exclusion criteria:</td><td>In the present report, we discuss the findings of this workshop dedicated to enhancing the use of EEN as a treatment option in the treatment of pediatric CD in Canada. Twenty pediatric stakeholders attended the one-day workshop, including three nurses, two dietitians and 15 pediatric gastroenterologists. Participants completed a premeeting assignment identifying experience in their pediatric practice with barriers and enablers to using EEN related to the following influencers: health system (internal and external), patient/family, EN, physician/care team-related or other. These results were further ranked according to priority, highlighting similar barriers and enablers to the use of EEN as described in the literature.</td></tr>
<tr><td>Notes</td><td colspan="4">Author’s Conclusion:
EEN is an extremely safe but underused treatment for induction of remission in pediatric CD in North America. Guidelines from both the NASPGHAN IBD Committee as well as the recent ECCO/ESPGHAN guidelines recommend use of EEN as first-line induction therapy in pediatric CD. During this thematic workshop focused on improving the framework for successful implementation of EEN therapy in pediatric CD in Canada, the panel ranked the need for EEN, the health care resources needed for a home EN program and cost implications as the top three barriers to its use. Identifying and understanding the barriers enables us to work on targeted strategies to overcome them, and help clinics implement and improve their success using EEN. Overcoming the barriers is the next step in the process.

Until we improve our understanding of the environmental and dietary triggers of CD, the effectiveness of EN will continue to rely on exclusion of the ‘prediagnosis’ diet. A standardized yet individualized approach (ie, by considering the caloric and other nutrient requirements of each patient) will optimize the use of limited dietetic resources, ideally with additional support for home nutrition programs. Polymeric formulas (which tend to be less expensive and more palatable) may be better suited if the oral route is chosen, with the option of dietetic guidance to flavour the formula used to avoid taste fatigue. Reducing the cost of EEN to the family will require ongoing advocacy for reimbursement by provincial ministries of health and private insurance companies. Further research to enhance our understanding of the mechanisms of action and the optimal application of EEN (or partial EN with additional dietary modifications) is necessary. Until such time, EEN should be recommended and supported as a highly effective and safe treatment modality in CD.</td></tr>
<tr><td>Outcome measures/results</td><td></td><td>Factor</td><td>Barriers</td><td>Enablers</td></tr>
<tr><td></td><td></td><td>Health System internal (hospital health authority)</td><td>• Insufficient clinic resources; allied health</td><td>• Adequate numbers of trained team members</td></tr>
</table>

			staff, knowledge, space*	(nurses, dietitians, social work/psychology/child health) and dedicated space for teaching *
		Health system external (provincial/regional)	• Funding for supplies, formula	• Coverage for EEN supplies and formula* • Supportive home service
		Patient/ family	• Fear of NG tube and/or loss of food • Difficulty sustaining diet • Limited support to family/socialization	• Involving parents/family in feeding choice • Support of diet, acknowledging it may be difficult • Supportive dietitian throughout pocess
		Enteral nutrition	• Exclusivity of enteral nutrition with no/limited oral intake* • Cost of enteral nutrition* • Taste • NG Tube	• Evidence-based/reduced need for steroids • Few side effects • Oral option possible; recipes
		Physician/care team-related	• Lack of institutional experience or critical mass to “keep it going” * • Lack of standardization of enteral nutrition approach*	• Consistent and systematic approach to EEN (protocols, tools, talking points, defined roles for team members)* • Conviction of physician and team to support EEN • Quality review process • Resource sharing
		* Barriers and enablers identified as highest priority.		

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)

<table>
<tr><td colspan="4">19. Dziechciarz P, Horvath A, Shamir R, Szajewska H. Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment Pharmacol Ther 2007;26(6):795-806. [141]</td></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>Meta-analysis
1-</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:
-no attempt to identify unpublished studies
-low methodological quality and small sample sizes of included trials
-lack of standardization of outcome measures and marked clinical heterogeneity, variation in the length of the trials (follow-up) and in the duration of the intervention
-use of concomitant treatment was allowed in some trials (increasing risk of bias)</td><td>Total no. patients: n= 394 (11 trials)

Inclusion criteria: randomized and quasi-randomized (i.e., allocating participants according to date of birth, the number of hospital records, etc.) controlled trials ; children up to 18 years of age, both with newly diagnosed CD and with relapsed disease; Patients in the experimental groups received enteral formula, including elemental (i.e., formulations of amino acids), semielemental (i.e., formulations of amino acids plus oligopeptides), or polymeric (whole protein) formula; Patients in the control group received corticosteroids or other types of enteral nutrition

Exclusion criteria:</td><td>We performed this meta-analysis to compare the effectiveness of enteral nutrition and corticosteroids in the treatment of acute CD in children, to investigate which type of enteral formula is most effective, including elemental formula, semielemental formula and polymeric formula and to determine short-term and long-term advantages of enteral feeding, if any.</td></tr>
<tr><td>Notes</td><td colspan="3">Author’s Conclusion:
Limited data suggest similar efficacy for EN and corticosteroids. As the number of patients needed to provide a definite answer is too large, future studies should focus on detailed outcome measurements including growth and quality of life.</td></tr>
<tr><td>Outcome measures/results</td><td>Primary outcome measures:
remission (percentage of subjects achieving remission); time until remission; duration of remission or time until the first relapse; relapse (number of</td><td colspan="2">We included 11 RCTs (n = 394). Seven RCTs (n = 204) compared EN with corticosteroid therapy. On the basis of pooled results of four RCTs (n = 144), we found no significant difference in the remission rates between groups (relative risk, RR 0.97, 95% CI 0.7–1.4, random effect model). Four RCTs (n = 190) compared two EN regimens. One of the four RCTs (n = 50) revealed a significant increase in the percentage of patients achieving remission in the total EN group compared</td></tr>
</table>

	relapses per patient year during follow-up) *secondary outcome measures:* growth parameters (weight gain, length/height gain); compliance (acceptance of treatment); quality of life; adverse effects	with the partial EN group (RR 2.7, 95% CI 1–7.4). Because of lack of data, formal pooling of results was not possible for many outcomes (e.g., time until remission, duration of remission, growth data).

20. 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(10):3069-74. [142]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Cohort study 2-	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:94 (51,4%)* *Study limitations:* *-retrospective study design* -bias of changing treatment paradigms with time -lack of propensity score matching -more accurate measure of intervention	*Total no. patients*: n= 183 • EEN group n=43 • Steroid group n=46 *Inclusion criteria:* *Exclusion criteria:* given EEN and CS concurrently; failure to commence early TP; inadequate follow-up/data; primary anti-TNF induction for fistulising perianal disease; failure to continue TP or ceased due to intolerance	We performed this cohort study to evaluate the Impact of first-line induction therapy on medium-term outcomes in the setting of early thiopurine (TP) use in children with Crohn's disease, in particular whether choice of exclusive enteral nutrition (EEN) over corticosteroids (CS) for induction impacts clinical outcomes at 12 and 24 months. -EEN: a sole therapy using polymeric feeds either oral or NG tube to induce remission for a minimum period of 6 weeks (Nutrison (1 kcal/ml, Nutricia, UK, 4 g protein, 3.9 g fat/100 ml) through nasogastric tube (NGT) or resource protein (1.25 kcal/ml, Nestle, 9.4 g protein, 3.5 g fat/100 ml) orally based on their preference and dietetic consultation) -Early TP: defined as introduction within 6 months of diagnosis (Therapeutic TP levels were defined as 6TG levels >250 pmol/8 × 10^8 red blood cells) -Steroid dependency: defined as 10 mg/day prednisolone or clinical relapse within 3 months of tapering steroids
Notes	-Height *Z* scores −1.64 corresponding to <5th percentile was denoted as the presence of growth failure - BMI *Z* scores were calculated using Centre for Disease Control (CDC) growth charts and BMI *Z* scores <−1, <−2, and <−3 defined grade 1, grade 2, and grade 3 thinness, respectively, based on international expert guidelines - Clinical remission was defined as PCDAI ≤ 10 and biochemical remission CRP < 5 mg/l with PCDAI ≤ 10 - Relapse was defined as PCDA > 15 on more than one occasion 1 week apart and/or CRP > 5 mg/l with clinically active disease. A PCDAI > 30 was considered moderate to severe pediatric CD -Endoscopic scores were determined retrospectively by authors separately based on electronically stored endoscopic images and reports description using the validated Simple Endoscopic Scoring system for Crohn's disease (SES-CD). Mild, moderate, and severe endoscopic disease activity was defined as SES-CD 4–10 mildly active, 11–19 moderate active, and 19 severe active CD ***Author's Conclusion:*** In the setting of early TP commencement, EEN induction is superior to CS induction for reducing growth failure, CS dependency, and loss of response to IFX over the first 2 years.		

Outcome measures/results	steroid dependency (relapse <3 months of tapering first course CS or inability to wean <10 mg prednisolone); need for IFX (Infliximab use); linear growth; surgical resections in those first treated with CS versus EEN over the first 2 years	Choice of EEN over CS induction was associated with reduced linear growth failure (7 vs. 26 %, p = 0.02), CS dependency (7 vs. 43 %, p = 0.002), and improved primary sustained response to IFX (86 vs. 68 %, p = 0.02). Combined CS/IFX-free remission and surgical resection rates were similar.

21. Li G, Ren J, Wang G, Hu D, Gu G, Liu S, Ren H, Wu X, Li J. Preoperative exclusive enteral nutrition reduces the postoperative septic complications of fistulizing Crohn's disease. Eur J Clin Nutr. 2014 Apr;68(4):441-6. [144]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective trial 2-	*Countries:* *Centres:* Jinling Hospital *Setting:* *Funding Sources:* Research Talents of Jiangsu Province, China; National Science Foundation of China *Dropout rates:* n=61 (33,2%) *Study limitations:* - influence of EEN use on the inflammation of the diseased intestine and the output of ECFs could not be assessed (retrospective design) -sump drain may influence differently in elder and younger patients -missing data (operation time, length of resected bowel)	*Total no. patients*: n=184 • EEN group n=55 • Controls n=68 *Inclusion criteria:* *Exclusion criteria:* patients who underwent temporal enterostomy rather than definitive operation for resection of fistulas; patients who underwent emergency surgeries and operations for perianal disease	Our aim was to investigate the influence of preoperative 3-month Exclusive enteral nutrition (EEN) on the incidence of intra-abdominal septic complications (IASCs) and to clarify the risk factors of IASCs in fistulizing CD. EEN group -preopeative 3-months EEN with exclusion of a normal diet Controls -no preoperative 3-month EEN
Notes	***Author's Conclusion:*** Preoperative EEN reduced the risk of postoperative IASCs after operation for ECFs in CD. In addition, age at operation may be another factor of influence.		

Outcome measures/results	Changes in serum albumin and C-reactive protein CRP (at the time of operation and preoperative); pre-operative data to identify independent risk factors affecting the incidence of postoperative IASCs; post-operative data about options of medication treatments and the incidence of IASCs	Patients were similar in gender, age, fistula conditions and perioperative medications in the EEN and non-EEN groups. The EEN group had a significantly higher serum albumin level and lower CRP at operation, and suffered a lower risk of IASCs (3.6% vs 17.6%, P<0.05). Two years after operation when follow-up ended, the two groups had comparable cumulative risk of IASCs (P=0.109). A logistic regression analysis identified age at operation and preoperative EEN as independent risk factors of postoperative IASCs.

22. 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(2):246-253. [93]

Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
RCT 1+	*Countries:UK* *Centres:* Alder Hey Children's NHS Foundation Trust *Setting:* *Funding Sources:* *Dropout rates:n= 7 (17,1%)* *Study limitations:* -The assumptions used for the power analysis were too optimistic -lack of fecal calprotectin data from all patients	*Total no. patients*: n= 41 • Elemental formula group n= 15 • Polymeric formula group n=19 *Inclusion criteria:* Children who were newly diagnosed with active CD (clinical, radiological and endoscopic); Pediatric Crohn's Disease Activity Index (PCDAI) >11 *Exclusion criteria:* Children with only large bowel disease	elemental formula (EF) group -6 weeks of an enteral Amino-acid based feed*: 130kcal, 4.0g protein, 16.5g carbohydrate, 5.1g fat, ratio of n3:n6 fatty acids 13:1, 17% LCT, 83% MCT, 5.4% energy from linoleic acid, 0.45% energy from α-linolenic acid, 71mg Calcium, 0.72µg Vitamin D, 8.2mg Vitamin C, 1.8mg Vitamin E α-TE polymeric formula (PF) group -6 weeks of an enteral polymeric formula: 130kcal, 4.3g protein, 16.8g carbohydrates, 5.1g fat, ratio of n3:n6 fatty acids 2:1, 50% LCT, 50% MCT, 3% energy from linoleic acid, 1.5% energy from α-Linolenic acid, 124mg Calcium, 1.01µg Vitamin D, 20.8mg Vitamin C,3.5mg Vitamin E α-TE *Composition per 100mL
Notes	***Author's Conclusion:*** There was no significant difference between EF and PF in inducing remission. One-third of children maintained remission. Changes in plasma polyunsaturated fatty acid status were subtle and may be relevant; however, further evaluation is recommended.		
Outcome measures/results	*Primary outcome measure:* clinical remission (PCDAI <11) at the end of week 6 *Secondary outcome*	Thirty-four children completed the study; EF: 15 (7 M, 8 F), PF: 19 (13 M, 6 F). The mean age was (years) EF: 12.6, PF: 11.7. Ninety-three percent of children (14/15) achieved remission in the EF group and 79% (15/19) in the PF group. One-third of patients maintained remission for 2 years. Mean time to relapse (days); EF: 183 (63–286), PF: 162 (53–301). Most children who relapsed used feed as a treatment for that relapse (EF: 9/10 and PF: 8/13). With PF, an increase of eicosapentanoic acid (EPA) and alpha linolenic acid was	

	measures: fecal calprotectin and plasma fatty acid status at 0 and 6 weeks of treatment; relapse rate at 24 months following induction of remission; patients' choice of treatment for the first relapse	found with a reciprocal decrease in arachidonic acid (AA). With EF, AA and EPA levels were reduced with a significant decrease in docosahexaenoic acid. Fecal calprotectin measurements decreased significantly but did not normalize at the end of week 6.

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)

23. Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2007(3):CD005984. [150]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic review 1-	*Countries:* *Centres:* *Setting:* *Funding Sources:Canadian Institutes of Health Reseach (CIHR) Knowledge Translation Branch; the Canadian Agency fo Drugs and Technologies in Health (CADTH); the CIH Institutes of Health Services and Policy Research; Musculoskeletal Health and Arrthritis, Gender and Health, Human Development, Child and Youth Health; Nutrition, Metabolism and Diabetes; and Infection and Immunity; Olive Stewart Fund* *Dropout rates:* *Study limitations:*	*Total no. patients*: n=84 (2RCTs) *Inclusion criteria:* Randomised controlled trials which compared enteral nutrition with no intervention, placebo or with any other intervention; patients of any age with Crohn's disease whose disease was in remission at the time of entry into the study, Remission should have been defined with a recognized Crohn's disease activity index; types of interventions: Enteral nutrition supplements (polymeric, elemental or semi-elemental) administered by any route (e.g. oral, nasogastric o gastrostomy); Controls: no intervention, placebo or other interventions; report of occurrence of clinical of endoscopic relapse (expressed as a percentage of the number of patients randomized); report on secondary endpoints: improvements in anthropometric measurements (including weight and height), improvements in quality of life, occurrence of adverse events *Exclusion criteria:*	The aim of this systematic review was to summarise the available evidence concerning the use of enteral nutrition for the maintance of remission in Crohn's disease.
Notes	***Author's Conclusion:*** The available evidence suggests that supplementary enteral nutritional may be effective for maintenance of remission in Crohn's disease.		

	Whilst larger studies are needed to confirm these findings, enteral nutritional supplementation could be considered as an alternative or as an adjunct to maintenance drug therapy in Crohn's disease.	
Outcome measures/results	Primary outcome measure: occurrence of clinical of endoscopic relapse (expressed as a percentage of the number of patients randomized) secondary outcome measures: improvements in anthropometric measurements (including weight and height), improvements in quality of life, occurrence of adverse events	Two studies were identified that met the inclusion criteria and were included in the review. Statistical pooling of the results of these studies was not possible because the control interventions, and the way outcomes were assessed differed greatly between the two studies. In one study (Takagi 2006), patients who received half of their total daily calorie requirements as elemental diet and the remaining half by normal diet had a significantly lower relapse rate compared to patients who received unrestricted normal diet (9 of 26 versus 16 of 25; OR 0.3, 95% CI 0.09 to 0.94). In the other study (Verma 2001), elemental and polymeric feeds (providing between 35 and 50% of patients' pretrial calorie intake in addition to unrestricted normal food) were equally effective for maintenance of remission and allowing withdrawal of steroid therapy (8 of 19 versus 6 of 14; OR 0.97, 95% CI 0.24 to 3.92).

24. 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 Mar;28(3):335-40. [157]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
cohort study 2-	*Countries:* *Centres:* Yokkaichi Social Insurance Hospital *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:*	*Total no. patients*: n= 40 • EN group n= 20 • Control group n= 20 *Inclusion criteria:* age between 15 and 75 years; endoscopic and histological diagnosis of CD; patient required resection for ileal or ileocolic (including ileocecal) CD;patient had experienced EN therapy including elemental diet infusion at least one time before operation; patient agreed to continue with the assigned treatment (with or without EN) for 5 years after operation; patient agreed to have ileocolonoscopy when clinical symptoms occur *Exclusion criteria:* patients with colonic CD alone; patients with diffuse small bowel CD; patient received corticosteroids, immunosuppressive drugs, or infliximab following	Before surgery, all patients had experienced elemental diet infusion. Patients with a good EN-theraopy compliance were assigned to EN group, patients with a poor compliance were assigned to the control group Intervention group (EN group) - continuous enteral elemental diet infusion starting 1 or 2 weeks postoperatively, administration during the nighttime (1 kcal/mL with an osmolarity of 760 mosm/L; amino acids, very little fat, vitamins, trace elements, major energy source was dextrin); a low-fat diet (20–30 g/day) during the daytime, Patients were advised to take 35–40 kcal/kg body weight/day, approximately half of the total calories to come from elemental diet Control group

		operation	- no dietary restriction during entire study period
Notes	-All patients received mesalamine (Pentasa 3,000 mg/day) as a prophylactic medication during the study (no patient received corticosteroid, immunosuppressive drugs, or infliximab except patients who developed recurrence) - The clinical disease activity was assessed as CD activity index (CDAI); recurrence was defined as CDAI ≥200 -When a patient developed clinical symptoms, ileocolonoscopy was conducted to investigate endoscopic inflammation - recurrence will be initially treated with corticosteroids (prednisolone 20–60 mg/day) and if recurrence could not be managed with prednisolone, infliximab (Remicade 5 mg/kg/day) at weeks 0, 2, and 6 as induction therapy, and then at 8-week intervals as maintenance therapy was to be given. During infliximab therapy, concomitant azathioprine (Imuran 25–50 mg/day) was to be added if patients agreed to receive immunosuppressants ***Author's Conclusion:*** The outcomes of this study suggest that EN therapy reduces the incidence of postoperative CD recurrence.		
Outcome measures/results	recurrence requiring biologic therapy or re-operation	In the EN group, four patients could not continue tube intubation for elemental diet intake. Two patients (10 %) in the EN group and nine patients (45 %) in the control group developed recurrence requiring infliximab therapy ($P = 0.03$). The cumulative recurrence incidence rate requiring infliximab was significantly lower in the EN group vs the control group ($P = 0.02$). One patient (5 %) in the EN group and five patients (25 %) in the control group required reoperation for recurrence ($P = 0.18$). The cumulative incidence of reoperation was lower in the EN group vs the control group, the difference not being significant ($P = 0.08$).	

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 C – 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)

25. 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 Aug;68(8):959-63. [167]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
cohort study 2++	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:*	*Total no. patients*: n= 48 *Inclusion criteria: patients with* Enterocutaneous fistula (ECF) treated with short-peptide-based EN for 3 months *Exclusion criteria:*	This study was performed to identify predictors of response to EN in CD, which may lead to a better selection of fistula patients for this therapy. Therefore patients with ECF were treated with short-peptide-based EN for 3 months and were followed up for at least 6 months.
Notes	***Author's Conclusion:*** In CD patients with ECF, lower CRP and higher BMI are associated with higher possibility of closure after EN treatment. EN therapy can lead to a closure of ECF in a certain proportion of patients. EN therapy could also ameliorate inflammatory condition and improve nutrition status.		
Outcome measures/results	Inflammatory parameters (erythrocyte sedimentation rate, C-reactive protein (CRP) and platelet count); Nutrition status (body weight, body mass index (BMI), hemoglobin, serum albumin (ALB), serum prealbumin and total protein	In total, 30 out of 48 patients were confirmed with a successful closure of fistula after 3 months' EN therapy. The average closure time was 32.4±8.85 days. Inflammatory parameters (erythrocyte sedimentation rate, C-reactive protein (CRP) and platelet count) improved significantly after EN therapy in all enrolled patients. Specifically, the improvement of CRP after therapy in closed group was more important compared with that in unclosed group (P=0.035). Nutrition status (body weight, body mass index (BMI), hemoglobin, serum albumin (ALB), serum prealbumin and total protein (TP)) improved as well (P<0.05). Similarly, after treatment, the improvement of serum albumin (P=0.046) and prealbumin (P=0.006) in closed group was much more important than those in unclosed group. Logistic regression analysis discovered that a decreased CRP level and an elevated BMI level would be beneficial to the response to EN in CD patients with ECF.	

	(TP))	

26. Visschers RG, Olde Damink SW, Winkens B, Soeters P, van Gemert WG. Treatment strategies in 135 consecutive patients with enterocutaneous fistulas. World J Surg. 2008;32:445-453. [168]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Retrospective Study 2+/-	*Countries:* *Centres:* *Setting:* *Funding Sources:* Netherlands Organisation for Health Research and Development to Steven W. M. Olde Damink *Dropout rates:* *Study limitations:*	*Total no. patients*: n= 135 *Inclusion criteria:* patients with Enterocutaneous fistulas (ECF) treated according to the SOWATS guideline *Exclusion criteria:* Patients with gastroduodenal, pancreatic, biliary, and perianal fistulas	We performed this study to assess the SOWATS guideline and determine prognostic factors for outcome of patients with enterocutaneous fistulas (ECF), and to define a more detailed therapeutic approach including the convalescence time before restorative surgery. Therefore data of patients with ECF treated according to the SOWATS guideline were analyzed.
Notes	SOWATS treatment guideline components: Sepsis, Optimization of nutritional state, Wound care, Anatomy (of the fistula), Timing of surgery, and Surgical strategy ***Author's Conclusion:*** Application of the SOWATS guideline allowed a favorable outcome after a short convalescence period. Abdominal wall defects and preoperative hypoalbuminemia are important prognostic variables.		
Outcome measures/results	Primary outcome measure: time of convalescence prior to restorative surgery secondary outcome measures: prognostic factors for fistula closure and mortality	A total of 135 patients were treated at our unit. Overall closure was achieved in 118 patients (87.4%). Restorative operations for fistula closure were performed after a median of 53 days (range: 4–270 days). Restorative operations were successful in 97/107 patients (90.7%). Thirteen patients (9.6%) died. An abdominal wall defect was the most predominant negative prognostic factor for spontaneous closure (odds ratio [OR] = 0.195, confidence interval [CI] 0.052–0.726, $p = 0.015$). A strong relation was found between preoperative albumin level and surgical closure ($p < 0.001$) and mortality ($p < 0.001$).	

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)

<table>
<tr><td colspan="4">27. Akobeng AK, Thomas AG. Refeeding syndrome following exclusive enteral nutritional treatment in Crohn disease. J Pediatr Gastroenterol Nutr. 2010 Sep;51(3):364-6. [177]</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study details/limitations</td><td>Patient characteristics</td><td>Interventions</td></tr>
<tr><td>Case report
3</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:</td><td>Total no. patients: n=2
Inclusion criteria:
Exclusion criteria:</td><td>We report 2 children with acute CD who developed the refeeding syndrome following treatment with exclusive enteral nutrition.</td></tr>
<tr><td>Notes</td><td colspan="3">Author’s Conclusion:
Malnourished children with CD are at risk for developing the refeeding syndrome when they are provided with enteral nutrition. Clinicians caring for these children should be aware of the syndrome to allow the identification and monitoring of patients at risk.</td></tr>
<tr><td>Outcome measures/results</td><td colspan="3">PATIENT 1

A white boy presented at the age of 10 years with a 7-month history of diarrhoea, abdominal pain, poor appetite, and weight loss. Laboratory investigations included haemoglobin, 8.3 g/dL (11.5–14.5); erythrocyte sedimentation rate, 35 mm in the first hour; platelet count, 675 × 10^9/L; albumin, 17 g/L (30–45); and orosomucoid, 4087 mg/L (300–1200). A barium contrast study showed terminal ileitis with longitudinal ulceration and bowel wall thickening. At colonoscopic examination, there was a cobblestone appearance of the mucosa of the caecum. Histological analysis of biopsy specimens showed active chronic inflammation with granulomata. The clinical, radiological, endoscopic, and histological features were consistent with a diagnosis of CD. Following the diagnosis, the patient was treated with a 6-week course of exclusive polymeric diet as primary therapy for CD. Within a few days of starting the polymeric diet, his serum phosphate concentration, which was normal initially, had dropped to 0.77 mmol/L (1.0–1.8). Oral phosphate supplements were commenced, and the serum phosphate concentration normalised within 48 hours to 1.28 mmol/L.

Following the initial treatment, he remained reasonably well but required intermittent courses of polymeric diet for acute exacerbations of the disease, without any untoward events. At the age of 13 years, he was readmitted to hospital because of an acute exacerbation of disease. He complained of abdominal pain, diarrhoea, and weight loss. His admission weight was 26.5 kg and his</td></tr>
</table>

		height was 148.9 cm. Using sex- and age-related UK growth and height curves , weight-for-height, weight-for-age, and height-for-age were calculated to be 67%, 60%, and 94%, respectively. His body mass index (BMI), calculated as weight (kg)/height (m^2), was 12 (<0.4th centile). His z scores for weight, height, and BMI were -2.9, -1.04, and -3.9, respectively. He was started on exclusive polymeric diet treatment. Two days after starting the feeds, he developed an acute episode of breathlessness and tachycardia. His pulse was 128 beats/minute and blood pressure was 87/50 mmHg. Blood tests revealed hypophosphatemia with a serum phosphate level of 0.61 mmol/L (1.0–1.8). Other results included corrected calcium, 2.2 mmol/L (2.2–2.7); magnesium, 0.75 mmol/L (0.65–1.00); sodium, 131 mmol/L (135–145); and potassium, 4.1 mmol/L (3.5–5.00). A diagnosis of refeeding syndrome was made, and he was initially treated with an intravenous phosphate infusion followed by oral phosphate supplements. When he was reviewed in the clinic about 6 weeks after commencing exclusive polymeric feeds, he was clinically improved. His weight was recorded as 32.65 kg and his height was 149.3 cm. His BMI had improved to 14.7, which was between the 0.4th and second centiles. His BMI z score was -1.1. He was put on polymeric diet supplements in addition to unrestricted normal diet. **PATIENT 2** An Asian girl presented at the age of 11 years with a history of diarrhoea, abdominal pain, erythema nodosum, and weight loss. Her admission weight was 18.7 kg and her height was 134.5 cm. Using age-related UK growth and height curves , weight-for-height, weight-for-age, and height-for-age were calculated to be 62%, 52%, and 93%, respectively. Her BMI, calculated as weight (kg)/height (m^2), was 10.3 (<0.4th centile). Using age-related UK growth and BMI curves, weight, height, and BMI standard deviation scores (z scores) were calculated. The z scores for weight, height, and BMI were -3.46, -1.45, and -4.23, respectively. Initial laboratory investigations included haemoglobin, 8.6 g/dL (11.5–14.5); erythrocyte sedimentation rate, 55 mm in the first hour; platelet count, 588 × 10^9/L; albumin, 21 g/L (30–45); and orosomucoid, 4158 mg/L (300–1200). At colonoscopic examination, there was evidence of patchy areas of ulceration throughout the colon. Histological analysis of mucosal biopsy specimens confirmed active inflammation throughout the colon and terminal ileum with granulomata. The clinical, endoscopic, and histological features were consistent with a diagnosis of CD. Following the diagnosis, the patient was started on a 6-week course of exclusive polymeric diet as primary therapy for CD. The aim was to provide her with about 120% of her estimated average requirement (1845 kcal) by day 3. She received the feeds orally during the first week but subsequently required a nasogastric tube. Within 4 days of starting the polymeric diet her serum phosphate level dropped to 0.63 mmol/L (1.0–1.8). Other investigations included sodium, 133 mmol/L (135–145); potassium, 4.6 mmol/L (3.5–5.00); corrected calcium, 2.25 mmol/L (2.2–2.7); and magnesium, 0.65 mmol/L (0.65–1.00). Oral phosphate supplements were commenced and the serum concentrations had normalised after 24 hours to 1.41 mmol/L

Recommendation 29:

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

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

<table>
<tr><td colspan="4">28. Jones VA, Dickinson RJ, Workman E, Wilson AJ, Freeman AH, Hunter JO. Crohn's disease: maintenance of remission by diet. Lancet. 1985 Jul 27;2(8448):177-80. [243]</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study details/limitations</td><td colspan="2">Patient characteristics</td><td>Interventions</td></tr>
<tr><td>RCT
1-</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:</td><td colspan="2">Total no. patients: n=20
• TPN group n = 13
• Elemental diet group n=7

Uncontrolled trial n=77

Inclusion criteria: patients with active Crohn’s disease (Crohn’s Disease Activity Index [CDAI] >150)

Exclusion criteria:</td><td>In 20 patients with Crohn’s disease remission was induced with TPN or an elemental diet (E028). When patients entered remission (CDAI <150) they were randomly allocated to the following diet regimes:

unrefined carbohydrate, fibre-rich diet

Exclusion diet
-patients excluded specific foods to which a patient was intolerant; patients introduced a single food each day, starting with those such as chicken and fish, which experience has shown to be unlikely to provoke symptoms, leaving until later those such as cereals and diary products; food that provoked symptoms was subsequently qvoided</td></tr>
<tr><td>Notes</td><td colspan="4">The procedure for the identification of specific food intolerance has been followed by 77 patients. 33 had gone into remission with TPN, 25 with E028, and 19 with an exclusion diet.
Author’s Conclusion:</td></tr>
<tr><td>Outcome measures/results</td><td>Length of remission</td><td colspan="3">20 patients with Crohn's disease took part in a controlled trial in which remission was maintained by either an unrefined carbohydrate fibre rich diet or a diet which excluded specific foods to which a patient was intolerant. 7 out of the 10 patients on the exclusion diet remained in remission for 6 months compared with none out of the 10 on an unrefined carbohydrate fibre rich diet (p less than 0.05, Fisher's exact test). In an uncontrolled study an exclusion diet allowed 51 out of 77 patients to remain well on the diet alone for periods of up to 51 months, and with an average annual relapse rate of less than 10%.</td></tr>
</table>

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)

<table>
<tr><td colspan="4">29. Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013 Nov;38(10):1156-71. [252]</td></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>review article
2+</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:</td><td>Total no. patients:
Inclusion criteria:
Exclusion criteria:</td><td>The aim of this review was to examine the evidence linking diet to IBD causation or activity and to conclude with suggestions of practical dietary advice for people with IBD based on the evidence available. Therefore we performed a review of the published literature on diet and IBD in combination with ‘Crohn's disease’ ‘Ulcerative colitis’ ‘diet’ ‘nutrition’ and ‘enteral’ ‘fatty acid’ and ‘food additives’.</td></tr>
<tr><td>Notes</td><td colspan="3">Author’s Conclusion:
There is little evidence from interventional studies to support specific dietary recommendations. Nevertheless, people with IBD deserve advice based on ‘best available evidence’ rather than no advice at all, although dietary intake should not be inappropriately restrictive. Further interventional studies of dietary manipulation are urgently required.</td></tr>
<tr><td>Outcome measures/results</td><td colspan="2">Investigated topics: Enteral nutrition, Dietary supplementation with Omega 3 fatty acids; Dietary supplementation with curcumin; Dietary component modification:Sugar and fibre, Nanoparticles, Milk and dairy products, Lactose,; Avoidance of various specific dietary components; Vitamin and mineral supplementation; Prebiotics; Fermentable Oligo-, di-, monosaccharides and polyols;

Investigated topics-evidence from experimental studies: ‘Western diet’; Emulsifiers and detergents; Prebiotics; Soluble plant fibres;</td><td>Enteral nutrition with a formula-defined feed is effective treatment for CD, but approximately 50% of patients relapse within 6 months of return to normal diet. There is no direct evidence of benefit from any other specific dietary modification in CD, but indirect evidence supports recommendation of a low intake of animal fat, insoluble fibre and processed fatty foods containing emulsifiers. Foods tolerated in sustained remission may not be tolerated following relapse. Some evidence supports vitamin D supplementation. In ulcerative colitis (UC), evidence is weaker, but high intakes of meat and margarine correlate with increased UC incidence and high meat intake also correlates with increased likelihood of relapse.
Dietary guidance
Taking into account the evidence presented above, noting the caution necessary in extrapolating from epidemiological correlations and laboratory studies, we would suggest that the following represents reasonable dietary advice for patients with IBD:

Dietary guidance for patients with CD

1. In about two-thirds of patients, remission of CD may be achieved, usually over about 3 weeks, by stopping all normal food and taking a formula-defined liquid diet (‘enteral nutrition’), with ap-</td></tr>
</table>

	effects of dietary components on the gut microbiota; Antioxidants, curcumin, olive oil and various other putative beneficial dietary components	propriate flavouring, as the sole feed. This is of course fairly tedious and will usually only be the first choice treatment for a minority of adults, but may more commonly be first choice treatment for children and adolescents. 2. Unfortunately, about 50% of patients treated by enteral nutrition relapse within 6 months of return to a normal diet. 3. The mechanisms by which enteral nutrition benefits CD are unclear and no specific food exclusion or inclusion has yet been proven definitively to benefit patients 4. The following advice is therefore based on a combination of evidence from interventional studies together with more indirect (and therefore probably less reliable) evidence based on statistical associations between risk of CD and diets in individuals and across countries. This evidence suggests that it may be reasonable to have a diet that – *Is low in animal fat* – guidelines suggest that a low-fat intake is approximately 30% of energy requirements, which equates to 90 g fat for someone who has an intake of 2500 kcal/day.*Avoids foods that are high in insoluble fibre* – stringy or fibrous vegetables such as green beans, corn on the cob (whole maize), tomato skins, orange pith, potato skins and wheat bran. *Avoids processed fatty foods* – often high in fat and usually contain emulsifiers – these are detergents that alter the behaviour of the intestinal lining – exposure to dish-washing detergents should also be minimised by careful rinsing.*Includes supplementary vitamin D* – up to 1200 IU/day.*Dairy products if tolerated can be consumed* to help ensure adequate calcium intakes. Dietary guidance for patients with UC 1. Short-term use of total bowel rest with intravenous feeding has proved ineffective in active UC and therefore, the general conclusion has been that diet has little role in causation of UC. 2. There is, however, evidence from several studies that risk for UC, and risk of relapse in patients who have UC, is increased in those with a high intake of red meat or margarine. 3. One small study showed that about one in five patients benefited from exclusion of milk and cheese. This study has yet to be repeated and strict avoidance of dairy products is not justified. 4. Lactose intolerance has probably been overemphasised as a clinical problem. Half the world's population does not retain the intestinal enzyme (lactase) necessary for lactose absorption into adult life, and a double-blind controlled trial failed to show correlation of symptoms with ingestion of 240 mL of lactose-containing milk in people with proven lactase deficiency. This evidence suggests that it may be reasonable to have a diet that –

		Is low in meat – particularly red meat and processed meats, e.g. restricting their intake to no more than once per week. *Avoids margarine*. There is weak evidence that olive oil might be protective. *Strict avoidance of dairy products and/or lactose is not justified* on the basis of current evidence.

30. Richman E, Rhodes JM. Review article: evidence-based dietary advice for patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013 Nov;38(10):1156-71. [252]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
review article 2+	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:*	*Total no. patients*: *Inclusion criteria:* *Exclusion criteria:*	The aim of this review was to examine the evidence linking diet to IBD causation or activity and to conclude with suggestions of practical dietary advice for people with IBD based on the evidence available. Therefore we performed a review of the published literature on diet and IBD in combination with 'Crohn's disease' 'Ulcerative colitis' 'diet' 'nutrition' and 'enteral' 'fatty acid' and 'food additives'.
Notes	***Author's Conclusion:*** There is little evidence from interventional studies to support specific dietary recommendations. Nevertheless, people with IBD deserve advice based on 'best available evidence' rather than no advice at all, although dietary intake should not be inappropriately restrictive. Further interventional studies of dietary manipulation are urgently required.		
Outcome measures/results		Enteral nutrition with a formula-defined feed is effective treatment for CD, but approximately 50% of patients relapse within 6 months of return to normal diet. There is no direct evidence of benefit from any other specific dietary modification in CD, but indirect evidence supports recommendation of a low intake of animal fat, insoluble fibre and processed fatty foods containing emulsifiers. Foods tolerated in sustained remission may not be tolerated following relapse. Some evidence supports vitamin D supplementation. In ulcerative colitis (UC), evidence is weaker, but high intakes of meat and margarine correlate with increased UC incidence and high meat intake also correlates with increased likelihood of relapse.	

31. Cabré E, Mañosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases - a systematic review. Br J Nutr. 2012 Jun;107 Suppl 2:S240-52. [253]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**

Systematic review 1-	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:*	*Total no. patients*: *Inclusion criteria:* randomised controlled trials (RCT) of fish oil or omega-3 PUFA therapy in both active and inactive UC or CD; reporting at least one of the primary or secondary outcomes; no limitation on either the length of therapy or the form it was given (capsules, liquid, enteric coated preparation), including nutritional supplements and enteral formula diets; Concomitant IBD therapies were allowed if they were balanced between the study groups *Exclusion criteria:* Studies dealing with conventional diets enriched with fish foods; Papers reporting pooled results in UC and CD, or in active and inactive patients; Studies reporting only surrogate outcomes, such as serum/tissue levels of cytokines, eicosanoids or other inflammatory markers	We aimed to systematically review the available data on the performance of omega-3 PUFA as therapeutic agents in patients with UC and CD. Therefore we systematically searched for RCT of fish oil or omega-3 PUFA therapy in both active and inactive ulcerative colitis or Crohn's disease, without limitation on either the length of therapy or the form it was given, including nutritional supplements and enteral formula diets.
Notes	***Author's Conclusion:*** The present systematic review does not allow to make firm recommendations about the usefulness of omega-3 PUFA in inflammatory bowel disease.		
Outcome measures/results	*Primary outcome measures:* remission rate (for active patients); relapse rate (for patients in remission) *Secondary outcome measures:* change in disease activity scores (either clinical or endoscopic); time to remission; time to first relapse; adverse events; hospitalisation rate; steroid sparing effect; disease activity at the end of follow-up period; quality of life	A total of 19 RCT were finally selected for this review. Overall, available data do not allow to support the use of omega-3 PUFA supplementation for the treatment of both active and inactive inflammatory bowel disease. Negative results are quite consistent in trials assessing the use of omega-3 PUFA to maintain disease remission, particularly ulcerative colitis, and to a lesser extent Crohn's disease. Trials on their use in active disease do not allow to draw firm conclusions mainly because the heterogeneity of design (ulcerative colitis) or their short number (Crohn's disease). In most trials, the appropriateness of the selected placebo is questionable.	

32. 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 Feb 28;2:CD006320. [258]

Study Type/ Evidence Level	Study details/limitations	Patient characteristics	Interventions
Systematic review 2++	*Countries:* *Centres:*	*Total no. patients*: n= 1039 • Intervention n= 523	We conducted this study to systematically review to examine the efficacy and safety of n-3 for

	Setting: *Funding Sources:* *Dropout rates:* *Study limitations:* -clinical heterogeneity among the included studies (different preparations of omega-3 fatty acids, with different compositions and different delivery systems, different placebos, post-operative setting, only pediatric patients)	• Controls=516 *Inclusion criteria:* Randomized placebo-controlled trials of fish oil or n-3 therapy administered for at least six months; reporting at least one of the primary or the secondary outcomes; published in any language; Studies published in an abstract form if enough data were provided to assess the reported outcomes; Crohn's disease patients (diagnosed using established criteria) who were in remission at the time of recruitment; no age restrictions; Intervention with fish oil or n-3 supplementation given in any form (capsule, enteric coated or liquid) but with a defined dose; Co-interventions were allowed only if they were balanced between the study groups *Exclusion criteria:*Studies in which the intervention group received diet enriched with fish products were excluded; Studies reporting only surrogate outcomes (e.g. serum or tissue levels of cytokines or inflammatory markers)	maintenance of remission in Crohn's disease (CD) and to evaluate the adverse events associated with fish oil or n-3 for maintaining remission in CD.
Notes	***Author's Conclusion:*** Evidence from two large high quality studies suggests that omega 3 fatty acids are probably ineffective for maintenance of remission in CD. Omega 3 fatty acids appear to be safe although they may cause diarrhea and upper gastrointestinal tract symptoms.		
Outcome measures/results	*Primary outcome measure:* relapse rate during the observation time *Secondary outcome measures:* change in disease activity scores; time to first relapse; adverse events (diarrhea, nausea, vomiting, halitosis, heartburn, alterations in low density lipoproteins, alterations in glucose level, increase in bleeding time and abdominal pain) recorded, if available: admission rate, use of steroids, disease activity at the end of follow-up period	Six studies with a total of 1039 patients were eligible for inclusion. The two largest studies were rated as low risk of bias for all assessed items. Four studies were rated as unclear risk of bias for randomization and allocation concealment. Two studies were rated as high risk of bias for incomplete outcome data and selective reporting. There was a marginal significant benefit of n-3 therapy for maintenance of remission. Thirty-nine per cent of patients in the n-3 group relapsed at 12 months compared to 47% of placebo patients (6 studies, 1039 patients; RR 0.77, 95% CI 0.61 to 0.98). A GRADE analysis rated the overall quality of the evidence for the primary outcome (i.e. relapse) as very low due to unexplained heterogeneity (I^2 = 58%), publication bias, and a high or unknown risk of bias in four studies in the pooled analysis. When two large studies at low risk of bias were considered the benefit was no longer statistically significant. Thirty-seven per cent of patients in the n-3 group relapsed at 12 months compared to 42% of placebo patients (2 studies, 738 patients; RR 0.88, 95% CI 0.74 to 1.05). No significant heterogeneity was identified for this pooled analysis (I^2 = 0%). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate due to sparse data (294 events). No serious adverse events were recorded in any of the studies but in a pooled analyses there was a significantly higher rate of diarrhea (4 studies, 862 patients; RR 1.36 95% CI 1.01 to 1.84) and	

	and quality of life	upper gastrointestinal tract symptoms (5 studies, 999 patients; RR 1.65, 95% CI 1.25 to 2.18) in the n-3 treatment group.

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)

<table>
<tr><td colspan="4">33. 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):1-13. [264]</td></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>Meta-analysis
1++</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:

Study limitations:
- studies investigating probiotic treatments on the induction and maintenance of remission in UC: variations in inclusion and exclusion criteria, the treatment and control interventions, schedules and concentrations of the probiotics, observation intervals, procedures used to assess the disease activity, concomitant medications, the ethnicity of the patients and the lifestyles of the enrolled patients</td><td>Total no. patients:n= 1547 (20RCTs)
• intervention n= 777
• Controls n=770

Inclusion criteria: randomized controlled studies comparing probiotics with standard treatments used for IBD or placebo; adult and pediatric studies; IBD patients were diagnosed based on the definite diagnostic standards

Exclusion criteria: Reviews, case reports, abstracts, presentations of meetings, uncontrolled tests and basic research studies</td><td>This systematic review verified the findings of high-quality randomized controlled trials (RCTs) which investigated the therapeutic effects of probiotics on IBD.</td></tr>
<tr><td>Notes</td><td colspan="3">Of these 20 studies three were conducted on the response rate to probiotic treatment, four studies examined the remission induction rate and two studies evaluated both the response and remission induction rates of UC patients, five studies focused on the maintenance therapy for UC, two studies on the maintenance therapy for an ileal pouch, one study was performed on the remission induction therapy for CD and four studies examined the effects of probiotics on the maintenance therapy for CD.
Author's Conclusion:</td></tr>
</table>

	In summary, the present study identified 20 high-quality RCTs which investigated the effects of probiotics on the induction or maintenance of remission in IBD. From the results of the validation of these RCTs, probiotic treatment is a practical option for UC patients as both remission induction and maintenance therapy, but such treatment is not effective in CD patients. Because there were many variations in the conditions among the studies, future studies on the value of probiotic treatment in IBD should consider the effects of different probiotics and different regimens, together with the specific patient populations which are most likely to benefit from probiotic treatment.	
Outcome measures/results	interventions used for treatment and control: disease severities, administration procedures, number of enrolled patients, observation intervals; articles associated with remission induction therapy for IBD: remission or response rates of the probiotic treatment and control groups; articles associated with maintenance therapy for IBD: relapse rates of the diseases	After the quality assessment, 20 RCTs which investigated the effects of probiotics on the induction or maintenance of remission in IBD were identified. From the results of the validation of these RCTs, beneficial effects of probiotic treatments to improve the response rate and remission rate on the remission induction therapies [risk ratio (RR) 1.81; 95 % confidence interval (CI) 1.40–2.35 and RR 1.56; 95 % CI 0.95–2.56, respectively] were verified. Furthermore, probiotic treatments exhibited effects equal to mesalazine on the maintenance of remission in UC (RR 1.00; 95 % CI 0.79–1.26). In contrast, no significant effect of probiotic treatments was shown in either the induction or maintenance of remission in CD.

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)

34. 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 Nov 23;11:CD001176. doi: 10.1002/14651858.CD001176.pub3. [280]			
Study Type/ Evidence Level	**Study details/limitations**	**Patient characteristics**	**Interventions**
Systematic Review 1-	*Countries:* *Centres:* *Setting:* *Funding Sources:* *Dropout rates:* *Study limitations:* - the generalizability and external validity of these results must be questioned (for each comparison, with the exception of VSL#3 versus placebo for chronic pouchitis, only one trial was eligible) - GRADE analyses indicate that the overall quality of evidence ranges from low to very low -occurrence of risk of bias in the included studies and very serious imprecision	*Total no. patients*: n=517 (13RCTs) *Inclusion criteria:* Randomized, controlled trials with parallel arm placebo-controlled trials, crossover placebo-controlled trials, and trials comparing two active agents; Adult patients (age ≥ 18 years) who had undergone IPAA (for chronic ulcerative colitis and were at risk of, or had developed acute or chronic pouchitis; eligible interventions: 1. Oral metronidazole 20 mg/kg/day or 500 mg twice dail2. 2.Oral VSL#3 probiotic bacterial formulation containing 300 billion bacteria per gram of viable lyophilized bacteria with four strains of *Lactobacilli* (*L. acidophilus*, *L. delbrueckii* subspecies *Bulgaricus*, *L. plantarum, L. casei*), three strains of *Bifidobacterium* (*B. infantis, B. longum, B. breve*) and one strain of *Streptococcus salivarius* subspecies *Thermophilus*; 6 g/day), 3 g/day , 3 g twice daily, 3 g once per day; 3. Bismuth carbomer foam enemas containing 513 mg bismuth citrate (270 mg metallic bismuth) complexed with carbomer (a synthetic high-molecular weight polymer of acrylic acid cross linked with poly alkenyl polyether) administered once nightly; 4. Glutamine suppositories containing 1 g of L-glutamine in a polyethylene glycol base administered twice daily; 5. Butyrate suppositories containing 40 mmol sodium butyrate in a poly-	We performed this review to determine the efficacy and safety of medical therapies (including antibiotics, probiotics, and other agents) for prevention or treatment of acute or chronic pouchitis. Therefore a databased literature search of published RCTs were performed to determine which of the currently utilized empiric medical therapies for pouchitis can be substantiated with valid data from controlled trials.

		ethylene glycol base administered twice daily; 6. Ciprofloxacin 1000 mg daily; 7. Rifaximin 400 mg orally three times daily; 8. *Lactobacillus GG* in two gelatine capsules orally twice daily versus microcrystalline cellulose-only gelatine placebo capsules ; 9. Budesonide enema 2 mg/100 mL at bedtime plus oral placebo tablets; 10. Allopurinol 100 mg twice daily; 11. Tinidazole 500mg daily; 12. *Bifidobacterium longum* BB-536 *Exclusion criteria:*	
Notes	-Pouchitis was variably defined by 1) solely clinical criteria; 2) clinical criteria in combination with endoscopic and histologic criteria; or 3) PDAI. Pouchitis was categorized by disease activity, as active (defined clinically as the presence of mild-to-severe symptoms or by a PDAI ≥ 7) or in remission (absence of symptoms or by a PDAI < 7), or by disease duration as acute (symptom duration ≤ 4 weeks) or chronic (symptom duration > 4 weeks). ***Author's Conclusion:*** For acute pouchitis, very low quality evidence suggests that ciprofloxacin may be more effective than metronidazole. For chronic pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo for maintenance of remission. For the prevention of pouchitis, low quality evidence suggests that VSL#3 may be more effective than placebo. Well designed, adequately powered studies are needed to determine the optimal therapy for the treatment and prevention of pouchitis.		
Outcome measures/results	Primary outcome measures: proportion of patients with clinical improvement or remission of pouchitis in patients with acute or chronic pouchitis (treatment of pouchitis); the proportion of patients with no episodes of pouchitis after IPAA (prevention of pouchitis) secondary outcome measure: proportion of patients who developed at least one adverse event	Thirteen studies (517 participants) were included in the review. Four studies assessed treatment of acute pouchitis. One study (16 participants) compared ciprofloxacin and metronidazole; another (26 participants) compared metronidazole to budesonide enemas; another (18 participants) compared rifaximin to placebo; and the fourth study (20 participants) compared *Lactobacillus GG* to placebo. Four studies assessed treatment of chronic pouchitis. One study (19 participants) compared glutamine to butyrate suppositories; another (40 participants) compared bismuth enemas to placebo; and two studies (76 participants) compared VSL#3 to placebo. Five studies assessed prevention of pouchitis. One study (40 participants) compared VSL#3 to placebo; another (28 participants) compared VLS#3 to no treatment; one study (184 participants) compared allopurinol to placebo; another (12 participants) compared the probiotic *Bifidobacterium longum* to placebo; and one study (38 participants) compared tinidazole to placebo. Three studies were judged to be of high quality. Two studies were judged to be low quality and the quality of the other studies was unclear. **Treatment of acute pouchitis:** The results of one small study (16 participants) suggest that ciprofloxacin may be more effective than metronidazole for the treatment of acute pouchitis. One hundred per cent (7/7) of ciprofloxacin patients achieved remission at two weeks compared to 33% (3/9) of metronidazole patients. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to high risk of bias (no blinding) and very sparse data (10 events). There was no difference in the proportion

		of patients who had at least one adverse event (RR 0.18, 95% CI 0.01 to 2.98). Adverse events included vomiting, dysgeusia or transient peripheral neuropathy. There were no differences between metronidazole and budesonide enemas in terms of clinical remission, clinical improvement or adverse events. Adverse events included anorexia, nausea, headache, asthenia, metallic taste, vomiting, paraesthesia, and depression. There were no differences between rifaximin and placebo in terms of clinical remission, clinical improvement, or adverse events. Adverse events included diarrhea, flatulence, nausea, proctalgia, vomiting, thirst, candida, upper respiratory tract infection, increased hepatic enzyme, and cluster headache. There was no difference in clinical improvement between *Lactobacillus GG* and placebo. The results of these studies are uncertain due to very low quality evidence. **Treatment of chronic pouchitis:** A pooled analysis of 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 VLS#3 patients maintained remission at 9 to 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). Adverse events included abdominal cramps, vomiting and diarrhea. There was no difference in effectiveness between glutamine and butyrate suppositories for maintenance of remission. There was no difference in clinical improvement or adverse event rates between bismuth carbomer foam enemas and placebo. Adverse events included diarrhea, worsening symptoms, cramping, sinusitis, and abdominal pain. The results of these studies are uncertain due to very low quality evidence. **Prevention of pouchitis:** The results of one small study (40 participants) suggest that VSL#3 may be more effective than placebo for prevention of pouchitis. Ninety per cent (18/20) of VSL#3 patients had no episodes 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). Another small study (28 participants) found that VLS#3 was not more effective than no treatment for prevention of pouchitis. *Bifidobacterium longum,* allopurinol and tinidazole were not more effective than placebo for prevention of pouchitis. The results of these studies are uncertain due to very low quality evidence.

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)

<table>
<tr><td colspan="4">35. Battat R, Kopylov U, Szilagyi A, Saxena A, Rosenblatt DS, Warner M, Bessissow T, Seidman E, Bitton A. Vitamin B12 deficiency in inflammatory bowel disease: prevalence, risk factors, evaluation, and management. Inflamm Bowel Dis. 2014 Jun;20(6):1120-8. [296]</td></tr>
<tr><th>Study Type/ Evidence Level</th><th>Study details/limitations</th><th>Patient characteristics</th><th>Interventions</th></tr>
<tr><td>Systematic review
2++</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:</td><td>Total no. patients: n= 3732 (42 articles)

Inclusion criteria:

Exclusion criteria: Articles not pertaining to the investigated topic; Case studies, letters, comments, review articles, and studies analyzing patients nil per os or on total parenteral nutrition; Publications identified as duplicates</td><td>This systematic review examines whether IBD predisposes to vitamin B_{12} (cobalamin, Cbl) deficiency. We provide an approach to the management of abnormal Cbl values in IBD based on current literature and consensus-based guidelines.</td></tr>
<tr><td>Notes</td><td colspan="3">This systematic review of Cbl deficiency in CD and UC included studies analyzing both serum Cbl levels and absorption tests.
No mention of eligibility criteria for included studies.
Author’s Conclusion:
This literature does not support an association of Crohn's disease in general, regardless of ileal involvement, with Cbl deficiency. Only ileal resections greater than 20 cm in Crohn's disease predispose to deficiency and warrant treatment. Based on these findings, we suggest a diagnostic and therapeutic algorithm. All findings and recommendations require verification in further studies using confirmatory biomarkers as per diagnostic guidelines for Cbl deficiency. Serum Cbl levels alone are likely insufficient to diagnose deficiency in asymptomatic patients.</td></tr>
<tr><td>Outcome measures/results</td><td>prevalence, risk factors, clinical significance, evaluation, and management of Cbl deficiency in IBD</td><td colspan="2">Crohn's disease without ileal resection, regardless of disease location in the ileum, did not increase the risk for Cbl deficiency. Ileal resections greater than 30 cm were associated with Cbl deficiency in Crohn's disease, whereas those less than 20 cm were not. The effects of 20 to 30 cm resections were inconsistent. Ulcerative colitis did not predispose to deficiency. All studies failed to use confirmatory biomarker testing as stipulated by diagnostic guidelines for Cbl deficiency.</td></tr>
</table>

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)

<table>
<tr><td colspan="4">36. Pironi L, Cornia GL, Ursitti MA, Dallasta MA, Miniero R, Fasano F, Miglioli M, Barbara L. 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(2):143-8. [306]</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study details/limitations</td><td>Patient characteristics</td><td>Interventions</td></tr>
<tr><td>controlled trial
2++</td><td>Countries:
Centres:
Setting:
Funding Sources:
Dropout rates:
Study limitations:</td><td>Total no. patients: n= 30
• Folinic acid group n= 15*
• Folic group n=15*
(* ten patients affected by Crohn's disease and five patients affected by ulcerative colitis in each group)

Inclusion criteria: patients with inflammatory bowel disease (IBD)

Exclusion criteria:</td><td>Folinic acid group
- treatment with salicylazosulfapyridine (SASP) (1g twice daily at meal times); intake of 15 mg/day of folinic acid for one month

Folic group
- treatment with salicylazosulfapyridine (SASP) (1g twice daily at meal times);intake of 15 mg/day of folic for one month</td></tr>
<tr><td>Notes</td><td colspan="3">Author’s Conclusion:
It was concluded that: a) both folic and folinic acid could restore and enlarge the body stores of folate in patients with IBD treated with SASP, when administered at the dose of 15 mg daily for one month; b) folinic acid seems to be more efficient in enlarging the body stores of the vitamin than folic acid.</td></tr>
<tr><td>Outcome measures/results</td><td>plasma folate concentration, red blood cell (RBC) folate concentrations</td><td colspan="2">After one month the mean increase in RBC folate concentration was significantly greater after folinic therapy then after folic acid therapy (910 +/- 383 versus 570 +/- 212 ng/ml; p less than 0.01), while no difference was observed in the mean increase of plasma folate level (19.8 +/- 6.6 versus 18.5 +/- 5.0 ng/ml).</td></tr>
</table>