Clinical Nutrition 28 (2009) 415–427

Contents lists available at ScienceDirect

Clinical Nutrition

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

ESPEN Guidelines on Parenteral Nutrition: Gastroenterology

André Van Gossum [a], Eduard Cabre [b], Xavier Hébuterne [c], Palle Jeppesen [d], Zeljko Krznaric [e], Bernard Messing [f], Jeremy Powell-Tuck [g], Michael Staun [d], Jeremy Nightingale [h]

[a] Hôpital Erasme, Clinic of Intestinal Diseases and Nutrition Support, Brussels, Belgium
[b] Hospital Universitari Germans Trias i Pujol, Department of Gastroenterology, Badalona, Spain
[c] Hôpital L'Archet, Service de Gastro-entérologie et Nutrition, Nice, France
[d] Rigshopitalet, Department of Gastroenterology, Copenhagen, Denmark
[e] University Hospital Zagreb, Division of Gastroenterology and Clinical Nutrition, Zagreb, Croatia
[f] Hôpital Beaujon, Service de Gastro-entérologie et Nutrition, Paris, France
[g] The Royal London Hospital, Department of Human Nutrition, London, United Kingdom
[h] St Mark's Hospital, Department of Gastroenterology, Harrow, United Kingdom

ARTICLE INFO

Article history:
Received 19 April 2009
Accepted 29 April 2009

Keywords:
Guidelines
Clinical practice
Evidence-based
Parenteral nutrition
Crohn's disease
Ulcerative colitis
Short bowel syndrome
Intestinal failure
Malnutrition
Undernutrition

SUMMARY

Undernutrition as well as specific nutrient deficiencies has been described in patients with Crohn's disease (CD), ulcerative colitis (UC) and short bowel syndrome. In the latter, water and electrolytes disturbances may be a major problem.
The present guidelines provide evidence-based recommendations for the indications, application and type of parenteral formula to be used in acute and chronic phases of illness.
Parenteral nutrition is not recommended as a primary treatment in CD and UC. The use of parenteral nutrition is however reliable when oral/enteral feeding is not possible.
There is a lack of data supporting specific nutrients in these conditions.
Parenteral nutrition is mandatory in case of intestinal failure, at least in the acute period.
In patients with short bowel, specific attention should be paid to water and electrolyte supplementation.
Currently, the use of growth hormone, glutamine and GLP-2 cannot be recommended in patients with short bowel.

Summary of statements: Parenteral nutrition in Crohn's disease

Subject	Recommendations	Grade	Number
Indication	PN is indicated for patients who are malnourished or at risk of becoming malnourished and who have an inadequate or unsafe oral intake, a non (or poorly) functioning or perforated gut, or in whom the gut is inaccessible. Specific reasons in patients with CD include an obstructed gut, a short bowel, often with a high intestinal output or an enterocutaneous fistula.	B	4.1
Active disease	Parenteral nutrition (PN) should not be used as a primary treatment of inflammatory luminal CD. Bowel rest has not been proven to be more efficacious than nutrition per se.	A	3.5
Maintenance of remission	In case of persistent intestinal inflammation there is rarely a place for long-term PN. The most common indication for long-term PN is the presence of a short bowel.	B	3.7
Perioperative	Use of PN in the perioperative period in CD patients is similar to that of other surgical procedures.	B	3.6
Application	When indicated, PN improves nutritional status and reduces the consequences of undernutrition, providing there is not continuing intra-abdominal sepsis	B	1
	Specific deficits (trace elements, vitamins) should be corrected by appropriate supplementation.	B	1
	The use of PN in patients with CD should follow general recommendations for parenteral nutrition.	B	1

(*continued on next page*)

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis; PN, parenteral nutrition.

E-mail address: espenjournals@espen.org.

0261-5614/$ – see front matter
doi:10.1016/j.clnu.2009.04.022

Summary of statements: Parenteral nutrition in Crohn's disease			
Subject	**Recommendations**	**Grade**	**Number**
Route	Parenteral nutrition is usually combined with oral/enteral food unless there is continuing intra-abdominal sepsis or perforation. Central and peripheral routes may be selected according to the expected duration of PN	C	3.2
Type of formula	Although there are encouraging experimental data, the present clinical studies are insufficient to permit the recommendation of glutamine, n-3 fatty acids or other pharmaconutrients in CD.	B	4.3
Undernutrition	Parenteral nutrition may improve the quality of life in undernourished CD patients.	C	3.4
Summary of statements: PN in ulcerative colitis			
Subject	**Recommendations**	**Grade**	**Number**
Indication	Parenteral nutrition should only be used in patients with UC who are malnourished or at risk of becoming malnourished before or after surgery if they cannot tolerate food or an enteral feed	B	9
Active disease	There is no place for PN in acute inflammatory UC as means of enabling bowel rest.	B	10
Maintenance of remission	Parenteral nutrition is not recommended.	B	11
Application	Treat specific deficiencies when oral route is not possible.	C	5
Type of formula	The value of specific substrates (n-3 fatty acids, glutamine) is not proven.	B	10.2
Summary of statements: Short bowel syndrome (intestinal failure)			
Subject	**Recommendations**	**Grade**	**Number**
Indication	Maintenance and/or improvement of nutritional status, correction of water and electrolyte balance, improvement in quality of life.	B	15
Route			
Post-op period	Predictions on the route of nutritional support needed can be made from knowledge of the remaining length of small bowel and the presence or absence of the colon. PN is likely to be needed if the remaining small bowel length is very short (e.g., less than 100 cm with a jejunostomy and less than 50 cm with a remaining colon in continuity). With longer lengths parenteral nutrition, water and electrolytes may be needed until oral/enteral intake is adequate to maintain nutrition, water and electrolyte status.	B	17.1
Adaptation phase	Patients with a jejunostomy have little change in their nutritional/fluid requirements with time. Patients with a colon in continuity with the small bowel have an improvement in absorption over 1–3 years and parenteral nutrition can often be reduced or stopped. Dietary counseling is important for those with a retained colon and may facilitate intestinal adaptation. In patients with a jejunostomy and a high output stoma advice on oral fluid intake and drug treatments are vital.	B	17.2
Maintenance/ Stabilization	Parenteral nutrition, water and electrolytes (especially sodium and magnesium should be continued when oral/enteral intake is insufficient to maintain a normal body weight/hydration or when the intestinal/stool output is so great as to severely reduce the patient's quality of life. Assuming strict compliance with dietary/water and electrolyte advice, after 2 years, dependency on PN is likely to be long-term.	B	17.3
Type of formula	No specific substrate composition of PN is required per se.	B	16
	Specific attention should be paid to electrolyte supplementation (especially sodium and magnesium).	B	16, 17
	Currently, the use of growth hormone, glutamine or GLP-2 cannot be recommended.	B	18

1. Crohn's disease

1.1. What influence does CD exert on nutritional status and on energy and substrate metabolism?

1.1.1. Acute phase

Undernutrition or protein–energy malnutrition, which is a prominent feature of CD, develops largely as a result of the systemic inflammatory response.

Anorexia, inadequate food intake, reduced absorption, increased intestinal loss and altered protein synthesis, all contribute to a significantly reduced nutritional status.

Deficiencies of micronutrients (vitamins, minerals and trace elements) are common especially in the acute phase of CD or after extensive surgery.

In children and adolescents a decrease in growth velocity may occur as a consequence of systemic inflammatory response, nutritional disturbances and due to drugs (e.g., steroids).

Comments: A low Body Mass Index (BMI) and recent weight loss in CD reflect poor nutritional status as well as poorly controlled disease. The systemic inflammatory response, poor or decreased oral intake (precipitated by anorexia, vomiting, fasting for tests) are the primary causes of malnutrition while several other factors contribute significantly, including nutrient malabsorption, increased nutrient requirements and increased resting energy expenditure in septic or underweight patients.[1,2]

Malnutrition is very common in CD, with an incidence ranging from 25 to 80%.[3] There is significant influence of small bowel involvement on body weight in CD, suggesting that individuals with small bowel disease have a higher risk of inadequate nutrition, probably because of simultaneous malabsorption, protein losing enteropathy and decreased energy intake.[4] CD patients with small bowel resection have lower bone mineral content, lean body mass, and BMI compared with those without small bowel resection. A negative nitrogen balance caused by reduced intake, increased intestinal losses, and steroid induced catabolism occurs in more than 50% of patients with active CD.

Resting energy expenditure (REE) may vary depending on inflammatory activity, disease extent and nutritional status.[5] Today it is generally accepted that total energy expenditure is similar to that in healthy subjects, but REE has been found to be increased, normal or even reduced.[2,6] It is slightly increased if calculated in relation to fat free mass (FFM) when this is low.[7] Changes in substrate metabolism, with reduced oxidation of carbohydrates and increased oxidation of lipids, are similar to the alterations in patients during starvation and are not disease specific.[8] They are mostly reversible when patients receive adequate nutritional support. An intake of 25–30 kcal/kg/day is usually adequate to meet energy and nutritional requirements.

The severity of the clinical picture, reduced intake, increased fecal losses, and diarrhea can each decrease serum concentrations of potassium, magnesium, calcium and phosphate.[9]

Regarding water-soluble vitamins, lower serum concentrations and deficits of vitamin B12 are well documented, depending on

the involvement or resection of the distal ileum.[10,11] Measurement of serum concentrations of ascorbic acid, nicotinic acid and biotin, unfortunately are not useful for estimating inadequate supply.

Homocysteine levels are significantly elevated in CD.[12] Elevated levels correlate with both low B12 and folate levels, but folate deficiency is the more important factor.

When patients are grouped according to the length of resected small bowel, a significant reduction of selenium and glutathione peroxidase in both plasma and erythrocytes was only found in patients with resection of >200 cm. The increased production of reactive oxygen species from activated neutrophils in CD may reduce plasma concentrations of antioxidant vitamins and result in increased oxidative stress. The reduced free radical scavenging action of zinc and selenium as a result of their deficiency may contribute to the continued inflammatory process.[13,14]

Plasma antioxidant vitamins (ascorbic acid, alpha- and beta-carotene, lycopene, and beta-cryptoxanthin) can be lower in CD patients than in control subjects but are of uncertain clinical significance.[15] Vitamin E levels correlate with both total blood cholesterol and total blood lipid concentration.[16]

The lower plasma concentrations of retinol seen in active CD usually remain subclinical and are normalized after treatment, without the necessity for supplementation.[17] Low concentrations of 25(OH)-vitamin D are however found in more than half of patients. Decreased levels of vitamin K are also associated with reduced bone mineral density.[18]

Malnutrition is a common in children with CD as in adults and may result in reduced skeletal muscle function and growth retardation. In children and adolescents with CD, growth retardation has been described in up to 40% and two-thirds of them have weight loss and decrease in muscle mass and body fat. Significant numbers of adolescent patients have decrease in height and/or growth velocity below the 3rd centile and this may precede other symptoms of CD. Growth retardation persists in 20–40% of patients and final body height is below the 5th centile in 7–30 % of patients. This can be explained by the fact that CD usually starts at a young age and may impair growth, and it has previously been demonstrated that earlier onset of CD more greatly affects adult height.[19] Nutritional treatment may restore growth velocity, after a period of retardation, but ultimate height still falls short of genetic potential.[20]

1.1.2. Remission

Nutritional status of CD patients in remission is not uniform; there is a spectrum from severe protein energy malnutrition to an apparently normal.

Undernutrition, if present, is mainly due to malabsorption resulting from previous surgery, with bile acid induced diarrhea, steatorrhoea, or from the development of short bowel syndrome, bacterial overgrowth, or drug treatment. Anorexia and inadequate food intake are issues even in patients in remission.

Specific deficits of micronutrients (vitamins, minerals and trace elements) require special attention. Deficiency of vitamin B12, folate and/or iron can lead to severe anemia.

Comments: Nutritional status, body mass index (BMI) and other parameters vary from apparently normal to significantly decreased in CD patients compared to healthy controls.[21] While weight loss and low bone mineral density are well documented in CD, few studies have focused on other components of body composition, specifically lean body mass and fat stores. Lean body mass has been shown to be significantly reduced in CD patients even when predominantly in clinical remission. There is emerging evidence that reduced muscle function may be a common feature in CD patients who are in remission.[22] This feature may remain undetected as these patients would typically be classed as well-nourished according to routine assessment measures.[23]

In CD patients, reduced body weight was found to be related to reduced body fat mass (FM), whereas fat free mass (FFM) was maintained.

Although weight loss is a known problem, excessive weight gain does occur and may mask underlying malnutrition (e.g., changes in lean body mass or bone mass or nutritional deficiencies). Patients of normal weight or who are overweight may look healthy and thus would not typically be considered for nutritional screening or assessment. Preliminary data showed that one-third of patients with inactive CD were overweight.[24]

In the presence of similar energy intake, REE does not seem to contribute to lower BMI, although nutrient malabsorption is higher in malnourished patients with CD in remission.[25] Alterations of substrate metabolism are still present in quiescent disease.[4] The non-protein respiratory quotient has been shown to be significantly lower in CD compared to healthy controls, indicating increased lipid oxidation. This increased lipid oxidation might explain the reduced fat stores found in Crohn's patients.[26] The intake of energy and nutrients in most CD patients is sufficient and comparable to that of a healthy population.

Bone mineral content and lean body mass are significantly lower in patients with CD compared with patients with UC and healthy subjects.[27] In untreated patients, osteopenia caused by nutritional deficits (including protein, vitamin D and calcium) and by inflammatory cytokines may develop as the disease progresses. There is a strong link between osteopenia and steroid therapy.[28] Osteoporosis is more likely with a diagnosis of CD, low body mass index in women, and postmenopausal status.[29]

In remission, deficiencies of macronutrients are rare. Serum vitamin B12 and folate should however be measured annually in patients with ileal CD.[30] Anemia could be caused by deficits of iron, vitamin B12 and folate,[31,32] which should direct investigation and treatment.

1.2. What influence does nutritional status exert on outcome?

Undernutrition has a negative impact on the clinical course, the rate of postoperative complications and mortality.

Comments: The key influences on outcome include water and electrolyte equilibrium, volume deficits, and protein-energy malnutrition.[33,34]

Preoperative undernutrition increases the likelihood of postoperative complications (especially anastomotic breakdown)[35–37] [**IIA**].

There is a high rate of sepsis in CD patients, a high rate of pneumonia and an increase in MRSA and other resistant infections. Hospital stay is prolonged significantly.

Also it is obvious that costs (both direct and indirect) are high.[38]

1.3. What are the goals of parenteral nutrition therapy?

1.3.1. Prevention and treatment of undernutrition

In patients with CD, parenteral nutrition may correct or prevent undernutrition but should be used only when oral/enteral feeding is not possible [B].

1.3.2. Bowel rest

Although the fecal stream is likely to play a role in the pathogenesis of CD, there is no evidence that bowel rest combined with parenteral nutrition may be beneficial in refractory CD [B].

Current theories on the immunopathogenesis of CD emphasize a T helper cell type 1 response probably directed against antigens of the commensal flora. The susceptibility genes so far identified[39] are associated with innate recognition of microbial products or epithelial barrier function.[40] The over expression of pro-inflammatory cytokines and increased production of matrix degrading enzymes by fibroblasts and macrophages are probably responsible for ulceration and fistula formation. Bowel rest might influence this process, beneficially[41] or otherwise[42] by altering intestinal flora[43] or changing the immunological responses to it. Lack of intestinal stimulus by food will affect intestinal motility and could predispose to bacterial overgrowth,[42] or could result in reduction of intestinal flora.[41]

A retrospective Canadian study[44] suggested that "bowel rest" and parenteral nutrition could be beneficial in refractory CD. The concept seemed attractive because it had long been known that surgical diversion of the fecal stream away from inflamed parts of the intestine could result in reduction in the inflammation, though it ignored the potential importance of food's trophic effect on the intestinal mucosa. Early clinical trials[45,46] of treating severe colitis, both UC and CD, with parenteral nutrition with no nutrients by mouth or via the intestine proved unpromising; while improvement of nutrition was beneficial, no benefit arose from reducing oral or enteral intake [**IIA**]. The Canadian group's prospective controlled trial, in which TPN with bowel rest was compared with nasogastrically administered enteral formula or partial parenteral nutrition with food,[47] showed no statistically significant difference between the three small groups and suggested that it was the improvement of nutrition that was most important [**IB**]. Further uncontrolled studies continued to be published suggesting that parenteral feeding as part of a therapeutic package could play a role in Crohn's colitis.[48] Since the early nineties all the emphasis has been on enteral nutrition and its role in primary therapy in CD,[49] which has been accepted, particularly in pediatric practice. Though Greenberg et al's study if anything suggested a slight, non significant advantage for parenteral feeding with nothing by mouth, there has been little work to examine potential clinical benefit from total parenteral nutrition with nil by mouth since. The argument that enteral feeding is as good and carries fewer side effects and lower expense has prevailed. On present evidence this argument holds good. It is unlikely that there will be a controlled trial done with a sample size big enough to demonstrate whether TPN with nil by mouth is (a) marginally more effective or (b) as effective as enteral feeding.

1.3.3. Improvement of growth

Growth is impaired in most children with CD at some stage. Adequate nutrition should be given, but primarily by the oral and/or enteral route. PN should be used if enteral feeding cannot be tolerated (in addition to the indications given at the start of this manuscript) (B).

Growth failure in CD is the result of the inflammatory response and malnutrition.[50] Any treatment which affects either can be expected to have a beneficial effect on growth. Parenteral nutrition has no known advantage in this respect over enteral nutrition – reviewed elsewhere.[49] Specific nutrient deficiencies such as zinc, vitamin D for example should be addressed and then appropriate energy and nitrogen supplied by the simplest, safest route acceptable to the patient.

1.3.4. Improvement of quality of life

Improvement of chronic malnutrition improves quality of life but this is not specific to parenteral nutrition.

Comments: Malnutrition affects quality of life in gastroenterology patients including those with CD.[51] Impaired functional status has been observed despite apparently normal nutritional status in patient with quiescent CD.[22] Obviously, quality of life may be altered in CD patients who required long-term parenteral nutrition.[52] However, long-term home parenteral nutrition may improve rehabilitation and its social components[53] [**III**].

1.3.5. Primary therapy for active CD

Parenteral nutrition should be not used as a primary treatment in patients with inflammatory luminal CD [A].

Comments: Although a few uncontrolled trials showed some benefit of parenteral nutrition in CD colitis, the only prospective trial comparing parenteral, enteral or oral food failed to slow any advantage of parenteral nutrition and bowel rest[47] [**IB**].

1.3.6. Perioperative nutrition

As for other underlying diseases, parenteral nutrition in the perioperative period should be given to prevent or treat malnutrition in patients who are not likely to be fed orally and/or enterally.

1.3.7. Maintenance of remission

Parenteral nutrition is not recommended for maintenance of remission [B].

Patients in whom remission is induced by parenteral nutrition may have a lower recurrence rate if maintained on subsequent artificial liquid diet.[54] Continued parenteral nutrition is clearly not a practical approach to maintenance of remission.

1.4. Practical implementation of PN

1.4.1. Which patients should receive PN? When is PN indicated?

Parenteral nutrition is indicated when nutrition cannot be maintained via the intestine in the following situations:

1. ***Obstructed bowel not amenable to feeding tube placement beyond the obstruction.***
2. ***Short bowel resulting in severe malabsorption or fluid and electrolyte loss which cannot be managed enterally.***
3. ***Severe dysmotility making enteral feeding impossible.***
4. ***A leaking intestine from high output intestinal fistula, or surgical anastomotic breakdown.***
5. ***Patient intolerant of enteral nutrition whose nutrition cannot be maintained orally***
6. ***Unable to access the gut for enteral feeding [B].***

Comments: Malnutrition is a common comorbidity that places patients at risk of complications, infections, long length of stay, higher costs, and increased mortality. Malnutrition is frequent in CD patients, thus nutrition support has become an important

therapeutic adjunct in the care of these patients. For patients unable to feed themselves, nutrition can be delivered via the parenteral or enteral routes. If the gut can be used safely, enteral nutrition is the preferred feeding method for CD patients needing nutritional support.[55] The advantages of enteral nutrition are stimulatory effects on gastrointestinal structure and function and reduced cost when compared to parenteral feeding. If the gastrointestinal tract cannot be used safely, parenteral nutrition is recommended.[56]

Exclusive parenteral nutrition can achieve high rates of remission, but this is not usually necessary since exclusive elemental and polymeric enteral regimes can yield similarly good results.[57] Greenberg and colleagues[47] undertook a multicentre controlled trial in which 51 patients with active CD were randomly assigned to total parenteral nutrition, defined-formula diets (tube feeds), or partial parenteral nutrition plus a low residue diet. There was no difference in response rates or remissions at one year [**IB**]. Similar results were reported by other investigators in both prospective[58,59] and retrospective studies[60] [**IIA**]. When nutritional support is indicated to treat the active phase of CD, enteral nutrition should be considered first. As for the treatment of malnutrition, PN can be considered in cases of small bowel obstruction, severe malabsorption, high output fistula, and intolerance of enteral nutrition.

In a European study 19% of patients treated with home parenteral nutrition suffered from CD,[61] the majority of them having a short bowel [**III**].

A survey on the utilization of parenteral nutrition during the in-patient management of inflammatory bowel diseases was recently performed in the United States[62] [**III**]. This study showed that only 64% of CD patients had an accepted indication for PN, e.g., malnutrition, fistulizing or obstructive CD, or recent surgery.

1.4.2. Are there contraindications to PN in CD?

The contraindication to PN in CD are similar to the contraindications to PN in other diseases [B].

Comments: There is no specific contraindication for using parenteral nutrition in patients with CD in comparison to other diseases. Nevertheless, it should be remembered that the inflammatory bowel diseases (IBD) themselves constitute an independent risk factor for the development of venous thromboembolism.[63]

1.4.3. Do specific parenteral formulas (e.g.: glutamine, omega-3 fats, etc.) offer any benefit in the treatment of CD?

Although there is a good rationale for the use of glutamine, n-3 fatty acids and other pharmaconutrients in the parenteral nutrition of patients with CD, there is currently insufficient enough evidence to recommend their use [B].

Comments: Glutamine is a conditionally essential amino acid with specific trophic effects upon intestinal epithelium. In animal models of intestinal inflammation, glutamine supplementation increases glutamine plasma concentration, reduces intestinal damage, improves nitrogen balance and may improve the course of the disease.[64,65]

The usefulness of glutamine supplementation – either enteral or parenteral – in CD has however scarcely been studied. To date, only two small RCT have compared glutamine-enriched enteral formulas to standard formulas or placebo[66,67] [**IB**]. Neither of them was able to demonstrate any benefit to the glutamine-supplemented groups. There is only one RCT comparing glutamine-enriched to standard parenteral nutrition, which was as adjuvant therapy in 24 patients with an acute attack of inflammatory bowel disease (19 of them with CD)[68] [**IB**]. The primary end points were the plasma concentration of glutamine, and intestinal permeability assessed by urinary lactulose: D-xylose ratio. There were no differences in these parameters between the glutamine-supplemented and the non-supplemented groups. Also, changes in inflammatory and nutritional parameters, disease activity, length of TPN and hospital stay, and surgical requirements were independent of glutamine-supplementation.

The anti-inflammatory effects of n-3 fatty acids (fish oils) have been suggested as offering benefit in chronic inflammatory disorders such as IBD. Several trials have assessed the usefulness of oral administration of n-3 fatty acid supplements for maintaining remission in both UC and CD. Recent systematic reviews with meta-analysis of these studies[69,70] conclude that n-3 fatty acids may be effective for maintenance of remission in CD when administered in enteric coated capsules [**IB**]. However, there are not sufficient data to recommend the routine use of oral n-3 fatty acids for maintenance of remission in CD. To date, there appear to be no data on the efficacy of n-3 fatty acid enriched parenteral lipid emulsions in inflammatory bowel disease [**IV**].

No other pharmaconutrients given by the parenteral route have been adequately assessed in IBD.

1.4.4. What influence does drug treatment have on nutritional status?

Drug therapy (e.g., steroids, anti-TNF agents) may influence nutritional intake as well as body weight composition.

Comments: In CD patients, steroid therapy increases nutritional intake, promoting overall positive energy balance.[71] Successful use of the new anti-TNF therapies (e.g., infliximab, adalimumab) generally induces weight gain[72] [**IIA**].

In children, no significant changes in energy expenditure were observed following infliximab in fasting or parenterally fed patients[73] [**IIA**].

2. Ulcerative colitis

2.1. What influence does UC have on nutritional status as well as on energy and substrate metabolism?

Disease related undernutrition or protein energy malnutrition, weight loss and sub-optimal nutritional status including some specific deficiencies of micronutrients may be present at any stage of UC.

However, patients with UC are usually well-nourished when in remission.

Anemia is very common in UC, mostly caused by iron or folate deficiency.

Comments: There is a shortage of new epidemiological studies in UC regarding the prevalence of undernutrition, protein energy malnutrition and weight loss.[74–77] UC patients are generally considered less prone to deterioration in nutritional status than CD patients, especially during the remission of the disease.[78–80] Stable out-patients with UC have only a minimal increase in energy needs.[5] Body weight and body mass index are however significantly lower in acute exacerbations of UC patients compared with healthy controls.[81] In growing children, inadequate nutrition and active disease may result in a failure to thrive and growth retardation.

Changes in lean body mass, muscle function, and body fat in UC patients are insufficiently well documented. UC patients generally

have significantly higher fat mass and body mass index than patients with CD.[27] Active therapy can nonetheless improve physical performance and increase lean body mass.[82]

Several studies have assessed the prevalence of anemia in UC.[31,32,83] Severe anemia is mostly defined as hemoglobin under 100 g/l, but some investigators have included levels <120 g/l as borderline deficiency. In UC patients estimates of the prevalence of anemia range from 8.8 to 66.6%. A higher percentage of IBD patients develops mild anemia at least once during the chronic course of the disease.[84]

Iron deficiency which is a main cause of anemia, resulting from blood loss, is seen in up to 80% of patients with UC.[85] The high prevalence of hyperhomocysteinemia in UC and in CD is mostly related to a low folate level.[86,87]

Selenium deficiency and antioxidant deficiency have been described in UC.[13,88,89] Serum concentrations of several nutrients (beta-carotene, magnesium, selenium and zinc) were found to be significantly lower in UC patients than in controls.[78,90–92] Measurement of plasma concentrations however does not help in the diagnosis of deficiencies of most micronutrients. While older age is a significant risk factor, BMI, lean body mass and disease type (CD versus UC) are all correlated with the risk of osteoporosis.[93–97] Adrizzone showed (based upon the WHO guidelines) that only 8% of CD patients and 15% of UC patients had normal bone mineral density (BMD); 55% (CD) and 67% (UC) were osteopenic, and 37% (CD) and 18% (UC) were osteoporotic.[98] IBD patients have diffuse osteopenia, the degree of which is not substantially different in CD and UC; however, bone turnover is significantly higher in UC. Relative to that in respective controls, CD and UC patients have significantly ($P < 0.01$) lower serum total osteocalcin and 25-hydroxyvitamin D.[99]

2.2. Does disease activity influence oral nutritional intake?

Inadequate intake of protein and/or energy has been reported in acute UC. Nutritional intake is not compromised in remission.

2.3. What influence does drug treatment have on nutrition status?

There are no studies investigating the effect of drug treatment on nutritional status in UC. However, folic acid deficit may be related to sulfazalasine therapy.

Comments: Folic acid deficit has been reported frequently with sulfasalazine therapy in UC patients[100,101] [**IIA**]. Recent studies have shown normal or higher levels of folate. The possible explanation is that most UC patients on sulfasalazine now use concomitant folic acid supplements.

2.4. What influence does nutrition status exert on outcome?

There are no data available for UC.
As for any other clinical situations, it is assumed that undernutrition may affect the postoperative morbidity.

2.5. Is PN indicated in order to treat undernutrition in UC?

Except in complicated UC or in the perioperative period, PN is not indicated to treat undernutrition in UC.

2.6. Is parenteral nutrition indicated in the therapy of active UC?

Parenteral nutrition is indicated as an adjuvant to other forms of medical treatment – but not as a primary treatment – and is used in severe attacks of UC only when enteral nutrition is not tolerated or there are contraindications for its use (e.g., impending or established toxic megacolon, colonic perforation, or massive colonic bleeding) [B].

Comments: In contrast to CD, artificial nutrition – both enteral and parenteral – does not have a primary therapeutic effect in UC. The use of total parenteral nutrition as an adjuvant therapy for inflammatory bowel disease was traditionally based on certain theoretical advantages: 1) bowel rest would be beneficial because it diminishes motor and transport function of the diseased bowel; 2) a decrease in antigenic stimulation will eliminate the immunological responses to food, especially in the presence of impaired intestinal permeability. However RCT conducted in the eighties and early nineties[8–10,45,46,102] [**IB**] clearly demonstrated that parenteral nutrition is not a *sine qua non* for a good outcome in severe UC. Moreover, adverse events attributable to artificial nutrition are more frequent when the parenteral route is used, and the postoperative morbidity of those patients requiring colectomy is lower with enteral feeding.[10,102] In the light of these data, enteral nutrition should be the preferred modality of artificial nutritional support in severe UC unless it is not tolerated or there is a contraindication to its use. Contraindications include impending or established toxic megacolon, colonic perforation, and massive colonic bleeding.

2.6.1. Do specific parenteral formulas (e.g., glutamine, omega-3 fats, etc.) offer any benefit in the treatment of UC?

Although there is a good rationale for the use of glutamine, n-3 fatty acids and other pharmaconutrients in parenteral nutrition for patients with UC, there is currently no evidence to recommend their use in these patients [B].

The rationales for using glutamine, omega-3 fatty acids, and other specific nutrients are the same for UC as for CD (see Section 1.4.3). Available data on the use of these compounds in parenteral formulas for patients with UC are even more scarce. The single RCT assessing the effect of glutamine-enriched parenteral nutrition in inflammatory bowel disease included only five UC patients[68] [**IB**]. Systematic reviews and meta-analyses on the use of orally administered omega-3 fatty acids in inflammatory bowel disease fail to demonstrate any benefit of these compounds in UC[69,70] [**IA**]. There are no data on the efficacy of parenteral nutrition enriched in either n-3 fatty acids or other pharmaconutrients in UC.

2.7. What value does parenteral nutrition have in the maintenance of remission in UC?

Parenteral nutrition does not have any role in the maintenance of remission in UC [B].

Comments: Parenteral nutrition does not appear to have any role as primary treatment of UC. Early studies showed that relapse rates in UC patients receiving parenteral nutrition could be as high as 40–62% at two years.[103]

2.8. Contraindications and complications of parenteral nutrition

Despite not being the preferred route for artificial nutrition, there are no specific contraindications for the use of parenteral nutrition in UC. However, parenteral nutrition related morbidity has proved to be higher than that during enteral feeding [B].

Comments: Parenteral nutrition should be considered a second line modality of artificial nutrition in UC. However, there is no

absolute contraindication for its use. Complications attributable to artificial nutrition are however more frequent with parenteral than with enteral nutrition. Catheter-related sepsis (which is obviously inherent to the parenteral route), metabolic complications (e.g., hyperglycemia) and deranged liver function tests are the most prevalent complications of PN in these patients.[102,104] In a recent survey on the utilization of parenteral nutrition in hospitalized patients with inflammatory bowel disease in the USA, the use of parenteral nutrition was associated with higher in-hospital mortality (OR 2.5; 95% CI: 1.93–3.24), length of stay (13.7 vs. 5.7 days, $P < 0.001$) and hospital charges ($51,729 vs. $19,563, $P < 0.001$)[62] [**III**].

3. Short bowel (Intestinal failure)

3.1. Definition

Two definitions of intestinal failure have recently been published. The principle underlying both is that there is a failure of absorption by the intestine

1. "Reduced intestinal absorption so that macronutrient and/or water and electrolyte supplements are needed to maintain health and/or growth. Undernutrition and/or dehydration result if no treatment is given or if compensatory mechanisms do not occur.[105]
2. "Results from obstruction, dysmotility, surgical resection, congenital defect or disease – associated loss of absorption and is characterized by the inability to maintain protein–energy, fluid, electrolyte or micronutrient balance".[106]

The severity of intestinal failure can be classified according to the type of nutritional support given/needed: mild if oral/dietary adjustments and/or oral salt and water are given; moderate if enteral nutrients and/or salt and water are given; and severe if parenteral nutrients and/or saline is given.

Intestinal failure can be classified as acute (temporary or reversible) or chronic. Acute can be subdivided into hyperacute (type 1 using the Hope Hospital classification[107]) which includes short term perioperative patients or those undergoing chemotherapy and the subacute type who have usually had complications following abdominal surgery and often have enterocutaneous fistulas and/or obstructed bowel and may undergo corrective surgery 3–6 months later (type 2 using the Hope Hospital classification). Chronic intestinal failure patients are those with a non-reversible, long-term situation that needs long-term nutrient and/or water and electrolyte therapy (type 3 using the Hope Hospital classification).

There are three main types of patient with a short bowel; those who have had a jejuno-ileal resection, colectomy and formation of a stoma (*Jejunostomy*); those who have had a jejuno-ileal resection and a jejuno-colic anastomosis (*Jejunum-colon*) and those who have had a predominantly jejunal resection, and have more than 10 cm of terminal ileum and the colon remaining (*Jejunum–ileum*). Jejunostomy and jejunum-colon patients are most commonly encountered.[108,109]

The most common reasons for a short bowel in adults are superior mesenteric artery thrombosis, CD and irradiation damage. A short bowel more commonly arises in women than men, possibly because women start with a shorter length of small intestine than men.

As lipid is absorbed over a longer length of intestine than carbohydrate and protein, fat malabsorption (steatorrhoea) may be an obvious problem and can be associated with fat soluble and essential fatty acid deficiencies. As B_{12} and bile salts are absorbed in the distal ileum there may be B_{12} deficiency, and unabsorbed bile salts or long chain triglycerides can worsen diarrhea in patients with a retained colon.[110]

Frequently the remaining bowel type and length is unknown and the patient is said to have "ileostomy diarrhea".[111] As stomal fluid has a sodium concentration of about 100 mmol/l (range 80–140) it is easy for these patients to develop dehydration (salt and water depletion) especially if the output exceeds 2 l/24 h. If less than 100 cm jejunum remains most patients will lose more from their stoma than they take in orally (net secretor status) and will need parenteral support. Magnesium depletion is common in these patients, partly because of a loss of secretions and a failure of absorption which is made worse by unabsorbed fatty acids binding to intraluminal magnesium.[112] In addition secondary hyperaldosteronism resulting from sodium depletion increases urinary magnesium and potassium losses.[113]

3.2. What influence does the disease exert on nutritional/fluid status as well as on energy and substrate metabolism?

A short bowel may impair absorptive capacities of the gut and provoke dehydration with electrolyte disturbances as well as acute renal failure. In the acute phase, sepsis or inflammatory processes may increase the energy expenditure.

Ongoing sepsis or active disease (e.g., CD) increases catabolism, and despite the provision of apparently generous amounts of energy (even given parenterally) the patient may not gain weight or muscle mass. Sepsis is the main cause of death in these patients (especially subacute/type 2 patients) and thus the most important part of their management is in trying to locate and treat sepsis.[106,107]

Patients with a small bowel stoma may have an increased output not only from having a short remaining length of small bowel (e.g., less than 200 cm from the DJ flexure) but also from partial small bowel obstruction, abdominal sepsis, active disease, drug cessation (steroids or opiates), prokinetic drugs (e.g., metoclopramide) and from small bowel infection (e.g., *Clostridium difficile*). Bacterial overgrowth in dilated areas of bowel may contribute to a high output and may also aggravate the malabsorption.[114]

A high stomal output (typically more than 2 l daily) will result in dehydration (salt and water depletion). If more than 60 cm of terminal ileum has been resected then vitamin B_{12} supplementation is very likely to be needed, and some patients need this even after more limited resection.

3.3. What influence does nutritional/fluid status exert on outcome?

A poor nutritional status may alter the quality of life and increase the risk of morbidity and mortality.

A patient of low weight is likely to have problems of undernutrition which include general tiredness, weakness, loss of concentration, prolonged sleep, risk of infections, poor wound healing, reduced growth/sexual development, lower body temperature. These result in high dependency nursing, increased hospital stay and increased morbidity and mortality. Water and electrolyte (especially sodium and magnesium) depletion cause postural hypotension, thirst, muscle cramps, tremor and poor concentration. Renal failure may result if left untreated. Many patients are labeled as having "ileostomy diarrhea" and are given incorrect advice to increase their hypotonic fluid intake.[115]

3.4. What are the goals of nutritional/fluid therapy

The goals of parenteral support are to correct nutritional status, and to maintain fluid and electrolyte balance, in order to optimize quality of life.

The overall aim of parenteral support is to restore and maintain nutritional adequacy and thus to help achieve a good/normal quality of life. This is partly met by restoring or maintaining a normal body weight and growth/sexual maturation in children. It also involves achieve hydration (salt and water balance) and a normal serum (red blood cell) magnesium. There should be no vitamin or micronutrient deficiencies. These goals are achieved in conjunction with consideration of the patient's height, weight, and usual weight in health/desired body weight. A target weight can usually be set and an appropriate amount of energy given to meet this over an appropriate interval. Asking about thirst, measuring postural systolic blood pressure and measuring random urine sodium concentration all help to assess hydration.[116]

Since the connection to a central line impairs the mobility and quality of life of the patients, parenteral regimens should be designed to be provided on as few nights as possible but still to ensure correct fluid balance. This can be difficult if there are high stomal fluid losses. Even then it may be better to have intravenous fluids only (no nutrition) on some days, since they can generally be given more quickly than high osmolality nutritional admixtures. In general PN is given overnight so the patient can appear normal during the day and may go to work or undertake other duties and activities. Some use portable pumps and infuse during the day, which may also be more physiological. It can be difficult for patients to take normal meals, as they may have to regularly empty their stoma bags. Sometimes taking no fluid for half an hour before and after food can reduce the sudden high output with food even if it does not reduce the total daily stomal output. More details are given in the ESPEN guidelines on Home Parenteral Nutrition.

3.5. Do patients require specific substrate (PN) composition?

PN composition must be adjusted to fulfill the needs of the individual single patient. This will depend on the extent of malabsorption, and enteric losses, and will influence the prescription of energy and amino acids, and especially of water, electrolytes and minerals [B]. Each PN cycle (usually nocturnal) should be complete and adjustment will be made on the number of cycles per week [C]. 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. Currently, no specific substrate composition is mandated per se, but every micronutrient should be given in order to avoid deficiency and to promote protein/energy efficiency [B].

Comments: Energy and protein: 2/3 of calories as glucose and 1/3 from lipid emulsion ($\geq$20%) seems a good compromise. No more than 1 g/kg/day of standard lipid emulsions can be recommended, because greater amounts prove a significant independent factor for chronic cholestasis and progression through liver fibrosis to cirrhosis, even in the optimal case of "normonutrition".[117] Total energy (including protein) should comprise between 0.85 and 1.5 times the REE. Nitrogen needs should be given as amino acids at 1–1.5 g/kg/day, to take into account increased digestive protein losses.[118,119] Ideally, digestive balance, either negative or positive[110,120,121] has to be summated with the IV infusion to reach the final level of the needs [**IIA**]. The second adjustment is achieved with the attempt to decrease the number of IV infusions per week; indeed the patient usually prefers, for obvious QOL reason, a minimum number of "complete" IV infusions per week.[122]

Gastrointestinal fluid balance (enteral fluid intake less stomal or stool output(s)) should be more than about 1.4 kg/day to be confident that the patient will not be dependent on parenteral support for hydro-mineral reasons.[121] In general a gastrointestinal output of more than 1.4 kg has similar significance. Around 20% of SBS patients remain dependent on parenteral supplies of water and sodium but become independent of parenteral protein and energy; this is especially the case in end-jejunostomy patients.[120] Then, water and sodium input should be given to obtain positive balances (avoid dehydration, tiredness, masked hypokalemia) and tailored according to each individual's needs, independently of protein energy needs.

For other nutrients, old studies have demonstrated that every mineral and most of the vitamins and trace metals (especially zinc) have to be in positive balance(s) to promote nitrogen retention.[123] Furthermore, dramatic clinical deficits were recognized in the pioneering era of HPN, when vitamin(s) or trace metal(s) had been omitted for various periods of time (from weeks to months) (see ESPEN HPN guidelines). It is accordingly recommended that *total* micronutrient requirements should be given via the IV route [**B**]. Some of them should be given in increased amounts because of the increased digestive losses (e.g., zinc, magnesium). Special effort should be made to avoid magnesium deficit given the interactions with sodium, potassium and calcium negative balances[112,113] [**IIA**]. Recently, pseudo gout has been demonstrated as being significantly associated with hypomagnesemia during HPN.[124]

3.6. What role does PN have in short bowel?

3.6.1. Post-operative phase

In the early phase after massive enterectomy, the main goal is to assure hemodynamic stability by providing water and electrolytes (e.g., intravenous normal saline or a balanced electrolyte solution such as Hartman or Ringer solution, 1–4 l/day, depending upon intestinal losses) [B].

Most patients with a short bowel require parenteral nutrition for the first 7–10 days after the resection but not necessarily in isolation [C].

Comments: In the early phase after massive enterectomy, the immediate goals are survival and hemodynamic stability aided by the provision of water and electrolytes. Nutritional therapy should not be introduced until the patient is hemodynamically stable.

To avoid sodium and water depletion from the stomal losses in patients with a jejunostomy it is easiest to rehydrate with mainly intravenous normal saline (2–4 l/day) while keeping the patient "nil by mouth"[125] [**IIb**]. After 1–2 days, oral food and restricted oral liquid are progressively introduced. The aim is to maintain good hydration status with a urine volume of at least 800–1000 ml with a random urine sodium concentration greater than 20 mmol/l.[114] Blood glucose concentration must be monitored at least daily while on PN and should be below the actual recommendations for acutely ill patients. There is currently no evidence for providing intravenous glutamine in order to increase intestinal adaptation.

Many patients with a short bowel require parenteral nutrition for the first 7–10 days. However, parenteral nutrition should not be started until the patient is hemodynamically stable and fluid/electrolyte balance has been reached [B]. Patients should receive about 25–33 kcal/kg and 1–4 l/day depending upon stomal/stool losses. Intravenous lipids should account for 20–30% of infused calories but may be increased in the short-term in the case of glucose intolerance. After 2 weeks the frequency of lipid administration may be reduced to 1–2 times a week to reduce the risk of

cholestasis [C]. Enteral nutrition should be initiated and progressively increased depending on the gut tolerance; a standard enteral diet is recommended if a colon is present in continuity. If a jejunostomy is present the enteral feed needs to be of lower osmolarity (e.g., around 300 mOsm/kg) and contain at least 100 mmol/l of sodium [A].

Initially, H2-antagonists or proton pump inhibitor (PPI) are started (and typically continued for six months) because acid hypersecretion may occur, even if there is a lack of direct evidence in man. The pH of the stomal output can be checked and should be >6 if adequate PPI is being absorbed. In the early stage, intravenous administration may be needed as the absorption of oral medicine may not be predictable. Acid suppression has the other important effect of reducing gastric fluid secretion, but may also prevent deconjugation of bile salts and may decrease endogenous pancreatic lipase excretion.

Loperamide hydrochloride or diphenoxylate reduce intestinal motility and intestinal losses by approximately 20–30%.[126,127] Typical doses of loperamide are 4 mg taken four times a day. If not effective, codeine phosphate (30–60 mg, 2–4 times daily) or tincture of opium may be necessary. In some cases, the effect of loperamide and opiate drugs both together may be greater. These drugs must be taken half an hour before food.

In adults, octreotide significantly reduces daily jejunostomy output (though may be no better than omeprazole). The greatest reductions in intestinal output are in those with a net secretory output. The volume of intravenous fluids may be reduced. Long acting octreotide/somatostatin preparations have not been assessed in large studies.[128–130] A recent small study with the long-active derivative of octreotide showed no benefit.[131] Long-term use of octreotide could reduce splanchnic protein synthesis, thereby reducing mucosal protein incorporation and villus growth rate. It could also increase the risk of cholelithiasis formation in patients with short gut.

3.6.2. Adaptation phase

Appropriate enteral and/or oral nutrition should be initiated as soon as possible and progressively increased depending on the tolerance of the gut and the patient.

Special attention must be paid to sodium, potassium and magnesium balance. Oral hydration in patients with a jejunostomy should include a glucose–saline replacement solution (with a sodium concentration of 90 mmol/l or more) [A].

In patients with a jejunostomy (and indeed in some with a retained colon) it is important to restrict the use of oral hypotonic drinks (tea, coffee, juices, beer, etc.) which cause sodium loss from the gut, and of hypertonic solutions that may contain sorbitol or glucose which cause both sodium and water loss[132,133] [**IB**]. Patients should be encouraged to drink a glucose–saline replacement solution (sodium 90 mmol/l or more). Several commercially available oral rehydration solution (ORS) formulas are available; although probably the best is that hitherto recommended by the World Health Organization (WHO) (the potassium chloride component can be omitted). Patients with a short bowel should be cautioned against consumption of plain water and should be invited to drink ORS whenever they are thirsty. The patients should be encouraged to sip these ORS solutions in small quantities all day long (cold with flavoring may make the solution more palatable).[134]

Patients with stomal losses of less than 1200 ml daily can usually maintain sodium balance by adding extra salt[135] [**IIA**]. Large amount of sodium chloride (8–14 capsules of 500 mg each) are effective but may provoke digestive intolerance with vomiting. Attention must be paid to the magnesium balance. In addition to sodium losses, significant losses of magnesium occur in the intestinal effluent and in the urine. Given that important magnesium deficiency may develop despite a normal serum magnesium concentration, it is ideal to measure 24-h urine magnesium loss.[136] Magnesium deficiency may be associated with: (a) calcium deficiency because hypomagnesemia impairs parathyroid hormone release[137,138]; and (b) potassium deficiency because hyperaldosteronism (from sodium depletion) increases renal retention of sodium at the expense of magnesium and potassium which are lost in high amounts in the urine. Oral supplementation of magnesium (often with 1-alpha calciferol) is not always successful and intravenous supplementation may be required[112] [**IIA**]. To correct hypokalaemia in patients with a high output stoma, sodium/water depletion must first be corrected to avoid hyperaldosteronism, and serum magnesium should also be brought into the normal range.

3.6.3. Maintenance/Stabilization phase

According to the length of residual small bowel as well as the type of anatomy (preserved colon or not), patients with short bowel may need long-term parenteral nutrition [B]. In some of them, the main problem is related to stabilizing their water and electrolyte balance. In some (usually with a retained colon) appropriate adaptive hyperphagia, and intestinal adaptation may improve nutritional status sufficiently that PN can be reduced or stopped [B].

Comments: Measurement of intestinal absorptive capacity is beneficial when considering dietary treatment of the individual short bowel patient.[114] Patients can be categorized as having problems with sodium or protein–energy balance, or both, and balance studies may quantify the degree of intestinal insufficiency.[121] This enables the physician to identify patients with suspected irreversible intestinal failure, either due to sodium or energy malabsorption, and those in whom dietary manipulations alone are more justifiable. Recommendations are always dependent upon remaining intestinal physiology.

The consequences of dietary manipulations, however, not only on nutrient, electrolyte and fluid absorption, but also on overall quality of life, must be taken into consideration when guiding short bowel patients.[119] Dietary manipulations may affect the palatability of food and the sense of satiety, which may be of importance when encouraging the patients towards an increased energy intake. Dietary manipulations may also affect abdominal sensation; discomfort, bloating and passing of air are common in this context, and changes in fecal consistency and fecal incontinence may seriously impair quality of life. The patient's autonomy should be respected and nurtured by efforts of physicians and dieticians in support of the patient who faces intestinal failure. Some patients prefer the hyperphagia, large stool volumes, fatigue and chronic dehydration in order to avoid a life tied to a central line and parenteral supplements[110] [**IIa**]. Others see parenteral supplements as a place of refuge escaping the demands of constant hyperphagia and concomitant large stool volumes and abdominal discomfort. Balance studies should not only be seen as tools of studying intestinal physiology in the short bowel syndrome, but they also give the individual patient a chance to experience the effect of extreme diets on fluid and energy absorption and on their well being.[139] Optimal nutritional care, guidance and support are of vital importance in the long-term management of the chronic short bowel syndrome.[140,141]

In patients with a preserved colon a high-carbohydrate, low (not increased) long-chain triglyceride diet is recommendable, and medium-chain triglycerides may be of benefit. A low oxalate diet with calcium supplements before meals is recommended to reduce the risk of calcium oxalate renal stone formation.

Manipulation of the fat: carbohydrate ratio does not generally affect energy absorption in patients with a jejunostomy, and the use of medium-chain triglycerides has not proved beneficial to overall energy absorption.

3.7. What role do pharmaconutrition and hormones as adjuvant therapy have in SBS?

The administration of growth hormone and glutamine have shown conflicting results in short bowel; growth-hormone-related side effects may affect quality of life. These treatment modalities are not recommended for routine use.

The data on the effects of glucagon-like peptide 2 so far are limited; this treatment should be reserved to controlled trials [B].

Comments: Intestinal adaptation is the process by which the body seeks to restore absorption of nutrients, minerals and water to that prior to an intestinal resection.[114] This occurs partly by the patient eating more food than normal (hyperphagia), partly by an increase in the absorptive area of the remaining bowel (structural adaptation) and/or partly by slower gastrointestinal transit (functional adaptation).

In recent years, increased attention has been addressed to the pharmacological enhancement of bowel adaptation aimed at weaning patients with intestinal failure from parenteral support.

Although the initial trials employing growth hormone and glutamine were positive, the subsequent controlled trials have demonstrated conflicting results[142–145] [**IB**].

Regarding improvements in wet weight absorption, the largest effects seem to be seen in studies employing the highest doses and mainly in short bowel patients with a preserved colon[146] [**IIA**]. The maximum effect reported on wet weight absorption is approximately 700 g/day, but it is not possible to determine if this effect is due to the combination of growth hormone and glutamine and a high-carbohydrate low-fat diet, oral rehydration solutions or the combination. The effects on wet weight absorption in jejunostomy short bowel patients without colon in continuity seem limited.

Regarding intestinal energy absorption, the effects seem to be limited in the high dose studies, whereas the low-dose growth hormone monotherapy study of Seguy et al. demonstrated an impressive effect of ~400 kcal/day.[145] This effect was, however, obtained at a higher dietary intake (~200 kcal/day) possibly reducing the true effect to around 200 kcal/day. The indirectly demonstrated effect on energy absorption by weaning from parenteral energy support in relation to somatropin (Zorptive™) treatment is ~450 kcal/day, but the 5.2 kg weight loss at week 18 after weaning from parenteral support raises concern.

The overall impression is that the effects of high doses of growth hormone are related to the wet weight absorption (or fluid retention) and mainly in patients with a preserved colon, whereas the effects on energy absorption are minor. With lower doses of growth hormone there may be an effect on energy absorption in short bowel patients with colon in continuity, whereas there is no effect on wet weight absorption regardless of intestinal anatomy. Since none of the studies have demonstrated ongoing effects after termination of treatment, there is a need for sustained treatment. Therefore, the presence and severity of adverse events raises concern. Thus, the swelling, fluid retentions symptoms, myalgia, arthralgia, gynecomastia, carpal tunnel syndrome, nightmares, and insomnia reported in the high-dose growth-hormone studies in short bowel patients may jeopardize the positive effects on quality of life, which should be the ultimate goal of such treatment.[147,148]

The physiologic effects of GLP-2 appear specific to the gut. This is concordant with the localization of the GLP-2 receptor. The peptide has intestinotrophic, anti-secretory, and transit-modulating effects in the short bowel patients, and the adverse events, even in supraphysiological doses, seem limited.[148,149] So far, the effects of GLP-2 are not clinically dramatic (e.g., an increase in wet weight absorption of 420 g/day), but in the first human trial, the dose of GLP-2 and the duration of therapy were chosen arbitrarily. The GLP-2 analog, teduglutide, which is more slowly degraded, doubled the effects seen in the study employing native GLP-2, increasing the wet weight absorption by ~750 g/day[150] [**IIA**]. Effects on energy absorption seem marginal (less than 250 kcal/day). The optimal dosage and administration of this new treatment to induce beneficial effects on intestinal secretion, motility, morphology, and (most important) absorption in short bowel patients are not known, but since the effect is seen in short bowel both with and without colon in continuity, it may eventually result in long-term improvements in nutritional and fluid status and independence of PN in a larger fraction of short bowel patients.

So far, among the hormonal factors, teduglutide is the only agent that has been able to induce significant intestinal growth in short bowel patients as evaluated by intestinal biopsies.[151] However, the increases in villus height of $38 \pm 45\%$ and crypt depths of $22 \pm 18\%$ in short bowel patients with a jejunostomy is still less significantly less than the increases in villus height demonstrated historically in patients with jejuno-ileal bypass operations, and the 200–300% increases in villus heights described in patients with enteroglucagonomas.[150] It remains to be demonstrated whether achieving intestinal growth of this magnitude is possible in patients with a jejunostomy, and indeed whether it is safe and improves intestinal absorption. Effective pharmacological manipulation may require combinations of growth factors. However, long-term treatment with any growth factor could be questioned due to the theoretical risks of stimulating tumor growth.[152] Therefore, at present, it is recommended that treatment of short bowel patients with intestinal growth factors is initiated in research settings only, and that close surveillance and monitoring of long-term effects is always part of the protocols.[148,153]

Conflict of interest

Conflict of interest on file at ESPEN (espenjournals@espen.org).

References

1. Kelly DG, Fleming CR. Nutritional considerations in inflammatory bowel diseases. *Gastroenterol Clin North Am* 1995;**24**:597–611.
2. Rigaud D, Cerf M, Angel AL, Sobhani I, Carduner MJ, Mignon M. Increase of resting energy expenditure during flare-ups in Crohn disease. *Gastroenterol Clin Biol* 1993;**17**(12):932–7.
3. Sawczenko A, Sandhu BK. Presenting features of infammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;**8**(11):995–1000.
4. Capristo E, Addolorato G, Mingrone G, et al. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. *Am J Gastroenterol* 1998;**93**:2411–9.
5. Kushner RF, Schoeller DA. Resting and total energy expenditure in patients with inflammatory bowel disease. *Am J Clin Nutr* 1991;**53**:161–5.
6. Stokes MA, Hill GL. Total energy expenditure in patients with Crohn's disease: measurement by the combined body scan tehnique. *J Parenter Enteral Nutr* 1993;**17**:3–7.
7. Chan ATH, Fleming R, O'Fallon WM, Huitzenga KA. Estimated versus mesaured basal energy requirements in patients with Crohn's disease. *Gastroenterology* 1986;**91**:75–8.
8. Wendland BE, Aghdassi E, Tam C, Carrrier J, Steinhart AH, Wolman SL, et al. Lipid peroxidation and plasma antioxidant micronutrients in Crohn disease. *Am J Clin Nutr* 2001 Aug;**74**(2):259–64.
9. Galland L. Magnesium and inflammatory bowel disease. *Magnesium* 1988; **7**(2):78–83.
10. Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. *Nutrition* 2006;**22**:1210–3.
11. Saibeni S, Cattaneo M, Vecchi M, Zighetti ML, Lecchi A, Lombardi R, et al. Low vitamin B_6 plasma levels, a risk factor for thrombosis, in inflammatory bowel

disease: role of inflammation and correlation with acute phase reactants. *Am J Gastroenterol* 2003;**98**:112–7.
12. Chowers Y, Sela BA, Holland R, Fidder H, Simoni FB, Bar-Meir S. Increased levels of homocysteine in patients with Crohn's disease are related to folate levels. *Am J Gastroenterol* 2000;**95**(12):3498–502.
13. Vucelic B, Buljevac M, Romic Z, Milicic D, Ostojic R, Krznaric Z, et al. Serum selenium concentracion in patients with ulcerative colitis and Crohn's disease. *Croat J Gastroenterol Hepatol* 1992;**1**:171–3.
14. Rannem T, Ladefoged K, Hylander E, Hegnhoj J, Jarnum S. Selenium status in patients with Crohn's disease. *Am J Clin Nutr* 1992;**56**(5):933–7.
15. Grisham MB. Oxidants and free radicals in inflammatory bowel disease. *Lancet* 1994;**344**:859–61.
16. Sampietro GM, Cristaldi M, Cervato G, Maconi G, Danelli P, Cervellione R, et al. Oxidative stress, vitamin A and vitamin E behaviour in patients submitted to conservative surgery for complicated Crohn's disease. *Dig Liver Dis* 2002;**34**: 696–701.
17. Rumi G, Szabó Imre, Vincze Áron, Matus Zoltán, Tóth Gyula, Mózsik Gyula. Decrease of serum carotenoids in Crohn's disease. *J Physiol Paris* 2000;**94**: 159–61.
18. Duggan P, O'Brien M, Kiely M, McCarthy J, Shanahan F, Cashman KD. Vitamin K status in patients with Crohn's disease and relationship to bone turnover. *Am J Gastroenterol* 2004;**99**(11):2178–85.
19. Alemzadeh N, Rekers-Mombarg LT, Mearin ML, et al. Adult height in patients with early onset of Crohn's disease. *Gut* 2002;**51**:26–9.
20. Sentongo TA, Semeao EJ, Piccoli DA, et al. Growth, body composition, and nutritional status in children and adolescents with Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000;**31**:33–40.
21. Geerling BJ, Badart-Smook A, Stockbrugger RW, Brummer RJ. Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. *Am J Clin Nutr* 1998;**67**(5):919–26.
22. Valentini L, Buening C, Pirlich M, et al. Impaired functional status despite apparently normal nutritional status in patients with quiescent Crohn's disease (CD). *Gastroenterology* 2005;**128**(4): A-551. 1999.
23. Suibhne NT, O'Morain C, O'Sullivan M. Protein undernutrition in Crohn's disease: an unrecognised problem? *Gastroenterology* 2005;**128**(4):A-312.
24. Hass DJ, Brensinger CM, Lewis JD, Lichtenstein GR. The impact of increased body mass index on the clinical course of Crohn's disease. *Clin Gastroenterol Hepatol* 2006;**4**:482–8.
25. Nachum V, Dotan I, Halack A, Niv E. Malabsorption is a major contributor to underweight in Crohn's disease patients in remission. *Nutrition* 2006;**22**: 855–9;
Capristo E, Mingrone G, Addolorato G, et al. Metabolic features of inflammatory bowel disease in a remission phase of the disease activity. *J Intern Med* 1998;**243**:339–47.
26. Mingrone G, Greco AV, Benedetti G, et al. Increased resting lipid oxidation in Crohn's disease. *Dig Dis Sci* 1996;**41**:72–6.
27. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Body composition in patients with inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2003;**98**:1556–62.
28. Frei P, Fried M, Hungerbuhler V, Rammert C, Rousson V, Kullak-Ublick GA. Analysis of risk factors for low bone mineral density in inflammatory bowel disease. *Digestion* 2006;**73**(1):40.
29. Asher K, Hayes M, Feldman S, Hunt M, Fried-Boxt E, Lichtiger S, et al. Do guidelines matter? Implementation of the ACG and AGA osteoporosis screening guidelines in Inflammatory Bowel Disease (IBD) Patients who meet the guidelines' criteria. *Am J Gastroenterol* 2006;**101**(7):1546–50.
30. Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. *Nutrition* 2006;**22**:1210–3.
31. Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anemia, and inflammatory bowel diseases. *Gut* 2004;**53**(8):1190–7.
32. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflamatory bowel disease. A systematic review of the literature. *Am J Med* 2004;**116**(7A):44S–9S.
33. Lindor KD, Fleming CR, Ilstrup DM. Preopertive nutritional status and other factors that influence surgical outcome in patients with Crohn's disease. *Mayp Clin Proc* 1985;**60**:393–6.
34. Higgens CS, Keighley MR, Allan RN. Impact of preoperative weight loss and body composition changes on postoperative outcome in surgery for inflammatory bowel disease. *Gut* 1984;**25**:732–6.
35. Couchino C, Sonnenbertg A. Cause of death in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2001;**7**:250–5.
36. Card T, Hubbard R, Logan RFA. Mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology* 2003;**125**:1583–90.
37. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Gastroenterology* 2002;**122**:1808–14.
38. Bernstein CN, Papineau N, Zajaczkowski J, Rawsthorne P, Okrusko G, Blanchard JF. Direct hospital costs for patients with inflammatory bowel disease in a Canadian Tertiary care University Hospital. *Am J Gastroenterol* 2000;**95**: 678–83.
39. Schreiber S, Hanpe J, Nikolaus S, Foelsch UR. Review article: exploration of the genetic aetiology of inflammatory bowel disease–implications for diagnosis and therapy. *Aliment Pharmacol Ther* 2004;**20**(Suppl. 4):1–8;
Schulte CMS. Bone disease in inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;**20**(Suppl. 4):43–9.
40. MacDonald TT, Di Sabatino A, Gordon JN. Immunopathogenesis of Crohn's disease. *JPEN J Parenter Enteral Nutr* 2005;**29**(Suppl. 4):S118–24 [discussion: S124-5, S184-8].
41. Schneider SM, Le Gall P, Girard-Pipau F, Piche T, Pompei A, Nano JL, et al. Total artificial nutrition is associated with major changes in the fecal flora. *Eur J Nutr* 2000;**39**(6):248–55.
42. van Saene HK, Taylor N, Donnell SC, Glynn J, Magnall VL, Okada Y, et al. Gut overgrowth with abnormal flora: the missing link in parenteral nutrition-related sepsis in surgical neonates. *Eur J Clin Nutr* 2003;**57**(4):548–53.
43. Linskens RK, Huijsdens XW, Savelkoul PH, Vandenbroucke-Grauls CM, Meuwissen SG. The bacterial flora in inflammatory bowel disease: current insights in pathogenesis and the influence of antibiotics and probiotics. *Scand J Gastroenterol Suppl* 2001;(234):29–40.
44. Ostro MJ, Greenberg GR, Jeejeebhoy KN. Total parenteral nutrition and complete bowel rest in the management of Crohn's disease. *JPEN J Parenter Enteral Nutr* 1985;**9**(3):280–7.
45. Dickinson RJ, Ashton MG, Axon ATR, Smith RC, Yeung CK, Hill GL. Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. *Gastroenterology* 1980;**79**:1199–204.
46. McIntyre PB, Powell-Tuck J, Wood SR, Lennard-Jones JE, Lerebours E, Hecketsweiler P, et al. Controlled trial of bowel rest in the treatment of severe acute colitis. *Gut* 1986;**27**:481–5.
47. Greenberg GR, Fleming CR, Jeejeebhoy KN, Rosenberg IH, Sales D, Tremaine WJ. Controlled trial of bowel rest and nutritional support in the management of Crohn's disease. *Gut* 1988;**29**:1309–15.
48. Sitzmann JV, Converse Jr RL, Bayless TM. Favorable response to parenteral nutrition and medical therapy in Crohn's colitis. A report of 38 patients comparing severe Crohn's and ulcerative colitis. *Gastroenterology* 1990;**99**(6):1647–52.
49. Lochs H, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Schutz T, et al. ESPEN guidelines on enteral nutrition: gastroenterology. *Clin Nutr* 2006;**25**(2): 260–74.
50. Ballinger A. Fundamental mechanisms of growth failure in inflammatory bowel disease. *Horm Res* 2002;**58**(Suppl. 1):7–10.
51. Norman K, Kirchner H, Lochs H, Pirlich M. Malnutrition affects quality of life in gastroenterology patients. *World J Gastroenterol* 2006;**7**:3380–5.
52. Richards D, Irving M. Assessing the quality of life in patients with intestinal failure on home parenteral nutrition. *Gut* 1997;**40**:218–22.
53. Van Gossum A, Vahedi K, Abdel-Malik, Staun M, Pertkiewicz M, Shaffer J, et al. Clinical, social and rehabilitation of long-term parenteral nutrition in patients: results of a Europen multicenter survey. *Clin Nutr* 2001;**20**:205–10.
54. 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**(Suppl. 10):S68–74.
55. Afonso JJ, Rombeau JL. Nutritional care for patients with Crohn's disease. *Hepatogastroenterology* 1990;**37**:32–41.
56. Zaloga GP. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes. *Lancet* 2006;**367**:1101–11.
57. Forbes A. Review article: Crohn's disease–the role of nutritional therapy. *Aliment Pharmacol Ther* 2002;**16**(Suppl. 4):48–52.
58. Wright RA, Adler EC. Peripheral parenteral nutrition is no better than enteral nutrition in acute exacerbation of Crohn's disease: a prospective trial. *J Clin Gastroenterol* 1990;**12**:396–9;
Zaloga G. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessment of outcomes. *The Lancet* 2006;**367**. 1001–1001.
59. Jones V. Comparison of total parenteral nutrition and elemental diet in induction of remission of Crohn's disease. *Dig Dis Sci* 1987;**32**(Suppl. 12):100S–7S.
60. Cravo M, Camilo M, Correia J. Nutritional support in Crohn's disease: which route? *Am J Gastroenterol* 1991;**86**:317–21.
61. Van Gossum A, Bakker H, Bozzetti F, Staun M, et al. Home parenteral nutrition in adults: a european multicentre survey in 1997. ESPEN-Home Artificial Nutrition Working Group. *Clin Nutr* 1999;**18**:135–40.
62. Nguyen G, Laveist T, Brant S. The utilization of parenteral nutrition during the in-patient management of inflammatory bowel disease in the United States: a national survey. *Aliment Pharmacol Ther* 2007;**26**:1499–507.
63. Miehsler W, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenslager T, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut* 2004;**53**:542–8.
64. Fujita T, Sakurai K. Efficacy of glutamine-enriched enteral nutrition in an experimental model of mucosal ulcerative colitis. *Br J Surg* 1995;**82**:749–51.
65. Ameho CK, Adjei AA, Harrison EK, Takeshita K, Morioka T, Arakaki Y, et al. Prophylactic effect of dietary glutamine supplementation on interleukin 8 and tumour necrosis factor alpha production in trinitrobenzene sulphonic acid induced colitis. *Gut* 1997;**41**:487–93.
66. Den Hond E, Hiele M, Peeters M, Ghoos Y, Rutgeerts P. Effect of long-term oral glutamine supplements on small intestinal permeability in patients with Crohn's disease. *JPEN* 1999;**23**:7–11.
67. Akobeng AK, Miller V, Stanton J, Elbadri AM, Thomas AG. Double-blind randomized controlled trial of glutamine-enriched polymeric diet in the treatment of active Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000;**30**:78–84.
68. Ockenga J, Borchert K, Stüber E, Lochs H, Manns MP, Bischoff SC. Glutamine-enriched total parenteral nutrition in patients with inflammatory bowel disease. *Eur J Clin Nutr* 2007;**59**:1302–9.
69. MacLean CH, Mojica WA, Newberry SJ, Pencharz J, Hasenfeld Garland R, Tu W, et al. Systematic review of the effects of n-3 fatty acids in inflammatory bowel disease. *Am J Clin Nutr* 2005;**82**(3):611–9.

70. 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* 2007;**2**:CD006320.
71. Mingrone G, Benedetti G, Capristo E, De Gaetano A, Greco AV, Tataranni PA, et al. Twenty-four-hour energy balance in Crohn disease patients: metabolic implications of steroid treatment. *Am J Clin Nutr* 1998;**67**:118–23.
72. Franchimont D, Roland S, Gustot T, Quertinmont E, Toubouti Y, Gervy M, et al. Impact of infliximab on serum leptin levels in patients with Crohn's disease. *J Clin Endocrinol Metab* 2005;**90**:3510–6.
73. Steiner S, Pfefferkorn M, Fitzgerald J, Denne S. Protein and energy metabolism response to the initial dose of infliximab in children with Crohn's disease. *Inflamm Bowel Dis* 2007;**13**:737–44.
74. Rath HC, Caesar I, Roth M, Scholmerich J. Nutritional deficiencies and complications in chronic inflammatory bowel disease. *Med Klin* 1998;**93**:6–10.
75. Gee MI, Grace MG, Wensel RH, Sherbaniuk RW, Thomson AB. Nutritional status of gastroenterology outpatients: comparison of inflammatory bowel disease with functional disorders. *J Am Diet Assoc* 1985;**85**:1591–9.
76. Pirlich M, Schutz T, Kemps M, et al. Prevalence of malnutrition in hospitalized medical patients: impact of underlying disease. *Dig Dis* 2003;**21**:245–51.
77. Vranesic D. Assessment of nutritional status of the patients at department of gastroenterology. Zagreb, Croatia (223 pages, in Croatian, mentorship by Krznaric Z), PhD Thesis. 2006.
78. Geerling BJ, Badart-Smook A, Stockbrugger RW, Brummer RJ. Comprehensive nutritional status in recently diagnosed patients with inflammatory bowel disease compared with population controls. *Eur J Clin Nutr* 2000 Jun;**54**(6):514–21.
79. Heatley RV. Assessing nutritional state in inflammatory bowel disease. *Gut* 1986;**27**(Suppl. 1):61–6.
80. O'Sullivan M, O'Morain. Nutrition in inflammatory bowel disease. *Best Pract Res Clin Gastroenterol* 2006;**20**:561–73.
81. Klein S, Meyers S, O'Sullivan P, et al. The metabolic impact of active ulcerative colitis. Energy expenditure and nitrogen balance. *J Clin Gastroenterol* 1988;**10**:34–40.
82. Jensen MB, Houborg KB, Vestergaard P, et al. Improved physical performance and increased lean tissue and fat mass in patients with ulcerative colitis four to six years after ileoanal anastomosis with a J-pouch. *Dis Colon Rectum* 2002;**45**:1601–7.
83. Gasché C. Anemia in IBD: the overlooked villain. *Inflamm Bowel Dis* 2000;**6**:142–50.
84. Cronin CC, Shanahan F. Anemia in patients with chronic inflammatory bowel disease. *Am J Gastroenterol* 2001;**96**:2296–8.
85. Oldenburg B, Koningsberger JC, Berge Henegouwen GP, Van Asbeck BS, Marx JJ. Iron and inflammatory bowel disease. *Aliment Pharmacol Ther* 2001;**15**:429–38.
86. Roblin X, Germain, Phelip JM, Ducros V, Pofelski J, Heluwaert F, et al. Hyperhomocystéinémie et facteurs associés au cours des MICI: étude prospective chez 81 patients. *La Revue de Médecine Interne* February 2006;vol. 27(Issue 2):106–10.
87. Nakano E, Taylor CJ, Chada L, et al. Hyperhomocystinemia in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2003;**37**:586–90.
88. Sturniolo GC, Mestriner C, Lecis PE, D'Odorico A, Venturi C, Irato P, et al. Altered plasma and mucosal concentrations of trace elements and antioxidants in active ulcerative colitis. *Scand J Gastroenterol* 1998 Jun;**33**(6):644–9.
89. Andoh A, Hirashima M, Maeda H, Hata K, Inatomi O, Tsujikawa T, et al. Serum selenoprotein-P levels in patients with inflammatory bowel disease. *Nutrition* 2005 May;**21**(5):574–9.
90. Ringstad J, Kildebo S, Thomassen Y. Serum selenium, copper, and zinc concentrations in Crohn's disease and ulcerative colitis. *Scand J Gastroenterol* 1993 Jul;**28**(7):605–8.
91. Janczewska I, Bartnik W, Butruk E, Tomecki R, Kazik E, Ostrowski J. Metabolism of vitamin A in inflammatory bowel disease. *Hepatogastroenterology* 1991;**38**:391–5.
92. Fernandez-Banares F, Abad-Lacruz A, Xiol X, Gine JJ, Dolz C, Cabre E, et al. Vitamin status in patients with inflammatory bowel disease. *Am J Gastroenterol* 1989;**84**:744–8.
93. Ghosh S, Cowen S, Hannan WJ, et al. Low bone mineral density in Crohn's disease, but not in ulcerative colitis at diagnosis. *Gastroenterology* 1994;**107**:1031–9.
94. Jahnsen J, Falch JA, Aadland E, Mowinckel P. Bone mineral density is reduced in patients with Crohn's disease but not in patients with ulcerative colitis: a population based study. *Gut* 1997;**40**:313–9.
95. Schulte CM. Review article: bone disease in inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;**20**(Suppl. 4):43–9.
96. American Gastroenterological Association. Medical position statement: guidelines on osteoporosis in gastrointestinal diseases. *Gastroenterology* 2003;**124**:791–4.
97. Buchman AL. Metabolic bone disease in inflammatory bowel disease. *Am J Gastroenterol* 2007;**102**:S49–55.
98. Ardizzone S, Bollani S, Bettica P, et al. Altered bone metabolism in inflammatory bowel disease: there is a difference between Crohn's disease and ulcerative colitis. *J Intern Med* 2000;**247**:63–70.
99. Gilman J, Shanahan F, Cashman KD. Altered levels of biochemical indices of bone turnover and bone-related vitamins in patients with Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2006;**23**(7):1007–16.
100. Pironi L, Cornia GL, Ursitti MA, et al. Evaluation of oral administration of folic and folinic acid to prevent folate deficiency in patients with inflammatory bowel disease treated with salicylazosulfapyridine. *Int J Clin Pharmacol Res* 1988;**8**:143–8.
101. Halsted C, Gandhi G, Tamura T. Sulfasalazine inhibits the absorption of folates in ulcerative colitis. *N Engl J Med* 1981;**17**:1513–7.
102. González-Huix F, Fernández Bañares F, Esteve Comas M, Abad Lacruz A, Cabré E, Acero D, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993;**88**:227–32.
103. Matuchansky C. Parenteral nutrition in inflammatory bowel disease. *Gut* 1986;**27**(Suppl. 1):81–4.
104. Abad A, González-Huix F, Esteve M, Fernández Bañares F, Cabré E, Boix J, et al. Liver function tests abnormalities in patients with inflammatory bowel disease receiving artifical nutrition: a prospective randomized study of total enteral nutrition vs total parenteral nutrition. *JPEN* 1990;**14**:618–21.
105. Nightingale JM. Management of patients with a short bowel. *World J Gastroenterol* 2001;**7**:741–51.
106. O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol* 2006;**4**:6–10.
107. Lal S, Teubner A, Shaffer JL. Review article: intestinal failure. *Aliment Pharmacol Ther* 2006;**24**:19–31.
108. Gouttebel MC, Saint-Aubert B, Astre C, Joyeux H. Total parenteral nutrition needs in different types of short bowel syndrome. *Dig Dis Sci* 1986;**31**:718–23.
109. Carbonnel F, Cosnes J, Chevret S, Beaugerie L, Ngô Y, Malafosse M, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. *J Parenter Enteral Nutr* 1996;**20**:275–80.
110. Messing B, Pigot F, Rongier M, et al. Intestinal absorption of free oral alimentation in very short bowel syndrome. *Gastroenterology* 1991;**100**:1502–8.
111. Nightingale JMD, Woodward J, Small bowel/Nutrition Committee of BSG. Guidelines for the management of patients with a short bowel. *Gut* 2006;**55**(Suppl. 4):iv1–12.
112. Selby PL, Peacock M, Bambach CP. Hypomagnesaemia after small bowel resection: treatment with 1-hydroxylated vitamin D metabolites. *Br J Surg* 1984;**71**:334–7.
113. Shils ME. Experimental production of magnesium deficiency in man. *Ann N Y Acad Sci* 1969;**162**:847–55.
114. Nightingale JM, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gallstones in patients with a short bowel. *Gut* 1992;**33**:1493–7.
115. DuPont AW, Sellin JH. Ileostomy diarrhea. *Curr Treat Options Gastroenterol* 2006;**9**:39–48.
116. Messing B, Joly F, Jeppesen PB. Short Bowel Syndrome. Home Parenteral Nutrition. In: Bozzetti F, Staun M, Van Gossum A, editors. Washington DC, USA: Cabi Ed; 2006. p. 57–77.
117. Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000;**132**:525–32.
118. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology* 2003;**124**:1111–34.
119. Messing B, Joly F. Guidelines for management of home parenteral support in adult chronic intestinal failure patients. *Gastroenterology* 2006 Feb;**130**(2 Suppl. 1):S43–51. Review.
120. Nightingale JM, Lennard-Jones JE, Walker ER, et al. Jejunal efflux in short bowel syndrome. *Lancet* 1999;**336**:765–8.
121. Jeppesen PB, Mortensen PB. Intestinal failure defined by measurements of intestinal energy and wet weight absorption. *Gut* 2000;**46**:701–6.
122. DiBaise JK, Matarese LE, Messing B, et al. Strategies for parenteral nutrition weaning in adult patients with short bowel syndrome. *J Clin Gastroenterol* 2006;**40**(5 Suppl. 2):S94–8.
123. Rudman D, Millikan WJ, Richardson TJ, et al. Elemental balances during intravenous hyperalimentation of underweight adult subjects. *J Clin Invest* 1975;**55**:94–104.
124. Richette P, Ayoub G, Lahalle S, et al. Hypomagnesemia associated with chondrocalcinosis: a cross sectionel study. *Arthritis Rheum* 2007;**57**:1496–501.
125. Sladen GE, Dawson AM. Interrelationships between the absorptions of glucose, sodium, and water by the normal human jejunum. *J Clin Invest* 1975;**55**:728–37.
126. Tytgat GN, Huibregtse K. Loperamide and ileostomy output-placebo-controlled double-blind crossover study. *BMJ* 1975;**2**:667–8.
127. King RFGJ, Norton T, Hill GL. A double-blind crossover study of the effect of loperamide hydrochloride and codeine phosphate on ileostomy output. *Aust New Zeal J Surg* 1982;**52**:121–4.
128. Cooper JC, Williams NS, King RFGJ, et al. Effects of a long acting somatostatin analogue in patients with severe ileostomy diarrhea. *Br J Surg* 1986;**73**:128–31.
129. Lémann M, de Montigny S, Maché S, et al. Effect of octreotide on water and electrolytes losses, nutrient absorption and transit in short bowel syndrome. *Eur J Gastroenterol Hepatol* 1993;**5**:817–22.
130. O'Keefe SJD, Peterson ME, Fleming R. Octreotide as an adjunct to home parenteral nutrition in the management of permanent end-jejunostomy syndrome. *J Parenter Enteral Nutr* 1994;**18**:26–34.
131. Nehra V, Camilleri M, Burton D, et al. An open trial of octreotide long-acting release in the management of short bowel syndrome. *Am J Gastroenterol* 2001;**96**:1494–8.

132. Griffin GE, Fagan EF, Hodgson HJ, et al. Enteral therapy in the management of massive gut resection complicated by chronic fluid and electrolyte depletion. *Dig Dis Sci* 1982;**27**:902–8.
133. Kennedy HJ, Al-Dujaili EAS, Edwards CRW, et al. Water and electrolyte balance in subjects with a permanent ileostomy. *Gut* 1983;**24**:702–5.
134. Hunt JB, Elliott EJ, Fairclough PD, et al. Water and solute absorption from hypotonic glucose-electrolyte solutions in human jejunum. *Gut* 1992;**33**:479–83.
135. Rodrigues CA, Lennard-Jones JE, Thompson DG, Farthing MJG. What is the ideal sodium concentration of oral rehydration solutions for short bowel patients? *Clin Sci* 1988;**74**(Suppl. 18):69.
136. Fleming CR, George L, Stone GL, et al. The importance of urinary magnesium values in patients with gut failure. *Mayo Clin Proc* 1996;**71**:21–4.
137. Anast CS, Winnacker JL, Forte LR, Burns TW. Impaired release of parathyroid hormone in magnesium deficiency. *Clin Endocrinol Metab* 1976;**42**:707–14.
138. Hylander E, Ladefoged K, Madsen S. Calcium balance and bone mineral content following small-intestinal resection. *Scand J Gastroenterol* 1981;**16**:167–76.
139. Newton CR, Gonvers JJ, McIntyre PB, et al. Effect of different drinks on fluid and electrolyte losses from a jejunostomy. *J R Soc Med* 1985;**78**:27–34.
140. Nightingale JM, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gallstones in patients with a short bowel. *Gut* 1992;**33**:1493–7.
141. Avery ME, Snyder JD. Oral therapy for acute diarrhea. The underused simple solution. *N Engl J Med* 1990;**323**:891–4.
142. Scolapio JS, Camilleri M, Fleming CR, Oenning LV, Burton DD, SEbo TJ, et al. Effect of growth hormone, glutamine, and diet on adaptation in short bowel syndrome: a randomized, controlled study. *Gastroenterology* 1997;**113**: 1074–81.
143. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, cross-over, placebo controlled study. *Gut* 2000;**47**:199–205.
144. Ellegard L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant human growth hormone increases body weight and lean body mass sin patients with short bowel syndrome. *Ann Surg* 1997;**225**:88–96.
145. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. *Gastroenterology* 2003;**124**:293–302.
146. Byrne TA, Wilmore DW, Iyer K, Dibaise J, Clancy K, Robinson MK, et al. Growth hormone, glutamine, and an optimal diet reduces parenteral nutrition in patients with short bowel syndrome: a prospective, randomized, placebo-controlled, double-blind clinical trial. *Ann Surg* 2005;**242**:655–61.
147. Messing B, Blethen S, Dibaise JK, Matarese LE, Steiger E. Treatment of adult short bowel syndrome with recombinant human growth hormone: a review of clinical studies. *J Clin Gastroenterol* 2006;**40**(5 Suppl. 2):S75–84.
148. Jeppesen PB. Growth factors in short-bowel syndrome patients. *Gastroenterol Clin North Am* 2007;**36**:109–21.
149. Kitchen PA, Goodlad RA, FitzGerald AJ, Mandir N, Ghatei MA, Bloom SR, et al. Intestinal growth in parenterally-fed rats induced by the combined effects of glucagon-like peptide 2 and epidermal growth factor. *J Parenter Enteral Nutr* 2005;**29**:248–54.
150. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. *Gut* 2005;**54**:1224–31.
151. Martin GR, Wallace LE, Sigalet DL. Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2004;**286**:G964–72.
152. Thulesen J, Hartmann B, Hare KJ, Kissow H, Orskov C, Holst JJ, et al. Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice. *Gut* 2004;**53**:1145–50.
153. Steiger E, DiBaise JK, Messing B, Matarese LE, Blethen S. Indications and recommendations for the use of recombinant human growth hormone in adult short bowel syndrome patients dependent on parenteral nutrition. *J Clin Gastroenterol* 2006;**40**(5 Suppl. 2):S99–106.