Use of Macro- and Micronutrients for Nutrition Support in Inflammatory Bowel Disease

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The appropriate use of nutritional treatment in the management of inflammatory bowel disease has been an unresolved issue. There is no disagreement that replacement therapy is indicated when nutrient deficiency is present. Problems arise with the use of macronutrients as either primary or adjunctive treatment for the disease – especially in patients who are not obviously malnourished, with the use of the parenteral route when oral intake is adequate (bowel rest), or with the appropriate use of micronutrients for current or future deficiency. There are two factors (among others) that have prevented clarification of these issues: the difficulty in assessing nutrient deficiency, and the long and multistaged nature of the natural history of these deficiencies. In light of these considerations, I will review the need for and the use of enteral nutrition and total parenteral nutrition in inflammatory bowel disease as adjunctive (not primary) treatment, and the provision of macronutrients parenterally at home. In addition, I will discuss the recognition of deficiency states and the use of cobalamin, iron, calcium, and vitamin D. The use of enteral nutrition and total parenteral nutrition as primary treatment for inflammatory bowel disease is discussed in the chapter by Jeejeebhoy.

Impact of Inflammatory Bowel Disease on Nutritional Status

The difficulty in identifying a gold standard for nutritional assessment is well known [1]. Moreover, in the presence of chronic illness the most commonly used techniques have many problems. Many experts agree that unintentional loss of
more than 10% of body weight in 6 months is a prognosticator of clinical outcome, at least in cancer patients [2]. However, in chronic disease this measure can be confounded by errors in recall of weight and by changes in body water (for example, dehydration, edema). The use of percent of ideal body weight may require different cut-off values from previously healthy patients, as those with chronic disease may not maintain ideal body weight, and yet may not be malnourished. Serum albumin has been used traditionally as a measure of protein nutrition, but inflammatory disorders can decrease the rate of albumin synthesis, increase the rate of albumin degradation, and cause increased transcapillary losses or protein-losing enteropathy. Finally, the ability to maintain immune competence is often compromised in chronic illness.

The difficulty in assessing macronutrient reserves presents a problem in monitoring the need for replacement, especially in the face of a chronic and progressive disease with a variable course. Because of the greater variability in the course of Crohn’s disease than of ulcerative colitis, I will concentrate the discussion mainly on the former disease. In Crohn’s disease in particular such reserves might also be affected by the chronic use of catabolic agents (prednisone) or by repeated surgical interventions, but there is no correlation between disease activity and resting energy expenditure [3]. In Crohn’s disease there is a modest increase in resting energy expenditure correlated with weight loss [4], as would be expected if mean fat-free mass were decreased. For the most part, however, patients with inflammatory bowel disease studied for the effect of nutritional intervention have not been segregated using nutritional indices. Apart from the heterogeneous patient population, other problems with studies include the use of diets with variable composition, small sample size, and high percentage of withdrawal from the diet arm of the study.

Similar problems in assessment and staging of micronutrient deficiency occur in patients with inflammatory bowel disease who have anemia or osteopenia. In addition, drugs used in inflammatory bowel disease can affect micronutrient status. Sulfasalazine can inhibit folate absorption, and corticosteroids reduce calcium absorption. Before exploring the issues regarding micronutrient replacement in patients with inflammatory bowel disease, I will consider some issues involving macronutrient nutritional support, namely the role of bowel rest, the use of enteral supplements to prevent mucosal atrophy, the value of perioperative or adjunctive treatment, and the value of total parenteral nutrition at home.

**Bowel Rest versus Nutritional Repletion in Crohn’s Disease**

Even before the experimental data in animal models of inflammatory bowel disease showed the important role of intestinal microflora in producing local disease, bowel rest with parenteral feeding was promoted as possibly beneficial. This strategy was supported by the exacerbation of disease activity resulting from re-
introduction of small bowel fluid into excluded bowel [5]. However, when short-term remission rates in patients with Crohn’s disease were compared using either total parenteral nutrition or enteral nutrition in four separate studies, no difference was found [6]. There have been no prospective, randomized controlled trials that use placebo controls compared with enteral feeding. However, the overall remission rate after enteral nutrition in one meta-analysis was around 60% [7], significantly higher than the 20–40% for placebo-treated patients with mild or moderately active Crohn’s disease [8–10].

There is no single diet that is uniformly effective for patients with inflammatory bowel disease. In general, restrictive diets should be discouraged, and there is no evidence for the value of exclusion diets. In one prospective, randomized controlled trial of an exclusion diet with subsequent rechallenge and double-blinded challenge following remission of Crohn’s disease initiated by an elemental diet, the identified problematic foods varied markedly, and often did not persist on rechallenge or double-blinded challenge [11]. Thus there is insufficient evidence to warrant the routine use of exclusion diets for patients with Crohn’s disease.

Can Enteral Feeding Reverse Total Parenteral Nutrition-Induced Intestinal Mucosal Atrophy in Humans?

When macronutrient malnutrition is suspected, enteral feeding is commonly chosen, if that route is available. If total parenteral nutrition is used, data from rodents show that mucosal mass diminishes, and that enteral supplements are protective against this complication. Unlike the situation in the rat, evidence for mucosal atrophy in humans produced by total parenteral nutrition is minimal [12]. The morphometric data show very small and inconsistent changes in only a few patients (including a few with inflammatory bowel disease), and the functional changes (increased permeability, brush border enzyme activity, bacterial translocation) are also no different from enterally fed controls. The effect of glutamine supplements on total parenteral nutrition with limited or no enteral feeding has been examined [12]. In none of the glutamine supplement studies was the morphology or function of the intestine examined, so no conclusions can be drawn about the value of either supplemental enteral nutrition or specific nutrients in conditions when enteral feeding was limited.

There are problems with the use of glutamine in total parenteral nutrition solutions, especially regarding stability of the amino acid, and the fact that it is not viewed as an essential amino acid. Thus it is not routinely used. Glutamine dipeptides are more stable and soluble, but are not yet available in the USA. There have been several studies in humans examining the effects of glutamine on various clinical outcomes, mostly in cancer patients, and none in inflammatory bowel disease [13]. The two best prospective, randomized controlled trials were performed in bone marrow transplant recipients [14, 15]. One study showed a
decrease in complications, better nitrogen balance, and shorter hospital stay [14], and the other did not. Some of the confusion in the field may be related to the fact that under normal fed conditions, enteral glutamate and not parenteral glutamine (or glutamate) is the major gut oxidative substrate. Over 90% of enteral glutamate is catabolized by the human intestine [16], and this rate of oxidation is greater than that for enteral glutamine [17]. In fed piglets, the rate of intestinal catabolism of enteral glutamate exceeds the rate of intestinal uptake of arterial glutamine by fivefold [18]. Finally, the trophic effects of arterial glutamine on the rat intestine are mimicked by enteral glutamate [19]. It is possible that the variable results using enteral or parenteral glutamine could be related to inefficient uptake or use of this fuel source. Thus future studies in humans should test the value of enteral glutamate.

**Nutrition Support in Crohn’s Disease as Adjunctive Treatment**

The rationale for using perioperative nutrition support comes from observations in patients with protein-energy malnutrition where wound healing is impaired and immunocompetence is affected [20, 21]. In addition, 13 prospective, randomized controlled trials of 7–10 days of preoperative total parenteral nutrition given to 1,250 “malnourished” cancer patients (defined as those with more than 10% body weight loss, low plasma proteins, or abnormal prognostic indices) showed a decline in postoperative complications, but only by 10% [1]. However, the routine use of postoperative total parenteral nutrition in similar patients seen in general surgery increased the rate of postoperative complications by 10% in patients who had not received preoperative total parenteral nutrition [1]. Of course, if the patient is not able to eat or receive enteral feed preoperatively or postoperatively, parenteral support is indicated. No comparable prospective studies are available for patients with either Crohn’s disease or ulcerative colitis. Uncontrolled studies in patients with inflammatory bowel disease have suggested that the use of total parenteral nutrition preoperatively reduces the complication rate [22, 23] and the amount of small bowel resected [24], but hospital stay might be prolonged [23]. Only in severely malnourished patients undergoing major surgery in the VA TPN Cooperative Study Group did total parenteral nutrition result in fewer noninfectious complications compared with controls [25]. Thus it is possible that in severely malnourished patients, 7–14 days of preoperative total parenteral nutrition might alter the clinical outcome. However, that degree of nutritional depletion, even if it could be accurately predicted in patients with inflammatory bowel disease, is only one of several factors that might influence surgical outcome in such patients. These factors might include the presence of sepsis preoperatively, the length of resection, the number of previous operations, and the extent of the procedure.
Use of Total Parenteral Nutrition in Patients with Gastrointestinal Fistulas

The management of fistulas in inflammatory bowel disease patients can be difficult, but no prospective, randomized controlled trials have evaluated the efficacy of nutrition support in such patients. In fact, most of the data available relate to fistulas from other causes. It is thought that total parenteral nutrition has improved the outcome in such patients, who often died from malnutrition and fluid and electrolyte losses. A retrospective analysis of small bowel fistula patients treated with total parenteral nutrition showed lower mortality rates, higher spontaneous closure rates, and higher surgical closure rates when compared with historical controls [26]. However, the overall closure rate of about 35% achieved with total parenteral nutrition was not maintained, as half the patients had reopened their fistulas by 3 months [27]. There may be a role for octreotide in closing fistulas in some patients with Crohn’s disease [28].

Home Parenteral Nutrition in Crohn’s Disease

Patients with a jejunostomy and <100 cm of jejunum, or those who have <50 cm of small bowel but an intact colon, often require long-term total parenteral nutrition [29]. The availability of home total parenteral nutrition has produced dramatic results in this small group of patients. These results have been documented in the North American Parenteral and Enteral Nutrition Patient Registry, from which the results from 1984 to 1994 are available [30] (Table 1). Oral rehydration treatment can sometimes obviate the need for home total parenteral nutrition, but usually requires greater sodium replacement than is present in most oral solutions, as these patients are in negative sodium balance. This result is reflected in the report that 70% of Crohn’s disease patients on home total parenteral nutrition are on full oral diets after 1 year. This result is similar to that found in patients with congenital bowel defects and chronic pancreatitis, and suggests that the remaining bowel can function well. In contrast, those on home total parenteral nutrition with ischemic disease, motility disorders, or radiation enteritis are much less likely to be weaned from this form of nutrition. The reported complication rate was no different (about 1 a year) in the Crohn’s disease patients whether on or off home total parenteral nutrition [30]. These results are consistent with results of the short-term trials: that is, total parenteral nutrition does not alter the natural history of the disease and does not provide long-term management except for those patients who cannot maintain adequate oral nutrition.

Patients on home total parenteral nutrition are at risk of several metabolic complications, some of which are unique to long-term total parenteral nutrition and others additive to the natural history of Crohn’s disease (Table 2). The most common problem relates to catheter infections, as readmission for sepsis occurs once every 12–30 months [30]. The usual organisms derive from skin or gut flora.
**Table 1.** Outcome of home parenteral nutrition (HPN) in chronic disorders (North American Parenteral and Enteral Nutrition Patient Registry 1984–94) [from 30]

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
<th>Age years</th>
<th>Survival % at 1 year</th>
<th>Status at 1 year, % full oral HPN</th>
<th>Complications/year HPN+</th>
<th>HPN–</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>562</td>
<td>36</td>
<td>96</td>
<td>70/25</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Ischemic bowel</td>
<td>331</td>
<td>49</td>
<td>87</td>
<td>27/48</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Motility disorder</td>
<td>299</td>
<td>45</td>
<td>87</td>
<td>31/44</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Congenital bowel defect</td>
<td>172</td>
<td>5</td>
<td>94</td>
<td>100/0</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>156</td>
<td>42</td>
<td>90</td>
<td>82/10</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Radiation enteritis</td>
<td>145</td>
<td>58</td>
<td>87</td>
<td>28/49</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Adhesive obstruction</td>
<td>120</td>
<td>53</td>
<td>83</td>
<td>47/34</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Small bowel transplant</td>
<td></td>
<td></td>
<td></td>
<td>59–83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Metabolic complications in patients on home parenteral nutrition

<table>
<thead>
<tr>
<th>Complication</th>
<th>Related factors or features</th>
<th>Unique for TPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone disease</td>
<td>Malabsorption, steroids, liver disease, vitamin D toxicity, Ca or Mg deficiency</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Al(OH)₃ toxicity</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver and gallbladder disease</td>
<td>Cholestasis, steatosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Nephrolithiasis, hypercalciuria (protein/acid load)</td>
<td>No</td>
</tr>
<tr>
<td>Hyperglycemic nonketotic coma</td>
<td>Hyperglycemia</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Abrupt cessation of glucose infusion</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Components of TPN solution</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>Osteomyelitis, endocarditis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TPN = Total parenteral nutrition.

Subclavian vein sites are least at risk, as are single lumen Silastic/polyurethane catheters. Use of urokinase flushes (2,500 U/ml) seem protective compared with heparin flushes. The value of high concentration antibiotic locks is still uncertain. For some reason there is a higher risk of sepsis in patients with Crohn’s disease, in smokers, and in patients with jejunostomies [30].

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Table 3. Inflammatory bowel disease is a predisposing factor for steroid-induced osteoporosis [from 31]

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients CD/UC</th>
<th>Method</th>
<th>% low bone mineral density or content</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>osteopenia (-1 to –2.5 SD)</td>
</tr>
<tr>
<td>Compston</td>
<td>1987</td>
<td>52/17</td>
<td>SPA</td>
<td>41 (CD), 14 (UC)</td>
</tr>
<tr>
<td>Pigot</td>
<td>1992</td>
<td>27/34</td>
<td>DEXA</td>
<td>59 (CD = UC)</td>
</tr>
<tr>
<td>Tromm</td>
<td>1994</td>
<td>53/23</td>
<td>CT</td>
<td>30 (CD), 9 (UC)</td>
</tr>
<tr>
<td>Bernstein</td>
<td>1995</td>
<td>26/23</td>
<td>DEXA</td>
<td>64/44:hip/spine (CD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43/48:hip/spine (UC)</td>
</tr>
<tr>
<td>Abitbol</td>
<td>1995</td>
<td>34/50</td>
<td>DEXA</td>
<td>43: lumbar spine</td>
</tr>
<tr>
<td>Silvennoinen</td>
<td>1995</td>
<td>78/67</td>
<td>DEXA</td>
<td>–</td>
</tr>
<tr>
<td>Bjarnason</td>
<td>1997</td>
<td>44/35</td>
<td>DEXA</td>
<td>78/54:hip/spine</td>
</tr>
</tbody>
</table>

CD = Crohn’s disease; CT = computed tomography; DEXA = dual-energy X-ray absorptiometry; SPA = single photon absorptiometry; UC = ulcerative colitis.

Common Metabolic Complications in Inflammatory Bowel Disease Patients, Especially Crohn’s Disease

Bone disease is a common complication in all patients with Crohn’s disease, not just those on home total parenteral nutrition. Anemia of chronic disease is also very common, and must be differentiated from iron and cobalamin deficiency. The following discussion pertains, therefore, to all patients with inflammatory bowel disease (but mostly Crohn’s disease), whether receiving macronutrient nutritional support or not. One major problem in dealing with these complications is the inability to accurately diagnose the condition, just as in the case of macronutrient malnutrition.

Osteoporosis

The diagnosis of osteoporosis is usually made by finding a bone mineral density or content >2 or 2.5 SD below the age/sex-matched control group. Osteopenia usually denotes a lesser degree of bone mineral loss, corresponding to a bone mineral density from –1 to –2.5 SD from the mean. In various studies of patients with inflammatory bowel disease a large proportion (30–78%) have been found to be osteopenic (Table 3), with fewer patients having osteoporosis (4–41%) [31]. In general, the incidence of either condition is higher in Crohn’s disease than in ulcerative colitis. The important clinical outcome of low bone density is bone fragility, manifested by fracture, and unfortunately the bone density itself does not correlate linearly with fragility [32]. Other factors of importance include a
family history of osteoporosis, sedentary lifestyle, chronic glucocorticoid or anti-convulsant treatment, early (before 50 years) natural or surgical menopause, testicular failure, and cigarette smoking.

Evaluation in any patient with inflammatory bowel disease to determine the need for preventive therapy for osteoporosis should therefore start with a search for other risk factors [33]. Patients at higher risk for developing osteoporosis include those who are postmenopausal, are immobilized, are chronic smokers (especially those with chronic obstructive airways disease), have a family history, are on chronic glucocorticoids, and who have malabsorption of calcium or vitamin D (for example, those with chronic liver disease or loss of ileal function). Because most patients with inflammatory bowel disease who will be at high risk include those on chronic glucocorticoids, initial categorization for the risk of osteoporosis should be confined to those patients taking such drugs [34]. Those on glucocorticoids who are at high risk for steroid-induced osteoporosis are those on >7.5 mg/day of prednisone, or who have an expected duration of treatment of over 1 year. Those patients at risk should then receive an initial assessment that includes spinal bone density, urinary calcium, plasma 25-OH vitamin D, and serum testosterone (if hypogonadism is suspected). Following this assessment and identification of patients at low(er) and high(er) risk for steroid-induced osteoporosis, preventive measures can be instituted to supplement the existing nutritional support, as follows:

(i) Patients at low risk include males or premenopausal women with no additional risk factors, if steroid treatment at any dose is given for >6 months, or the dose is >7.5 mg/day of prednisone for <1 year. In these patients the dose of corticosteroids should be kept as low as possible, and be taken before 08:00 h to minimize inhibition of endogenous steroids. Patients should maintain as much physical activity as possible, stop smoking, and avoid excessive alcohol. Calcium and vitamin D intake should be maintained at adequate levels (1 g and 400–800 U/day, respectively). Gonadal hormones should be replaced in postmenopausal women, if feasible. Vitamin D deficiency should be corrected with 50,000 IU/week of vitamin D3 or 40 μg/day of calcifediol. Thiazide diuretics to increase calcium retention should be considered if urinary calcium exceeds 4 mg/kg/day.

(ii) Patients are at high risk for steroid-induced osteoporosis if treatment is for >1 year at any dose, or for >3 months at a dose >7.5 mg/day of prednisone in the presence of any risk factors. These patients should be evaluated for more specific treatment with either a bisphosphonate, nasal calcitonin, or sufficient calcifidiol (10–100 μg/day), or combinations of these, to keep the urinary excretion under 300 mg/day.

Anemia/Iron Deficiency
Separation of iron deficiency from anemia of chronic disease is a troubling aspect of the nutritional management of inflammatory bowel disease patients, especially those with Crohn’s disease. A major problem for diagnosis is that the
The diagnostic usefulness of the serum ferritin test [from 41]

<table>
<thead>
<tr>
<th>Serum ferritin μg/l</th>
<th>Test result</th>
<th>Iron deficiency anemia, %</th>
<th>Likelihood ratio (present/absent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Very positive</td>
<td>59</td>
<td>1.1</td>
</tr>
<tr>
<td>15–34</td>
<td>Mod. positive</td>
<td>22</td>
<td>4.5</td>
</tr>
<tr>
<td>35–64</td>
<td>Neutral</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>65–94</td>
<td>Mod. negative</td>
<td>3.7</td>
<td>9.5</td>
</tr>
<tr>
<td>&gt;95</td>
<td>Very negative</td>
<td>5.9</td>
<td>75</td>
</tr>
</tbody>
</table>

deficiency develops over time, so that the deficiency state occurs in stages. The various diagnostic tests do not all become positive during the same stage of deficiency [35]. Thus there is not a single test that can be used to determine whether iron deficiency is present. In addition, the tests vary in sensitivity. For example, serum (or red cell) ferritin can be abnormal as early as lack of iron is detected in the bone marrow, but the cut-off value of <15 μg/l is not sufficiently sensitive (Table 4). Values from 15 to 34 μg/l still carry a likelihood of deficiency of nearly 5, and deficiency is consistent with even higher values. Patients may have higher values if they are not yet sufficiently deficient, or if their chronic inflammatory condition raises the level of serum ferritin, which is an acute phase reactant. In such cases, values of serum ferritin may be about twice those in Table 4 to have the same diagnostic value. Thus many other tests have been used to assess body iron status (Table 5) [36].

Zinc protoporphyrin and transferrin saturation (in the presence of raised serum transferrin) are increased relatively early in iron deficiency, but both may be normal in patients with chronic inflammation. Because the “gray” area for serum ferritin, from 15 to 100 mmol/l, is difficult to interpret (Table 4), it seems logical to combine the assay of serum ferritin with another measure of disease severity. Many attempts have been made, with variable results. The most recent efforts involve soluble transferrin receptor (TfR) in plasma, a truncated form of the membrane receptor which is present as a TfR-Tf complex. The TfR number on the cell surface is a reflection of the iron status, increasing as deficiency develops. The log transformation of the ferritin value from the same patients has been suggested as part of a ratio of TfR/log ferritin (TfR-F index) to normalize the TfR values in patients with anemia of chronic inflammation [37]. It remains to be seen if this or related measures stand up to repeated testing. One of the simplest tests for iron deficiency in the presence or absence of chronic inflammation is the response to treatment. Interpretation may be complex in patients with inflammatory bowel disease, because the response may be truncated by the chronic disease, or by malabsorption of iron. In some cases it is appropriate to use parenteral iron,
Macro- and Micronutrients for Nutrition Support in IBD

Table 5. Assessment of functional body iron status [from 36]

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Reference range (adults)</th>
<th>Diagnostic use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional iron</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13–18 (M), 12–16 (F)</td>
<td>Severity of anemia</td>
</tr>
<tr>
<td>Red cell indices</td>
<td>MCV 80–94, MCH 27–32</td>
<td>Reduced when iron supply is low</td>
</tr>
<tr>
<td>Red cell zinc protoporphyrin</td>
<td>&lt;70 µg/dl RBC</td>
<td>↑ Protoporphyrin and ↓ RBC ferritin</td>
</tr>
<tr>
<td>RBC ferritin</td>
<td>3–40 µg/cell</td>
<td>↑ Protoporphyrin and ↓ RBC ferritin</td>
</tr>
<tr>
<td>Serum transferrin receptor</td>
<td>2.8–8.5 mg/l</td>
<td>↑ In early iron deficiency, with measure of stores identifies ACD</td>
</tr>
<tr>
<td><strong>Tissue iron supply</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum iron</td>
<td>10–30 µmol/l</td>
<td>Very rapid T/2, low in infections</td>
</tr>
<tr>
<td>Serum transferrin</td>
<td>47–70 µmol/l</td>
<td>Raised in iron deficiency</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>16–60%</td>
<td>↓ In deficiency if transferrin is high, high in iron overload</td>
</tr>
<tr>
<td><strong>Iron stores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>15–300 µg/l</td>
<td>Lower in children, higher in adult males; &lt;15 means deficiency, 15–100 indeterminate in ACD</td>
</tr>
<tr>
<td>Response to EPO</td>
<td>NA</td>
<td>If cannot use storage iron, indices may be NL, anemia will respond</td>
</tr>
<tr>
<td>Tissue iron</td>
<td>Liver (3–33 µmol/g dry wt) Marrow-Prussian blue stain</td>
<td>Useful for iron overload Absent in deficiency, positive in ACD</td>
</tr>
</tbody>
</table>

ACD = Anemia of chronic disease; EPO = erythropoietin; MCV = mean cell volume; MCH = mean corpuscular hemoglobin; RBC = red blood cell.

diluted in saline and given intravenously rather than intramuscularly [38]. In other cases recombinant erythropoietin may be given, allowing the use of storage iron in patients with anemia of chronic inflammation [36].

Anemia/Cobalamin Deficiency

Like deficiency of bone minerals and iron, cobalamin deficiency occurs in stages [39], and the appropriate diagnostic test depends in part on the stage in which the patient resides. The loss of ileum results in patients with Crohn’s disease being at high risk for cobalamin malabsorption, a condition that leads not only to inability to assimilate dietary vitamin (about 2 µg/day), but also leads to loss of body stores through the enterohepatic circulation (about 5–10 µg/day). Serum cobalamin (B₁₂) levels are diagnostic when very low (<125 pg/ml), but deficiency may be present in many patients with values up to 200 pg/ml, and very
occasionally with serum cobalamin concentration up to 350 pg/ml if accompanied by anemia or consistent neurologic findings [40]. When cobalamin deficiency is suspected in a patient with serum concentrations from 125 to 200 pg/ml, further workup should include measurement of serum methylmalonic acid and homocysteine (both raised), and if confusion persists, following the response to cobalamin replacement. In some instances the most sensitive assay for deficiency may be a measure of holo-TCII content, as TCII loses its cobalamin before haptocorrins, the other cobalamin binding proteins in serum [39]. Treatment of deficiency traditionally involves injections of the vitamin (1 mg/month), but for patients with short bowel syndrome, nasal cobalamin preparations are available as an alternative.

**Recommendations for the Adjunctive Use of Parenteral Nutrition Support in Inflammatory Bowel Disease in Adults** [1]

(i) Bowel rest is not necessary to achieve clinical remission.
(ii) Parenteral treatment is useful in patients who cannot tolerate intestinal feeding and who require nutritional support.
(iii) Home total parenteral nutrition provides an important long-term treatment for patients who do not have adequate gut function.

**Detection and Treatment of Common Micronutrient Deficiencies in Patients with Inflammatory Bowel Disease**

(i) Consideration should be given to the stage of bone mineral, iron, or cobalamin deficiency in an individual patient.
(ii) The diagnostic tools chosen should be appropriate for that stage of deficiency.
(iii) The success of treatment should be followed using the most appropriate index.
(iv) The concomitant use of either enteral or total parenteral nutrition should not necessarily be considered adequate management for these deficiency states.

**References**

Discussion

Dr. Khoshoo: Is there a difference in the response between acute fistulas and chronic fistulas with respect to the use of total parenteral nutrition (TPN)?

Dr. Alpers: I don’t know that it’s ever been stratified in that way. The biggest differential that I find is the severity of the post-fistula obstruction. Most fistulas in Crohn’s disease occur with a partial obstruction just beyond the fistula, whether it’s recognized or not. How complete that is, or how much of an abscess there is around that area, will determine the response. If there is a partial obstruction due to an acute abscess and you’re able to control the abscess by medical means and therefore to decrease the amount of postoperative, post-fistula stricture, that will decrease the pressure in the gut which I think is involved in causing the fistula. Those patients may do better but I can’t quote you a study that confirms that.

Dr. Seidman: Our group has been studying the use of parenteral iron as a factor in peroxidative injury. We know that patients with inflammatory bowel disease are under peroxidative stress and we know that TPN patients receive parenteral iron. Do you think the use of parenteral iron might increase infection rates and therefore reduce any benefit there might be in using TPN to prevent postoperative infections, because of the very nature of the iron load given parenterally in those patients?

Dr. Alpers: What dose of iron are you using?

Dr. Seidman: It depends on whether they are being treated for anemia concurrently, in which case it would be 100–200 μg/kg; otherwise I think it’s of the order of 15 μg/kg.

Dr. Alpers: I don’t have a specific answer for you. I’m not a fan of mixing medications or therapeutic goals. If you determine that the patients needs iron, I would give it separately, particularly as there are ways to give it safely with a minimum of side effects. I wouldn’t be in favor of adding it to the TPN mixture. Now if you’re asking whether, when added to the mixture, it could affect the response rate, the answer is theoretically yes, but there are so many other variables involved that I wouldn’t know how to evaluate it.

Dr. Bistrian: Most hyperalimentation services do not put iron into TPN solutions. It’s incompatible with three-in-one solutions in any quantity. When it was put in at all, it was put in usually in the range of 2–4 mg/day. That amount of iron will slightly raise the serum iron but will have no impact on hemoglobin, so most people just discontinued it. There’s a particular risk in giving iron in any quantity when individuals are acutely ill. In the rehabili-
ation of children with kwashiorkor, giving iron in the rehabilitation formula increases mortality. There’s excellent experimental evidence that large amounts of iron increase the growth of pathogens in the serum, so you should never give iron, even to patients with iron deficiency, during acute illness. It is better to transfuse the patient.

**Dr. Alpers:** Of course, there are other reasons for not giving large amounts of iron too, because of the side effects that you get from the preparation.

**Dr. Bistrian:** Actually, total dose infusion of iron is something we do quite commonly in our home TPN patients. It’s a convenient way to give it to those who have continued iron losses while on home TPN. We do not routinely provide iron with the TPN because patients with even the shortest guts can absorb some iron and there are cases of iron overload when even small amounts of iron are added to the home TPN formula. We wait until iron deficiency develops and then, rather than give iron on a continuous basis because of the risk of catheter infections, we wait until they’re well and then give a total dose infusion of 200–500 mg of iron, which is extraordinarily well tolerated.

**Dr. Van Gossum:** I’m puzzled that about 65% of the patients who are considered to be refractory to steroids respond to TPN. How can you explain that? This percentage is as good as for drugs like anti-TNF or even better than IL-10, for example.

**Dr. Alpers:** I think it depends on what your outcome is. If, for example, your outcome is a Crohn’s disease activity index or diarrhea, you know you will get an improvement on TPN, because nothing is going into the intestinal lumen, accepting that there are some patients who are secreting even in the absence of enteral intake. But that aspect will certainly improve. There are other aspects, such as the patient with anorexia feeling better because he doesn’t have to eat and is not being pressured to eat. So there are several reasons why a person on TPN might feel better. But as soon as you stop the TPN, the symptoms generally return. Whether this is really a recrudescence of the disease or simply stress on the unused gastrointestinal tract isn’t really clear. Much of the response seen with TPN is rapid and early. The patients feel better right away. I think this is one of the reasons why the short-term remission rates with TPN are considerably higher than longer-term rates.

**Dr. Lochs:** Do you really think it is important to determine in cases of deficiency whether it is an expression of inflammation or an expression of a low nutrient intake? I would like to quote our papers on iron supplementation in Crohn’s disease. We did not attempt to determine whether these patients were iron deficient because of increased inflammatory activity or from a low intake, but when we replenished them with iron, their disease activity decreased, their well-being increased, and their anemia improved. So maybe that if you have anemia or if you are deficient, let’s say, in calcium or whatever, the reason why you are deficient is not the most important factor, don’t you think?

**Dr. Alpers:** Thanks for that comment. I want to make sure I made myself clear. I didn’t mean to say that if you really are iron deficient it matters how you got that way. What I meant to say was that there are many people who have anemia in Crohn’s disease who are **not** iron deficient; they have the anemia of chronic disease. Those people will not respond to iron. I would agree that if you really are iron deficient, you should respond, but I would say the majority of patients whom I see with Crohn’s disease who have hemoglobin concentrations of 11 or 12 g/dl are not really iron deficient. They are often put on iron without even a check of their reticulocyte count afterwards to see if they responded. They’re just maintained on iron when in fact they’re not really iron deficient.

**Dr. Lochs:** I’m not sure whether this anemia of chronic disease really exists in Crohn’s disease. We have looked at a large number of patients with Crohn’s disease – you may know of the paper we published in the *New England Journal of Medicine*. We only studied those with a hemoglobin below 10 g/dl, but when we gave them parenteral iron 80% of them improved, both with respect to their hemoglobin and also to their Crohn’s disease activity index. The 20% who did not improve responded to erythropoietin.
Dr. Alpers: You’re absolutely correct, but I think this is the issue of stratification again. A man with a hemoglobin concentration of less than 10 mg/dl has a considerable loss of body iron. People with anemia of chronic inflammation usually don’t drop their hemoglobin down to that level, though there are exceptions. When anemia is more severe it should respond. But we see a lot of patients in the higher range who don’t respond to iron.

Dr. Van Gossum: In patients with chronic anemia, when would you consider the administration of erythropoietin?

Dr. Alpers: I would first want to make sure that they were not iron deficient. If they were iron deficient, then I would give them iron. If they couldn’t take oral iron I would give them parenteral iron. If then I was left with a degree of anemia which I thought was important for the patient, I would consider erythropoietin, but that’s going to be in a very small number of patients, particularly if you don’t accept fatigue as a symptom of anemia. I think fatigue is multifactorial, not only from cytokines, but also from depression.

Dr. Belli: You spoke about liver involvement. With regard to TPN-associated liver disease, we recently demonstrated that this can be related to oxidative stress, and this was confirmed by data in the American Journal of Physiology [1]. Don’t you think that the cumulative effect of oxidative stress and Crohn’s disease could be deleterious and requires us to be very cautious in view of the possibility of causing liver damage?

Dr. Alpers: Yes. Thank you. But on the other hand I think we need to be clear that not all liver responses are the same. So the cholestatic response that we tend to see much more in younger children may not be the same as the fatty liver or other abnormal responses that we tend to see more often in the adult.

Dr. Rolandelli: I’d like to expand on the comments you made about perioperative nutritional support. There are data showing that when you compare TPN versus no TPN or TPN versus enteral nutrition, the patients who do not get TPN have a lower rate of infectious complications that are not necessarily related to TPN. For example, in the VA Cooperative Study [2], those patients who were severely malnourished did get benefit but those who were only mildly malnourished had a higher incidence of septic complications. In another study involving laparotomy for trauma, patients who received enteral nutrition had fewer pneumonias [3]. Another point that I’d like to make, expanding on what we discussed with Dr. Jeejeebhoy earlier, is that there is no good study showing a reduction in postoperative complications after surgery for Crohn’s disease or ulcerative colitis with the use of nutritional support. However, there are good data to show that the use of steroids and the presence of infection before surgery predisposes to abscesses.

Dr. Alpers: The difficulty with this whole area is that the techniques you’re talking about – the administration of TPN and surgery – although they should be standardized and routine, are in fact very operator dependent. Particularly with some of the older studies of TPN, where it was not quite as routine as it is nowadays, I really don’t think you can assume that it was safely administered at that time, so I simply can’t answer that particular question. You’re quite right that the difference in infectious complication could be related to the presence of enteral feeding, but the opposite interpretation is just as possible.

Dr. Van Gossum: In patients receiving long-term parenteral nutrition, what is your recommendation about manganese administration, with respect to the risk of brain toxicity?

Dr. Alpers: I’m still unaware of any well-documented case of manganese deficiency in man. I’m not convinced that manganese needs to be given routinely.

Dr. Van Gossum: But should we avoid giving complexes containing manganese, because of the reports of brain toxicity and neurological disorders [4]?

Dr. Alpers: I think it’s not a good idea to give it routinely in the long term.

Dr. Winter (South Africa): Intravenous fat emulsions are unfortunately very expensive and this limits their general use. What would be your advice as to the requirement for intravenous fat for long-term TPN?
Dr. Alpers: As you know, the requirement is relatively low. You can fulfill it by very small amounts of Intralipid or even, if the patient can take it, by 10–15 ml of corn oil a couple of times a week by mouth. There are some advantages to giving lipid, if volume overload is a problem, but I don’t think anybody should be wedded to a particular percentage of lipid in long-term TPN.

Dr. Winter (South Africa): We’ve had the occasional problem of steatosis and liver dysfunction in these patients which seems to be reversed by increasing the fat intake.

Dr. Alpers: Yes, but I think time does it too. If you just continue with the same dose that you’re on, the liver function tests tend to normalize.

Dr. Jeejeebhoy: I’d like to point out that a lot of patients who are on intravenous supplementation because of inflammatory bowel disease don’t get it because of energy restriction, they get it because they cannot maintain their fluid and electrolyte balance. In particular the maintenance of magnesium levels can be very troublesome in a lot of patients. So the major need for intravenous supplementation of patients who have no colon and no ileum is fluid and electrolyte supplementation. Giving magnesium is helpful because not only does this cure magnesium deficiency but there’s evidence that magnesium and citrate are important in preventing renal stones.

Dr. Alpers: We give oral sodium supplementation (using concentrations >110 mEq/l) along with magnesium gluconate. Using that we can markedly diminish the numbers that require TPN for fluid and electrolyte replacement.

References