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Nutritional Issues in the Short Bowel Syndrome – Total Parenteral Nutrition, Enteral Nutrition and the Role of Transplantation

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Abstract

In this review, I focus on the extreme of the short bowel syndrome where the loss of intestine is so great that patients cannot survive without intravenous feeding. This condition is termed short bowel intestinal failure. The review outlines the principles behind diagnosis, assessing prognosis and management. The advent of intravenous feeding (parenteral nutrition) in the 1970s enabled patients with massive (>90%) bowel resection to survive for the first time and to be rehabilitated back into normal life. To achieve this, central venous catheters were inserted preferably into the superior vena cava and intravenous infusions were given overnight so that the catheter could be sealed by day in order to maximize ambulation and social integration. However, quality of life has suffered by the association of serious complications related to permanent catheterization – mostly in the form of septicemias, thrombosis, metabolic intolerance and liver failure – from the unphysiological route of nutrient delivery. This has led to intense research into restoring gut function. In addition to dietary modifications and therapeutic suppression of motility, novel approaches have been aimed at enhancing the natural adaptation process, first with recombinant growth hormone and more recently with gut-specific glucagon-like peptide-2 analogues, e.g. teduglutide. These approaches have met with some success, reducing the intravenous caloric needs by approximately 500 kcal/day. In controlled clinical trials, teduglutide has been shown to permit >20% reductions in intravenous requirements in over 60% of patients after 6 months of treatment. Some patients have been weaned, but more have been able to drop infusion days. The only approach that

predictably can get patients with massive intestinal loss completely off parenteral nutrition is small bowel transplantation, which, if successful (1-year survival for graft and host >90%) is accompanied by dramatic improvements in quality of life.

Introduction

It should be noted that the severity of the short bowel syndrome (SBS) varies from mild to severe, and that the degree of severity is directly related to the loss of absorption capacity. For example, the management of *mild disease* is easy and based on increased oral supplementation to overcome the reduced efficiency of absorption, for example oral B_{12} supplementation in patients with ileal resection, whilst the management of *severe disease* includes intravenous supplementation of water, electrolytes and nutrients.

Definition of Severe Short Bowel Syndrome or Short Bowel Syndrome and Intestinal Failure

SBS and intestinal failure (SB-IF) is the most severe form of the syndrome and can only be managed with long-term use of intravenous nutrition, i.e. home (HPN) or total parenteral nutrition (TPN). It is this condition that we will focus on in this article. It has been defined as a condition that results from surgical resection, congenital defects or disease-associated loss of absorption, and is characterized by the inability to maintain protein energy when on a conventionally accepted normal diet [1].

Prediction of Short Bowel Syndrome and Intestinal Failure

Studies performed by Messing et al. [2] in France have indicated that patients with massive intestinal resection or loss can be categorized into those who are likely to become permanently dependent on parenteral nutrition (PN) and those who are not. Measurements suggest that patients with <80 cm of small intestine plus colon are likely to become independent of parenteral support (PS). However, those who have lost their colons as well, i.e. those with end-jejunostomies, will likely need >200 cm of small intestine to remain independent of PS. Of course, this assumes that the remaining small intestine is functionally normal. If it is diseased, as in Crohn's disease, then greater lengths of small intestine will be required.

Clinical Determination of Short Bowel and Intestinal Failure

The best practical way of assessing whether a patient has SB-IF is to measure 24-hour urine output volumes plus sodium content when they are off all intravenous infusions and eating normally. If the 24-hour urine volume is greater than 1 liter and if urinary sodium is greater than 20 mEq/day, then it is not present. These measurements are also very useful in gauging intravenous fluid and electrolyte requirements in patients requiring TPN or HPN.

Adaptation

The remarkable thing about the intestine is its ability to adapt to the loss of length. Consequently, it is important to reassess absorption in the months following intestinal loss to reassess PS requirements. Some patients might well become independent of intravenous infusions in the 2 years following resection. The process of adaptation begins almost immediately following resection or loss, and can continue for over 2 years [3, 4]. Adaptation is characterized by villous hyperplasia, which increases the absorptive surface 200-fold. In the days before the advent of intravenous feeding, this process allowed some patients to survive with only 15 cm of small intestine [5]. Villous hyperplasia is far more evident in studies in experimental animals than in humans. The hyperplasia is associated with increased digestive enzyme secretion, muscular hypertrophy, delayed food transit through changes in motility and increased blood flow. The net result is increased absorption. These features are illustrated in figure 1. Probably the driving force for adaptation is the increased contact between food and the remaining mucosa resulting from the associated hyperphagia. Studies have shown that adapted patients usually consume 1.5–2.0 times the recommended dietary allowance for protein and calories [6]. Studies of ours have revealed that food-induced pancreatic secretion is also twice normal (fig. 2) [6, 7].

General Principles of Management

(1) It must be remembered that most food digestion occurs in the jejunum and proximal jejunum. Consequently, digestion is rarely a problem and there is no indication for pancreatic enzyme supplementation to improve absorption in SB-IF patients.

(2) The reason why we have an extraordinary long small intestine is to allow for the reabsorption of the massive quantities of fluid (>7 liters/day) and elec-

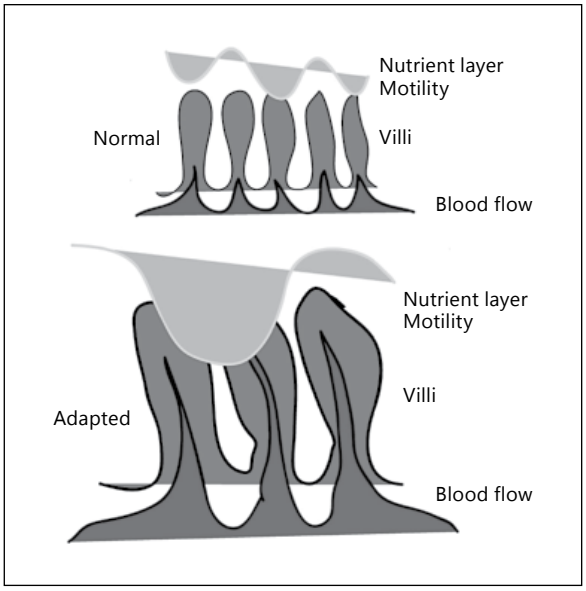

Fig. 1. Key factors in intestinal adaptation.

trolytes that are secreted by the upper gastrointestinal tract to ensure optimal enzymatic digestion. Consequently, fluid and electrolyte depletion is the earliest event in SBS.

(3) As mentioned above, digestive function and absorption improves with time because of adaptation, but absorptive capacity must be rechecked over the course of time to reassess basic needs.

(4) As mentioned above, digestion is not the problem, transit is. Consequently, it is important to tailor management to keep food in contact with the remaining intestinal surface for as long as possible.

Practical Management

(1) Avoid dietary restriction [8]. Remember hyperphagia is part of the adaptation response.

(2) Prolong nutrient-mucosa contact time. Break down normal meals into small frequent meals, supplement with nutrient-dense liquids and use drugs to reduce motility. Patients need to understand that they have to change the way they eat; they must train themselves to 'nibble like rabbits'. This reduces the load on the remaining intestine and ensures a longer contact time between food and the absorptive mucosa. The most effective way is to provide continuous slow enteral feeding. This was beautifully illustrated by Joly et al. [9] in their random-

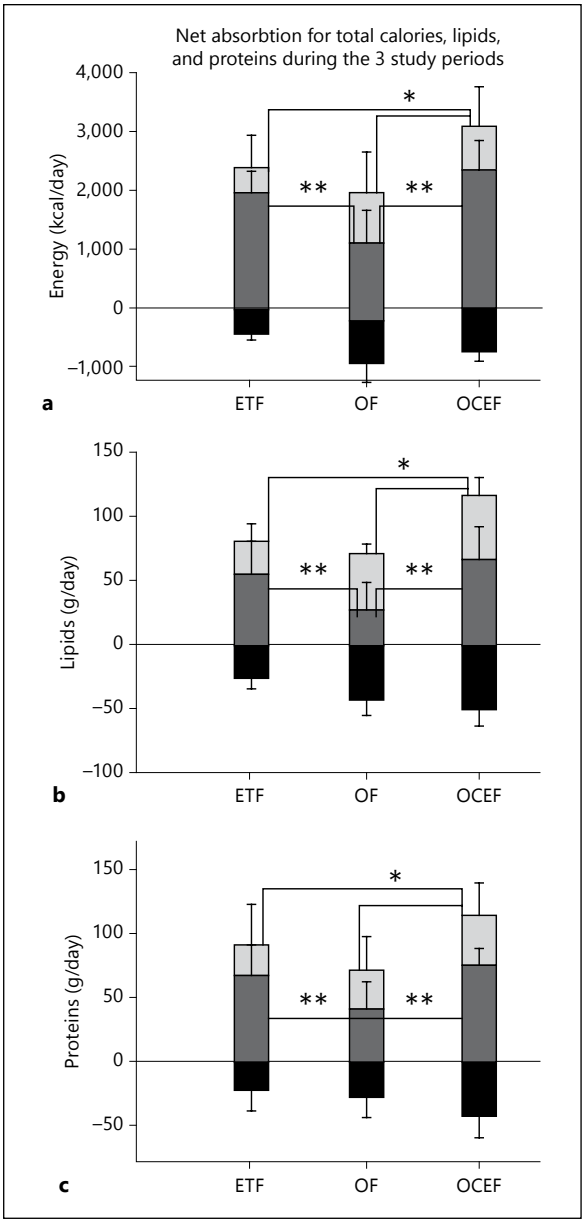

Fig. 2. A randomized crossover study compared absorption between isocaloric tube feeding and OF in 15 SBS patients >3 months after short bowel constitution. An OF period combined with enriched (1,000 kcal/day) tube feeding was also tested. Means ± SD. Net absorption for total calories (**a**), lipids (**b**) and proteins (**c**) during the 3 study periods. In the *histograms*, intakes (light grey) and losses (in black) are above and below the zero line, respectively, the dark grey being the net absorption (intake losses). Total caloric, lipid and protein intakes (light grey bars) were significantly higher with OF combined with tube feeding (OCEF) than with OF and enteral tube feeding (ETF; * p = 0.001). Net absorption for total calories, lipids and proteins (dark grey bars) was significantly higher with ETF and OCEF than with OF (** p 0.001) with permission [9].

ized crossover study of 15 SBS patients; they compared absorption between isocaloric tube feeding and oral feeding (OF), and then a combination of OF and 1,000 kcal/day tube feeding. Figure 2 shows that absorption of calories, lipids and protein was significantly higher with exclusive enteral tube feeding than OF. The combination enhanced absorption further, illustrating the importance of hyperphagia in maximizing absorption in SB-IF patients.

(3) Opiates are the most effective antimotility agents to use in this situation to increase nutrient-mucosa contact time. However, it is best to avoid opiates in the long term and use their derivatives such as Imodium, which have little central side effects. Imodium should be given in much higher quantities, i.e. up to 16 mg 6 hourly, than recommended for people with normal intestines because of the reduced absorption of medications and high therapeutic index.

(4) Studies have shown that with adaptation, colonic bacterial fermentation increases dramatically and can result in a net salvage of up to 1,000 kcal/day in the form of short-chain fatty acids [10]. Consequently, in order to maximize absorption, patients with SB-IF with colons should be given diets enriched with complex carbohydrates.

(5) Previously, patients with SB-IF were encouraged to limit the amount of fat they consumed in order to reduce steatorrhea. However, when formally tested, it was shown that the amounts of calories absorbed were higher when patients consumed a high-fat diet despite the fact that stool fat also increased [11, 12].

(6) One of the key principles of SB-IF management is to restrict water consumption. The reason for this is that the mucosa of the duodenum and jejunum is freely permeable to fluid and electrolytes and cannot maintain a concentration gradient. Thus, in patients with end jejunostomies, the consumption of water will draw electrolytes accompanied by water from the body and exacerbate dehydration and electrolyte deficiencies. In order to prevent this, the use of WHO-type solutions is encouraged. With these solutions, salt and glucose are actively taken up across the mucosa by specific transport mechanisms into the body accompanied by water. Thus, it is always important to encourage patients to take fluids containing sugar and salt in the ratios suggested by the study by Lennard-Jones [13] shown in figure 3. The problem is that patients are tired of drinking these solutions. A pragmatic alternative is to use flavored sport drinks, such as Gatorade. Blenderized soups are also very useful if they contain salt and a carbohydrate source such as pasta, rice or potato.

(7) Another approach is the suppression of secretion. The use of acid suppressants such as H_2 antagonists or proton pump inhibitors is encouraged early following intestinal loss when gastric secretion is increased. Long-term use is, however, contraindicated as acid secretion decreases with time and complete suppression will lead to bacterial overgrowth in the remnant intestine and exacerbation of fluid and electrolyte losses [6, 7]. The most dramatic therapeutic approach to the suppression of secretion is to use octreotide. In a study of 8 well-adapted patients with severe SB-IF, we were able to show that injections of octreotide 50 μg t.i.d. resulted in 50% reductions in stomal fluid and electrolyte losses [6, 7] (fig. 4). Interestingly, while fat absorption was not affected, there was

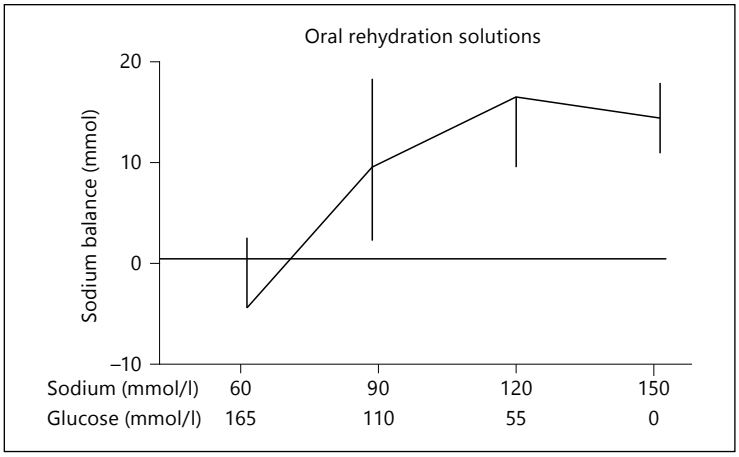

Fig. 3. The physiological basis for WHO rehydration fluids. Sodium balance is only achieved when luminal concentrations exceed 70 mmol/l with glucose concentrations of 140 mmol/l (Lennard-Jones [13]).

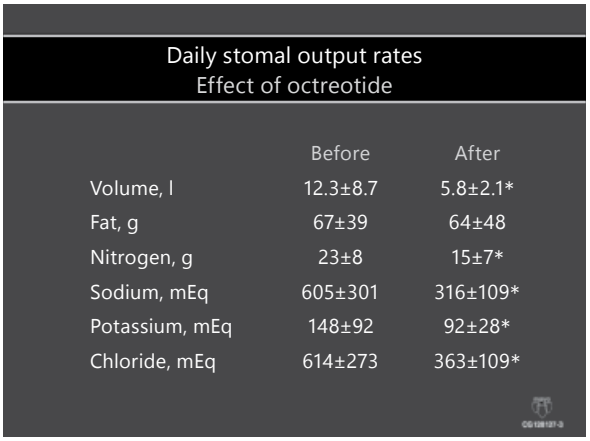

Fig. 4. The effect of octreotide, a long-acting somatostatin analogue, on end-jejunostomy losses in hyperphagic SB-IF patients [7].

a significant increase in nitrogen reabsorption, presumably because of the ability of the drug to reduce motility thereby increasing food-mucosa contact time.

We performed studies in this group of patients to examine the effects of octreotide on mucosal growth (fig. 5), using primed continuous 8-hour intravenous infusions of isotope-labeled leucine [7]. The results showed that despite the beneficial effects of the drug, i.e. decreased fluid and electrolyte secretory losses, it had negative effects on mucosal protein synthesis and villous growth, thus countering the physiological adaptation process. Consequently, we only recommend short courses of octreotide to control extremely high secretory stomal losses before adaptation has had time to establish itself.

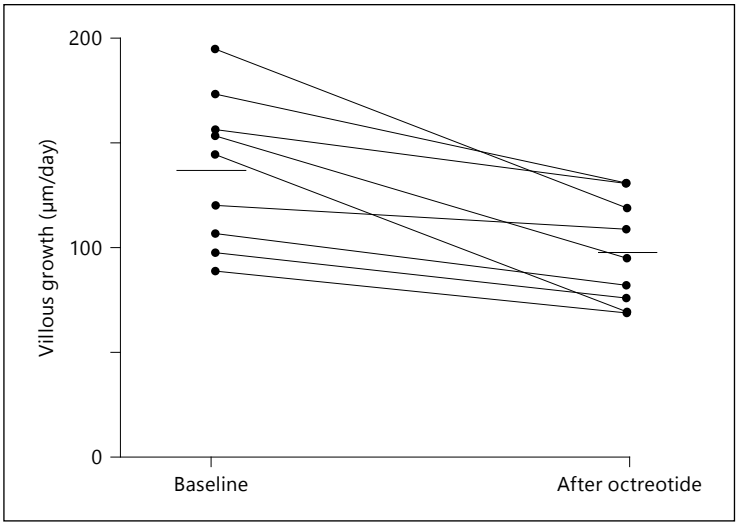

Fig. 5. Octreotide inhibits mucosal protein synthesis and may have anti-adaptational properties [7].

(8) Another approach is to increase adaptation. Much attention has recently been devoted to developing gut hormonal approaches enhancing the natural adaptation process. The first hormone to be used was recombinant growth hormone. Several studies (initially uncontrolled, later controlled) showed that injections of recombinant growth hormone increased electrolyte and energy absorption in SB-IF patients. Perhaps the best of these is the one reported by Seguy et al. [14] (fig. 6). Despite using lower and more physiological doses, their results were very positive, with significant increases in energy, nitrogen, carbohydrate and D-xylose absorption. However, in its marketed form, Zorptive, the drug has been little used in clinical practice primarily because it can only be used during a short time frame and because of its high side effect profile. A Cochrane review [15] of all the controlled trials came up with the following conclusion: 'The results suggest a positive effect of human growth hormone on weight gain and energy absorption. However, in the majority of trials, the effects are short-lived returning to baseline shortly after cessation of therapy. The temporary benefit calls into question the clinical utility of this treatment. To date, the evidence is inconclusive to recommend this therapy'.

Perhaps the most exciting recent developments in the therapeutic management of SB-IF is the protease-resistant form of glucagon-like peptide GLP-2. GLP-2 is secreted by L-cells in the distal bowel. Many of their properties are those seen in natural adaptation. For example, the peptide slows gastric emptying, reduces gastric secretion, increases mucosal blood flow, stimulates the growth of small and large intestine, increases epithelial proliferation and reduc-

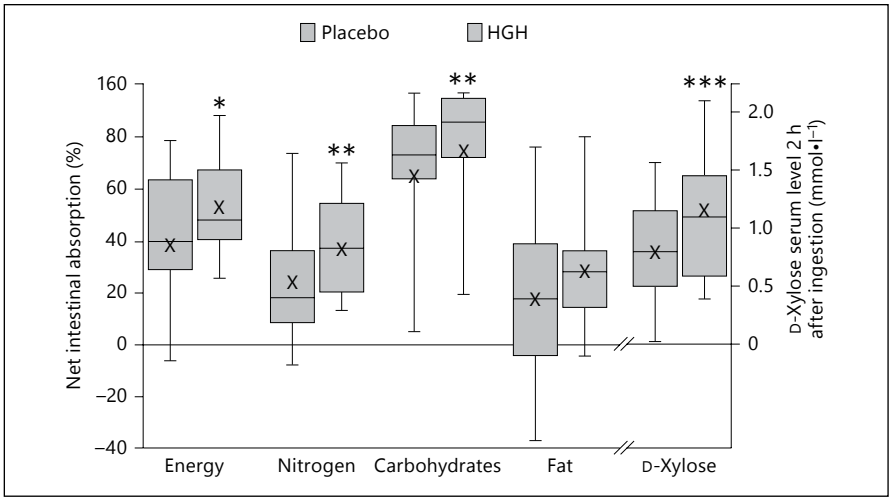

Fig. 6. Three weeks of human growth hormone (HGH) increases intestinal absorption of macronutrients with permission [14]. Lower dose (physiological) recombinant HGH significantly affected energy (440 kcal/day), nitrogen and carbohydrate absorption in 12 SBIF patients (Crohn's disease 3/12, residual small intestine mean 43 cm range 0–120 cm, 9/12 had colons, 9/12 colon: study design: randomized double-blind, placebo controlled, cross-over trial GH 0.05 mg/kg/day for 3 weeks placebo controlled, cross-over trial GH 0.05 mg/kg/day for 3 weeks). * $p < 0.002$, ** $p < 0.04$, *** $p < 0.02$, vs. placebo.

es apoptosis [16]. Thus, unlike growth hormone, its effects are specific to the small intestine. With chemical engineering, the substitution of a glycine molecule for alanine in natural GLP-2 made the product, teduglutide, protease resistant, thus increasing its half-life from minutes to several hours [17]. This is important as it can now be given as a single daily injection.

Two multicenter, multinational randomized controlled trials which verify the potency and efficacy of the drug in reducing intravenous fluid requirements have now been completed. Because the condition is relatively rare, sufficient numbers could only be achieved with international collaborations through 29 sites in 10 countries (USA and Europe). In the first study [18], two dose levels were compared to placebo in 84 patients. Surprisingly, the lower dose (0.05 mg/kg per day) proved more effective in achieving the primary end point of 'clinically significant' (>20%) reductions in intravenous fluid requirements to maintain normal renal function as defined by a stable plasma creatinine and urine volume of 1–2 l/day (46 vs. 6%, $p = 0.01$). Secondary benefits included increased fasting plasma citrulline, a marker of enterocyte function, and increased lean body mass. In the second confirmatory study, a more simple randomized controlled trial was conducted between placebo and the teduglutide dose of 0.05 mg/kg per day (fig. 7) in 86 patients [19]. Here, 63% achieved >20% reduction in PS

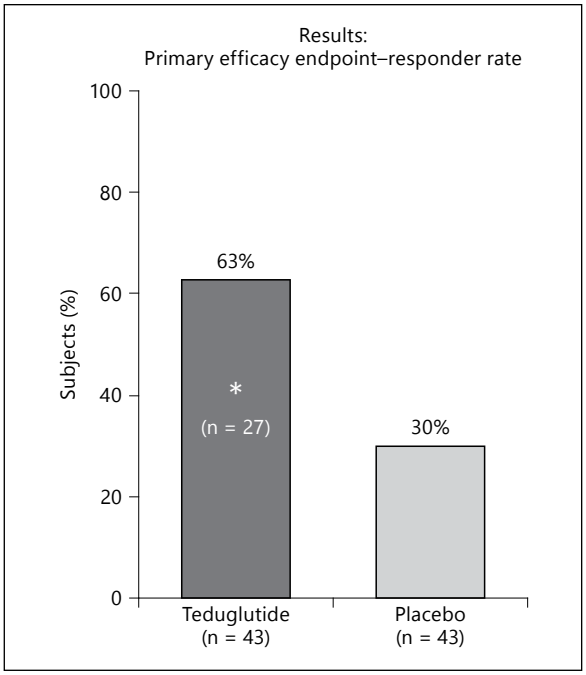

Fig. 7. The long-acting protease-resistant modification of the gut peptide GLP-2, teduglutide, reduced intravenous fluid requirements by >20% in 63% of SB-IF patients within 6 months, which translated into a shorter duration of intravenous infusion and total weaning back to normal food in 4 patients (Jeppesen et al. [19]). * $p < 0.002$, vs. placebo (Cochran-Mantel-Haenszel test).

Fig. 8. A common side effect of teduglutide is swelling of the stoma, which indicates the powerful effects the drug has on the residual bowel.

compared to 43% on placebo ($p = 0.002$). Importantly, this translated into more patients being able to drop the frequency of intravenous infusions, and 11 patients were successfully and completely weaned from intravenous therapy during the two studies [20]. Interestingly, the time of weaning varied from 12 to 110 weeks on the drug. There is no doubt about the potent hypertrophic effects of this drug, which can readily be seen with endoscopy and examination of the stoma, which commonly enlarges considerably, as shown in figure 8.

Table 1. Three-year analysis of the Mayo Clinic HPN Program [21]

Patients: 63
Short bowel: 40
Chronic obstruction: 23
Hospitalizations: 73% (average stay: 11 days)
71% were due to catheter infections (*Staphylococcus epidermidis:* 12, fungi: 8)
• 70% of them required catheter replacement
• 2 weeks of intravenous antibiotics
25% for catheter replacement for thrombosis or damage
All had intermittent abnormalities in complete blood cell count, urinary excretion, and renal and liver tests

Another interesting fact was the high placebo response. There is no clear explanation, but it is possible that adaptation continues longer than previously thought, or it could be that tighter management in the clinical trial setting allowed further intravenous fluid reductions. The drug has now been marketed. Postmarketing surveillance will be essential to rule out unanticipated long-term side effects, e.g. neoplastic changes bearing in mind its proliferative properties, but to date the safety profile looks good.

Problems with Home Parenteral Nutrition

PS is the only life-sustaining form of medical treatment for SB-IF. However, PS is expensive, impairs quality of life (QoL) and is associated with serious complications, such as catheter sepsis, central venous thrombosis and liver failure (table 1) [21, 22].

Quality of Life

Many studies have examined this and found that QoL is severely impaired. This is not surprising, as patients lose their freedom as they are tethered to intravenous catheters for the rest of their days. This severely limits social intercourse and the ability to return to a normal occupation and lifestyle. They also have to be vigilant in preserving catheter sterility, as breaks in the line will result in bacteremia, septicemia and repeated hospitalizations.

Complications of Total Parenteral Nutrition

It must be appreciated that although TPN has allowed patients to survive without significant gut function and food absorption, feeding into the right side of the heart can never substitute for feeding through the gut and portal

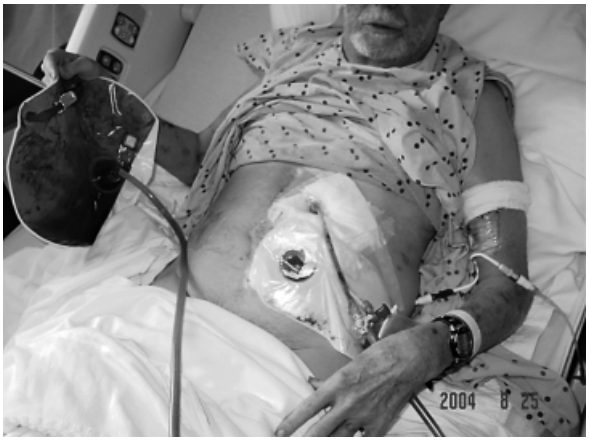

Fig. 9. Illustration of the complexity of the management of patients with massive intestinal resection. This elderly patient had suffered thrombosis of his superior mesenteric artery resulting in gangrene of all of the small intestine from the ligament of Treitz. He was managed with gastrostomy with jejunal extension and central feeding via a peripherally inserted central catheter. Massive stomal losses were associated with recurrent bouts of catheter sepsis and progressive liver dysfunction. A small bowel transplant was performed with successful removal of all these tubes and reestablishment of normal eating.

vein. Even the freshest of foods is heavily colonized by microbes, which are safe if they stay intraluminal but could be fatal if they enter the systemic circulation. Consequently, the prime function of the gut, other than absorption, is to break down food into a sterile solution that can be absorbed into the portal vein, sensed by the pancreas and assimilated by the liver. To achieve this, microbe quantities are progressively diminished by the action of gastric acid, pancreatic enzymes and bile, and finally sterilized by the action of the gut immune system, which surrounds the lumen and engulfs any remaining bacteria. If you contrast this to TPN, it is easy to understand that the chief complications are septicemia, metabolic instability, liver dysfunction and progressive occlusion of the central veins through trauma of the intima by repeated catheterization. A further problem is that systemically administered nutrients are not as well assimilated and utilized by the liver. Consequently, it is always important to maintain oral intake for hepatic nutrition, even if most is malabsorbed.

Complications are directly related to the quality of catheter care at home (fig. 9). Our analysis showed that some patients never experienced catheter infections, whilst others had to be rehospitalized every few weeks [22]. Other risk factors for catheter infections included the presence of a high-output

Table 2. Indications for TPN failure

Medicare indications
(1) Life-threatening sepsis
(2) Venous thrombosis – loss of access
(3) Liver disease – progressive fibrosis, cholestasis, cirrhosis

jejunostomy, chronic obstruction and gut stasis leading to bacterial overgrowth and Crohn's disease.

Perhaps the most life-threatening complication is liver failure. While minor liver function test abnormalities are common and not serious, progressive cholestasis, liver fibrosis and cirrhosis, and eventual liver failure is devastating and uniformly fatal unless a successful liver-small bowel transplant is performed. Luckily, the complication only occurs in ~5% of patients. The etiology is complex and involves repeated infections, absence of oral intake, an extremely short bowel and too many PN calories in the form of fat or dextrose.

Small Bowel Transplantation

The efficacy of small bowel transplantation (SBTx) lagged behind that for renal and liver transplantation until recently, when the Intestine Transplant Registry participants announced that 'a new era has dawned' as outcome now is very similar to that of liver transplantation, i.e. 1-year survival of graft and host >90% due to improved surgery and immunosuppression [23].

In the USA, Medicare has accepted 'TPN failure' as the chief indication for SBTx. The chief criteria are summarized in table 2. It is important to stress that although the novel pharmaceutical approaches to reduce PN requirements certainly contribute to an improved outcome and QoL, only SBTx can *predictably* get patients off intravenous infusions and make them nutritionally autonomous. We have argued that consideration for SBTx should be made early in patients with risk factors for developing liver failure (e.g. ultrashort bowel <50 cm without colon), as this will preserve the liver and obviate the need for a combined liver-small intestine transplant [24].

To illustrate theses points, we conducted a prospective 2-year study of 46 consecutive patients transplanted between June 2003 and July 2004 [25]. PN was stopped completely by day 17 after transplantation. After a mean follow-up time of 21 months, 40/46 (87%) were well with good graft function. Perhaps, most importantly, average QoL, measured with a QoL tool based on a validated self-administered questionnaire containing 26 domains and 130 questions, was

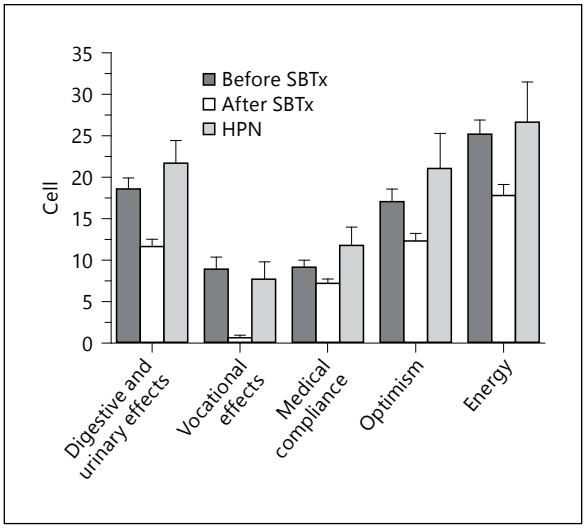

Fig. 10. QoL was significantly improved when patients with intestinal failure dependent on HPN were successfully transplanted. Results were evaluated by comparison to nontransplanted HPN patients. Key improvements following SBTx in some of the 26 domains that improved specifically (split by period) are shown. Means ± SE [25].

dramatically improved. A summary of some of the key improvements is shown in figure 10. It should also be noted that we evaluated baseline QoL compared to HPN in patients who declined transplantation and showed that the indices of QoL in transplanted patients prior to transplantation were significantly lower, indicating the gravity of their illness.

Despite these exciting observations, there remains a reluctance to refer patients with Medicare indications for SBTx, as evidenced by the review by Pironi et al. [26] in Europe. They found that only 15% of HPN patients with Medicaid criteria for 'TPN failure' and small bowel transplant were referred to a center for transplantation, and only 36% of adults and 43% of children with HPN liver failure were described as needing immediate transplantation [26]. The explanation for the reticence is unclear, particularly since SB-IF-associated liver failure is generally a fatal condition, and also because late referral is associated with poor outcomes [23]. The most likely explanations involve unfamiliarity with the procedure and the paucity of experienced centers offering transplantation because the volume is small and the specific skills needed to perform the surgery, and manage the problems, scarce.

Conclusion

There have been significant advances in different approaches to the complex management of patients with SB-IF over the last decade, which have fuelled our armamentarium of therapeutic options and translated into improved quality of

care. However, all these forms of therapy have side effects and potentially serious long-term complications, and so we need to be vigilant in our surveillance, thorough in our multidisciplinarian management [27] and continue to seek safer forms of therapy that return QoL towards normal.

Disclosure Statement

Stephen O'Keefe in the past acted as an advisor to NPS pharmaceuticals in the development of their multicenter clinical trials of teduglutide, and has received support from them for investigator-initiated studies.

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