AGA Technical Review on Short Bowel Syndrome and Intestinal Transplantation

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The normal human small intestine length is generally considered to be between 3 and 8 meters, depending upon whether radiologic, surgical, or autopsy measurements are made.[1–5] Short bowel syndrome (SBS) occurs when there is <200 cm of bowel remaining. This is an approximate length as most methods of residual intestine measurement (such as radiologic contrast studies, pathology of the resected specimen, and perioperative measurement of unweighted intestine) are not especially accurate. Because absorption is related to the amount of residual intestine, it is more important to document the amount of remaining, viable intestine.

Those patients at greatest nutritional risk generally have a duodenostomy or a jejunoileal anastomosis with <35 cm of residual small intestine, jejunocolic or ileocoloic anastomosis with <60 cm of residual small intestine, or an end jejunostomy with <115 cm of residual small intestine.[6–8] It has been suggested that intestinal failure is better defined in terms of fecal energy loss rather than residual bowel length.[9] Given the observations that fecal energy loss does not always correlate well with residual bowel length,[9] and the significant individual variability in jejunal absorption efficiency,[10] it is reasonable to consider a more standardized approach to defining intestinal failure and "functional" SBS from a clinical standpoint. However, fecal energy loss is a function of both energy intake and energy absorption. Patients who are unable to increase their oral intake sufficiently or are unable to absorb sufficient energy despite significantly increased intake, are defined as patients with intestinal failure and require parenteral nutrition support. A standardized diet may be useful for clinically defining functional SBS, although there is insufficient data with regard to what the composition of such a diet optimally should be.

Methods

Most available data on the treatment of SBS are based on retrospective analyses of case series (type II-3 or type III data) and are often few in number, because of the trolled trials were undertaken (type 1 and type IIb data), and the studies are described in detail. Data and reports were obtained from extensive PubMed and Medline searches using several key words, including SBS, various conditions predisposing to SBS, parenteral nutrition, enteral nutrition, relevant specific nutritional deficiencies, intestinal surgery, and intestinal transplantation. In addition, surgical and gastroenterological texts, published national and international scientific meeting abstracts, and the extensive manuscript/abstract files of the authors were reviewed. Expert opinion was sought for the few areas in which no suitable published reports existed (e.g., TPN cycling and preparation of the patient for home TPN). Human data and reports were reviewed exclusively.

Patients with functional SBS who have severe malabsorptive processes related to refractory sprue, chronic intestinal pseudo-obstruction syndrome, or congenital villus hypoplasia are not the specific focus of this technical review, although most of the medical and nutritional management problems and therapies are similar, if not identical.

Incidence and Prevalence of Short Bowel Syndrome

It is unclear how many individuals in the USA suffer from SBS, but based on the numbers in Europe, the incidence may be ≃2 per million.[11] More recent data from 1993 indicated the incidence and prevalence of home parenteral nutrition, for which SBS was the most prevalent indication, increased slightly to 2–3 per year

Abbreviations used in this paper: CMV, cytomegalovirus; CTP, Child-Turcotte-Pugh; CVC, central venous catheter; ESLD, end-stage liver disease; GLP-I, glucagon-like peptide I; ITR, Intestinal Transplant Registry; IVC, inferior venous catheter; LCT, long-chain triglyceride; LILT, longitudinal intestinal lengthening and tailoring; MCT, medium-chain triglyceride; ORS, oral rehydration solution; SBS, short bowel syndrome; SCFA, short-chain fatty acid; SRSB, segmental reversed small bowel; SVC, superior venous catheter; UNOS, United Network of Organ Sharing.

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per million inhabitants and 4 per year per million, respectively.[12,13] The most recent European survey, in 1997, indicated the incidence of home TPN increased slightly to ≃3 per million and the prevalence had increased to 4 per million.[14] SBS constituted the largest single group of patients who required home TPN (35%). In comparison, the most recent data for incidence and prevalence in the USA is from 1992. At that time, it was estimated based on extrapolated data from the Oley Foundation Home TPN Registry that ≃40,000 patients required TPN each year.[15] Approximately 26% of the patients in the Oley registry had SBS, although some patients with a primary TPN indication of malignancy or radiation enteritis may have had SBS as well. These numbers for either Europe or the USA do not reflect patients with SBS who never required TPN or for whom TPN could be discontinued successfully. Approximately 50%–70% of the short bowel patients who initially require TPN can be weaned off TPN successfully in optimal settings with better outcomes in children.[6,16] Therefore, the number of patients with SBS may be substantially greater than previously estimated. A registry of short bowel patients, including those who require TPN permanently, transiently, and not at all, should be implemented.

Pathophysiology of Short Bowel Syndrome

SBS may be a congenital or acquired condition. Infants born with intestinal atresia (jejunal or ileal) constitute the congenital forms. Otherwise, SBS results from surgical resection of bowel. This is usually related to multiple resections for recurrent Crohn's disease, massive enterectomy made necessary because of a catastrophic vascular event (such as a mesenteric arterial embolism or venous thrombosis, volvulus, trauma, or tumor resection in adults, and in children, gastroschisis, necrotizing enterocolitis), intestinal atresias, and extensive aganglionosis. Functional SBS may also occur in cases of severe malabsorption where the bowel length is often intact. Such conditions may include chronic intestinal pseudo-obstruction syndrome, refractory sprue, radiation enteritis, or congenital villus atrophy. Severe nutrient and fluid malabsorption occurs following extensive small intestinal resection. Patients with <100 cm of jejunum remaining generally have a net secretory response to food.[17]

Patients can be grouped into 2 distinct subgroups: those with intact colon in continuity and those without colon in continuity. In patients with SBS, the colon becomes an important digestive organ. The colon absorbs (SCFAs) (see below discussion regarding soluble dietary fiber).[8,18,19]

How Does the Remaining Intestine Adapt Following Resection?

Patients often clinically adapt to the significantly reduced energy absorption associated with SBS through hyperphagia. However, the intestine adapts as well to ensure more efficient absorption per unit length. After massive enterectomy, the intestine hypertrophies and becomes more efficient in nutrient absorption; there is slight lengthening, but more importantly, diameter and villus height increase, effectively increasing the absorptive surface.[20–23] This process may evolve over 1 or 2 years.[6,8,24] Several factors are important determinants in the functional adaptation process and clinical outcome.[6,25,26] These include the presence or absence of the colon and ileocecal valve, length of remaining bowel, health of the remaining bowel, patient age, and comorbid conditions. Although the length of remaining bowel necessary to prevent dependence on TPN is ≃100 cm in the absence of an intact and functional colon or 60 cm in the presence of a completely functional colon,[6,8] the degree of adaptation and TPN dependence may be highly individualized. In infants, adaptation to full enteral nutrition has been reported with as little as 10 cm of residual intestine.[24] However, Carbonnel et al. found small bowel length, determined radiographically, to be an independent risk factor for loss of nutritional autonomy in 103 patients, of which 24 became TPN dependent.[7] In addition, those with a jejunostomy were at increased risk for TPN dependence and those with a jejunal-ileal anastomosis were at decreased risk. Patients with active Crohn's disease, radiation enteritis, carcinoma, or pseudo-obstruction involving their remaining bowel will have a blunted adaptation response.

Animal models of SBS have suggested several gut hormones are involved in postresection intestinal adaptation. These include enteroglucagon, glucagon peptide II, epidermal growth factor, growth hormone, cholecystokinin, gastrin, insulin, and neurotensin.[27] There is little data on the role of either endogenous or exogenous hormones on intestinal adaptation in humans.

Despite the fact that, normally, most nutrients are absorbed in the proximal jejunum, the residual ileum is able to adapt and to assume the role of macronutrient absorption. However, the specialized cells of the terminal ileum, where vitamin B_{12} /intrinsic factor receptors are located and where bile salts are reabsorbed, cannot be

Effects of Massive Enterectomy on Gastrointestinal Motility and Transit Time

Following small intestinal resection, dysmotility may develop, which may predispose to bacterial overgrowth in the residual intestine. In addition, resection of the ileocecal valve allows colonic bacteria to enter and populate the small intestine.[28] Bacterial overgrowth may negatively impact on digestion and nutrient assimilation, as bacteria compete for nutrients with the enterocytes. Diagnosis may be more difficult using breath tests because of more rapid intestinal transit in short bowel patients. Endoscopically obtained small bowel aspirate for culture may be required. Treatment can be undertaken with oral metronidazole, tetracycline, or other antibiotics.

Following jejunal resection, gastric emptying of liquids is more rapid, although intestinal transit may still remain normal because of the braking effect of the ileum.[29] Gastric emptying is significantly slower in patients who have residual colon in continuity and is similar to normal controls. The loss of inhibition on gastric emptying and intestinal transit in patients without colon is related to a significant decrease in peptide YY (PYY), glucagon-like peptide I (GLP-I), and neurotensin.[30] PYY is normally released from L cells in the ileum and colon when stimulated by fat or bile salts. Obviously, these cells are missing in patients who had distal ileal and colonic resection. Those patients with the shortest residual jejunum (<100 cm residual) exhibit the most rapid liquid gastric emptying.[29] Solid emptying may also be more rapid in these patients. Rapid gastric emptying may contribute to fluid losses in patients with SBS.

Medical Therapy of Short Bowel Syndrome

The goal of medical therapy is for the patient to resume work and a normal lifestyle, or as normal of one as possible. This is undertaken via the use of specific measures to gradually decrease the requirement for TPN, and at best, to eliminate its need. The most important aspects of the medical management of the patient with SBS are to provide adequate nutrition, including both macro- and micronutrients (to prevent energy malnutrition and specific nutrient deficiencies), to provide sufficient fluid (to prevent dehydration), and to correct and prevent acid-based disturbances. Most macronutrients, including carbohydrate, nitrogen, and fat, are absorbed

Table 1. Dietary Macronutrient Recommendations for Short Bowel Syndrome

	Colon present	Colon absent
Carbohydrate	Complex carbohydrate 30–35 kcal/kg per day Soluble fiber	Variable 30–35 kcal/kg per day
Fat	MCT/LCT 20%–30% of caloric intake ± low fat/high fat	LCT 20%–30% of caloric intake ± low fat/high fat
Protein	Intact protein 1.0–1.5 g/kg per day ± peptide-based formula	Intact protein 1.0–1.5 g/kg per day ± peptide-based formula

LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

Macronutrient Assimilation and Dietary Therapy

Typically, patients who have undergone massive enterectomy require TPN for the first 7–10 days. Nutritional therapy should not be introduced until the patient is hemodynamically stable and fluid management issues are relatively stable. The goal is to provide patients with ≃25–35 kcal/kg per day depending upon whether nutritional support is for maintenence or correction of undernutrition and 1.0–1.5 kg per day of protein (Table 1). Additional energy and protein are required by children, especially infants and neonates. Some debate exists whether the patient's actual body weight or ideal body weight should be used in this calculation. For the postoperative patient, standard enteral formula is recommended. These should be instituted gradually as tolerated. Once patients are able to eat, they should be encouraged to eat a regular diet, but modified as described below. There is no value in separating liquids from solids in the diet. Such practices have no effect on macronutrient, electrolyte or mineral absorption, fecal volume, or fecal weight.[18]

Proteins and amino acids. Dietary protein is first digested, and then absorbed as dipeptides and tripeptides. Therefore, it was reasoned that dietary protein provided in a predigested form would be more readily absorbed. However, nitrogen absorption is the macronutrient least affected by the decreased intestinal absorptive surface. Therefore, the utility of peptide-based diets in such patients is generally without merit. McIntyre et al. compared energy, nitrogen, and fat absorption, as well as stool weight in 7 patients, all with end-jejunostomy and <150 cm (range, 60–150 cm) of remaining small intestine. These patients were fed with either a peptide-based or an essentially isocaloric and isonitrogenous polymeric formula. Although the study was small, no differences

electrolyte, mineral, or fluid absorption.[32] Uncontrolled data from Levy et al. supports these findings.[33] However, in a small study of 6 patients, all with 90–150 cm of residual jejunum and end-jejunostomy, data from Cosnes et al. suggests nitrogen absorption may be improved with the use of a peptide-based diet. Energy, other macronutrient, electrolyte, mineral, and fluid absorption was unaffected.[34] Therefore, the clinical effect of the modestly increased nitrogen absorption was insignificant. It must be recognized that all the studies described above were very small, the study populations somewhat heterogeneous, the various peptide constituents and their concentrations in these various formulas differed significantly, and there was variation in the type and amount of fat (long-chain triglycerides [LCTs] versus medium-chain triglycerides [MCTs]). It is therefore difficult to make definitive comparisons between studies.

The amino acid glutamine, together with glucose, is the preferred fuel for the small intestinal enterocyte.[35] Rodent TPN models suggested that both parenteral or enteral glutamine supplements could effect more rapid and significant bowel adaptation following massive enterectomy.[36,37] Therefore, it was thought glutamine supplementation in humans would have a similar effect. Although an early case series of 10 patients suggested that glutamine, combined with growth hormone supplementation and a high complex carbohydrate diet could result in decreased stool output and increased absorption of energy, protein, carbohydrate, sodium, and water,[38] 2 subsequent double-blinded, randomized placebo-controlled trials failed to confirm any of these effects.[39,40] In addition, Scolapio et al. showed that glutamine and growth hormone supplementation did not lead to morphological changes in the intestine.[39] Glutamine-supplemented oral rehydration solution (ORS) (see fluid and electrolyte management) was associated with decreased Na absorption and a trend toward decreased fluid absorption in a small controlled trial in 6 patients.[40,41] All of the patients studied by Byrne et al. had colon in continuity[38]; it is likely the treatment-associated increase in energy absorption was related solely to the increased complex carbohydrate diet discussed above. Treatment with growth hormone and glutamine in the setting of SBS has been associated with significantly increased extracellular fluid and peripheral edema.[39,42,43] Therefore, treatment with glutamine and growth hormone cannot be recommended.

Lipid. Luminal digestion of lipid may be impaired because of impaired bile salt reabsorption related to resected ileum (>100 cm).[44] Therefore, treatment to increase the duodenal bile salt concentration to a concentration greater than the level at which micellar solubilization of lipid occurs.[45–47] Unfortunately, this therapy has been associated with significantly increased fecal volume, at least in those patients with intact colon. A preliminary, open-labeled study of 4 patients (2 with colon in continuity) indicated treatment with the conjugated bile acid cholylsarcosine (6 g/day) was associated with an increase in fat absorption of 17 ± 3 g/day without any effect on stool wet weight.[48] As a conjugated bile acid, cholylsarcosine is resistant to colonic bacterial deconjugation, although 1 of the 4 patients did experience a significant increase in wet stool output and another experienced nausea. Cholestyramine is not useful in patients with >100 cm of ileal resection, and may actually worsen steatorrhea because of the binding of dietary lipid.[49]

Although dietary fat restriction may result in increased fecal fat losses, there is no difference in the percentage of fat absorbed between high fat (75% nonprotein calories derived from fat)/low carbohydrate and low fat/high carbohydrate, isocaloric and isonitrogenous diets.[50] In addition, stool weight did not differ between diets. Because fat is energy-dense (9.0 kcal/g) when compared to carbohydrate (4.0 kcal/g), fat restriction may ultimately deprive the patient of a necessary source of energy. Up to 65% of dietary carbohydrate may be malabsorbed and lost in the feces without degradation by colonic bacteria.[31]

The colon also absorbs MCTs (C8-C10), possibly related to the fact that MCTs are water soluble. In a study of 10 short bowel patients with colon in continuity and 9 patients with no residual colon, [randomized in a cross-over design to consume an LCT diet based on ordinary dietary fat, consisting of 20% carbohydrate, 24% protein, and 56% fat versus an MCT-LCT diet, where 50% of the LCT was replaced with MCT (margarine, MCT oil)],[51] those patients with intact colon absorbed 96% ± 3% of C8 and 87% ± 6% of C10, versus 63% ± 25% for C8 and 57% ± 28% for C10, respectively, in patients with no residual colon ($P = 0.007$ for C8 and $P = 0.004$ for C10) from the mixed LCT-MCT diet. Significantly increased energy absorption (≃2.1 MJ/day; 500 kcal/day) was found in patients with colon, but the LCT-MCT diet did not result in increased energy absorption when compared to the LCT diet in patients with an end-jejunostomy or ileostomy whose fecal output was also increased. MCT contain 8.3 kcal/g. Some, but not all, LCT can be replaced by MCT in the diet. In a short bowel patient eating 10.5 MJ/day (2500 kcal/day),

can be replaced with MCT. However, LCTs are still necessary to provide essential fatty acids, and primarily linoleic fatty acid, which is not found in MCTs. In addition, excessive intake of MCT may result in nausea, vomiting, and ketosis.

Carbohydrates. Rarely is the proximal jejunum resected in patients who require massive enterectomy. Because most intestinal disaccharidases are present in highest concentration proximally, it would stand to reason such patients would be unlikely to benefit from a lactose-free diet. Marteau et al. studied 14 short bowel patients in whom a lactose-free diet was compared to a diet containing 20 g/day containing ≤4 g milk.[52] Lactose absorption, breath hydrogen, subjective symptoms of flatulence, and diarrhea were similar regardless of which diet was consumed. This data confirmed the findings of an earlier controlled study in 17 short bowel patients where it was also reported that lactose absorption was enhanced when provided in yogurt rather than via milk.[53] Regardless, in the absence of significant jejunal resection, lactose should not be restricted in the diet of the short bowel patient. The amount of lactose found in a glass of milk (20–25 g) is generally well tolerated even in patients with an end-jejunostomy.[53] Because most lactose is found in milk-based foodstuff, which are also the most important source of dietary calcium, dietary lactose restriction will result in insufficient dietary calcium intake.

The role of soluble fiber. Soluble nonstarch polysaccharides and some starches[54] are not generally absorbed by the small intestine. Soluble fiber is water soluble and found primarily in the following (in descending order of concentration): oatmeal, oat bran, psyllium (Metamucil, Procter and Gamble, Cincinnati, OH; Konsyl, Konsyl Pharmaceuticals, Ft. Worth, TX), barley, artichokes, strawberries, legumes, prunes, grapefruit, and squash. Soluble fiber and starches pass undigested into the colon where colonic bacteria ferment them not only to hydrogen and methane, hence patient "gas" complaints, but also to SCFAs, including butyrate, proprionate, and acetate. SCFAs are the preferred fuel for the colonocyte.[55] Therefore, in the patient with SBS, the colon becomes an important machine for energy absorption. Approximately 75 mmol of SCFA are produced from 10 g of unabsorbed carbohydrate.[56] Patients with SBS, but intact colon in continuity were able to decrease fecal energy loss by 1.3–3.1 MJ/day (310–740 kcal) when they were fed a diet consisting of 60% carbohydrates.[57] Colonic metabolism of unabsorbed carbohydrate was indicated by decreased fecal carbohydrate losses in intact colon to absorb up to 2.2–4.9 MJ (525–1170 kcal) daily from dietary fiber.[8,9,57] Colonic energy absorption may also increase somewhat during the postresection adaptation phase, related to increased colonic bacterial carbohydrate fermentation.[10,58] This may be related to increased colonic bacteria in patients with SBS as well as an increase in the concentration or activity of various enzymes, such as β-galactosidase, over time during the adaptation period.[58] Because SCFAs stimulate sodium and water absorption,[42] patients might be expected to experience decreased fecal fluid and sodium loss, but this has not been observed clinically.[57]

Table 2. Vitamin and Mineral Supplements for Patients With Short Bowel Syndrome

Vitamin A	10000–50000 units daily[a]
Vitamin B_{12}	300 μg subcutaneously monthly for those w/ terminal ileal resections or disease
Vitamin C	200–500 mg
Vitamin D	1600 units DHT daily; may require 25-OH- or 1,23 (OH_2)-D_3
Vitamin E	30 IU daily
Vitamin K	10 mg weekly
Calcium	See text
Magnesium	See text
Iron	As needed
Selenium	60–100 μg daily
Zinc	220–440 mg daily (sulfate form)
Bicarbonate	As needed

NOTE. The table lists rough guidelines only. Vitamin and mineral supplementation must be monitored routinely and tailored to the individual patient, because relative absorption and requirements may vary.

[a]Use cautiously in patients with cholestatic liver disease.

Vitamins. Micronutrients often require supplementation (Table 2). Because water-soluble vitamins are absorbed in the proximal jejunum, it is unusual for deficiencies to develop in short bowel patients (except in those who have high jejunostomies or duodenostomies), although these patients generally require TPN. Thiamine deficiency has been reported and became an important issue during a recent parenteral vitamin shortage.[59] Patients have presented with Wernicke's encephalopathy, beriberi, and severe metabolic alkalosis.[60] If thiamine deficiency is suspected, whole blood thiamine concentration is not helpful; this reflects recent nutritional intake. Erythrocyte transketolase activity should be determined and empiric therapy begun with 100 mg of parenteral thiamine daily. Biotin deficiency has rarely been reported in patients with SBS.[61] It is manifested in a scaly dermatitis, alopecia, lethargy, hypotonia, and lactic acidosis. Therapy consists of parenteral biotin supplementation of 0.3–1 mg daily, although this is not currently commercially available. Vitamin B_{12} supple-

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