Nutrition Support of Infants With Short Bowel Syndrome

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INTRODUCTION

Short bowel syndrome (SBS) is a clinically complex disorder resulting from alterations of normal intestinal anatomy and physiology and producing a variety of nutritional, infectious, and metabolic complications. It is usually defined functionally and is considered to be present when the patient has malabsorption in conjunction with a shortened small intestine.[1] After resection, the residual small bowel undergoes intestinal adaptation, a process characterized by mucosal hyperplasia, villus lengthening, increased crypt depth, and bowel dilatation.[2,3] Oral nutrients and hormones stimulate this intestinal adaptation. Among the hormones, enteroglucagon is an important growth-promoting agent in addition to other growth factors such as epidermal growth factor, prostaglandin E_2, and human growth hormone analogs. The intestinal enterocyte is the target of these factors and, within the cell, the synthesis of polyamines responsible for rapid growth is the most essential step for the development of hyperplasia after resection.[4] The prognosis of patients with SBS has changed in recent decades. Although the presence of an ileocecal valve markedly improves prognosis, some children have survived massive resection and adapted well even in the absence of an ileocecal valve.[5] This disorder, which used to be fatal, is now often compatible with long-term survival and potentially even a normal life course. The establishment of surgical techniques and intestinal transplantation is currently further improving the future of these patients. Nevertheless, the main clinical challenge in SBS lies in managing the many nutritional problems that occur as a result of malabsorption secondary to the reduced absorptive surface area.

PATHOPHYSIOLOGY

The major consequence of resection of the small intestine is malabsorption. This is due primarily to reduction of the absorptive surface area with a concomitant loss of digestive enzymes and transport carrier proteins.[6] Malabsorption of rapidly digested carbohydrates produces osmotic diarrhea. Proteins produce fewer symptoms when malabsorbed. Malabsorption of fat creates little additional fluid loss from the small intestine. Fat-soluble vitamins may also be malabsorbed in patients with SBS. Therefore, vitamin-deficiency states are common.

The extent of micronutrient and macronutrient malabsorption depends to some degree on the area of the bowel resected and the functional characteristics of the segment lost and the segment remaining. Important differences exist in the physiology of the proximal versus the distal small intestine, and these differences have a major impact on the management of patients with SBS. The jejunum has long villi, a large absorptive surface, and a significant concentration of enzymes and transport carrier proteins. Large junctions between the epithelial cells characterize the epithelium, making it relatively porous, and allowing free and rapid flux of water and electrolytes from the vascular to the intraluminal space. The jejunum is also the site of greatest nutrient absorption in the small intestine. Rapid mixing, digestion, and subsequent carrier-mediated transport of monosaccarides, amino acids, and dipeptides occur here predominantly. In contrast, the ileum is characterized by shorter villi, more lymphoid tissue, less absorptive capacity, and a tighter epithelium.[7] The tighter junctions allow less flux of fluid from the vascular space to the lumen, making this epithelium more efficient for the absorption of fluid and electrolytes. The ileum is also responsible for the absorption of vitamin B12 and bile salts through site-specific receptors. Infants with a jejunostomy and a major ileal resection will be extremely susceptible to fluid losses from osmotic diarrhea, especially in association with carbohydrate feedings. Those with jejunal resection may tolerate such feedings better with less fluid loss. The ileum can develop the absorptive capacity of the jejunum for various macro- and micronutrients, but site-specific carrier-mediated transport of vitamin B12 and bile salts will never occur in the jejunum after ileal resection. Reabsorption of bile salts also may be impaired after extensive ileal resection, and luminal bile salt concentrations may fall below the critical micellar concentration. Fats cannot be solubilized and may then be malabsorbed to a greater degree. In addition, many gastrointestinal hormones are produced in the ileum, especially those that affect small intestinal motility, such as enteroglucagon and peptide YY.[8] Thus, ileal resection may also impair regulation of gut motility. Overall, intestinal adaptation after massive ileal resection may be somewhat more difficult than after jejunal resection.

POSTOPERATIVE TOTAL PARENTERAL NUTRITION

The management of infants with SBS is best considered in stages.[1] The immediate postoperative period is characterized by a transient ileus, and all nutrients necessary for basic metabolic needs must be given parenterally. At this first stage of therapy, it is also appropriate to start repleting any nutrition deficiencies present at the time of resection. The evaluation of these deficiencies is done through clinical assessment including anthropometric measurements and laboratory determinations.

With initiation of total parenteral nutrition (TPN), fluid requirements must be calculated and these can be categorized into maintenance therapy, deficit therapy, and replacement therapy.[9] The required maintenance volume of TPN can be determined by calculating the infant's maintenance fluid needs and subtracting from this calculated volume other fluid intakes, such as enteral fluids and intravenously administered medications. During this stage, patients may develop large water and electrolyte secretions once the initial ileus resolves, and gastric fluid and ostomy losses may be high. Excessive fluid and electrolyte losses need to be replaced based on the measured volume and the electrolyte content of these secretions with the use of a separate fluid and electrolyte solution.

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This may seem troublesome, but the more economical use of parenteral nutrition solutions, a more flexible response to rapidly changing fluid losses, and the decreased need for laboratory monitoring will compensate for the additional effort. Close monitoring of fluid and electrolyte balance is particularly important during infancy when sudden fluid shifts can rapidly lead to severe dehydration, kidney failure, or fluid overload.[10]

In addition, caloric requirements must be determined. Ideally, TPN should provide adequate non- protein calories to prevent further catabolism and promote protein accrual. Ideal body weight should be used to determine caloric intake. The amount of calories must provide for growth of the infant. Additional requirements must be taken into consideration including increases due to fever, cardiac failure, surgery, and sepsis. Macronutrients must be initiated in a stepwise fashion.

During the neonatal period, dextrose should be started at a rate of 4 to 7 mg · kg^{-1} · min^{-1} and then increased in gradual increments by 1 to 2 mg · kg^{-1} · min^{-1} to 12 to 15 mg · kg^{-1} · min^{-1}. This approach allows an appropriate response of endogenous insulin and prevents hyperglycemia and glucosuria. Hyperglycemia leads to hyperinsulinemia, causing significant changes in potassium and phosphorus metabolism and episodes of profound hypoglycemia after the abrupt discontinuation of TPN. To avoid hypoglycemia, the infusion rate should be tapered by 50% for at least 1 h before discontinuation of TPN. Excessive carbohydrate infusion can result in alteration of the immune defense system, development of hepatic steatosis, and excess carbon dioxide production with CO_2 retention.[11]

Protein provides 4 kcal/g and should not be included in the calculated caloric intake because most of the infused amino acids should be used for endogenous protein synthesis. To promote efficient protein use and growth of infants, approximately 150 to 200 non-protein calories are required per gram of nitrogen. This amounts to 24 to 32 non-protein calories per gram of protein. The protein requirement of infants is 2 to 3 g · kg^{-1} · d^{-1}, being higher in premature and malnourished patients. The amino acid formulation used for TPN in infants in the United States is usually TrophAmine. This solution has reduced concentrations of potentially hepatotoxic amino acids such as methionine, glycine, and alanine. It provides the essential amino acids (including taurine, tyrosine, and histidine), aspartic acid, and glutamic acid in adequate amounts as judged by an appropriate amino acid profile in plasma.[12,13] In neonates, cysteine is an essential amino acid and needs to be provided separately.[14] Beyond infancy, the addition of cysteine HCl to home parenteral nutrition solutions leads to plasma taurine concentrations within the normal reference range.[15] Cysteine HCl doses of 30 to 40 mg/g of amino acids are recommended if TrophAmine is used as the amino acid formulation.

Fat emulsions are required for the prevention of essential fatty acid deficiency and as a calorie source. A 20% lipid emulsion is preferred over a 10% lipid emulsion because of its lower phospholipid content per gram of fat. Fat may contribute 30% to 40% of total non-nitrogen calories but should not exceed 60%. In patients with respiratory failure, fat is a preferred source of calories because of its low respiratory quotient. Currently available lipid emulsions in the United States contain only long-chain fatty acids provided by soybean oil or combinations of soybean and safflower oil as their fat source. Long-chain fatty acids are essential for normal growth, maintenance of cell integrity, and as precursors of prostaglandins, prostacycline, thromboxane, and leukotrienes.[16] Lipid emulsions containing a mixture of medium- and long-chain triacylglycerols have been used in Europe and South America for some time.[17,18] They may have the advantage of providing additional calories without the risk of causing hypertriglyceridemia or hyperglycemia. These emulsions are likely to be replaced by emulsions containing structured lipids with medium- and long-chain fatty acids on the same glycerol backbone. Optimal oxidation of fatty acids requires carnitine, which may be an essential nutrient in premature infants and infants with SBS. The appropriate dose ranges from 10 to 50 mg · kg^{-1} · d^{-1}. Parenteral administration is recommended because oral carnitine supplementation seems to be insufficient to restore low carnitine levels in patients with SBS and severe malabsorption.[19]

Micronutrients in TPN also include electrolytes, vitamins, trace minerals, and iron. Special consideration in patients with SBS must be given to calcium and phosphorus because these patients may have higher requirements. However, to avoid precipitation in the TPN solution, the product of calcium and phosphorus should be less than 300 mEq/L. Vitamins, trace minerals, and iron constitute an essential component of nutrition therapy. Pediatric multivitamins and adult multivitamins are not interchangeable because of differences in concentrations of individual vitamins and the lack of vitamin K in adult formulations. Trace minerals should include zinc, copper, selenium, manganese, molybdenum, and iodide. Infants with SBS may have significant gastrointestinal losses of zinc requiring additional supplementation.

Other additives to TPN that have been considered beneficial include glutamine, arginine, and ω-3 fatty acids. These compounds have various positive effects including those on the immune system.[20,21] However, their potential use in TPN of infants requires further study.

Several factors have been associated with the duration of TPN in infants with SBS.[22] These include hepatobiliary disease, presence of bacterial overgrowth, and tolerance of enteral feedings. In addition, length and type of residual intestine are major determinants of the ability to wean the infant off TPN. The presence of an ileocecal valve also may play a role, but this has recently been refuted.[22] As a general rule, patients at the time of neonatal resection with longer than 25 cm of small intestine with an ileocecal valve or those with longer than 40 cm of small intestine who do not have an ileocecal valve have a reasonably good prognosis.

Complications of TPN include catheter sepsis, fluid and electrolyte imbalances, disturbances in acid–base status, dysfunction of the hepatobiliary system, and metabolic complications including hyperammonemia, hyper- and hypoglycemia, hypertriglyceridemia, metabolic bone disease, and hypercalciuria. Liver disease is extremely common in infants with SBS. Factors associated with cholestatic liver disease can be divided into three categories: 1) those related to TPN such as glucose overload causing steatosis,[23,24] recurrent episodes of sepsis, hepatoxicity of certain ingredients of TPN solutions,[25,26] lipid peroxidation with free radical formation,[27] and photosensitivity of lipid emulsions;[28] 2) those related to the shortened intestine such as disturbance of the enterohepatic circulation of bile acids, decreased bile flow, and the formation of biliary sludge;[29] and 3) those related to the lack of enteral feeding such as non-stimulation of insulin-like growth factor-1 and other growth factors that affect the liver and cholecystokinine, which promotes gallbladder emptying and bile flow.[22]

Several therapeutic strategies have been proposed to reduce liver damage. Lipid peroxidation can be reduced by decreasing light exposure to the fat emulsion and by ensuring adequate intake of vitamins C and E.[20] Other treatments proposed are ursodeoxycholic acid, cholecystokinin, and *S*-adenosylmethionine. A clinical effect of these interventions has yet to be proven.[20] Overall, early exposure of the gastrointestinal tract to nutrients is the best treatment for hepatobiliary dysfunction associated with long-term TPN.

Therefore, infants with SBS should be aggressively weaned off TPN. However, if they cannot be weaned, they are candidates for receiving therapy at home. Patients on long-term home parenteral nutrition have a better quality of life when compared with patients remaining in the hospital for long periods for nutritional therapy.[30] Receiving parenteral nutrition at home is safer, with lower sepsis rates and longer duration of central venous catheters.[31] In addition, home parenteral nutrition has a beneficial effect on the child's behavior and family dynamics.[32]

ENTERAL NUTRITION

In the second stage of the care of patients with SBS, enteral nutrition is initiated promptly to promote intestinal adaptation. This adaptive response depends on the presence and quality of enteral nutrients in the gut, with complex nutrients stimulating adaptation to a greater degree.[33] The benefits of trophic feeding compared with TPN in improving intestinal length, mucosal mass, and brush border enzyme activity have been established.[21,34] Enteral nutrition also plays a role in maintaining normal gut flora and immunocompetence and in decreasing the incidence of bacterial translocation.[35] In adults, complex proteins are often used for their stimulant effect on gut adaptation. However, in infants with SBS, enteral feedings are usually started with elemental or semi-elemental diets containing free amino acids or small peptides rather than intact protein (Table I). It is not clear why infants with SBS tolerate elemental diets better than diets containing intact protein. One reason may be that infants have a "leaky gut" favoring sensitization to cow's milk or soy protein. In fact, allergic reactions to these proteins are common in infants with SBS.[22,36] Bines et al. noticed a remarkable fall in intestinal permeability (using lactulose) in four children with SBS after they were switched from a protein hydrolysate formula to a formula containing free amino acids and glutamine (Neocate, SHS North America, Rockville, MD, USA; Table I) as the protein source.[37] These investigators also observed a significant increase in disaccharidase activities and reduction in patient morbidity 12 mo after starting the amino acid–based formula.[37] They speculated that elimination of dietary antigen and/or ingestion of glutamine with the formula could have contributed to the observed improvement in intestinal function.

The type of fat in the formula (Table I) also may be important in enteral nutrition of infants with SBS. There is experimental evidence that diets containing a high proportion of fat in the form of medium-chain triacylglycerols stimulate mucosal adaptation to a lesser degree than those containing predominantly long-chain fatty acids.[38] However, in infants with significant ileal resection, luminal bile acid concentrations may not be sufficient to absorb large quantities of long-chain fat. In such infants, a mixture of medium- and long-chain triacylglycerols in the diet may be preferable because medium-chain fats do not require micellar formation for intestinal absorption.[39]

Most commonly, enteral nutrition is provided in a continuous fashion to maximally saturate carrier proteins and optimally use intestinal function. Continuous feedings also reduce emesis.[1] The feedings are started slowly and the concentration is increased as tolerated to 0.67 kcal/mL (or 20 kcal/oz) in infants. Higher concentrated formulas may cause osmotic diarrhea. Initial advancement of concentration rather than rate of infusion of the enteral feeding solution allows the transition from parenteral to enteral feeding to be conducted without overloading the patient with fluid. Subsequently, the volume of enteral feedings can be gradually increased as the volume of parenteral feedings is decreased. These changes should be isocaloric. A marked increase in stool loss ($>$50% of previous volume or amounts larger than 40 to 50 mL $\cdot$ $kg^{-1} \cdot d^{-1}$) or ostomy output strongly positive for reducing substances suggests that enteral feedings should not be advanced. In patients with an intact colon, a decrease in stool pH below 5.5 is indicative of carbohydrate malabsorption. Advancing feedings in these patients is likely to result in a significant increase in osmotic diarrhea. If diarrhea persists, addition of fiber to the formula may increase absorption and decrease stool quantity. Fiber, by producing short-chain fatty acids, may also play a role in intestinal adaptation.[40] Starches should be avoided in the nutrition of infants with SBS. They are rapidly hydrolyzed in the upper gastrointestinal tract, producing an osmotic load that may exceed the absorptive capacity of the shortened intestine. In comparison, hydrolyzed fats exert little effect on the fluid flux across the small intestine because of micellar formation.[33] Medications such as loperamide to slow intestinal transit have been used with some success.[41]

In addition to intragastric feedings, feedings by mouth should be initiated promptly and can be started with solids around nasogastric tubes without difficulty after age 4 mo. This permits the infant to maintain oral motor skills and lessens the likelihood of feeding difficulties once tube feedings are discontinued. Solid food items high in protein and fat and low in carbohydrate such as meats are preferred.

BREAST MILK

The use of breast milk in SBS deserves special consideration. A continuous infusion of small amounts of breast milk in a group of infants with SBS resulted in a shorter duration of TPN than did a similar infusion of a protein hydrolysate formula in a control group.[22] This suggests that breast milk may be beneficial for infants with SBS. Breast milk contains high levels of immunoglobulin A, nucleotides, leukocytes, and other components that bolster the neonate's immune system.[42] Moreover, the presence of glutamine and growth factors such as growth hormone and epidermal growth factor in breast milk may play a role in intestinal adaptation by affecting enterocyte growth and brush border enzyme activity.[43] Breast milk also provides a protective colonic bacterial flora. Lactoferrin, a glycoprotein found in high concentrations in breast milk, delivers iron to the intestinal epithelium, stimulates proliferation and differentiation of crypt cells, influences brush border enzyme activity, and functions as a scavenger for iron to prevent free radical–mediated tissue damage.[44] All these properties make breast milk an attractive nutritional alternative to formulas for young infants with SBS.

FACTORS INTERFERING WITH ENTERAL NUTRITION

Intestinal motility and mucosal immunity are disrupted in infants with SBS and predispose them to bacterial overgrowth, leading to deconjugation of bile salts, depletion of the bile acid pool, incomplete micellar solubilization of fats, and, consequently, to steatorrhea and malabsorption of fat-soluble vitamins. Bacterial overgrowth also competes with the host for vitamin B12[45] and perhaps other nutrients. Treatment is initiated with antibiotics that affect anaerobic bacteria and is usually given intermittently.

Excessive fluid secretion frequently occurs in SBS, manifesting clinically with protracted diarrhea. Elevated serum gastrin levels, which are often present in patients with SBS, may cause secretory diarrhea interfering with nutrient absorption. H_2 receptor antagonists can be used to avoid gastric hypersecretion.[46] Somatostatin analogs have been used with mixed results.[41] Cholestyramine is sometimes helpful in decreasing the concentration of bile acids in the colon but may interfere with fat absorption.

The compromised intestinal function becomes a major problem in ensuring adequate intake of micronutrients. Trace minerals and vitamins are often less well absorbed and are more likely to become deficient than are macronutrients. Malabsorption of fat-soluble vitamins, especially A, D, and E, is common. Trace metal deficiencies are likely to occur, with iron and zinc being most common. Selenium absorption also may be impaired.[1] Low serum levels of calcium and magnesium are frequently observed. Supplemental vitamin D and calcium may correct the calcium deficiency, but magnesium deficiency is more difficult to treat. Enterally administered magnesium salts often result in osmotic diarrhea, although some magnesium salts are better tolerated than others.[47] After ileal resection, infants should be monitored carefully for vitamin B12 deficiency. Parenteral administration of vitamin B12 may be required every 1 to 3 mo. In contrast to adults, vitamin B12

TABLE I.

COMPARISON OF ELEMENTAL AND SEMI-ELEMENTAL PRODUCTS FOR INFANTS FROM BIRTH TO 12 MO OF AGE

Per 100 kcal	Neocate*	Alimentum†	Nutramigen‡	Pregestimil§	Vivonex Pediatric‖
Form	Powder	Liquid	Powder	Powder	Powder
Flavor	Unflavored	Unflavored	Unflavored	Unflavored	Unflavored
Energy (kcal/ml)	0.67	0.67	0.67	0.67	0.8
% Protein	12	11	11	11	12
% Fat	41	48	45	48	25
% Carbohydrate	47	41	44	41	63
Protein equivalent (g)	3.1	2.75	2.8	2.8	3
Protein source	L-amino acid	Hydrolyzed casein	Hydrolyzed casein	Hydrolyzed casein	L-amino acid
Fat (g)	4.5	5.54	5	5.6	2.94
Linoleic acid (g)	0.67	1.9	0.82	1.04	0.39
% MCT	5	50	0	55	68
% LCT	95	50	100	45	32
Carbohydrate (g)	11.7	10.2	11	10.2	15.75
Minerals					
Calcium (mg)	124	105	94	115	121.5
Phosphorous (mg)	93.1	75	63	75	100
Magnesium (mg)	12.4	7.5	11	11	25
Iron (mg)	1.85	1.80	1.8	1.8	1.25
Zinc (mg)	1.66	0.75	1	1	1.5
Manganese (mg)	0.09	0.008	0.025	0.025	0.25
Copper (mg)	0.124	0.075	0.075	0.075	0.15
Iodine (μg)	15.4	15	15	15	15
Sodium (mg)	37.3	44	47	47	50
Potassium (mg)	155.1	118	110	110	150
Chloride (mg)	77.2	80	86	86	125
Selenium (μg)	3.73	2.8	2.8	2.8	3.75
Chromium (μg)	3.56	Not stated	Not stated	Not stated	5.69
Molybdenum (μg)	4.75	Not stated	Not stated	Not stated	9.4
Vitamins					
Vitamin A (μg RE)	122.7	90	90	114	93.8
Vitamin D (μg)	2.175	1.13	1.5	1.5	1.58
Vitamin E (mg TE)	0.765	2.01	1.35	2.68	2.52
Vitamin K (μg)	8.79	15	8	12	5
Vitamin C (mg)	9.26	9	12	12	12.5
Thiamin (mg)	0.093	0.06	0.08	0.08	0.19
Riboflavin (mg)	0.138	0.09	0.09	0.09	0.225
Vitamin B6 (mg)	0.123	0.06	0.06	0.06	0.26
Vitamin B12 (μg)	0.17	0.45	0.3	0.3	0.375
Niacin (mg)	1.54	1.35	1.0	1.0	2.5
Folic acid (μg)	10.2	15	16	16	26
Pantothenic acid (mg)	0.62	0.75	0.5	0.50	0.629
Biotin (μg)	3.1	4.5	3	3	12.5
Choline (mg)	13.1	8	12	12	25
Inositol (mg)	23.3	5	17	17	7.5
Osmolarity at standard dilution (mOsm/kg water)	342	370	320	340	360

* SHS North America, Rockville, MD, USA 1999.
† Ross Products Division, Columbus, OH, USA, Abbott Laboratories, 1999.
‡ Mead Johnson Pediatrics, Evansville, IN, USA, Mead Johnson & Co., 1999.
§ Mead Johnson Pediatrics: Evansville, IN, USA, Mead Johnson & Co., 1999.
‖ Clinical Products Division, Minneapolis, MN, USA, Sandoz Nutrition Corporation, 1999.
LCT, long-chain triglycerol; MCT, medium-chain triacylglycerol

deficiency can rapidly develop in infants with SBS and periodic attention to this possibility is required.

SURGICAL OPTIONS

Infants who are unsuccessful in achieving intestinal adaptation require other therapeutic alternatives. Surgical options include maneuvers to slow intestinal transit, increase mucosal surface areas, improve intestinal motility, and increase intestinal length.[33] Most recently, intestinal transplantation and combined transplantation of small intestine and liver have changed the prognosis for infants dependent on long-term TPN.[33] However, with aggressive nutrition therapy, most infants with SBS have a good chance of intestinal adaptation. Careful attention to detail and close moni-

toring for complications, deficiencies, and acute changes in the clinical course are key to the optimal care of these patients.

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