# Current Management of Short Bowel Syndrome

Intestinal failure refers to a condition that results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance.[1] The short bowel syndrome (SBS) is a type of intestinal failure caused by intestinal resection leading to a shortened intestinal remnant and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet. SBS accounts for approximately three-fourths of intestinal failure patients in adults and more than one half in children. The pathophysiologic changes that occur in SBS relate primarily to the loss of intestinal absorptive surface and more rapid intestinal transit. The consequences of malabsorption of nutrients include malnutrition, diarrhea, steatorrhea, specific nutrient deficiencies, and fluid and electrolyte imbalance. These patients are at risk for other specific complications, which include an increased incidence of cholelithiasis, gastric hypersecretion, nephrolithiasis, and liver disease.

The history of SBS is one of long-standing interest but more recent advancements. Koeberle[2] reported the first patient surviving massive resection of the small intestine in 1880. The clinical consequences of diarrhea and malabsorption were described by Senn in 1888.[3] Mall[4] reported using reversed intestine segments to improve these symptoms in 1896. Functional adaptation after massive resection was well documented by Flint[5] in 1912. In 1935, Haymond[6] reviewed 257 cases of extensive (>8 feet resected) intestinal resection. He found that only 50 (20%) survived for more than 1 year and further suggested that loss of 50% of the intestine was the upper limit of safety. Simons and Jordan[7] reported 90 SBS patients (<4 feet remaining small intestine) in 1969. Mesenteric vascular disease was the most common diagnosis and mortality remained high. An important milestone was the demonstration by Wilmore and Dudrick in 1968 that parenteral nutrition (PN) would support nutritional

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status in SBS patients.[8] The development of home PN in 1970 revolutionized the long-term care of SBS patients and this modality rapidly became standard therapy.[9,10] More recently, the importance of optimal diet and potential pharmacologic therapy was introduced by Byrne and colleagues,[11] leading to the concept of intestinal rehabilitation. In 1990, Grant and colleagues[12] reported the first long-term survivor of a small bowel transplant who achieved enteral autonomy, ushering in a new avenue of treatment for SBS.

The incidence and prevalence of SBS are estimated to be 3 per million and 4 per million, respectively.[13] Thousands of patients are now surviving with SBS.[14] This condition occurs in approximately 15% of adult patients undergoing intestinal resection, with three fourths of these cases resulting from massive intestinal resection and one fourth from multiple sequential resections.[15] Massive intestinal resection continues to be associated with significant morbidity and mortality rates, which are related primarily to the underlying diseases necessitating resection.[15,16] Approximately 70% of patients who develop SBS are discharged from the hospital.[16] The overall 5-year survival is 75% for those leaving the hospital.[17] This improved survival rate has been achieved primarily by the ability to deliver long-term nutritional support. The overall outcome of these patients is often determined not only by their age and underlying disease but also by complications related to management of SBS.

SBS has been the topic of previous issues of *Current Problems of Surgery*. In 1971, Wright and Tilson highlighted the pathophysiology of SBS as management options were limited at that time.[18] Wilmore and colleagues[19] in 1997 emphasized new therapeutic approaches, particularly promising pharmacologic agents. This led to the concept of intestinal rehabilitation and the development of multidisciplinary teams. The current monograph reviews recent advances in our understanding of pathophysiology, medical management, and surgical therapy, especially intestinal transplantation.

## Etiology of the Short Bowel Syndrome

A variety of conditions requiring intestinal resection lead to SBS (Table 1). The causes of SBS vary by age group. In infants, necrotizing enterocolitis is the most common cause of SBS, followed by intestinal atresia, gastroschisis, and midgut volvulus.[20] In older children, postoperative SBS and malignancies become important reasons for resection. Trauma and

**TABLE 1.** Causes of the short bowel syndrome

| |
|---|
| Infants |
| Necrotizing enterocolitis |
| Intestinal atresia |
| Gastroschisis |
| Midgut volvulus |
| Children |
| Cancer |
| Postoperative complication |
| Trauma |
| Motility disorders |
| Adults |
| Postoperative complications |
| Irradiation/cancer |
| Mesenteric vascular disease |
| Crohn's disease |
| Trauma |
| Other benign causes |

motility disorders requiring resection are also potential mechanisms for SBS in this age group.

The etiology of SBS in adults may be changing. We have found that postoperative SBS, resection performed for complications of previous abdominal operation, has become the most common cause in adults.[21] This occurs after both open and laparoscopic procedures. Although this may be related to infarction secondary to vascular injury, volvulus, or hypotension, it most commonly occurs because of intestinal obstruction. Mesenteric ischemia remains an important predisposing factor. Mesenteric vascular disease is the common mechanism but ischemia secondary to drug abuse and hypercoagulable disorders is increasingly found. Malignancy, with or without radiation treatment, also accounts for a significant number of cases. Crohn's disease remains responsible for a significant number of SBS patients but may be declining with less aggressive resective therapy. Resection for trauma and other benign conditions, such as volvulus and intestinal pseudoobstruction, are other potential causes for SBS.

## Prevention of the Short Bowel Syndrome

Prevention of SBS is an important consideration given the morbidity and mortality associated with long-term treatment. Efforts at prevention can be divided into 2 periods: preoperative and intraoperative.

Preoperative strategies to prevent SBS are primarily related to the patient's underlying diagnosis. Postoperative SBS could be minimized by employing strategies to present adhesions, avoiding technical errors,

diagnosing intestinal ischemia in a timely fashion, and approaching the frozen abdomen cautiously.[21] Patients undergoing bariatric procedures should have mesenteric defects closed to prevent internal hernias and this diagnosis should always be entertained when these patients experience abdominal pain.[22] Unsuspected intestinal ischemia is increasingly recognized as a complication of laparoscopic procedures.[23] Intestinal ischemia from mesenteric vascular disease and hypercoagulability must be diagnosed in a timely fashion. This may permit attempts at revascularization. Intestinal viability should be carefully assessed intraoperatively and second-look procedures should be used judiciously.[24] Radiation enteritis can be reduced by minimizing bowel exposed to radiation.[25] Errors in diagnosis, aggressive resectional therapy, and postoperative complications contribute to SBS in patients with Crohn's disease.[26,27] SBS can be minimized in trauma patients by early diagnosis of vascular injuries, use of second-look procedures, and appropriate resuscitation.[28] Bowel-preserving strategies are now being used in infants with necrotizing enterocolitis, which may decrease the incidence of SBS because of this condition.[29]

There are several intraoperative strategies to prevent SBS.[30] The extent of resection should always be minimized where possible. Tapering or lengthening dilated segments and use of stricturoplasty in conditions such as Crohn's disease can obviate the need for resection. Avoiding extensive enterolysis and using cautious resection can prevent SBS in patients with extensive adhesions from conditions, such as radiation enteritis.[25]

## Factors Influencing Outcome

The clinical manifestation of SBS varies greatly among patients, depending on intestinal remnant length, location, and function; the status of the remaining digestive organs; and the adaptive capacity of the intestinal remnant (Fig 1). More recently the importance of other patient-related factors has also been recognized, including age, diagnosis, and body mass index.[16,31] Thus, although intestinal length is important, the outcome of SBS is not entirely dependent on a given length of remaining intestine.

Intestinal remnant length is the primary determinant of outcome in SBS. The length of the small intestine reported in adults varies between 12 and 20 feet (360-600 cm), depending on how it is measured and the height and sex of the individual.[32-34] The duodenum measures 10-12 inches (25-30 cm). The length of the small intestine from the ligament of Treitz to the ileocecal junction is generally approximately 16 feet (480 cm), with the

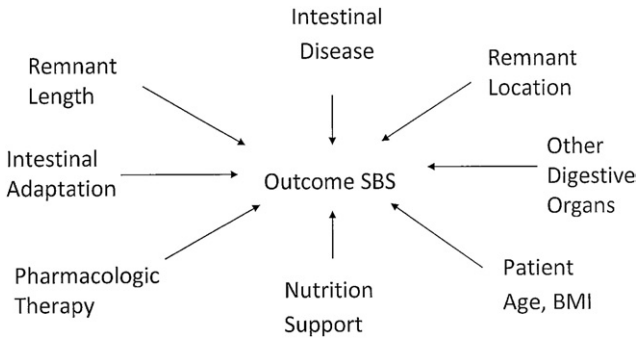


**FIG 1.** Factors affecting the outcome of short bowel syndrome.

proximal two fifths being jejunum and the distal three fifths being ileum. Resection of up to one half of the small intestine is generally well tolerated. Although adult patients with less than 180 cm of small intestine, approximately one third the normal length, may develop SBS, permanent PN support is likely to be needed in patients with less than 120 cm of intestine remaining without colon in continuity and less than 60 cm remaining with colonic continuity.[17,35]

In infants, the intestinal length is 125 cm at the start of the third trimester and 250 cm at term. The length then doubles again as the child reaches adulthood.[20,36] Children with less than 75 cm small intestine may develop SBS. Children are further classified as short small bowel (>38 cm), very short small bowel (15-38 cm), and ultrashort small bowel (<15 cm).[20] These categories predict those that are most likely to become PN-independent and survival vs need for PN and mortality.

The site of resection is also an important factor. Patients with an ileal remnant generally fare better than those with a jejunal remnant. The ileum has specialized absorptive properties for bile salts and vitamin $B_{12}$, unique motor properties that prolong transit time, a hormone profile different from the jejunum, and a greater capacity for intestinal adaptation.[37,38] L cells in the terminal ileum secrete several hormones that might influence appetite, gastrointestinal motility, intestinal absorption, and intestinal adaptation, including peptide YY, neurotensin, and glucagon-like peptides 1 and 2 (GLP-1 and GLP-2). The presence of the ileocecal junction improves functional capacity of the intestinal remnant.[38] Although previously this had been largely attributed to a barrier function and transit prolonging property of the ileocecal valve, this advantage may actually be related to the special-

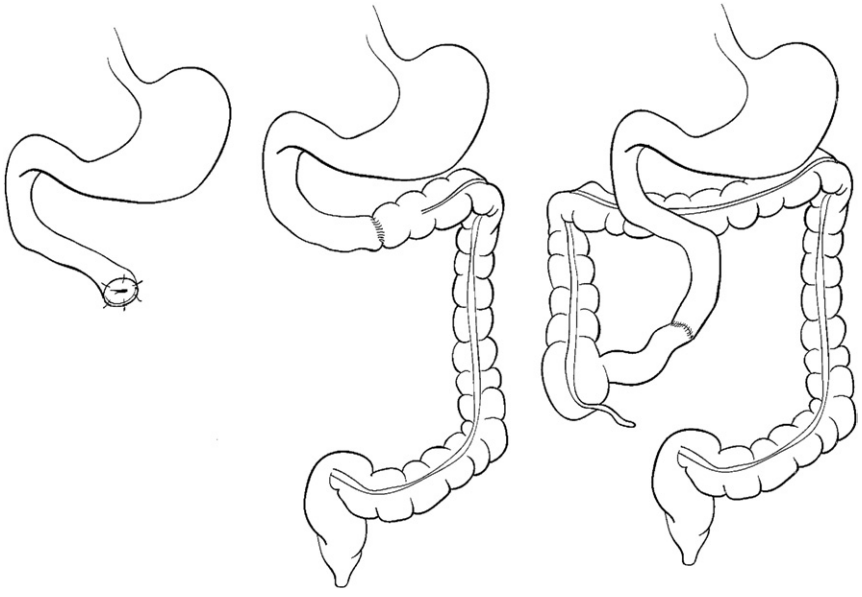

**FIG 2.** Intestinal anatomy in short bowel syndrome Type 1 anatomy (left) is a proximal jejunostomy. Type 2 anatomy (center) is a jejunocolostomy. Type 3 anatomy (right) is a jejuno-ileo-colostomy.

ized properties of the terminal ileum itself, which is usually resected with a loss of the ileocecal junction.

The status of the other digestive organs also contributes to the outcome. The stomach influences oral intake, mixing of nutrients, transit time, pancreatic secretion, and protein absorption. Pancreatic enzymes are important in the digestive process and particularly influence fat absorption. The colon absorbs fluid and electrolytes, slows transit, and participates in the absorption of energy from malabsorbed carbohydrates.[39] The colon will absorb up to 15% of the daily energy requirements and thereby reduce PN needs.[39-41] Compared with an end jejunostomy (Type 1 anatomy), a jejunoileal anastomosis with an intact colon (Type 3 anatomy) is equivalent to 60 cm of additional small intestine, and a jejunocolic anastomosis (Type 2 anatomy) is equivalent to approximately 30 cm of additional small intestine[35] (Fig 2). The importance of the colon in functional adaptation of infants is less clear but appears to be critical in children with very short and ultrashort small bowel.[42]

The underlying disease leading to resection is an important patient-related outcome factor. Patients with inflammatory disease (eg, Crohn's disease and radiation injury) in the intestinal remnant may have impaired intestinal function. They may also be at increased risk of hepatobiliary

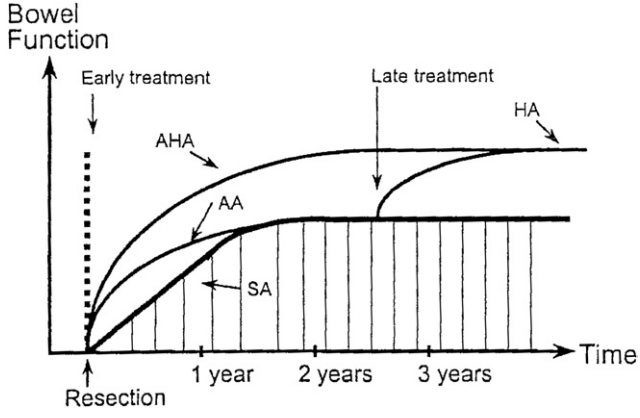


**FIG 3.** Schematic presentation of intestinal adaptation. SA, spontaneous adaptation; AA, accelerated adaptation, HA, hyperadaptation; AHA, accelerated hyperadaptation. (Reprinted with permission from Jeppesen.[44])

disease.[43] The cause of resection will also influence outcome because of the effect on other digestive organs. Patients with malignancy and trauma often have involvement of other organs.[28]

Long-term treatment and survival are influenced by the patient's age and other medical conditions. Infants and young children have the potential for intestinal growth but typically have caloric needs 2 to 3 times those of adults to support normal growth and development.[20] Elderly patients generally have a less favorable outcome.[17] Paradoxically, obesity has also been recognized recently as an important positive determinant of SBS outcome.[31]

## Intestinal Adaptation

The small intestine has the ability to adapt to compensate for the reduction in absorptive surface area caused by intestinal resection.[19,44,45] This adaptive process occurs within the first year or 2 after resection in adults and improves intestinal absorptive capacity (Fig 3).[44] Intestinal failure is considered permanent when specialized nutritional support is required beyond this initial 2-year period. Whether or not the adaptive response can be significantly accelerated or augmented (hyperadaptation) pharmacologically is uncertain but is 1 of the main goals of intestinal rehabilitation. Intestinal adaptation in children is influenced by growth and development and thus occurs over a longer period in younger children.[20] The overall intestinal adaptive response results from changes in intestinal structure, absorptive function, and motility.

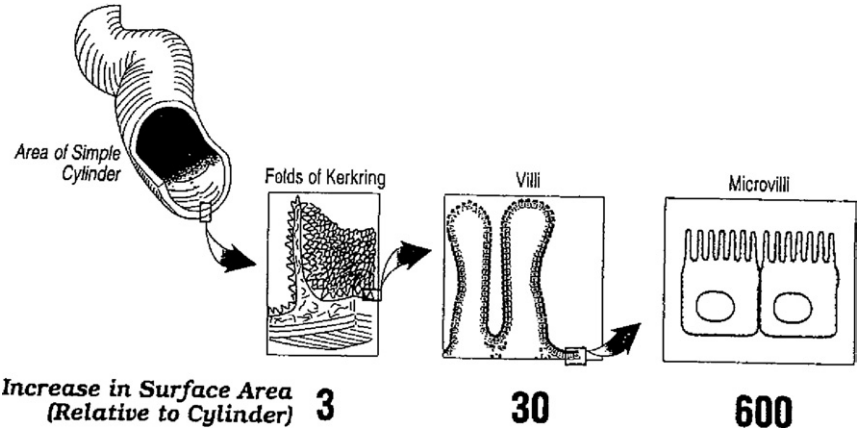


**FIG 4.** Morphologic structures of the small bowel that increase surface area. (Reprinted with permission from Wilmore et al.[19])

Structural adaptation after intestinal resection involves all layers of the intestine.[19,45] The intestine is not simply a cylindrical tube but contains folds (the folds of Kerkring) lined with finger-like villi composed of enterocytes, which are covered by microvilli. All of these structures contribute to the overall absorptive surface area (Fig 4). Mucosal DNA, protein synthesis, and crypt cell proliferation are increased within hours after resection. The total number of cells, the proportion of proliferating cells, and number of stem cells are increased in the crypt.[46] Villus lengthening occurs by overall increased number of cells as enterocytes migrate at a faster rate along as the villus. Interestingly, rates of apoptosis, or programmed cell death, increase in both crypt and villus enterocytes after resection. However, the proliferative stimulus dominates so that structural adaptation occurs. An expansion of intestinal progenitors and putative stem cells precedes crypt fission and an increase in the ratio of crypts to villi.[47] Microvilli along the epithelial surface also increase. Overall, the mucosal weight increases and mucosal folds enlarge. The colon may also undergo structural adaptation after intestinal resection.[48]

The thickness and length of the muscle layers also increase after resection. This results primarily from hyperplasia rather than hypertrophy of the muscle cells.[45] Muscle adaptation, however, occurs at a later time and only after more extensive resection than does mucosal adaptation. These changes in the components of the intestinal wall result in marked thickening of the intestinal wall as well as increased intestinal circumference (circular muscle) and length (longitudinal muscle). Thus, there is

an overall increase in mucosal surface area because of the increases in length and circumference of the remnant, villus hypertrophy, and increased microvilli length. These structural changes are more striking in experimental models than they are in humans.[49]

Intestinal motor activity is also altered by intestinal resection and is a biphasic motor response to varying degrees of distal resection.[50,51] Initial disruption of motor activity is followed by adaptation. Motility recordings in the canine small intestine are initially dominated by recurring bursts of clustered contractions in the distal segment of the intestinal remnant after limited resection and more generally after 75% resection.[51] These clusters are prolonged and associated with baseline tonic changes with extensive resection. With more limited resection, there is evidence of progressive motor adaptation with eventual slowing of transit and return of migrating motor complex cycling. This adaptation is less apparent after massive resection and is more prominent in the jejunum than in the ileum. These motility changes are accompanied by modest alterations in smooth muscle contractility. Clinical reports also demonstrate a biphasic adaptive motor response during the first year after resection. There is disrupted motor activity in the first few months after resection, but these changes occur only after extensive resection (remnant shorter than 100 cm). Long-term human studies demonstrate a shorter duration of the migrating motor complex cycle and fed pattern after resection.[52]

Functional adaptation clearly occurs after resection.[19,52,53] This is due in part to structural adaptation, which increases intestinal absorptive surface area. Both structural and motor adaptation leads to prolonged transit time, which will improve absorption. Although previously improved absorption by individual enterocytes has been discounted, more recent studies suggest improvement in certain transport capabilities.[54] There is evidence that there is up-regulation of the total number of transporters and an increase in intrinsic activity for transporters, particularly for glucose absorption, but this remains controversial.[54,55] Brush border enzyme activity also increases. Overall, the effect of these changes is that diarrhea diminishes, absorption increases, and nutritional status improves within months of resection.

Less well understood are any adaptive changes in the immune and barrier functions of the intestinal remnant during adaptation. In experimental studies, intestinal intra-epithelial lymphocytes shift to a more immature and less activated cell population.[56] Bacterial translocation to lymph nodes and peripheral blood is increased with massive resection.[57] Changes in immune and barrier function in adult SBS patients are not well studied.

**TABLE 2.** Factors influencing intestinal adaptation

| |
|---|
| Luminal factors |
| Gastrointestinal regulatory peptides |
| Nutrients |
| Secretions |
| Systemic factors |
| Cytokines |
| Growth factors |
| Hormones |
| Tissue factors |
| Immune system |
| Mesenchymal factors |
| Mesenteric blood flow |
| Neural influences |

The mechanism of intestinal adaptation has been studied extensively but is still not entirely understood. The degree of structural adaptation is related to the extent and site of resection.[19,45] Adaptation is greater with more extensive resections and the ileum has a greater adaptive capacity than jejunum. Subsequent resection elicits a further adaptive response. Luminal nutrients, secretions, and growth factors are important in achieving the maximal response but are not essential for adaptation to occur (Table 2).[19,45]

The early molecular events associated with this hyperplastic response are being investigated.[58-63] Intestinal resection results in increased levels of a variety of gene products in crypt and villus enterocytes within hours. There is an immediate increase in genes influencing cell proliferation, nutrient absorption and trafficking, and cellular homeostasis. Many of these are novel genes, not normally present in intestinal epithelium. This molecular response is spatially and temporally regulated. Proteomic analysis has also been performed after resection and many proteins are increased.[60] Proteins, such as fatty acid (FA) binding protein, may prove useful in monitoring the adaptive response. The specific triggers for these events are not clear, but there are many candidates. Gene expression is regulated by growth factors in a specific fashion [eg, epidermal growth factor (EGF) and GLP-2 but not Insulin-like growth factor (IGF)-1 up-regulate PC4 expression[61] and early but not late administration of GLP-2 expands progenitor cells].[47] Currently there is great clinical interest in manipulating the adaptive response pharmacologically.

## Medical Rehabilitation

The medical management of SBS requires tailoring to the clinical stage of the patient following massive intestinal resection. The early acute

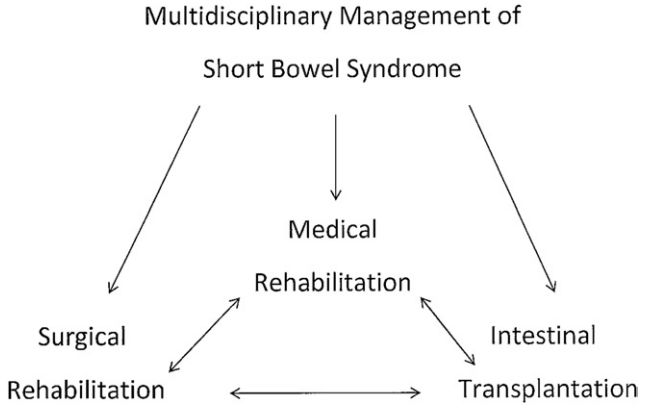


**FIG 5.** Multidisciplinary management of short bowel syndrome.

phase (1-3 months) involves stabilization of large fluid and electrolyte losses, maintaining fluid balance, and controlling acid/base balance. Diarrhea is generally severe during this period and enteral absorption is limited; therefore, PN support is required as the patient rebuilds stamina and recovers from surgical resection. Long-term vascular access must be established in this phase. During the intermediate phase (up to 24 months), the focus is placed on balancing nutrition support with the potential to begin PN reduction as enteral absorption improves based on clinical parameters of weight, oral intake, renal function, and hydration status. The use of medical treatments to maximize the absorptive capacity of the remaining intestine and prevention of the complications related to both the underlying pathophysiology and the nutritional therapy requires intensive monitoring. In the last phase (>24 months), continued efforts toward complete PN weaning should be attempted. However, in some patients stabilization may be reached and no further improvement in functional adaptation may be demonstrated.

The overall goal of medical rehabilitation is to return patients to as normal a lifestyle as possible with as little dependence on PN as can be achieved. Intestinal rehabilitation is the process of enhancing intestinal absorption and function through the use of modified diet, enteral nutrition, oral rehydration solution, motility and antisecretory agents, antibiotics, and enterotrophic medications.

A multidisciplinary approach is required for comprehensive and optimal care of patients with intestinal failure[64-68] (Fig 5). Expertise in the management of gastrointestinal disease, gastrointestinal surgical expertise for both children and adults, and ideally, organ transplantation provide the

appropriate therapeutic options. Nutritionists, nurse coordinators, psychologists, and social workers are also critical members of the team. Support from consultants, such as endocrinologists and appropriate radiologic and laboratory services, is called on as needed. Administrative support to coordinate this process and to maintain a clinical database is also required. Several reports have demonstrated the benefits of this multidisciplinary effort on patient outcome and early referral to an intestinal rehabilitation center is suggested.[64-68]

## Maintaining Nutritional Status

The main therapeutic objective in the management of SBS is to maintain the patient's nutritional status as defined in adults by a target body mass index of 20 to 25 kg/mg$^2$ and normalized macro- and micronutrient status. Most adult patients require 25 to 30 kcal/kg per day and 1.0 to 1.5 grams of protein per kilogram per day with appropriate additives. Goals in infants and children are age-specific and nutritional support in these patients has been recently summarized.[69] Maintenance of nutritional status requires in most instances continuous PN support in the early period after operation.

The appropriate composition of PN is based on age, body weight, and underlying condition. The presence of concurrent morbidities, such as hepatic, renal, pancreatic, pulmonary, or cardiovascular disease, calls for individual tailoring of the PN orders. Attention and frequent monitoring to the individual patient's requirement for optimal fluid replacement and electrolyte replacement is imperative. Enteral nutritional (EN) support via nasojejunal access or percutaneous enteral access should be started as soon as possible followed by careful monitoring of the patient's response and improvement in adaptation. If the patient can accomplish enteral intake, it should be 1500 mL greater than gastrointestinal tract output, which would allow for 1000 mL of urine output and 500 mL of insensible fluid loss.

Although the traditional view has been that EN should be held until bowel function has resumed, several clinical studies have challenged this traditional view and now support the early provision of EN for surgical patients in general within 24 to 48 hours of surgery.[70] Even in the strict nil per os (NPO) setting the fasting gastrointestinal tract is exposed to 500 to 1000 mL of gastric secretions daily complemented by 1 to 2 L of biliopancreatic secretions regardless of enterally administered nutrition. The presence of luminal nutrients results in postprandial hyperemia, which in turn prevents mucosal atrophy, attenuates the stress response,

maintains immunocompetence, preserves the gut flora, is associated with fewer septic complications, and is associated with cost savings.[71-74] Early EN in patients with SBS should have additional benefit in terms of intestinal adaptation but restrictions apply to hyper- and hypoosmolar solutions in SBS patients.

With time, an increasing amount of nutrients is absorbed by the enteral route. This is important for maximizing intestinal adaptation and allowing gradual reduction of PN. As the patient's condition improves and intestinal adaptation occurs, many patients can absorb the necessary nutrients entirely by the enteral route while becoming to a certain extent hyperphagic.[75,76] Enteral independence, defined as the ability to maintain adequate caloric intake without need for PN, is determined by (1) residual length of small bowel, (2) continuity of small bowel with large bowel, (3) presence of ileocecal valve, (4) the ability to respond with a certain degree of hyperphagia,[75,76] and (5) the presence or absence of a stoma. Classifying the patient into 1 of 3 anatomic types described earlier (Fig 2) helps to a certain extent predicting who will eventually wean from PN. Patients with more than 180 cm of small intestine remaining generally require no PN; those with more than 90 cm and colon in continuity will require PN for less than 1 year; and those with less than 60 cm of small intestine will likely require permanent PN, depending on the length of colon remaining.

Although initially administered continuously, PN can be switched to cyclical administration as soon as there is enteric intake by mouth or other stated routes. Continuous PN is given in the early phase, whereas cyclic PN will predominate the intermediate and late phases. Cyclic (discontinuous) PN is more convenient in adults. A recent review of 25 clinical studies in children and adults recieving long-term PN emphasizes the favorable risk-benefit profile of cyclic PN.[77]

The need for prolonged PN in patients with SBS can result in considerable societal costs (expenses, clinic visits, loss of time at work for caregivers) and morbidity and mortality. The quality of life is negatively affected and restrictions on travel can be onerous for PN patients. The very regimented lifestyle of a patient with SBS with 12 to 18 hours of PN infusion and line care poses major social life, travel, and professional restrictions. Published data on the quality of life assessment for patients on PN were recently reviewed by Richard and Carlson,[78] Winkler,[79] Howard,[80] and Huisman-de Waal and colleagues.[81] Assessment of quality of life must include emotional, physical, occupational, and social data. The European Quality of Life Instrument (EuroQoL) index offers a scale from 0 to 100 and examines the domains of mobility, self-care, main

activity, social relationships, pain, and mood.[78] Lowest scores of 50 to 60 are usually reported in the first year on PN assuming that the patient was previously in good health. Rising scores to 60 to 70 are reported after 4 to 5 years of therapy, with a score of 100 presenting the normal healthy population.[78] Three studies applying other quality of life instruments have reported on the decrease in quality of life in several domains while receiving PN.[82-84]

Although long-term PN certainly affects quality of life, SBS patients have additional anatomic issues (eg, stoma) and other medical conditions which further impact quality of life. A specific validated quality of life instrument for patients with SBS did not exist until recently based on a review of psychometric studies in patients on PN.[85,86] In 2010, Baxter and colleagues published a provisional questionnaire that was administered to 100 adult patients receiving home PN that showed high compliance rate and was well received by patients.[87]

The patients with SBS very often face complex psychosocial adjustment problems, which can be challenging to manage. Problems, such as grief reactions, depression, organic brain syndromes, drug dependency, and body image changes, have been described.[88] A number of home PN patients have been noted to use their central venous catheter for self-harm.[89] The impact of the chronic illness on the caregiver should also not be underestimated. Stressed families face additional worries because of the variability of PN expenses.[90,91] The cost of PN ranges from $75,000 to $150,000 per year depending on nutritional requirements and does not incorporate indirect costs, such as travel to appointments and opportunity costs of caregivers.[92]

Several studies have addressed long-term survival for patients receiving PN.[17] Messing and colleagues found that patients without malignancy requiring long-term PN have 1-, 3-, and 5-year survival rates of approximately 90%, 70%, and 60%, respectively.[17] Survival was negatively affected by end enterostomy, small bowel length $<50$ cm, and mesenteric ischemia as an etiology. Recent data from Italy have showed an actuarial survival rate of patients with intestinal failure of 88% and 78% at 3 and 5 years, respectively, which was influenced by the length of remnant intestine, age at the start of home PN, enteral independence, and, to some extent at least, the primary disorder.[93] Mortality in these patients is one third due to the underlying disease, in 50% due to other supervening illnesses, and in 10% to 15% because of PN therapy.

**TABLE 3.** Complications of short bowel syndrome and therapy

| |
|---|
| Catheter related |
| Infection |
| Loss of vascular access |
| Hepatobiliary |
| Intestinal failure associated liver disease |
| Cholelithiasis |
| Metabolic |
| Fluid and electrolyte abnormalities |
| D-Lactic acidosis |
| Micronutrient deficiency |
| Metabolic bone disease |
| Osteoporosis and osteomalacea |
| Renal |
| Chronic renal failure |
| Nephrolithiasis |
| Gastrointestinal |
| Gastric hypersecretion |
| Small bowel bacterial overgrowth |
| Changes in colonic flora |

## *Preventing Complications*

Patients with SBS are at increased risk for a variety of complications related to their underlying disease, pathophysiologic changes of SBS, and nutritional therapy. The complications are outlined in Table 3. Prevention of complications is important for improving quality of life, reducing costs, and improving long-term survival. Changes in therapy or administration of PN require careful monitoring and usually result in a multitude of laboratory studies and other clinical information. The use of an electronic medical record with recall and reminder capability in the management of SBS is mandatory to minimize complications.[94] At our institution we use an organ transplant patient tracking software that allows following nontransplant patients[95] (http://www.hksys.com/tra.html).

## *Catheter-Related Infections and Loss of Vascular Access*

Catheter-related infections and venous thrombosis with loss of vascular access are important complications in SBS patients requiring long-term parenteral support.[96] These 2 problems are related in that repeated infection predisposes to thromboses. SBS patients are at increased risk for infection because of their underlying intestinal disease, bacterial overgrowth, and presence of stomas. Furthermore, both complications are determinants of outcome and the need for intestinal transplantation.

Sepsis because of central line-associated bloodstream infections (CLABSIs) causes substantial morbidity and results in excess direct and indirect costs. The cumulative excess health care costs between 2001 and 2009 due to CLABSIs in the intensive care unit alone in the USA was $1.8 billion.[97] The US Centers for Disease Control and Prevention reported that CLABSIs are associated with a 12% to 25% mortality rate. Prevention programs have resulted in a reduction of central line-associated infections by 58%, saving up to 6000 lives and $414 million in 2009 alone.[97] Rates of line infection can be expressed as a true number of cases or can be reported as several cases per 1000 line days, which allows us to standardize rates between health care settings. Quality review and outcomes measurement of PN management is important. Rates of catheter-related blood infection higher than 2 per 1000 catheter-days are no longer acceptable.[98] Updated guidelines by the Healthcare Infection Control Practices Advisory Committee have been published.[99]

The American Society for Parenteral and Enteral Nutrition guidelines recommend that a central venous access device used for PN to be placed with its tip in the superior vena cava adjacent to the right atrium. Position of the catheters should be confirmed and, if necessary, followed serially radiologically because misplacement can occur.[100] This can be accomplished by placement of a centrally placed tunneled catheter (Hickman, Broviac, Groshong), ports, or a peripherally inserted central catheter (PICC). The use of a port for home PN is generally discouraged since ports seem to be susceptible to contamination on account of the frequent need for access. Based on retrospective data on adult patients receiving home PN, PICC lines may be associated with a higher incidence of catheter infections compared to central venous access devices.[101] Catheters for long-term PN with ethanol lock capability (silicone-based) are preferred over polyurethane and cabothane polymers. In general, centrally placed venous access devices are preferred over PICC access because the latter lack ethanol lock therapy capability. Ethanol lock therapy involves instillation of 70% ethanol, equal to the volume of the line, into the catheter lumen for 12 to 24 hours and then withdrawal when PN is resumed. In many centers, this has surpassed antibiotic lock therapy as a technique to prevent infections. Several studies have confirmed the efficiency and safety of ethanol lock therapy in pediatric and adult patients for treatment and prevention of CLABSIs.[102-107] Prospective data from 2008 have confirmed that the use of intraluminal ethanol in immunosuppressed hematology patients reduced catheter-associated bloodstream infection.[105]

The implementation of a specific central venous catheter postinsertion care bundle was associated with a significant reduction in CLABSI in a

setting where compliance with the central line insertion bundle was already high.[108] In this Veterans Affairs based study the intervention incidence density of 5.7 CLABSIs per 1000 catheter-days was reduced to an incidence density of 1.1 CLABSIs per 1000 catheter-days after implementation of the interventions. Using the catheters only for PN also reduces the risk of infection.

The epidemiology and microbiologic characteristics of bloodstream infections in long-term adult PN patients have been reported in a prospective cohort study. One fourth of infections were polymicrobial[96]; 55% were due to Gram-positive organisms. Coagulase-negative staphylococci account for 33% of infections. Twenty-two percent were fungal. Central venous thrombosis was seen in 44% of patients with a mean duration of 4.5 years of PN.[96] Because of the high prevalence of antibiotic resistance and fungal infections in these patients, broad spectrum antibiotics and antifungal therapy are appropriate empiric therapy in an ill patient. In patients with SBS—because of the chronicity of the underlying illness and the higher incidence of vascular thrombosis—not all line infections call for immediate removal of the catheter since progressive loss of access can become a major problem. Infections at the tunnel or exit site or suspected fungal infection should prompt early removal. Management algorithms are useful for guiding decisions.[53]

Prevention of catheter and venous thrombosis is also related to catheter type and insertion. The subclavian vein is the preferred site. Proper orientation of the tip is also important. Vascular access exhaustion because of vascular thrombosis sometimes results in placement of central catheters via the transhepatic or translumbar inferior vena caval approach. This was originally reported in bone marrow transplant and hemodialysis patients but subsequently has been used in patients recieving long-term PN.[109-111] Arteriovenous fistulas are another alternative.[112] The loss of vascular access should prompt referral for evaluation for intestinal transplantation.

There are no established guidelines that are specific for SBS patients or patients who are recieving long-term PN as far as screening or surveillance for susceptibility to infection and vaccination protocols are concerned. Prevention of infection through implementation of vaccination schedules however seems intuitively important and we follow the standard vaccination schedules for adults in the USA based on the Advisory Committee on Immunization Practices with the Centers for Disease Control and Prevention.[113] We aim to vaccinate all long-term PN patients against hepatitis A and hepatitis B on account of the potential to develop chronic liver disease. We also recommend administration of

pneumococcal prophylaxis, annual influenza vaccination, MMR, tetanus, pertussis, and shingles vaccination. We do not routinely screen for fungal exposure and TB but implement an evaluation if the imaging studies indicate exposure to pathogens based on past personal residential and travel history.

## Hepatobiliary Complications

Three types of hepatobiliary disorders occur with prolonged PN management in SBS patients: steatosis, cholestasis, and gallbladder sludge/stones. The term intestinal failure-associated liver disease (IFALD) is preferred for these entities because both SBS and PN contribute. IFALD is commonly defined as the persistent elevation of liver blood tests 1.5 times above the upper limit of normal.[114] The prevalence rates of IFALD between adults and children are variable with steatosis being more prominent in adults and cholestasis more prominent in children. In the adult PN population the incidence of elevated liver function tests has been reported between 25% and 100%. Similar findings have been reported in children.[20] Severe steatosis and cholestasis can progress to fibrosis, cirrhosis, and end-stage liver disease.

Prospective cohort studies have shown that the prevalence of complicated IFALD increases with longer duration of PN. Earlier cohort studies on adult patients followed between 1985 and 1996 showed that chronic cholestasis occurs in 65% after a median of 6 months (range, 3-132 months). Complicated liver disease occurred in 37% after a median of 17 months (range, 2-155 months). Of these patients, 17 showed extensive fibrosis after 26 months (range, 2-148 months), and 5 had cirrhosis after 37 months (range, 26-77 months). The prevalence of complicated IFALD was 26 $\pm$ 9% at 2 years and 50 $\pm$ 13% at 6 years. Six patients died of liver disease (22% of all deaths).[115] In another study of 42 adult patients in the USA receiving home PN for more than 1 year, 6 (15%) developed end-stage liver disease. All 6 patients died, at an average of 10.8 $\pm$ 7.1 months after the initial elevation of serum bilirubin.[116]

The etiology of IFALD is multifactorial (Fig 6) with a variety of postulated mechanisms having been put forward.[117] The relative importance of the events that lead to IFALD differ in adults and children. Two partially overlapping events of steatosis and cholestasis, however, present final common pathways. Steatosis can occur because of carnitine deficiency, essential FA deficiency, choline deficiency, or excess carbohydrates via PN. Cholestasis may result because of a lack of enteral stimulation, which in turn leads to bile stasis and bacterial translocation.

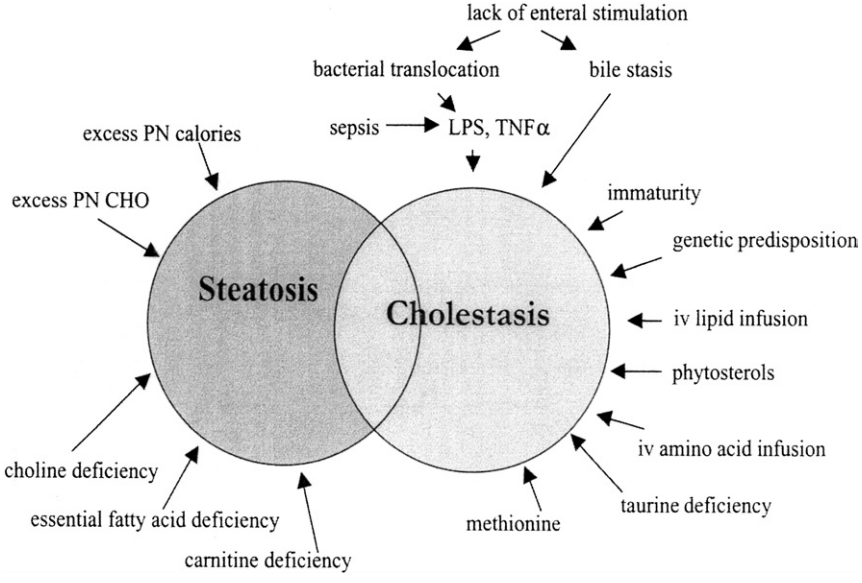


**FIG 6.** Postulated mechanisms of IFALD. (Reprinted with permission from Beath SV, Woodward JM. Intestinal failure-associated liver disease. In: Langnas AN, ed. Intestinal Failure: Diagnosis, Management and Transplantation. Malden, MA: Blackwell Publishing, 2008: 196.)

The clinical evaluation and management of patient with SBS and suspected IFALD require the elimination of other causes for the abnormal liver function tests (review of hepatotoxic medications, herbal supplements, biliary obstruction, hepatitis, infection), changes to the composition of PN (decrease dextrose, decrease fat emulsion, cyclical infusion), maximization of enteral intake, treatment of small intestinal bacterial overgrowth, and pharmacotherapy with ursodeoxycholic acid.[117] The evaluation for liver disease includes routine laboratory studies that are done in every liver patient (metabolic, viral, autoimmune markers) and a liver biopsy. Noninvasive markers of fibrosis, such as FibroTest, SteatoTest, and NashTest, are available but are not Food and Drug Administration (FDA) approved.[118,119] Finally, consideration for small intestine transplantation for patients with IFALD should be entertained.

Traditional lipid emulsion is prepared from soybean oil that is composed of long-chain triacylglycerols with a high amount (>60%) of polyunsaturated FAS. Soybean oil is a reliable source of essential FA in the form of linoleic acid ($\omega$-6 FA) and $\alpha$-linolenic acid ($\omega$-3 FA). In the USA, Intralipid (Fresenius Kabi, Uppsala, Sweden) and Liposyn (Abbott Laboratories, Chicago, IL) are FDA approved and are based on safflower and/or soybean with high concentrations of

ω-6 FA, phytosterols, and vitamin E. Elevated levels of phytosterols have been shown to be associated with paralysis of bilirubin transport mechanisms in the hepatocyte membrane. The major morbidity because of soybean-based lipid appears to be cholestasis, which may be an important part of IFALD in children and adults. Recent studies have emphasized the necessity of reducing the total soy lipid dose, either alone in a protocol of lipid minimization or in concert with additional non-soy lipid calories, such as a fish oil emulsion.

The advent of pure ω-3 fish oil based emulsion (omega-3 FA) (omegaven; Fresenius Kabi) has provided a new option in preventing IFALD and has been heralded by some as a major breakthrough in the management of pediatric IFALD.[120,121] Omegaven is approved in Europe and Asia only and may be accessed in the USA through compassionate release, or under the auspices of an FDA-approved trial. Although published studies in children suggest a benefit in improving cholestasis, it is not clear if this is purely an effect of the fish oil emulsion or whether it is a result of the minimization of soy-based lipid. There is presently no evidence to suggest that overall outcomes are improved; however, it has become an important part of the treatment armamentarium in treating IFALD in infants. Data for omegaven in the adult population are limited. For a 75-year-old woman with 12 cm of small bowel in continuity with ascending colon the administration of an omega-3-enriched lipid emulsion added to the PN regimen reversed cholestasis and was associated with histologic improvement on serial liver biopsy.[122]

SMOFlipid 20% (Fresenius Kabi) is an intravenous lipid emulsion containing soybean oil (30%), medium-chain triglycerides (30%), olive oil (25%), and fish oil (15%) developed to provide energy, essential FAS, and long-chain ω-3 FAS as a mixed emulsion containing α-tocopherol.[123] Data in adults with SMOFlipid indicate that hepatic integrity was maintained in adults.[124]

Cholelithiasis occurs in 30% to 40% of adult patients with SBS and 20% of pediatric patients.[20,42,125,126] Factors that predispose these patients to gallstone formation include altered hepatic bile metabolism and secretion, gallbladder stasis, and malabsorption of bile acids. Depending on the dominant mechanism, either mixed pigment stones or cholesterol stones may occur. Biliary sludge forms within a few weeks of initiating PN in the absence of enteral intake but rapidly disappears when enteral nutrition is resumed. Long-term PN is associated with gallbladder stasis and alters hepatic bile metabolism and thus is an important contributing factor. Because patients receiving PN develop both cholelithiasis and hepatocellular dysfunction, they require careful clinical evaluation to distinguish between the

2.[125,126] Intestinal mucosal disease and resection, particularly of the ileum, cause bile acid malabsorption leading to lithogenic bile and the formation of cholesterol stones. Colon preservation does not affect the incidence of cholelithiasis.[41] The risk for cholelithiasis is significantly increased if less than 120 cm of intestine remains after resection, the terminal ileum has been resected, and PN is required.

The incidence of cholelithiasis can be minimized by providing nutrients enterally when feasible to prevent stasis. Lipid infusion also stimulates gallbladder emptying. Patients totally dependent on PN may be treated with intermittent cholecystokinin injections to prevent stasis and formation of sludge, although we do not generally use this. Cholelithiasis appears to lead to complications more frequently in SBS patients compared to the general population. This requires more complicated surgical treatment. Thus, prophylactic cholecystectomy is recommend in SBS patients when laparotomy is being undertaken for other reasons.[125,126] Given the similar development of gallbladder disease in children, this recommendation should also be considered in the pediatric population.

## *Metabolic Complications*

Metabolic complications are common in patients with SBS because of their tremendous fluid and electrolyte losses and the need to replace these with specialized solutions[127] (Table 3). Intravascular volume must be maintained to prevent dehydration and renal dysfunction. Hyperglycemia and hypoglycemia are frequent complications of patients receiving a large amount of their calories parenterally. Hypocalcemia is a common problem related to poor absorption and binding by intraluminal fat. Hypomagnesemia is a major challenge because oral supplementation is usually associated with a severely cathartic effect.[128,129] Maintaining adequate levels of calcium, magnesium, and vitamin D supplementation are important to minimize bone disease in the long term. Both metabolic acidosis and alkalosis can occur.

D-lactic acidosis (D-lactate encephalopathy) is a rare neurologic syndrome that results from bacterial fermentation of unabsorbed nutrients, particularly simple sugars.[130] Symptoms can occur after intake of high-carbohydrate feedings and include altered mental status, slurred speech, and ataxia.[130] Lactate reduces colon pH, permitting the growth of acid-resistant anaerobes capable of producing D-lactate.[131-133] Impaired metabolism of D-lactic acid may also contribute to elevated serum D-lactic acid levels. D-lactic acid is not measured by standard laboratory tech-

niques for lactic acid determination. Thus, an increased anion gap but normal lactate level in the appropriate clinical setting mandates measurement of D-lactic acid. D-lactic acidosis is treated by minimizing overall caloric intake or by a low-carbohydrate diet. Administering intestinal antibiotics may be appropriate, but the optimal duration of such treatment is unclear, and the recurrence rates are significant. Uchida and colleagues have reported the successful combination of probiotic *Bifidobacterium brebe* and *Lactobacillus casei* powder (Yakult Co Ltd, Tokyo, Japan) and kanamycin, 400 mg $d^{-1}$, in an effort to eliminate D-lactic acid producing lactobacilli in a 22 year old with SBS and D-lactic acidosis.[134] Finally, intestinal tapering enteroplasty has been reported to resolve D-lactic acidosis in an SBS patient with dilated bowel.[135]

Specific nutrient deficiencies need to be prevented and monitored closely. These include iron and vitamin deficiencies as well as deficiencies of micronutrients, such as selenium, zinc, and copper. Because fat is poorly absorbed, FA deficiency can also occur. Although medium-chain FA can supplement the diet enterally, parenteral lipids are required in patients who depend primarily on that route. Serum-free FA levels and triene-to-tetraene ratios may need to be monitored periodically to determine the need for supplementation and response to treatment. In general, the enteral intake must greatly exceed the absorptive needs to ensure that these needs are being met.

## Metabolic Bone Disease

Metabolic bone disease (MBD) is increased in SBS patients requiring PN, including osteoporosis and osteomalacia.[136-140] A substantial prevalence of low bone mass has been described in these patients according to dual-energy X-ray absorptionmetry measurements of bone mineral density with the prevalence of osteoporosis in PN-treated patients ($T$-score $< -2.5$) being reported between 33% and 67%. MBD leads to a fracture rate of 10%.[135-137] The etiology is multifactorial, including increased calcium excretion, calcium deficiency, vitamin D deficiency, toxic components of PN, and underlying disease.[139] The incidence of MBD is increased further after intestinal transplantation.[140]

We screen the bone health at intake visit and perform close follow-up with dual-energy X-ray absorptionmetry scanning as indicated and based on published guidelines (National Osteoporosis Foundation [2008]. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation[141]; http://www.nof.org). The World Health Organization Fracture Risk Assessment Tool (FRAX)[142] is

available online and provides a useful application to give the 10-year probability of fracture[143] (http://www.shef.ac.uk/FRAX/).

The monitoring of vitamin D status, parathyroid hormone, testosterone levels, and the close collaboration with the endocrine consultant are part of the effort to reduce the significant morbidity and mortality from osteoporosis. The plethora of available medications allows us to tailor the treatment individually.[144] The availability of injection-based drugs for osteoporosis is helping our SBS patients who have erratic mucosal absorption patterns. Growth hormone favorably affects bone turnover and bone mineral density and is another therapeutic option.[145]

## Renal Complications

Both nephrolithiasis and renal dysfunction are potential complications of SBS.[42] Hyperoxaluria due to increased oxalate absorption from the colon is 1 common mechanism.[42,146] Oxalate is normally bound to calcium in the intestinal lumen and is not absorbed. Decreased availability of calcium secondary to reduced intake or binding by intraluminal fat secondary to fat malabsorption and bile salt deficiency leaves free oxalate in the lumen. Thus, the oxalate is absorbed in the colon and forms calcium oxalate in the urine. Nephrolithiasis is unusual in patients with intestinal resection and jejunostomy but occurs in one fourth of such patients with an intact colon within 2 years of resection.[42] The chronic deposition of oxalate crystals with hyalinization and interstitial fibrosis in the tubules presents a longer term problem to renal function. The resultant development of end-stage renal disease is well known.[147] Other causes of renal failure include acute metabolic derangements and chronic obstruction.[148,149] Reports of successful renal transplantation in patients with SBS and chronic renal failure with long-term survival have been published.[150-152]

Nephrolithiasis can be prevented by maintaining a diet low in oxalate, minimizing intraluminal fat, monitoring vitamin C supplementation, supplementing calcium citrate orally, and maintaining a high urinary volume. Foods with high oxalate content include chocolate, tea and cola, spinach, celery, carrots, and other fruits and vegetables. Cholestyramine, which binds oxalic acid in the colon, is another potential treatment.

## Gastrointestinal Complications

There are a few well-recognized gastrointestinal complications of SBS. Gastric hypersecretion is an important early problem. Alterations in the

gut bacteria, such as bacterial overgrowth, are also important changes that are being studied in the context of the gut microbiome.

Gastric hypersecretion is a common problem in both adult and pediatric patients with SBS.[153-156] Massive intestinal resection can cause gastric hypersecretion because of parietal cell hyperplasia and hypergastrinemia. This phenomenon is usually transient, lasting several months. The etiology has not been completely elucidated but presumably involves loss of an inhibitor from the resected intestine. The associated hyperacidity exacerbates malabsorption and diarrhea. Clinical development of peptic ulcer disease may also occur. Approximately one fourth of patients undergoing massive resection develop this complication.[153] Treatment of gastric acid secretion may improve absorption but also prevents peptic ulcer disease. Control of acid secretion by histamine-2 ($H_2$) receptor antagonists or proton pump inhibitors should be initiated in the perioperative period after resection and maintained until the increased acid production resolves. Some patients, however, continue to have symptoms of peptic ulcer disease that eventually require surgical intervention.[153,157] Gastric resective therapy should be avoided when possible.

Small bowel intestinal bacterial overgrowth (SIBO) is a well-recognized long-term complication associated with both intestinal disease and resection.[158-165] SIBO may result from impaired motility or stasis caused by obstructive lesions. Achlorhydria is also a contributing factor.[166] This condition is defined by overgrowth of more than $10^5$ colony forming units per milliliter of bacteria in the proximal small bowel.[163] The limitations of available diagnostic tests (hydrogen breath testing and duodenal aspiration with quantitative bacterial culture) need to be recognized.[164,165]

SIBO has several detrimental effects. Histologically there is villus blunting and inflammation. Bacterial deconjugation of luminal bile salts impairs bile salt reabsorption. Bacteria also metabolize intraluminal vitamin $B_{12}$ and compete for enteral nutrients. Depending on the bacterial species present, secretory diarrhea may also occur. Typically, the patient presents with increased flatulence, bloating, crampy abdominal pain, changes in stool habits, foul smelling bowel movements, or intolerance to enteral feedings. Because these are common symptoms in SBS patients, bacterial overgrowth requires a high degree of suspicion for diagnosis.

SIBO is treated with poorly absorbed antibiotics empirically, which are adjusted based on sensitivities. Cycling of antibiotics may be necessary due to induction of bacterial resistance. Probiotics are another potential therapy, either alone or with antibiotics. Because SIBO may result from a mechanical obstruction or a blind loop which can be relieved by

operation, radiographic evaluation should be performed. However, it is often a primary motor abnormality, which requires intermittent therapy with antibiotics.

The large bowel flora have gained recent attention in the context of the obesity epidemic.[167-170] The human microbiome consist of as many as 10 to 100 trillion microorganisms, representing at least 10-fold more cells than exist in the human body.[171] Little is known about the microbiome with intestinal failure.[172] Joly and colleagues reported in 2010 on 11 patients with jejunocolonic anastomosis that the microbiome was unbalanced with a high prevalence of Lactobacillus along with a subdominant presence and poor diversity of *Clostridium leptum*, *Clostridium coccoides*, and Bacteroidetes compared to 8 healthy controls.[173] *Lactobacillus mucosae* was detected within the fecal and mucosa-associated microbiota of SBS patients, whereas it remained undetectable in controls.[173] Analysis of the microbiome after small bowel transplant showed that the posttransplant microbial community was found to be dominated by Lactobacilli and Enterobacteria, both typically facultative anaerobes. This represents an inversion of the normal community that is dominated instead by the strictly anaerobic Bacteroides and Clostridia.[174] We would anticipate that with the evolution of knowledge of the human microbiome in health and disease in future years, more data will become available regarding the microbiome in SBS patients and perhaps open new avenues of treatment.

## Maximizing Enteral Absorption

The measures taken to maximize enteral absorption focus on (1) dietary and (2) pharmacologic interventions.

***Dietary Therapy.*** Certain measures can be taken to maximize enteral nutrient absorption. High stomal or rectal output (defined as losses >1500 mL/24 hours) are usually due to a combination of high osmotic load, gastrointestinal secretion, gastric hypersecretion, exocrine pancreatic insufficiency in the setting of mucosal disease, and foreshortened length of small and large bowel. Diet recommendations for patients are determined by whether the colon is in continuity and the remnant length. The macronutrient and oral fluid recommended to patients are based on bowel anatomy. The jejunum is more permeable than the ileum. SBS patients often are hyperphagic. The role of diet modification to diminish symptoms associated with severe malabsorption requires extensive education and monitoring to maintain compliance. As absorption improves with time, frequent modifications of the diet occur. Plasma citrulline concen-

trations have been proposed as a possible marker of absorptive enterocyte mass, but the utility of such measurements has been questioned.[175,176]

Hypoosmolar diets are started initially to minimize gastrointestinal fluid losses. Ingestion of a glucose-electrolyte oral rehydration solution with a sodium concentration of at least 90 mmol/L will optimize water and sodium absorption in the proximal jejunum and prevent secretion into the lumen.[177,178] Oral fluid intake should be limited in the acute post-resection phase with gradual increase to 2 to 3 L sipped throughout the day. Hyperosmolar oral fluids should be avoided. In patients with remaining colon water and sodium handling are generally more significant; however, adequate dietary sodium is required.

Patients with colon in continuity should consume 5 to 6 meals per day composed of complex carbohydrates that provide 50% to 60% of calories, restrict simple sugars, and take 20% to 30% of calories as protein.[179] The diet should be low (20%-30%) in fat. Lactose-containing diets have been shown to be well tolerated by some patients, but their use must be assessed on an individual basis especially if a previous intolerance may have been present. Lactose-reduced products are also commonly available and may allow for continued milk consumption with the benefit of improving dietary calcium intake. A goal of 2 grams of calcium daily is generally recommended. Five to 10 grams per day of soluble fiber should be given for net secretors.

Patients without colon should take 4 to 6 meals; 40% to 50% of calories should be provided by carbohydrates; protein should provide 20% to 30%, and fat should provide 0% to 40% of total calories with an emphasis on essential fats. Specific oxalate or lactose restrictions are not needed but isotonic rehydration solutions are advocated for the enhancement of enteral fluids and may be needed at a volume of 3 L sipped throughout the day. Net secretors may benefit from 5 to 10 grams per day of soluble fiber.

***Pharmacologic Therapy.*** Medications used for the treatment of SBS are shown in Table 4. Antidiarrheal therapy includes loperamide hydrochloride, diphenoxylate and atropine, codeine, paregoric, and tincture of opium. The effect of these agents may decrease over time and require alterations in therapy. Bile acids spilled into the colon can stimulate electrolyte and water secretion, which results in loose to watery stools.[180] The bile acid resin cholestyramine may have a role in patients with distal ileal resection. Pancreatic enzymes should be replaced as appropriate. Antisecretory agents, such as histamine$_2$-blockers, proton pump inhibitors, octreotide acetate, and clonidine, will also decrease diarrhea.[166,181-185]

Antibiotics are indicated for SIBO.[158] No specific regimen exists and often the treatment course is dictated by the individual insurance plan

**TABLE 4.** Medical treatment of short bowel syndrome

| Treatment goal | Medications |
|---|---|
| Slow transit and decrease diarrhea | Loperamide |
| | Diphenoxylate |
| | Narcotics |
| | Cholestyramine |
| | Pancreatic enzymes |
| Reduce gastrointestinal secretion | $H_2$ receptor antagonists |
| | Proton pump inhibitors |
| | Octreotide |
| | Clonidine |
| Treat bacterial overgrowth | Antibiotics |
| | Probiotics |
| | Prokinetics |
| Pharmacologic treatment | Glutamine |
| | Growth hormone |

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coverage and tolerance of drugs. Recent data suggest potential benefits of pro- and prebiotics on intestinal mucosal immunity and intestinal barrier in SBS.[159]

Recognition that enteral absorption of drugs and supplements is erratic and inherently unpredictable has resulted in more use of other drug delivery platforms.[186] These include buccal, transdermal, and rectal applications. Transdermal clonidine has been shown to reduce diarrhea and sodium loss in patients with proximal jejunostomy.[184,185] Vitamin D replacement remains a major challenge in SBS and reports indicate that buccal drops and commercial portable ultraviolet indoor tanning lamps can help normalize vitamin D levels in these patients.[187] Antidepressant therapy remains a major challenge in these patients because nonenteric routes of drug administration are not available. Following drug levels for some compounds seems indicated and help from a psychiatric consultant should be sought.

Apart from the above well-described dietary and pharmacologic interventions, investigators have focused on the use of various hormones and growth factors that can promote intestinal growth or enhance absorptive function to achieve enteral independence (wean from PN). Over the last 15 years various investigators have reported the use of growth hormone combined with glutamine and a short bowel diet,[188-193] GLP-2 and its analog teduglutide,[189,194-198] and EGF therapy.[199-201] More recently the use of GLP-1 agonist exenatide has been reported in 5 patients with SBS.[202] The timing, dosage, duration of therapy, and route of delivery of such agents remain poorly defined.[198,200]

A recent Cochrane review focused on randomized controlled trials of human growth hormone with or without glutamine for patients with SBS.[203] This review suggested a positive effect of human growth hormone on weight gain and energy absorption. However, in most 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. The authors concluded that the evidence is inconclusive to recommend growth hormone and glutamine for SBS.[203] We do not use these agents routinely because of these conflicting results, cost, and potential side effects.

GLP-2 is a pleiotropic hormone that affects multiple facets of intestinal physiology, including growth, barrier function, digestion, absorption, motility, and blood flow.[204,205] GLP-2 is strongly associated with intestinal growth and postresection intestinal adaptation. Intestinal GLP-2 is produced in enteroendocrine L-cells of the distal jejunum, ileum, and colon. The downstream effects of GLP-2 include expansion of the intestinal mucosa by crypt cell growth and a reduction in enterocyte apoptosis.[206-208] Jeppesen and colleagues in 2001[195] performed balance studies where GLP-2 was given to 8 patients with SBS with no terminal ileum and colon at a dose of 400 $\mu$g subcutaneously twice per day for 35 days.[195] The intestinal absorption of energy improved 3.5% and body mass and lean body weight increased as did the 24-hour urine creatinine excretion. Jeppesen and colleagues in 2009 showed that GLP-2 dosed at 400 $\mu$g subcutaneously three times per day given in 11 SBS patients showed in 8 patients that completed the study that GLP-2 reduced fecal weight by approximately 1000 g/d and enabled SBS patients to maintain their intestinal fluid and electrolyte absorption at lower oral intakes.[196] The creatinine clearance improved 28%.

A synthetic analogue of GLP-2, Teduglutide (GATTEX or ALX-0600 NPS; Allelix Corp, Missisanga, Ontario) has shown promising results as reported in a randomized placebo-controlled trial. Initially in a proof of concept study in 2005 Jeppesen and colleagues[194] showed that Teduglutide administered subcutaneously for 21 days once or twice daily to 16 patients with SBS resulted in a decrease in fecal weight, increased jejunal villi height, crypt depth, and mitotic index. These findings led to a landmark international randomized control trial that involved 83 patients and was published in 2011.[197] Patients were randomized to 3 arms: placebo, Teduglutide at 0.05 mg/kg/d, and Teduglutide 0.1 mg/kg/d for 24 weeks. The primary endpoint was to seek a reduction of parenteral volume of more than 20% at week 20 and week 24 of treatment. Before database lock a Graded Response Score was introduced to define the

intensity and duration of response at the end of week 24. The study showed that 3 Teduglutide-treated patients were completely weaned off parenteral support. A reduction in total parenteral nutrition of 20% occurred at weeks 16-24 compared with baseline. Villus height, plasma citrulline concentration, and lean body mass were significantly increased with Teduglutide compared with placebo.[197] At the lower dose of 0.05 mg/kg/d, Teduglutide increased the graded response score significantly compared to placebo. Teduglutide is not FDA approved as of June 2011.[209]

GLP-1, like GLP-2, is released from ileal L cells and as 1 action inhibits gastric emptying ("ileal brake" mechanism).[202] Surgical loss of the ileum leads to L-cell mass loss and loss of the GLP-1-mediated inhibitory mechanism with resultant faster intestinal transit and nutritional depletion in SBS patients. Exenatide is a GLP-1 receptor agonist that is FDA approved since April 2005 for the treatment of Type II diabetes.[210] A recent publication reported on 5 patients with ileal resection—all receiving PN—that had fast intestinal transit before exenatide administration. All 5 patients showed immediate improvement in bowel frequency and form while on exenatide, allowing 3 patients to wean PN.[202] The lack of side effects (eg, hypoglycemia) should encourage design of a larger prospective randomized controlled trial of GLP-1 agonist(s) for the fast transit short bowel patients who seem to lack L-cell mass.

EGF also has undergone limited clinical trials.[201] Based on its demonstrated proabsorptive effects and enhancement of intestinal adaptation in experimental studies, a recombinant EGF was administered enterally to pediatric SBS patients. There was transiently increased carbohydrate absorption and improved tolerance to enteral feeding. This agent remains investigational.

## Surgical Rehabilitation

The primary goal of surgical rehabilitation for SBS is to increase intestinal absorptive capacity of the existing intestine using nontransplant surgical procedures. This can be achieved by procedures to improve the function of existing intestine or by increasing the area of absorption (Table 5). Recruiting additional intestine into continuity, relieving obstruction, or slowing intestinal transit will often improve absorption. Although intestinal lengthening procedures to expand the area of absorption are feasible in selected patients, ultimately the most significant increase in length is achieved by intestinal transplantation. The choice of

**TABLE 5.** Surgical strategies for short bowel syndrome

| |
|---|
| Preserving the intestinal remnant |
| Minimize resection |
| Restore continuity |
| Recruit additional intestine |
| Improving intestinal motility |
| Relieve obstruction |
| Taper dilated bowel |
| Prolong intestinal transit |
| Increasing absorptive area |
| Intestinal lengthening |
| Intestinal transplantation |

**TABLE 6.** Surgical therapy for the short bowel syndrome

| Intestinal anatomy | Clinical status | Surgical therapy |
|---|---|---|
| Adequate length with normal diameter (remnant >120 cm) | Enteral nutrition only<br>Recruit additional length | Optimize intestinal function |
| Adequate length with dilated bowel | Bacterial overgrowth | Treat obstruction<br>Intestinal tapering |
| Marginal length with normal diameter (remnant 60-120 cm) | Rapid transit<br>Need for PN | Recruit additional length<br>Procedures to slow transit |
| Marginal length with dilated bowel | Bacterial overgrowth<br>Need for PN | Intestinal lengthening |
| Short length with normal diameter (remnant <60 cm) | Need for PN | Optimize intestinal function |
| Short length with dilated bowel | Bacterial overgrowth<br>Need for PN | Intestinal lengthening |
| Short length | Complications of PN | Intestinal transplantation |

PN, parenteral nutrition.
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surgical therapy for SBS is influenced by intestinal remnant length and caliber and the clinical condition of the patient (Table 6).[16]

## *Preserving the Intestinal Remnant*

Approximately one half of adult patients with SBS after their initial discharge from the hospital will undergo further abdominal procedures.[153,211] Intestinal problems due to complications or underlying disease are the most common indication. An important goal in any reoperation in patients with SBS is to preserve the intestinal remnant length. Several strategies can be employed to achieve this when further intestinal disease requires operation.[153] Further resection can often be avoided using intestinal tapering to improve the function of dilated segments, employing stricturoplasty for benign strictures, and using

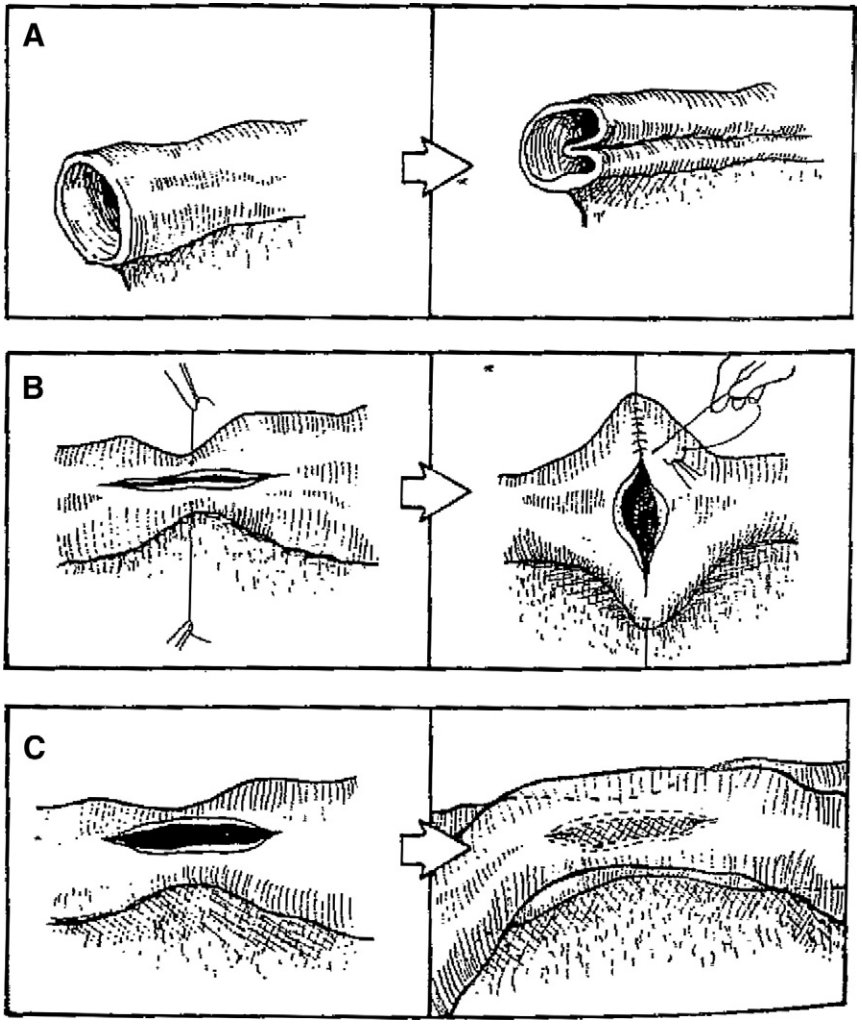


**FIG 7.** Techniques for preserving intestinal length include tapering of dilated segments rather than resection (A), stricturoplasty for strictures (B), and serosal patches for strictures and perforation (C). (Reprinted with permission from Thompson JS. Recent advances in the surgical treatment of the short bowel syndrome. Surg Ann 1990;22:110. © The McGraw-Hill Companies, Inc.)

serosal patching for certain strictures and chronic perforations (Fig 7). Tube enterostomy is another useful approach to controlling acute perforations and chronic fistula. Intestinal resection should be limited in extent when unavoidable. End-to-end anastomosis is favored both to prevent blind loops and to maximize functional length of the intestine. Paradoxically, there are situations, for example, radiation injury or intestinal

pseudoobstruction, where resection of often lengthy intestinal segments will result in overall improvement of function. Depending on the previous operations performed, SBS patients occasionally have intestinal segments that can be recruited into continuity at the time of reoperation. The length, location, and characteristics of the remnant should be carefully documented at the time of any operation to help guide subsequent management.

Most stricturoplasties can be performed in the fashion of a Heineke–Mikulicz pyloroplasty. The stricture is incised longitudinally and closed transversely. The incision should extend at least 1 cm proximal and distal to the stricture, but larger incisions may be required to achieve a satisfactory luminal orifice. The enterotomy can be repaired with either a single-layer or a 2-layer anastomosis. Longer strictures or multiple closely associated strictures can be opened with a side-to-side stapled anastomosis. Blind loops should be avoided, however, because of the risk of stasis and bacterial overgrowth.

Serosal patching is a useful technique for dealing with a nonhealing fistula, stricture, or other focal defect. It is performed by apposition of an adjacent serosal surface, usually either small intestine or colon to the intestine around the lesion. A single-layer seromuscular-to-seromuscular anastomosis is created in either an interrupted or a continuous fashion. The serosal patch becomes covered by normal mucosa from the adjacent tissue. This technique is most applicable to smaller defects because contraction of the patch does occur and could lead to a stenotic segment.

## *Restoring Intestinal Continuity*

An important clinical issue is whether to establish intestinal continuity in patients who have a colonic remnant.[212] Ostomies are performed in more than one half of patients at the time of resection leading to SBS. Ostomy formation is common in SBS patients because of the often emergent nature of their initial resection, questionable blood supply to the intestinal remnant, colonic disease, and anticipated poor functional outcome. In our experience only one fourth of SBS patients with an initial stoma have subsequent ostomy closure.[211,212]

There are several advantages to restoring continuity. The colon may improve intestinal absorption by increasing the absorptive surface area, deriving energy from short-chain FAS, and prolonging transit time, particularly if the ileocecal valve is intact.[213] The colon can serve as a "brake" to gastric emptying in SBS patients, perhaps mediated by peptide YY and other hormones secreted from the terminal ileum and colon.[37,38]

Eliminating a stoma may improve the quality of life and reduce the risk of central line infection.

Unfortunately, the response of the colon to luminal contents is somewhat unpredictable. Bile acids may cause a secretory diarrhea. Perianal problems can be quite disabling and decrease the patient's oral intake. Oxalate is absorbed primarily in the colon, and restoring continuity places the patient at increased risk for the formation of calcium oxalate stones. These issues need to influence decision-making.

Not all patients who initially have a stoma formed will eventually have continuity restored with a satisfactory outcome.[211,212] This decision should be considered on an individual basis, depending on the length of the intestinal remnant, the status of the ileocecal valve and the colon, and the patient's overall condition. Generally, at least 3 feet of small intestine is required to prevent severe diarrhea and perianal complications. Restoring continuity, however, should always be given strong consideration because of possible improvements in absorption. We have certainly become more aggressive in this regard. In some patients exchanging a proximal stoma for a more distal 1 is appropriate and may improve nutrition while preventing issues with disabling diarrhea.[214]

## *Improving Motility*

Patients with SBS may develop dilated intestine secondary to chronic obstruction or intestinal adaptation. The latter occurs more frequently in children. This may lead to stasis and bacterial overgrowth, which can further aggravate the malabsorption associated with the short remnant. Mechanical obstruction at an anastomosis or from adhesions or strictures related to the underlying disease process should always be sought in these patients and corrected using the techniques mentioned previously. These dilated segments, however, are often not associated with distal obstruction and tapering dilated segments may improve motility. Restoring more normal luminal size permits closure of the lumen during contraction of the wall, which improves peristalsis. Both simple imbrication of the redundant bowel and longitudinal transection with excision of intestine along the antimesenteric border have been employed. A continuous nonabsorbable suture line is usually most expeditious, particularly for lengthy segments. Excisional techniques are easily performed with stapling devices. Tapering enteroplasty has been demonstrated to improve intestinal function in SBS patients.[16] Blind loops may also be associated with dysmotility. They should be sought and eliminated, preferably by revising the anastomosis rather than resection.

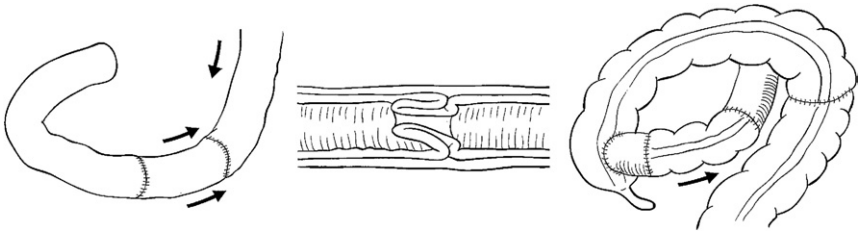

**FIG 8.** Techniques for slowing intestinal transit: antiperistaltic segment (left), intestinal valve (center), colon interposition (right).

**TABLE 7.** Clinical experience with procedures to prolong transit for short bowel syndrome[a]

| Procedure | Number of patients | Number of children (%) | Patients with clinicalimprovement (%) |
|---|---|---|---|
| Reversed segment | 60 | 6 (10%) | 47 (78%) |
| Intestinal valve | 32 | 7 (22%) | 24 (75%) |
| Colon interposition | 14 | 11 (78%) | 8 (57%) |

[a]From references 215, 216, 219, 220, 222, 223, 224, 225.

## *Prolonging Intestinal Transit*

Procedures designed to prolong intestinal transit time have been evaluated experimentally and performed clinically for several decades, but their efficacy remains questionable[215,216] (Fig 8). Most of the reports are anecdotal. These adjunctive procedures are often performed during the adaptive phase; hence, it is difficult to determine whether improvement in nutritional status and absorption were due to the surgical procedure or the normal adaptive process. Three procedures have been attempted in sufficient numbers to be considered. These include reversed intestinal segments, colon interposition, and artificial sphincters (Table 7).

***Reversed Intestinal Segments.*** Reversing segments of intestine to slow intestinal transit has been attempted for more than 100 years for a variety of conditions and is the surgical procedure that has been reported most extensively.[4,215] The antiperistaltic segment functions by inducing retrograde peristalsis distally and disrupting the motility of the proximal intestine. In addition, the disruption of the intrinsic nerve plexus slows myoelectrical activity in the distal remnant. Reversed segments also alter the hormonal milieu after resection.[217]

Most experimental studies of antiperistaltic segments demonstrate slowed intestinal transit, improved absorption, reduced weight loss, and

prolonged survival after intestinal resection, but some reports do not show a beneficial effect.[218,219] The variable outcomes may be explained by several factors, including variation in extent of resection, timing of the procedure, and use of different lengths of antiperistaltic segments. Reversed segments performed simultaneously with resection might alter the normal adaptive response.[217,218]

Ideally, the antiperistaltic segment slows intestinal transit without causing complete functional obstruction. Several technical details are important. The optimal length of the reversed segment would appear to be approximately 10 cm in adults and 3 cm in children. The reversed segment should be created as distal in the small intestinal remnant as feasible to receive the benefit of proximal absorptive surface. Care must be taken to identify a satisfactory vascular arcade to the segment and to avoid complete rotation of the mesentery during reversal to prevent intestinal ischemia.

Antiperistaltic segments have been reported clinically in more than 60 patients, of whom approximately 90% were adults.[215,216,219,220] The length of the segment has varied from 5 to 15 cm in adults in these reports. Clinical improvement has been reported in 80% of SBS patients in these anecdotal reports with slowed intestinal transit and increased absorption demonstrated. Although long-term function of antiperistaltic segments have been demonstrated, our experience suggests only 50% long-term clinical benefit.[220] Transient obstructive symptoms, intestinal ischemia, and anastomotic leak are potential problems. This procedure has been reported in patients with Crohn's disease with acceptable outcomes and does not appear to influence recurrence rates.[219,220] Obviously caution must be exercised in patients with mesenteric scarring or residual intestinal disease.

***Intestinal Valves.*** The effect of surgically constructed valves and sphincters on intestinal motility involves several different mechanisms. They create a partial mechanical obstruction, disrupt the normal motor pattern of the small intestine, and prevent retrograde reflux of colonic contents.[215,221] In experimental studies, intestinal valves and sphincters have been shown to prolong intestinal transit time, increase absorptive capacity, and improve survival after intestinal resection, although the results have been inconsistent. Effective valves usually result in some dilation of the proximal intestine and may cause, at least transiently, obstructive symptoms. Potential complications include necrosis of the valve, complete obstruction, and intussusception. Durability of the sphincter function of valves has been questioned and may be influenced by the technique of construction.

Several different techniques for creating intestinal valves and sphincters to replace the ileocecal valve have been reported. These include external constriction of the intestine, segmental denervation, and intussuscepting intestinal segments to increase intraluminal pressure, with the latter being employed most frequently. Intussuscepted or nipple valves should be 2 cm in length if created retrograde and 4 cm if the valve is prolapsed antegrade. We have generally created a retrograde sphincter similar to that employed in the continent ileostomy procedure but only 2 cm in length.[16,221] However, there is insufficient experience to claim superiority of this technique over another.

The reported clinical experience with intestinal valves and sphincters is less extensive than that with reversed segments. Intussuscepted valves have been reported as primary treatment of SBS in 25 adults and 1 infant[211,222]: 24 patients improved markedly; 1 had questionable benefit, and the other required takedown of the valve. The primary end points were improved diarrhea and maintenance of body weight. Ileocolic nipple valves were lost in one third of patients followed for more than 5 years in 1 study, again raising the issue of durability. Nipple valves have also been employed in 6 infants to cause dilation of the intestine to permit subsequent intestinal lengthening.[223]

***Colon Interposition.*** Interposing a colonic segment in the small intestinal remnant in either an isoperistaltic or an antiperistaltic fashion retards intestinal transit. Isoperistaltic interposition is performed proximally and functions by slowing down the rate at which nutrients are delivered to the distal small intestine.[215] The antiperistaltic colon interposition is placed distally, similar to the reversed small intestinal segment. Interposed colonic segments absorb water, electrolytes, and nutrients in addition to their effect on intestinal transit. Although it has been suggested that interposed colon might develop structural and functional similarities to the small intestine, this has not been substantiated.[224]

In experimental studies, isoperistaltic colon interposition generally resulted in slower transit time, less weight loss, and improved survival after resection. Results with antiperistaltic colon interposition, however, have been less consistent. The length of colon interposed seems to be less critical than with reversed segments of small intestine.

The use of colon interposition has been reported in 12 SBS patients, 11 of whom had isoperistaltic interposition.[215,224,225] Eleven of these patients were infants younger than 1 year of age. The interposed colon segment varied between 8 and 24 cm in length. All patients were PN-dependent preoperatively. Eight (57%) patients demonstrated sus-

tained clinical improvement. Six children, including 1 with an antiperistaltic colon, did not improve and subsequently died of sepsis or hepatic failure. Colonic stasis with bacterial overgrowth may have contributed. Overall, this experience suggests that isoperistaltic colon interposition may have some merit.

***Choice of Procedures.*** Procedures designed to slow intestinal transit should be applied cautiously in patients with nearly adequate remnant length and demonstrated rapid transit. They should be considered only after maximal adaptation has occurred. Reversed intestinal segments and artificial valves have the greatest appeal as procedures to slow intestinal transit. Antiperistaltic segments should be used in patients with longer remnants so the 10-cm segment used still leaves sufficient intestinal remnant for absorption. Valves should be considered in patients with shorter remnants because less bowel is used. In 1 experimental study, an intestinal valve was more effective than an antiperistaltic segment in prolonging transit time after resection. Colon interposition has largely been restricted to children where the small intestinal remnant is much shorter. Overall, these procedures are applicable to only a small proportion of patients with SBS and the efficacy of these procedures remains questionable.

## *Intestinal Tapering and Lengthening*

Some SBS patients will develop dilated intestinal segments that may be amenable to intestinal tapering and lengthening. These procedures are an attempt to optimize the volume-to-surface-area ratio of the intestine to improve contact time between luminal contents and absorptive surface. They should also improve motility and reduce stasis. The primary technique of longitudinal intestinal lengthening was initially described by Bianchi in 1980[226] (Fig 9). More recently an alternative technique called serial transverse enteroplasty (STEP) was reported by Kim and colleagues in 2003[227,228] (Fig 10). Using these approaches, the dilated segments are not only tapered, but the redundant intestine is preserved as additional length.

The Bianchi procedure is performed by transecting distal to the dilated segment to be tapered. Dissection is performed longitudinally for approximately 5 cm on the mesenteric edge of the bowel between the terminal branching vessels to create a space that permits longitudinal division of the bowel with a stapler. A hand-sewn anastomosis can also be employed. If the diameter of the bowel permits, the staple line can be imbricated as well. This procedure is repeated until the desired length of division is

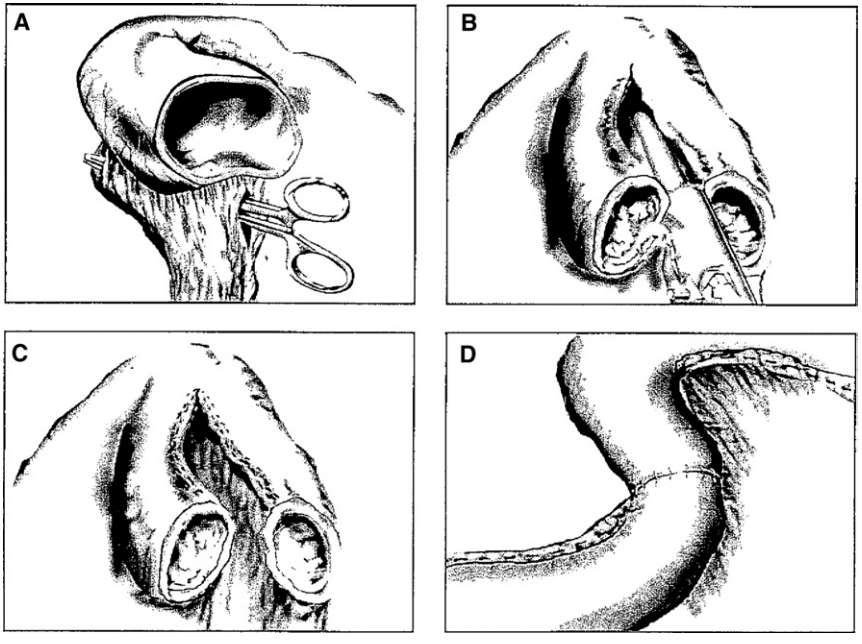


**FIG 9.** The Bianchi procedure. Longitudinal dissection between the blood vessels on the mesenteric border (A) permits the use of staples to divide the intestine longitudinally (B and C). The 2 parallel segments are then anastomosed end to end (D). (Reprinted with permission from Thompson JS. Surgical rehabilitation of the intestine in SBS. Surgery 2004;135:465.)

achieved. The 2 parallel longitudinal segments can then be anastomosed end-to-end to halve the diameter and double the length of the segment. Intestinal lengthening of segments up to 90 cm has been reported. Limitations of the Bianchi procedure include its technical difficulty, need for intestinal anastomosis, and risk of injury to intestinal blood supply. Obviously, longer segments are at greater risk for other complications, including leak and stricture formation.

In experimental studies, intestinal lengthening by the Bianchi procedure prolongs transit time but does not clearly improve absorption in the short term.[229] Intestinal lengthening causes motor disruption in the proximal intestine and alters the hormonal response to resection. The jejunum may yield better results than lengthening of ileum. However, this procedure has been demonstrated clinically to improve fat and carbohydrate absorption and slow transit time.[230] Stool frequency is reduced and clearance of intraluminal barium is improved. Thus, any short-term functional problems appear to resolve with time. The experimental studies suggest that

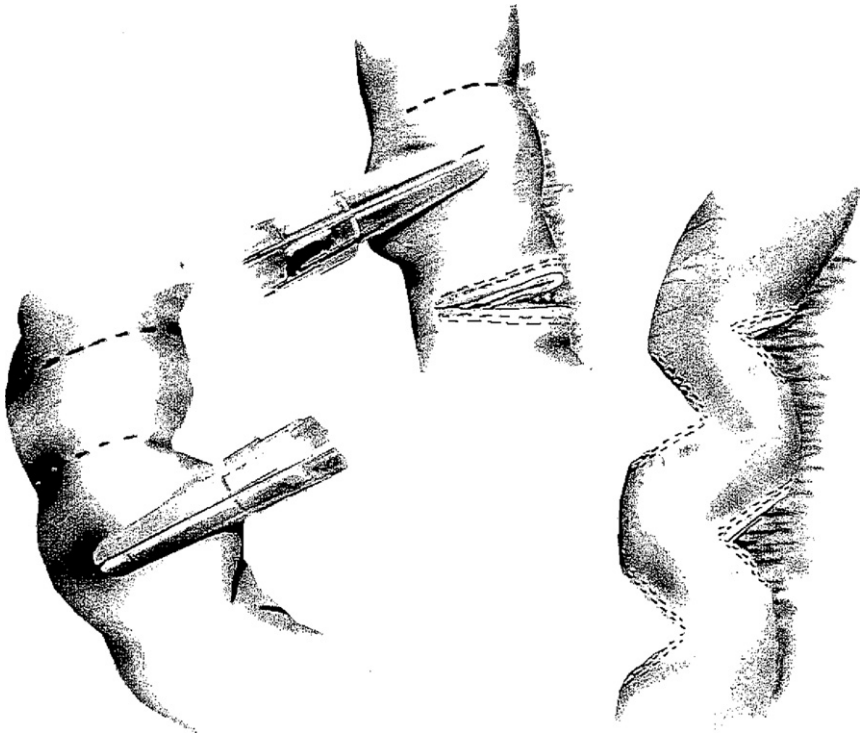

**FIG 10.** The STEP procedure. Several transverse application of a linear stapler from opposite directions on the bowel wall allowing the intestine to lengthen with reduced diameter. (Reprinted with permission from Thompson JS. Surgical rehabilitation of the intestine in SBS. Surgery 2004;135:465.)

lengthening should not be performed until postresection adaption has occurred.

Intestinal lengthening by the Bianchi procedure has now been reported in more than 150 patients, the vast majority being children.[226,228,231-236] After an initial prolonged ileus, significant improvement in absorptive capacity and nutritional status has been reported in 80% of these patients in the short term. PN weaning is achieved in more than one half of the patients. Early complications, such as necrosis of divided segments, anastomotic leak, and obstruction, occur in up to 20% of patients. Gastrostomy tubes are often placed because of the prolonged dysmotility that occurs. The close proximity of multiple staple lines can lead to enteroenteral fistulas, which can influence functional outcome and lead to a challenging reoperation. Although short-term results have been encouraging, our long-term results suggest that approximately one half of the

patients undergoing this procedure have sustained benefit for up to 10 years.[231] However, others report an 80% clinical improvement rate.[236] The overall mortality rate has been 15% to 20% but reflects patient selection rather than technical problems. Recurrent dilation can occur and may lead to further procedures, such as a STEP, although great care must be taken because of the already divided blood supply to the intestine. Ten percent of patients underwent intestinal transplant after longitudinal lengthening.[233]

The STEP procedure involves serial transverse applications of a linear stapler from alternating directions, in an overlapping fashion, which incompletely divides the bowel perpendicular to the long axis of the intestine. This can be done in a lateral side-to-side fashion or mesenteric-to-antimesenteric, although in either case, the staple lines must cross the midpoint of the diameter of the bowel to produce an appropriate overlapped pattern. Either approach preserves the blood supply from the mesenteric border. The length and spacing of the transverse division is determined by the diameter of the intestine, which is in general guided by the age and size of the patient. Multiple stapler applications are required and the lengthening achieved is determined by the length and number of firings. Although referred to in general terms as a "lengthening procedure," the net effect again is to alter the volume to surface area of the intestine to improve absorption and propulsive contraction. Grossly the net result is an increase in length and reduction in diameter. This procedure is less complicated than the Bianchi procedure because it avoids the extensive mesenteric dissection and the additional anastomosis. It is feasible for very short segments and those near the ligament of Treitz. It is also more applicable than the Bianchi procedure when the bowel diameter is asymmetrical along its length.

Improved maintenance of nutrition has been demonstrated in an animal model employing the STEP procedure.[227] D-xylose and fat absorption improved. Bacterial overgrowth was reduced. The STEP procedure does not appear to interfere with baseline or hormonally stimulated motility in the porcine small intestine.[237]

The experience with the STEP procedure has been quite favorable.[228,232,235] Initial short-term results in 72 patients demonstrate the feasibility and safety of the technique in the clinical setting. Eighty-eight percent of procedures are in children. The clinical improvement rate is 80%. Despite having multiple staple lines, the rate of leak following STEP is low. The functional benefits of a STEP seem to average 10 to 12 weeks after the procedure and over time there appears to be catch up growth and gradual improvement in enteral tolerance. Late complications

include obstruction from overly narrow STEP segments and recurrent dilation. Overall mortality rate is approximately 8% with subsequent intestinal transplantation in 5%. This is a more recent procedure so long-term data are not available. The outcomes of these procedures are heavily influenced by patient selection in terms of age, remnant length, hepatic function, and requirement for PN.

We recently compared our experience with both lengthening procedures.[232] Preoperative remnant length and final bowel length achieved was similar with both procedures (52% increase with STEP and 48% with Bianchi). PN requirements were similar before lengthening, but there was a trend toward increased weaning with STEP (60%) compared to Bianchi (55%). There was also a longer time to complete discontinuation of PN for Bianchi (8.4 months) compared to STEP (4.8 months). There was no difference in patient survival. Given the greater applicability and technical ease, the STEP procedure has become our preferred approach.

Many patients who undergo intestinal lengthening develop further dilation of the intestinal remnant. The feasibility of repeat STEP has been reported in several series in patients who underwent either the Bianchi or the STEP procedure.[238,239] Further nutritional benefit occurs with these repeat procedures. This is determined, of course, by change in absorptive surface and motility achieved. However, overall redilation may be a poor prognostic factor.[239]

Intestinal tapering and lengthening should be considered in 2 situations. Patients who remain PN-dependent after intestinal rehabilitation is 1 group. The goal here is to reduce or eliminate PN. Tapering enteroplasty can also be considered in the setting of dilated bowel and recurrent bacterial overgrowth. Here the primary goal is to restore intestinal motility and prevent bacterial overgrowth. The STEP procedure is the preferred alternative method to simple tapering. Adaptive dilation without obstruction is particularly common in children and thus most of the procedures have been preferred in this age group. However, we have been identifying more adults who are candidates for these procedures.[240] When the underlying cause of dilated bowel is obstruction, then the primary goal is to relieve the obstruction and enteroplasty may not be prudent at that time. Patients with cirrhosis are not suitable candidates. Performance of this procedure in neonates remains controversial.

Unfortunately, the lengthening procedures can be applied only to a fairly select group of patients. The intestinal diameter should be at least 4 cm to provide an adequate lumen size after tapering. The vascular anatomy must be favorable and dilation fairly uniform for the Bianchi procedure. Sequential operations, first employing a procedure, such as an

artificial valve to produce intestinal dilation and then performing the lengthening at a later time, have been used to expand the applicability of this technique. Efforts have also been directed at recruiting additional vascular supply to permit longitudinal lengthening. The STEP procedure should markedly increase the applicability of intestinal lengthening.

## Tissue Engineering

Techniques to expand intestinal surface area by taking advantage of the regenerative capability of the small intestine remain an active area of investigation for potential therapy of SBS. Early attempts at increasing surface area by serosal patching with regeneration from the margins of the wound were limited by marked contraction of the defects created so that only a modest gain in surface area was achieved.[241] Seeding a variety of conduits with isolated intestinal epithelial cells was largely unsuccessful because of limited growth.[242] An important step forward was the development of isolated organoid units to produce all the epithelial cell lineages.[243,244] The use of stem cells isolated from the intestine should lead to further progress in intestinal regeneration.[243-247]

Current techniques of experimental intestinal tissue engineering employ artificial biodegradable scaffolds in a 3-dimensional structure in which organoid units are seeded.[246,247] This results in regeneration of functional small intestine, which has been implanted into the intestinal tract.[245] Tissue-engineered structures have been demonstrated to improve body weight following intestinal resection. These segments are responsive to luminal contents and can be manipulated to affect growth, for example, angiogenesis.[248]

## Intestinal Transplantation

### *Background*

The development of intestinal transplantation must be placed in the context of patients and physicians faced with catastrophic clinical circumstances in the absence of reliable alternatives. The mortality rate of patients requiring PN for benign disease varies between etiologies but has been estimated at 20% to 25% at 5 years.[17,93,249] For infants, the risk for PN-induced liver disease is especially great. It is estimated that one half of the deaths in children receiving PN are due to liver failure.[249] Although the first successful intestinal transplant was reported in 1990, it was only a decade ago in 2001 that the USA federal government through Centers for Medicare and Medicaid Services (CMS) approved payment for intestinal transplantation at select centers meeting federal guidelines.

**TABLE 8.** Established indications for intestinal transplantation

| |
|---|
| Failure of TPN |
| Intestinal failure-associated liver failure |
| Thrombosis of ≥2 central veins |
| ≥2 episodes/yr severe sepsis especially fungemia |
| Selected malignancies |
| Neuroendocrine tumors, desmoid (postresection) |
| Diffuse mesenteric venous thrombosis with complications and failed nonsurgical therapy |
| Controversial/unestablished indications |
| Intestinal failure with frequent hospitalizations, narcotic dependency, or pseudoobstruction |
| Patient unwillingness to accept long-term parenteral nutrition (PN) |

TPN, total parenteral nutrition; PN, parenteral nutrition.

## *Indications*

The generally accepted indications for intestinal transplantation are restricted to life-threatening complications of intestinal failure (Table 8).[250,251] One common reason to consider intestinal transplantation is the development of IFALD and in that consideration it is important to determine whether the liver disease is reversible. If the liver disease is found to be irreversible, based either on biopsy findings or on clinical features, such as massive splenomegaly, ascites, encephalopathy, or gastrointestinal bleeding, the patient should undergo combined liver–small bowel transplantation. As early PN management strategies have evolved to include lipid minimization and alternate lipid preparations, such as fish oil based emulsions, there has been recognition of reversibility of IFALD and a greater emphasis has recently been placed on considering isolated small bowel transplantation for patients with potentially reversible PN-induced liver disease. Although irreversible IFALD was previously the top indication for transplant, it is being replaced by recurrent line infections and vascular access problems, as liver disease is increasingly prevented. Regardless of the type of transplant required, early referral and listing are important to ensure the patient their greatest opportunity to obtain a transplant.

The other common indications for intestinal transplantation are an irreversible permanent PN requirement along with episodes of sepsis or loss of venous access. Septic episodes that would prompt consideration for intestinal transplantation are typically catheter-related, especially those associated with yeast. Patients who have undergone multiple hospitalizations related to catheter sepsis, often requiring intensive unit care with the need for vasopressors, fall into this category. Other indications for intestinal transplantation are multi-antibiotic-resistant bacteremias or metastatic infections in sites, such as tricuspid valve or the

brain. Loss of venous access typically implies an inability to place a catheter in the subclavian or intrajugular veins and the use of extemporaneous sites, such as the hepatic veins or the inferior vena cava. A transplant evaluation is strongly recommended in patients with conditions having no meaningful hope of enteral nutrition, such as microvillus inclusion disease, tufting enteropathy, or intestinal aganglionosis. The use of intestinal transplant, either alone or as part of a multivisceral transplant, has been successfully employed in patients with desmoid tumors that have had massive bowel loss in the course of resection and also in selected patients with neuroendocrine malignancies. Caution must be taken in expanding the indications for intestinal transplantation away from life-threatening complications and toward indications, such as "poor personal tolerance of PN" or lifestyle issues, since there is clear evidence that these patients have worse survival following transplant than without it. Today with improved outcomes and large numbers of patient dying on the waiting list, a greater responsibility is being placed on the treating physician to make earlier referral to a transplant center.

The transplantation evaluation process for patients with intestinal failure requires a multidisciplinary group of health care professionals, including surgeons, gastroenterologists, dietitians, social workers, and nurse specialists. In essence the transplant team is charged with answering 2 questions: does the patient have indications for transplant and are there contraindications precluding transplant? Contraindications to transplant would include recent malignancy (with exceptions noted above) and insufficient cardiopulmonary reserve to tolerate surgery. Often the barriers to transplant are not medical but rather are social or psychological, related to addiction or poor compliance or a poor social network. Contrast studies, computed tomography scans, and magnetic resonance angiography or venography are often used to define anatomy and specifically vascularization fully. A liver biopsy is performed in patients with evidence of liver dysfunction to help select the appropriate type of transplantation procedure. During the evaluation process, other problems are addressed, including worsening liver failure, sepsis, difficult vascular access, and septic episodes. After the patient is identified as a potential candidate, he or she is placed on an active transplantation waiting list. The decision to list for transplant should not preclude active ongoing rehabilitation, however, and patients can be potentially moved back and forth between programs, depending on current clinical condition. This reinforces the importance of management of intestinal failure patients in specialized

centers offering both rehabilitation and transplantation, either at the one institution or through close relationships between centers.

## Operative Procedure

The donor operation begins similarly regardless of the organs being removed. Potential organ donors are matched with the recipients based on blood types, size, and medical necessity. Most patients with SBS have a loss of peritoneal domain, requiring the donor to be equal to or smaller in the size than the potential recipient, ranging to as low as 25% to 30% of recipient weight or even smaller in some cases. Although some success has been reported with reduced size donors, the number of intestine donors typically far exceeds the number of listed candidates, and except in extreme circumstances, a suitably sized donor can be found. Living donor intestine transplants have been reported, but for similar reasons as reduced-sized donors, have a very limited role in intestinal transplantation overall. Donors should be ABO blood group identical, although exceptions to this rule have been reported.[252] Human leukocyte antigen matching and a negative T-cell cross-match may be beneficial particularly for recipients of isolated small bowel allograft; however, donor logistics often prevent this from being performed prospectively. A cross-match performed after the transplant may still be useful in guiding immunosuppressive therapy postoperatively.

Procurement of the intestine for an isolated small bowel transplantation typically involves the removal of the liver and small bowel together with separation on the back table,[251] although the isolated graft can also be removed separately from the liver. The donor operation for a liver–small bowel transplantation is rather similar to a liver procurement, but no hilar dissection is performed and the aorta is divided just distal to the origin of the superior mesenteric artery, with care taken to remove as much aorta proximal to the celiac axis as possible. In some centers, stomach or segments of colon are included in the graft, which is removed en bloc.[250]

The back table preparation for the isolated small bowel graft involves removing a portion of the duodenum along with the head of the pancreas from the portal vein and superior mesenteric artery, while obtaining sufficient length of each vessel care is taken to not ligate early jejunal branches, and to mark the orientation of the vessels, which can become disorienting during implantation. For composite grafts, in the past some or all the pancreas and spleen were removed in preparation, although in general the pancreas is now included in the graft, with most centers removing the spleen. When included as part of the graft, addition of the

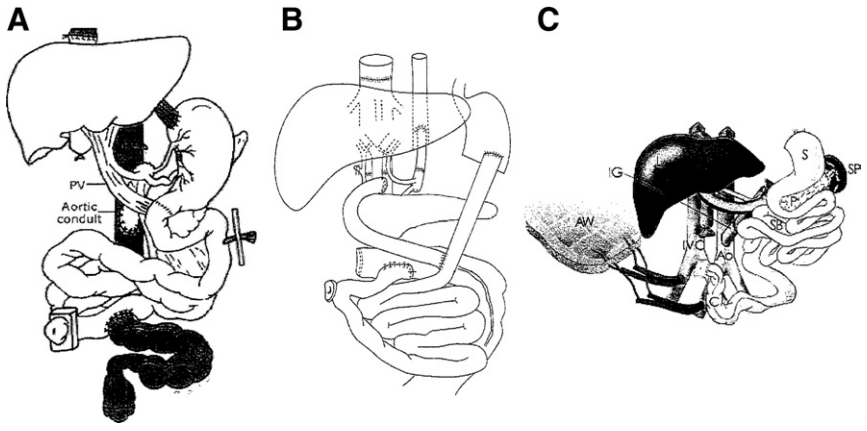


**FIG 11.** Surgical techniques for multivisceral transplantation. (A) University of Pittsburgh. (Reprinted with permission from Abu-Elmagd et al.[250]) (B) University of Nebraska. (Reprinted with permission from Grant et al.[253]) (C) University of Miami. (Reprinted with permission from Tzakis AG, Kato T, Levi DM, Defaria W, Selvaggi G, Weppler D, et al. 100 multivisceral transplants at a single center. Ann Surg 2005;242:480-93.)

spleen is associated with a potentially lower rate of post-transplant lymphoproliferative disorder (PTLD), but an increased risk of autoimmune hemolytic anemia.[250] The numerous intercostal arteries are ligated, and the distal end of the aorta is oversewn. Critical for the liver–small bowel graft is that no hepatic hilar dissection takes place, so the hepatobiliary-duodenal complex remains undisturbed.

The recipient operation typically makes use of prior incisions. For isolated small bowel transplantation, the infrarenal aorta is isolated, and the arterial anastomosis for the small bowel graft is typically performed between the donor superior mesenteric artery and the infrarenal aorta.[253] The venous drainage can be systemic or portal. Systemic drainage is preferred whenever liver disease is present. Often much of the recipient native intestine beyond the ligament of Treitz is removed before implantation to facilitate exposure; thus, the proximal graft is anastomosed to the most distally located and convenient loop of recipient bowel. An enterostomy is created to decompress the small bowel and to facilitate biopsies with a loop ileostomy being the most common type of stoma created for both liver–small bowel and isolated small bowel transplantations.

The liver–small bowel transplantation surgical technique leaves the donor hepatic hilar structures undisturbed (Fig 11), limiting the necessary back table dissection, and virtually eliminates any possible biliary tract

complications after transplantation. The liver–small bowel composite allograft is implanted orthotopically with arterial inflow through the donor aortic conduit anastomosed to the supraceliac aorta when possible. The arterial anastomosis has also been described using a large Carrel patch encompassing both the celiac and the superior mesenteric artery, typically to the infrarenal aorta. When the native foregut is left in situ, a portacaval shunt is necessary to decompress the recipient's viscera. As maintenance of native foregut appears to add little advantage to outcome, increasingly complete removal of the small intestine, duodenum, pancreas, spleen, and distal stomach is employed, obviating the need for a portacaval shunt. In this case, enteric reconstruction typically involves anastomosis between the remnant proximal stomach and donor jejunum, either directly or by Roux Limb.

After transplantation, the cornerstone of immunosuppressive management is the administration of tacrolimus and steroids. The majority of intestinal transplant programs now makes use of some form of induction therapy either with biological agents, such as Thymoglobulin, or with an interleukin-2-receptor blocking agents.[254-256] Reports have been made of other drugs being administered, including sirolimus, Campath, and mycophenolate.[257] Numerous other agents are administered as prophylaxis for infections, in particular, broad-spectrum antibiotics, antifungal agents, and antiviral drugs.

## Outcome

With improvements in immunosuppression, operative techniques, and critical care, patient and graft survival have steadily increased over time (Fig 12). Based on Organ Procurement and Transplantation Network (OPTN) data as of June 2011, there have been 2067 intestinal transplants and 629 liver-pancreas-intestine transplants performed in the USA. From these data, at present graft and patient survival both vary from 64% to 89% at 1 year based on age category (less than 1 year of age being worst), falling to 31% to 69% at 5 years for graft survival, and 33% to 76% for patient survival at 5 years. In larger centers, however, results are improved with 1-year patient survival around 80% for both isolated intestine and combined liver-intestine grafts, dropping to around 60% at 5 years. In general, clinical experience remains confined to a small number of programs with 83% of the cases being performed at 10 institutions. Analysis of the Intestinal Transplant Registry (ITR) data has shown that programs that have performed at least 10 transplantations have better patient survival rates than programs that have performed fewer than 10 transplantations and that patients who are called in from home have a

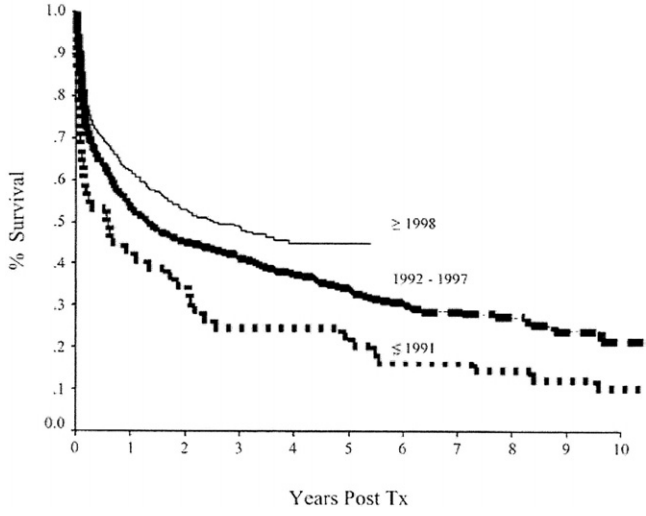


**FIG 12.** Graft survival rates after intestinal transplantation have improved over time. (Reprinted with permission from Grant et al.[257])

much higher survival rate than those that are hospitalized, which should encourage physicians to refer patients earlier. The most common causes of death following intestinal transplantation included sepsis, multiorgan system failure, graft thrombosis, rejection, and posttransplantation lymphoma.

Rejection episodes continue to be a major problem in small bowel transplantation, even with tacrolimus-based immunosuppression combined with some form of induction therapy. According to the ITR, graft rejection rates were 57% for intestine grafts, 39% for combined intestine and liver grafts, and 48% for multivisceral grafts.[258] The diagnosis of rejection is made based on histologic findings. Biopsy of the small bowel allograft is performed either on a protocol basis or on a basis of changes in clinical findings. Clinical findings that could be associated with rejection include diarrhea, increases of stoma outputs, bloody diarrhea, abdominal pain, or intolerance to feedings. Unfortunately, a noninvasive marker for the diagnosis of rejection episodes is not available.

Two important factors in intestinal transplant patients: increased levels of immunosuppression and an allograft colonized with enteric organisms—lead to frequent infections. Common sites for bacterial infections include the central line, surgical wound, and abdominal cavity. Bacteremia or fungemia may also develop because of allograft rejection,

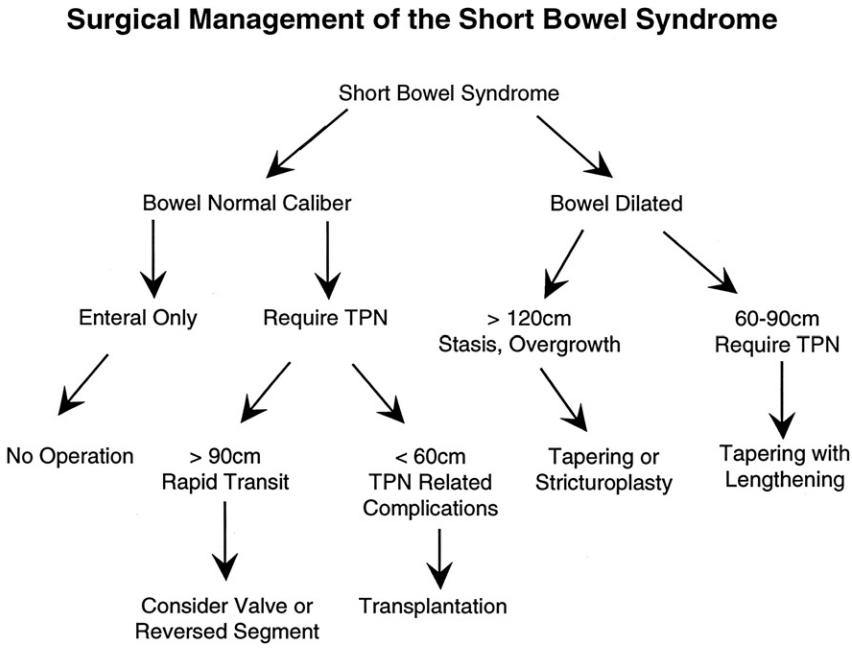


**FIG 13.** Surgical management of the short bowel syndrome. (Reprinted with permission from Thompson et al.[16])

infectious enteritis, or preservation injury. With any of these bowel injuries, there can be loss of the mucosa with eventual translocation of enteric organisms. The primary viral infections that occur after intestinal transplantation include herpesviruses, such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV). A variety of strategies have been proposed to either prevent or diagnosis both CMV and EBV infections. Molecular monitoring for both EBV and CMV DNA in blood is now routine in most transplant programs. Prophylactic measures include infusions of pooled immunoglobins and antiviral drugs, such as ganciclovir. The intestinal graft is the most common site of CMV infection. Treatment is based on the use of antiviral drugs, such as ganciclovir or foscarnet.

PTLD is an EBV-associated process that occurs after all solid organ transplantations. Intestinal transplant recipients appear to be at a high risk for PTLD than recipients of other organ transplants. This is likely due in part to the high level of immunosuppression needed to control rejection as well as the relatively young age of the recipients. The reported incidence of PTLD after intestinal transplantation are between 7% and 29%.[253,255,257] The treatment of PTLD often involves the lowering of

immunosuppression and the use of antiviral agents as first line of therapy.[254] Newer treatments being proposed include the use of a low-dose Cytoxan regimen to control PTLD without the side effects of more traditional chemotherapeutic regimens.[258] Rituximab, a monoclonal antibody directed to CD 20 positive B cells, is now being used to treat PTLD. Recently, the use of blood tests to measure qualitative and quantitative amounts of EBV DNA in the peripheral blood of transplant recipients has been advocated.[258] The measurements of EBV DNA are used in a hope to identify PTLD before it becomes clinically evident so that less toxic preemptive therapy can be administered.

More information about long-term nutritional outcome and quality of life is emerging. The functional status of the small bowel allograft is the foremost factor in determining the long-term quality of life for recipients. Although one third of recipients are discharged on PN, according to the ITR, 81% of recipients develop enteral autonomy. Pediatric patients develop good growth velocity. Intestinal transplantation has improved quality of life in almost all domains, but particularly in digestive function, vocational status, medical compliance, optimism, and energy.[92,259,260] More recent studies, however, suggest that quality of life remains lower than nontransplant controls. Data also demonstrate that intestinal transplantation becomes cost-effective compared to PN at 2 years.[92,261]

The increasing experience and improved outcome of intestinal transplantation support the clinical use of this treatment modality in the management of patients with intestinal failure. Listing patients for transplantation should not be viewed as a failure of intestinal rehabilitation, but rather an alternative pathway in getting patients to achieve the goal of intestinal failure treatment, which is the development of enteral autonomy. Both autologous reconstructive procedures and organ replacement procedures should be available in providing therapy for intestinal failure optimized to each individual patient (Fig 13).

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