REVIEWS

Short Bowel Syndrome and Intestinal Failure: Consensus Definitions and Overview

STEPHEN J. D. O'KEEFE,* ALAN L. BUCHMAN,† THOMAS M. FISHBEIN,§ KHURSHEED N. JEEJEEBHOY,‖ PALLE BEKKER JEPPESEN,¶ and JONATHAN SHAFFER#

*Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh, Pittsburgh, Pennsylvania; †Feinberg School of Medicine, Northwestern University, Chicago, Illinois; §Georgetown University, Washington, DC; ‖St Michael's Hospital, Toronto, Ontario, Canada; ¶Rigshospitalet, Copenhagen, Denmark; and #Hope Hospital, Salford, United Kingdom

Short bowel syndrome (SBS)–associated intestinal failure is a highly disabling condition that impairs quality of life and social integration. Although the condition is not uniformly fatal, it might lead to serious, life-threatening complications. The basic goals of medical treatment are to maintain fluid, electrolyte, and nutrient balances and to make appropriate modifications in disease management to avoid side effects. Various definitions have been proposed for SBS and intestinal failure within the medical literature, but many focus on different aspects of the conditions, leading to confusion. In the past, identifying the cause of intestinal failure was of little consequence, because all patients were managed on total parenteral nutrition at home. However, with the recent development of medical therapies such as recombinant growth hormone, octreotide, and glucagon-like peptide-2 analogues and with improvements in small bowel transplantation, many patients can be made nutritionally autonomous. To evaluate the relative efficacy of these therapies, there is now a need to develop consensus definitions so that patients can be properly categorized before therapy. To this end, a group of experts on the subject was convened to develop the following new definitions: "Intestinal failure 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." "Short-bowel syndrome results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet."

Short bowel syndrome (SBS) is a complex disease that can result from physical loss of portions of the small intestine or from loss of function.[1] Intestinal failure

nal loss caused by surgery, trauma, or infarction and less commonly congenital defect or a lessening of absorptive surface as a result of diffuse disease. Management of SBS is directed toward maintaining fluid, electrolyte, and nutrient balances (Table 1).[2,3] For the most severe forms of SBS, this has traditionally been accomplished with the use of TPN administered at home, whereas milder forms of the syndrome might be managed with less aggressive measures. These therapies have a long history of use, but recent advances in the treatment of SBS have begun to offer, for the first time, the opportunity for some patients to regain nutritional autonomy and be free from dependence on TPN or intravenous fluids.[2]

Identifying the patients who might qualify for new therapeutic strategies will depend on the accuracy of patient diagnosis and classification, which has been complicated by the multitude of definitions that exist for both SBS and intestinal failure. There is currently no consensus within the published literature as to the definition of either of these conditions. Definition of intestinal failure has been hampered by the fact that whereas in Chinese failure is defined as the complete loss of function, in English failure can include partial loss. With regard to short bowel, some definitions are anatomically based, whereas others describe the syndrome in functional terms. To optimize the outcomes from conventional management strategies and to evaluate new therapies, it is important to try to establish a precise definition of SBS and intestinal failure.

Recognizing the potential ramifications of the definitions of SBS and intestinal failure in this new era of treatment advances, a panel of experts in gastroenterology and clinical nutrition was convened to re-examine

Abbreviation used in this paper: SBS, short bowel syndrome.

Table 1. Clinical Consequences of SBS

Jejunal resection of 50%–60% is usually well tolerated.
Greater than 30% ileal resection is poorly tolerated.
Severe malabsorption occurs with residual small bowel <60 cm.
Deficiencies include fluid and electrolytes (mild and moderate cases)/plus nutrient absorption (severe cases).
Severe fluid and electrolyte loss is associated with end-jejunostomy.
Magnesium, calcium, and zinc deficiencies are common.

the definitions currently in use and to propose new definitions. This article summarizes their discussions, which examined the limitations and ambiguities surrounding current terminology in light of their experience with the clinical issues related to SBS.

Overview of Short Bowel Syndrome and Intestinal Failure

Incidence

The true incidence of SBS and intestinal failure in the United States is unknown, in part because of the lack of precise definitions. Surveys of clinicians have produced variable figures; some practicing gastroenterologists report never having seen a patient with SBS. Undoubtedly, some of their patients are those who have had minor, well-tolerated resections, and who thus do not require therapy. Registries of home TPN patients generally produce incidence figures representing the severe end of the SBS spectrum. The Oley Foundation estimated that 40,000 patients with intestinal failure were receiving home TPN in 1992, with approximately 35% of cases attributable to SBS.[4] Other estimates for the United States identify approximately 41% of SBS patients as dependent on parenteral nutrition (ie, they have SBS-associated intestinal failure) and another 12% as dependent on intravenous fluids and electrolytes alone (data on file; NPS Pharmaceuticals, Salt Lake City, UT; 2002). These figures are likely to be inaccurate, because they would not include patients with uncomplicated SBS.

Prognostic Factors in Short Bowel Syndrome

Among the factors associated with the prognosis of SBS-associated intestinal failure are the length of the residual small intestine, the presence of residual underlying disease, the presence or absence of the colon in continuity and of the ileocecal valve, and the nature of the primary disorder; prognostic factors also include the age of the patient and the status of enteral dependence or [5–8]

intestine lengths greater than 50 cm, but survival rates are much lower for patients with residual lengths less than 50 cm.[2] It is important to qualify these figures, because it is recognized that less than 10% of the 35% who die within this period are directly related to TPN complications, and most die of complications of the underlying disease, for example, cancer and heart failure.[5] Patients with shorter residual intestine are more likely to develop liver and kidney failure and to remain totally dependent on parenteral nutrition.[7,9,10]

Bowel Adaptation

The adaptation of the residual bowel is an important factor in determining whether the patient with a short bowel will progress to permanent intestinal failure and dependence on TPN. The adaptive process was first described in the 1950s and further characterized during subsequent decades.[11–13] During the first 6 months after surgery, a period of gastric hypersecretion usually occurs.[14,15] Other adaptive changes in SBS include mucosal hyperplasia, increased mucosal blood flow, and improved segmental absorption, together with increased pancreaticobiliary secretions. Functional improvement can take up to 2 years.[14] Thus, some patients with a short bowel might initially have intestinal failure and therefore be dependent on intravenous supplementation, but, with time, they might become nutritionally autonomous.

Because of the capacity for the remaining bowel to adapt, most of the intestine has to be lost before intestinal failure occurs. Evidence of loss of function includes vitamin B_{12} deficiency, malabsorption of bile acid and fat-soluble vitamins in isolated ileal resection, and the inability to maintain hydration and electrolyte stability.

Management of Short Bowel Syndrome

The management of SBS has recently been reviewed.[1] It is appropriate here to highlight some general principles (Table 2)[2,3] as they relate to the issue of disease definition.

Management of the malabsorption associated with SBS varies with the degree of severity. In mild cases, malabsorption can be overcome by increasing oral intake. In more severe situations, absorption can be enhanced with the use of antimotility agents that prolong nutrient-mucosa contact and, therefore, fractional absorption. Digestive function is far better preserved than absorptive function, because enzymes are secreted well in excess of requirements, and carbohydrate and protein digestion is virtually complete in the duodenum. In the extreme situation, for example, with the loss of all but the jeju-

Table 2. General Management Strategies for SBS

Fluids
Avoid drinking water without food
Spread fluid intake throughout the day
Sip liquids
Restrict hypotonic fluids
Drink oral rehydration solution containing salt and carbohydrates
Diet
Eat small, frequent meals balanced in nutrient content
Add salt to the diet (only for patient with colon in continuity)
Increase quantity of food intake
Follow a high complex-carbohydrate diet (patients with a colon)
Avoid osmotically active sweeteners, which might cause diarrhea
Drugs
Use antimotility agents
Use antisecretory agents
Consider growth factors to enhance adaptation and absorption
Surgery
Small bowel transplantation
Bowel-lengthening procedures

NOTE. These are based on current practice.[2,3] Management strategies might differ for SBS patients with or without a colon.

balances. Patients then become dependent on intravenous therapy. A state of permanent intestinal failure exists when patients remain dependent on intravenous therapy beyond the 2 years or so that are generally sufficient for intestinal adaptation. This group of patients needs to be identified early, because they will die without intravenous support and close metabolic and nutritional monitoring. Clear definition of the condition of SBS-associated intestinal failure is therefore important.

Evolution of Definitions: Short Bowel Syndrome and Intestinal Failure

The reported "normal" length of the small intestine varies considerably from 300–850 cm.[1,16] Although evidence suggests that patients with less than 200 cm of small bowel are likely to develop intestinal failure, this number is of little use in clinical practice, because outcome depends on the prognostic factors already mentioned, important among which are the quality of bowel remaining and whether the large bowel has been conserved. For example, loss of bowel in a patient with Crohn's disease or from radiation injury is likely to be far more serious than loss of bowel as a result of trauma.

The preservation of the colon is often a critical determinant of whether a patient will manage without intravenous supplements, because the colon helps conserve fluid and electrolytes and can salvage malabsorbed carbohydrate and protein through bacterial metabo-

bowel lengths ranged from 17–150 cm. Overall, the length of bowel remaining correlated with the patient's degree of nutritional autonomy (ie, independence from intravenous nutrition), but the configuration of the remaining bowel, namely whether there was any ileum or colon in continuity, also affected the prognosis. This study reported a high risk for loss of nutritional autonomy under conditions of (1) <35 cm of jejunum remaining in patients with jejunoileal anastomoses, (2) <60 cm remaining in patients with jejunocolic anastomoses, and (3) <115 cm remaining in patients with end-jejunostomies. Remarkably similar cutoff levels were reported by Messing et al[7] on the basis of an analysis of 124 patients with short bowel (<150 cm of small intestine remaining).

Function is not dependent on length alone, because 150 cm of diseased bowel might function less well than 75 cm of healthy intestine, as indicated above. For this reason, some definitions of SBS and intestinal failure have been based on measurements of the functional capacity of the remaining bowel. A study of 48-hour nutritional balance studies in patients dependent on home TPN, as compared with patients who were nutritionally autonomous, demonstrated that intestinal failure could be predicted by an absorption rate below 1.4 kg/day of wet weight and 84% of the calculated basal metabolic rate (4.9 megajoules [1171 kilocalories]/day of energy).[18] It is important to note that nutritional balance studies are very difficult to perform accurately in practice because they require the analysis of duplicate food portions and accurate stool collections. Furthermore, dietary intake rate can influence intestinal transit and therefore absorption rates. Consequently, dietary intake needs to be standardized to reveal reproducible measurements. Other investigators used the plasma citrulline test as an alternative measure of intestinal function.[21] Noting that citrulline in the fasting state can only be synthesized by the small intestine and is not incorporated into body proteins, they proposed that fasting plasma citrulline concentration should provide an index of residual functional enterocyte mass. Although the low plasma concentration of citrulline represents a potential problem in achieving an accurate determination, automated ion exchange chromatography specifically standardized for citrulline measurement has enhanced the precision and accuracy to <5%, making the test a practical measure of enterocyte function or mass. By equating citrulline levels to absorption, they suggested that a concentration of <5 μmol/L

Table 3. Medical Appropriateness of Small Bowel Transplantation

Category I
TPN failure because of venous thrombosis, recurrent sepsis, and liver failure
Category II
Small bowel
SBS with intestinal failure
Defective intestinal motility (hollow visceral myopathy, neuropathy, and/or total intestinal aganglionosis)
Impaired enterocyte absorptive capacity (microvillus inclusion disease, selective autoimmune enteropathy, radiation enteritis, extensive inflammatory bowel disease, and/or massive intestinal polyposis)
Failure of a previously transplanted small bowel graft
Small bowel/liver
Irreversible failure of the liver and intestine
Liver failure associated with total thrombosis of the protomesenteric system
Multivisceral
Combined organ failure and/or premalignant conditions of the gastrointestinal tract
Extensive thrombosis of the splanchnic vascular system
Massive gastrointestinal polyposis
Generalized hollow visceral myopathy or neuropathy
Contraindications
Life expectancy <5 years because of age-related debilitation and comorbidities
Ability to ingest oral nutrition
Unresectable malignancy
Serious, uncontrolled psychiatric illness that would hinder compliance at any stage of the transplant process
Neurologic disease independent of the disease process being treated
Drug or alcohol addiction
Human immunodeficiency virus positivity
Active and/or life-threatening infections that are uncorrectable
Severe body/organ system disease unrelated to the transplanted organs
Inability or unwillingness of the individual or legal guardian to give signed consent and to comply with regular follow-up requirements

NOTE. This is an example of where a precise definition of SBS with intestinal failure will help in assessing candidacy. (Based on BlueCross BlueShield Medical Policy Reference Manual, 2005.)

With the recent development of potent forms of hormone and gut peptide therapies such as growth hormone, octreotide, and glucagon-like peptide-2,[2,22–24] which have the potential to improve intestinal function sufficiently for some patients with intestinal failure to be weaned off home TPN, there is an urgent need to develop a practical working definition of SBS-associated intestinal failure. The same is true for the selection of patients with SBS–intestinal failure for small bowel transplantation. Table 3, which summarizes the medical appropriateness of small bowel transplantation (based on BlueCross BlueShield), illustrates this point, because the Category 2 candidacy for isolated small bowel transplan-

Current Definitions

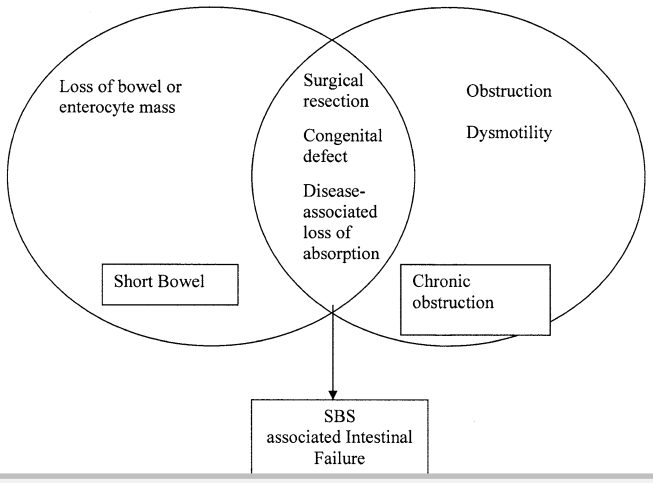
The National Institute of Diabetes and Digestive and Kidney Diseases defines intestinal failure as "reduced absorption of nutrients from the gastrointestinal tract resulting in the need for parenteral nutrition for survival."[25] This definition lacks precision, because it would include patients with anorexia, who also have inadequate absorption not because of intestinal failure but because of the inability or unwillingness to eat. Fleming and Remington[18] have defined intestinal failure as the "reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of food." This is a far more encompassing definition because it includes the need for loss of intestinal mass.

Proposed New Definitions

Recognizing the limitations and overlap in current definitions of conditions related to short bowel and intestinal failure, our group convened for the purpose of developing consensus definitions for both intestinal failure and SBS-associated intestinal failure to help practicing gastroenterologists categorize patients with short bowel and to provide uniformity of view when registering such patients with regulatory authorities or assessing their response to novel forms of therapy. The panel considered SBS as only one cause of the broader condition of intestinal failure (Figure 1).

Short Bowel Syndrome

The proposed new definition for SBS takes into consideration all of the previously noted factors and characteristics but makes SBS a subcategory of the broader condition of intestinal failure. "Short-bowel syndrome–intestinal failure results from surgical resection,



congenital defect or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balances when on a conventionally accepted, normal diet."

Intestinal Failure

The proposed new definition for intestinal failure builds on the concepts noted above. "Intestinal failure 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."

Conclusions

Consensus working definitions of SBS and intestinal failure have been proposed in this review to help the practicing gastroenterologist manage patients with intestinal failure caused by massive intestinal loss and, at the same time, to help in the evaluation of novel pharmacologic therapies.

References

1. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003;124:1111–1134.
2. Buchman AL. The medical and surgical management of short bowel syndrome. Med Gen Med 2004;6:12.
3. Jeejeebhoy KN. Short bowel syndrome: a nutritional and medical approach. CMAJ 2002;166:1297–1302.
4. Oley Foundation. North American home parenteral and enteral nutrition patient registry annual report. Albany, NY: Oley Foundation, 1994.
5. American Gastroenterological Association. Short bowel syndrome and intestinal transplantation: medical position statement. Gastroenterology 2003;124:1105–1110.
6. Carbonnel F, Cosnes J, Chevret S, et al. The role of anatomic factors in nutritional autonomy after extensive small bowel resection. JPEN J Parenter Enteral Nutr 1996;20:275–280.
7. Messing B, Crenn P, Beau P, et al. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 1999;117:1043–1050.
8. Nightingale JM, Lennard-Jones JE, Gertner DJ, et al. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. Gut 1992;11:1493–1497.
9. Banerjee A, Warwicker P. Acute renal failure and metabolic disturbances in the short bowel syndrome. Q J Med 2002;95:37–40.
10. Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000;132:525–532.
11. Althausen TL, Doig RF, Kohn U, et al. Digestion and absorption after massive resection of the small intestine: part 2. Gastroenterology 1950;16:126–139.
12. Dowling RH, Booth CC. Functional composition after small bowel resection in man. Lancet 1966;2:146–147.
13. Williamson RCN. Intestinal adaptation. N Engl J Med 1978;298:1393–1402.
14. Alpers DH. How adaptable is the intestine in patients with short-bowel syndrome? Am J Clin Nutr 2002;75:787–788.
15. Nightingale JM, Lennard-Jones JE, Walker ER, et al. Jejunal efflux in short bowel syndrome. Lancet 1990;336:765–768.
16. Crenn P, Haniche M, Valleur P, et al. Surgical versus radiological evaluation of remaining small bowel length (RSBL) in short bowel syndrome (SBS). Gastroenterology 1996;110:A321.
17. Fleming CR, Remington M. Intestinal failure. In: Nutrition and the surgical patient (clinical surgery international). London: Churchill Livingstone, 1981:219–235.
18. Jeppesen PB, Mortensen PB. Intestinal failure defined by measurements of intestinal energy and wet weight absorption. Gut 2000;46:701–706.
19. Nordgaard I, Mortensen PB. Digestive processes in the human colon. Nutrition 1995;11:37–45.
20. Royall D, Wolever TM, Jeejeebhoy KN. Evidence for colonic conservation of malabsorbed carbohydrate in short bowel syndrome. Am J Gastroenterol 1992;87:751–756.
21. Crenn OP, Vajedo K, Lavergne-Slove A. Plasma citrulline: a marker of enterocyte mass in villous atrophy associated small bowel disease. Gastroenterology 2003;124:1210–1219.
22. Byrne TA, Morrissey TB, Nattakom TV, et al. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. JPEN 1995;19:296–302.
23. O'Keefe SJO, Haymond MW, Bennet WM, et al. Long-acting somatostatin analogue and protein metabolism in patients with jejunostomies. Gastroenterology 1994;107:379–388.
24. Jeppesen PB, Sanguinetti EL, Buchman A, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut 2005;54:1224–1231.
25. National Institute of Diabetes and Digestive and Kidney Disease. Intestinal failure, short gut syndrome and small bowel transplantation. Last update: September 9, 2002. Available at: http://www.niddk.nih.gov. Accessed October 30, 2004.

Address requests for reprints to: Stephen J. D. O'Keefe, MD, MSC, University of Pittsburgh, Division of Gastroenterology, Hepatology, and Nutrition, 200 Lothrop St, Mezzanine Level C-Wing, Pittsburgh, PA 15213. e-mail: sjokeefe@pitt.edu; fax: 412-648-9378.

Dr Jeppesen has served as a consultant for NPS Pharmaceuticals.

Funding for the meeting of the panel of experts was provided by NPS Pharmaceuticals, Salt Lake City, Utah. The views contained are solely those of the expert panel.