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Review

Key issues in addressing the clinical and humanistic burden of short bowel syndrome in the US

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Abstract

Background:

The purpose of this analysis was to provide a concise report of the literature on the burden of intestinal failure associated with short bowel syndrome (SBS–IF) in adults, focused on clinical and humanistic issues important to clinicians and payers.

Scope:

A literature search was performed using the National Library of Medicine PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) with the search term ‘short bowel syndrome’ limited to adult populations and English-language reports published from January 1, 1965, to January 18, 2013. Citations were assessed for relevance and excluded articles focused on single case studies, colon fermentation, absorption of medications with PN/IV, surgical technique, mesenteric artery complications/surgery, and transplantation focus. Additional hand searches were performed using the terms ‘short bowel syndrome’ AND ‘cost’, and ‘home parenteral nutrition’ AND ‘cost’, along with the exclusion criteria described above.

Findings:

Despite advances in management in recent decades, SBS–IF continues to carry a high burden of morbidity and mortality. In the absence of sufficient intestinal adaptation following resection, many patients remain dependent on long-term parenteral nutrition and/or intravenous fluids (PN/IV). Although potentially life saving, PN/IV is costly, invasive, and associated with numerous complications and deleterious effects on health and quality of life. Surgical interventions, especially intestinal transplantation, are costly and are associated with substantial morbidity and high mortality. New therapies, which show promise in promoting intestinal rehabilitation and reducing dependence on PN/IV therapy, are the subject of active research.

Conclusions:

Overall, the available literature suggests that although SBS–IF affects a relatively small population, the clinical and humanistic burden is significant, and there is an unmet need for effective therapeutic options that target the underlying problem of inadequate absorptive capacity of the remaining intestine. Consequently, many patients with SBS–IF remain dependent on long-term PN/IV support, adding to the burden imposed by the underlying disorder.

Introduction

Intestinal failure associated with short bowel syndrome (SBS–IF) is a rare, chronic, and debilitating condition associated with either functional or anatomic loss of portions of the intestine, resulting in substantial morbidity and mortality^{1,2}. A variety of overlapping definitions of SBS–IF have been promulgated over the years that focus on different aspects of the condition; however, in 2006 an international expert group published a consensus definition, which

states that “SBS-IF 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”³. This definition considers SBS as a subcategory of – and one of the major recognized causes of – the more broadly defined condition of intestinal failure. Importantly, it acknowledges that outcomes in SBS-IF are dependent on complex, interrelated prognostic factors regarding intestinal absorptive capacity, including the quality, function, and length of remnant bowel^{1,4}.

Although the symptom complex varies among patients, SBS-IF is characterized by diarrhea, steatorrhea, abdominal pain, electrolyte disturbances, dehydration, and malnutrition⁵. Management is complex, requiring an individualized and comprehensive approach⁴. The goal of therapy broadly focuses on symptomatic management along with intestinal rehabilitation to promote absorption of fluid and nutrients⁶. Numerous factors such as oral food intake, remnant bowel length and anatomy, age and comorbid conditions affect the remnant bowel's ability to adapt following surgical resection^{2,4}. Patients who cannot meet their nutritional or fluid needs through oral intake require long-term parenteral support: that is, parenteral nutrition and/or intravenous fluid (PN/IV)². However, PN/IV has limitations: in addition to its cost, it is associated with numerous complications, some of which can themselves be life threatening.

In the past, there have been few options for the management of SBS-IF beyond nutritional support and treatments directed at symptoms and complications of malabsorption, with surgery and transplantation reserved as treatments of last resort. Recently, however, new targeted therapeutic strategies have been suggested to reduce reliance on PN/IV by enhancing intestinal function⁷. The objective of this review is to summarize the available literature on the burden of SBS-IF in adult patients, with a focus on its clinical and humanistic burden, to provide a context for assessment of current management and emerging treatment approaches.

Methods

To characterize the current management patterns, guidelines, and health outcomes among patients with SBS-IF, a literature search was performed using the National Library of Medicine PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>). The search terms were ‘short bowel syndrome’ [Title] NOT pediatric [All Fields] NOT infantile [All Fields] NOT infant [All Fields] NOT children [All fields] NOT ‘case reports’ [Publication Type]. The inclusive dates were January 1, 1965, to January 18, 2013. The English-language filter was applied.

The literature search yielded 382 citations. The citations were assessed for their relevance to the topic and excluded articles focused on single case studies of a particular side effect related to PN/IV, studies focused on colon fermentation or on absorption of medications in patients with PN/IV, studies that included pediatric patients, surgical technique papers, articles about mesenteric artery complications/surgery, and articles focused solely on transplantation. Additional hand searches were performed using the terms ‘short bowel syndrome’ AND ‘cost’, and ‘home parenteral nutrition’ AND ‘cost’, along with the exclusion criteria described above. Key medical textbook chapters also were included in the reviewed material. Although a comprehensive literature search was conducted, the review was not intended to be exhaustive or to provide an economic analysis of SBS-IF management.

The results of this review focus on articles published within the last 10 years. However, older articles were considered for inclusion if highly regarded or frequently referenced in the existing literature. Finally, the abstracts were reduced to 155 articles that underwent a more thorough review and assessment for relevance and/or redundancy, yielding a total of 67 citations for this article.

Resultant articles were categorized and assessed based on topic. Topic areas in this review included SBS-IF epidemiology and clinical burden, disease management (including PN/IV) and complications, new and emerging therapies, and SBS-IF and PN/IV-related quality of life (QoL) because these topics most accurately reflected the overall description of SBS-IF and its ramifications.

Since the time of the initial literature review, a novel therapy (teduglutide) has been approved in the United States for the treatment of adult patients with SBS who are dependent on parenteral support; the primary report on the results of the pivotal trial of this agent, published in December 2012, were also included.

Results

Adult patients with SBS-IF are highly heterogeneous, presenting with a wide range of underlying pathology, anatomy, residual intestinal function, and psychosocial characteristics. In adults, SBS-IF usually occurs following extensive surgical resection of the small intestine, sometimes including parts or all of the colon^{4,6,8}. The most common underlying causes of SBS-IF are complications of Crohn's disease that require multiple resections or infarction due to occlusion of the mesenteric vessels; other etiologies include malignancy, trauma, volvulus, complications of bariatric surgery, and recurrent intestinal obstruction or pseudo-obstruction⁴.

Epidemiology

The exact incidence of SBS-IF is unknown; surveys of clinicians have produced a range of estimates^{3,4}. Home PN/IV, for which SBS is a frequent indication, often serves as a surrogate marker for epidemiologic measurements. The most recent prevalence estimate in the United States is from 1992, based on extrapolated data from the Oley Foundation Home Parenteral and Enteral Nutrition Registry. At that time, it was estimated that about 40,000 US patients per year required home PN/IV support. Approximately 35% of the patients in the Oley registry had a diagnosis of SBS, yielding an estimate of 10,000 to 15,000 patients with SBS-IF⁹. It should be noted, however, that the number of patients may be substantially greater than this estimate because some patients dependent on PN/IV support because of malignancy or radiation enteritis may meet the criteria for a diagnosis of SBS-IF¹⁰. In addition, these estimated patient numbers do not reflect individuals with SBS-IF who had never required home parenteral support or for whom home parenteral support could be successfully discontinued.

European data suggest a projected incidence of two individuals per million per year in the United States¹⁰. A multicenter survey conducted in 1997 indicated that the incidence in Europe was approximately three individuals per million population per year with prevalence of approximately four per million, representing a modest increase from data collected in 1993¹¹. Another multicenter assessment outlined the demographic features of the SBS-IF population in Western Europe. In 41 centers from nine countries that enrolled 688 adults (>18 years of age), the average age of patients with SBS was 52.9 years; more patients were female (57%) than male (43%)¹².

Mortality estimates for the SBS-IF population are high. According to Schalamon *et al.*, overall SBS-IF-related mortality in adults ranges from 15% to 47% depending on patient age, underlying disease, and duration of PN/IV¹³. A recent US study by Boland *et al.* in 2010 estimated 1 and 5 year mortality rates to be 17% and 32%, respectively¹⁴. An earlier study by Messing *et al.* in a French population reported 2 and 5 year mortality estimates of 14% and 25%, respectively¹⁵. In multivariate analysis, survival was related negatively to end enterostomy, small bowel length <50 cm, and arterial infarction as a cause of SBS, but not to parenteral support dependence. The latter was related negatively to post-duodenal small bowel lengths <50 and 50–99 cm and to absence of terminal ileum and/or colon in continuity. Cutoff values of small bowel lengths separating transient and permanent intestinal failure were 100, 65, and 30 cm in end enterostomy, jejunocolic, and jejunoleocolic type of anastomosis, respectively. A review of 210 postoperative cases of SBS in the United States evaluated over 20 years revealed that 25% were caused by a postoperative complication: 67%

of those patients required long-term parenteral support (all patients with remnants <60 cm required parenteral support), and 13% of patients died⁸.

Impact of malabsorption

One of the major consequences of SBS-IF is malabsorption leading to dehydration and malnutrition. The severity of malabsorption and which deficiencies are present depend primarily on the remnant bowel length and anatomy, among other factors¹⁶. Underlying conditions, such as active Crohn's disease, may also impede the intact bowel from adapting^{16,17}. The presence of colon in continuity affects outcome because following resection the colon becomes an important digestive organ⁴.

Patients considered to be at the highest nutritional risk typically have one of the following: an end jejunostomy with <115 cm of small intestine remaining; a jejunocolic or ileocolic anastomosis with <60 cm of small intestine remaining; or a duodenostomy or a jejunoleal anastomosis with <35 cm of small intestine remaining¹⁸.

Resection of the first part of the small intestine (duodenum) by itself is rare and does not lead to SBS-IF, but it may cause dumping syndrome, poor tolerance of certain sugars, and malabsorption of calcium, iron, and folic acid¹⁶. Malabsorption due to resection of the jejunum is often transient because the last section of the small intestine (i.e., the ileum) can adapt rapidly to take over the jejunum's functions, including fat absorption¹⁹. However, survival may be limited if only a few centimeters of the jejunum are present¹⁷. The ileum is not able to compensate for the lack of enterohormones normally produced by the jejunum that aid in the regulation of gastric secretion¹⁶. Consequent increased acidity may cause damage to the mucosa, decreased transit, and inactivation of pancreatic enzymes, leading to poor absorption of lipids and proteins and potentially, steatorrhea¹⁶. Patients with jejunum resection may also experience transient electrolyte and fluid imbalance, as well as chronically low absorption of nutrients and excess sodium loss¹⁶.

The effects of malnutrition from SBS-IF range from weight loss to distinct clinical syndromes related to various micronutrient and macronutrient deficiencies (calcium; magnesium; potassium; selenium; zinc; iron; vitamin B₁₂; vitamins A, D, and K; carbohydrates; lactose; protein; and fat among others)^{16,17,19–22}. Malnutrition impairs the function of all body systems, leading to diminished overall health and QoL. Patients with malnutrition may be more susceptible to disease and have a greater propensity to experience complications from surgery or illness. Loss of muscle mass is associated with weakness and fatigue, and loss of body fat produces a feeling of coldness; gaunt appearance; dry, wrinkled skin; and dull hair, leading patients to appear to age prematurely.

Moreover, malnutrition may cause mood changes, such as apathy, depression, and irritability, which may in turn affect patients' willingness to adhere to treatment².

In addition to essential nutrients, medications may be malabsorbed, complicating comorbid conditions^{2,10}. Reduced fluid absorption in the distal regions of the bowel may induce severe dehydration and diarrhea^{10,16,21}. This, combined with sodium deficiency, may lead to hypotension and acute renal failure^{6,23}. Malabsorbed bile salts may enter the colon and stimulate water and fat secretion, causing diarrhea. Moreover, bile salt deficiency may lead to fat malabsorption, resulting in steatorrhea¹⁹. Gallbladder stasis often leads to gallstones, especially in male patients. Hypocalcemia is common and may cause bone demineralization and altered mental status²³. Other possible complications include metabolic acidosis, hyperammonemia, hypomagnesemia, reduced carbohydrate fermentation, and renal stones^{6,16,19,21,24}.

Impact of PN/IV

All patients with SBS initially need intravenous fluids and electrolytes, with the goal of gradually discontinuing parenteral support once the patient is taking oral nutrition². PN/IV support is usually given at night for an average of 5 (range, 3–7) days per week^{4,13,25}. Overnight infusions can improve nitrogen balance and result in decreased satiety, thereby leading to increased food intake during daylight hours; however, they can also be disruptive to sleep patterns because of frequent bathroom visits or discomfort from the procedure.

Many patients, especially those with very short intestinal remnants, require life-long parenteral support². A longer duration of PN/IV support is associated with an increased probability of continued dependency. One assessment found that patients have a 95% probability of irreversible intestinal failure after 2 years of PN/IV dependency¹⁵. Patients who are dependent on PN/IV are at risk for severe, chronic complications and death.

Complications account for an estimated 15% to 20% of all deaths among patients on long-term PN²⁶.

The most common complication of this invasive therapy is catheter-related infection²⁷, a cause of up to 70% of PN-related deaths⁶. Septicemia, in particular, is of major concern and has been associated with approximately 70% of hospitalizations among patients receiving PN. On average, these patients experienced an infection once per 31 months²⁸. The evidence suggests PN/IV patients require one to two hospital readmissions per year²⁶, with 0.34 catheter sepsis events per catheter-year and 0.07 catheter occlusions per catheter-year²⁹. Venous thromboses and catheter occlusions often occur and prevent adequate PN/IV support^{1,6}. Fracture or breakage, pinch-off syndrome, placement complication, and various other complications may also result from the central venous catheter (Table 1). Preliminary results suggest that including ethanol locks as part of the PN/IV protocol may substantially reduce bloodstream infections; however, because some patients have developed thromboses, caution should be taken³⁰.

Abnormal biochemical liver function and associated liver complications are common and may be a factor in PN-related mortality^{6,31,32}. An estimated 15% of patients dependent on PN/IV have end-stage liver disease (ESLD), for which the prognosis is poor. As Chan *et al.* found among 42 patients with PN/IV (mean follow-up, 6.7 years), six had ESLD, with a 100% mortality rate³². In general, the longer the duration of PN/IV dependence, the greater the increase in risk of developing ESLD. Buchman *et al.* reported that the majority of patients relying on PN/IV for more than 5 years will develop significant liver disease (severe fibrosis, cirrhosis, bilirubin >3.5 mg/dL for >1 month, ascites, portal hypertension or liver failure with factor V <50%)⁴. Promising new data suggest that intestinal-failure-related liver disease may be treated with lipid therapy modulation³³. However, the findings are investigational and future research is required. In addition, vitamin and mineral deficiencies are common in PN/IV

Table 1. Short bowel syndrome complications.

Central Venous Catheter Related	Parenteral Support Related ⁶⁷	Bowel Anatomy Related ⁶⁷	Other Considerations ^{2,4,6}
Infection Occlusion Breakage Central vein thrombosis	Hepatic Biliary	Malabsorptive diarrhea Malnutrition and dehydration Fluid and electrolyte disturbances Micronutrient deficiency Essential fatty acid deficiency Small bowel bacterial overgrowth D-lactic acidosis Oxalate nephropathy Renal dysfunction Metabolic bone disease Acid peptic disease Anastomotic ulceration/stricture	Susceptibility to disease Appearance of premature aging Apathy, depression, irritability, confusion High costs involved in care Impaired quality of life Increased risk of mortality

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