available at www.sciencedirect.com

The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland

www.thesurgeon.net

Short bowel syndrome

*Claire L. Donohoe, John V. Reynolds**

Department of Surgery, Trinity Centre for Health Sciences, Trinity College Dublin, St James' Hospital, Dublin 8, Ireland

ARTICLE INFO

Article history:
Received 17 February 2010
Accepted 13 June 2010

Keywords:
Short bowel syndrome
Intestinal adaptation
Intestinal failure
Intestinal transplant
Parenteral nutrition
Intestinal lengthening

ABSTRACT

The short bowel syndrome (SBS) is a state of malabsorption following intestinal resection where there is less than 200 cm of intestinal length. The management of short bowel syndrome can be challenging and is best managed by a specialised multidisciplinary team. A good understanding of the pathophysiological consequences of resection of different portions of the small intestine is necessary to anticipate and prevent, where possible, consequences of SBS. Nutrient absorption and fluid and electrolyte management in the initial stages are critical to stabilisation of the patient and to facilitate the process of adaptation. Pharmacological adjuncts to promote adaptation are in the early stages of development. Primary restoration of bowel continuity, if possible, is the principle mode of surgical treatment. Surgical procedures to increase the surface area of the small intestine or improve its function may be of benefit in experienced hands, particularly in the paediatric population. Intestinal transplant is indicated at present for patients who have failed to tolerate long-term parenteral nutrition but with increasing experience, there may be a potentially expanded role for its use in the future.

Introduction

The short bowel syndrome is a malabsorptive state usually following massive resection of the small intestine.[1] It generally occurs when there is less than 200 cm of bowel in situ.[2] Intestinal failure may be defined as a condition where faecal energy loss occurs and the patient is unable to increase oral intake or absorptive capacity sufficiently to maintain their nutritional status by the enteral route alone. These patients may become dependent on parenteral nutrition support to maintain their energy balance. Malabsorption of macronutrients and micronutrients may predominate as a clinical manifestation, whereas other patients may struggle to maintain fluid and electrolytes homeostasis.

Newer definitions of the syndrome have been proposed in order to better define and diagnose patients according to their likely requirement for surgical intervention and to evaluate new therapies.[1] These definitions are included in Table 1.

Epidemiology

The exact population prevalence of the syndrome is unknown. However, this may be estimated from numbers of patients on home total parenteral nutrition—of whom approximately one quarter to one-third have short bowel syndrome. Thus the estimated population prevalence is approximately 1 per million.[3] SBS is more likely to occur in

* *Corresponding author*. Tel.: +353 872271250.
E-mail address: reynoljv@tcd.ie (J.V. Reynolds).

1479-666X/$ – see front matter

Table 1 – Proposed consensus definitions of Short bowel syndrome and intestinal failure.[1]

Short bowel syndrome-intestinal failure results from surgical resection, congenital defect or disease-associated loss of absorption and is characterised by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balances when on a conventionally accepted, normal diet.
Intestinal failure results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterised by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance.

women (2:1), most likely due to the shorter length of the small intestine in women.[4]

Short bowel syndrome (SBS) results from resection of unviable intestine secondary to vascular insufficiency, Crohn's disease, malignancy or radiation in adults.[3] In the paediatric population congenital intestinal anomalies such as gastroschisis or atresia, or necrotising enterocolitis lead to insufficient intestinal length to maintain nutrition.[5]

Pathophysiology

Consequences of the SBS arise from an inability to absorb adequate macro- and/or micronutrients. There may be an inability to maintain nutritional intake and this may include vitamin and mineral deficiencies or could result in fluid and electrolyte imbalances. Additionally, loss of gastrointestinal hormonal production may alter bowel motility, transit and gastroduodenal emptying. The degree of functional impairment is dependent on a number of factors: length of intestine, segments of intact bowel, the absorptive quality of the remnant bowel, and inter-individual variability in efficiency of absorptive capacity and adaptation. Patients at greatest risk for developing malabsorption are summarised in Table 2.

Normal intestinal physiology

The normal small bowel length is estimated to be approximately 600 cm. Macronutrients such as carbohydrate, nitrogen and fat are predominantly absorbed within the first 100–150 cm of jejunum. The gastrointestinal tract processes 8–9 L of fluid per day. The majority of water ingested is reabsorbed and over 80% of this absorption occurs in the small bowel with only 100–200 ml of fluid egested in faecal material daily.

Table 2 – Patients at highest risk of developing short bowel syndrome.[28]

Anastomosis	PLUS length of residual small intestine
Duodenostomy or jejunoileal	<35 cm
Jejunocolic or ileocolic	<60 cm

Colon in continuity

The concept of colon in continuity is important to understanding the adaptation process which occurs in short bowel syndrome. The colon becomes an important digestive organ after loss of a critical mass of small bowel. It can help compensate for the lack of small bowel by reabsorbing water, electrolytes and short-chain fatty acids. By hormonal mechanisms, it can slow intestinal transit and stimulate intestinal adaptation. Up to 65% of carbohydrate intake may be lost in the faeces if not degraded by colonic bacteria.[6] The flora of the colon ferment malabsorbed carbohydrates to short-chain fatty acids, which when absorbed, can provide up to 500 kcal/day.[7] Medium chain fatty acids are water soluble and thus can be absorbed in the colon and these may be used as dietary supplements in cases of long-chain fatty acid malabsorption, which is not usually the case in SBS as these patients have intact pancreatic function. Accordingly, patients who have a jejunostomy and therefore, no colon in continuity, do not have the ability to reabsorb large amounts of gastrointestinal secretions. If they lose a critical mass of jejunum (with <100 cm remaining) they may have a net secretory response to food.

Loss of the ileocaecal valve

If the ileocaecal valve is resected, small bowel bacteria may overgrow due to small intestine dilation and slower motility.[8] Bacterial overgrowth has several negative consequences including competition for nutrients, inflammation, gastrointestinal bleeding, bacterial translocation and endotoxaemia, liver injury and D-lactic acidosis.[9]

Jejeunal resection

Most of the food absorbed daily is absorbed by the long villi of the jejunum, where most of the digestive enzymes are concentrated.[10] Following resection there is an initial and temporary reduction in nutrient absorption, until the remaining small intestine can adapt. In addition, hypertonic solutions, such as that provided by naso-enteral feeding, can exacerbate fluid losses by stimulating fluid secretion by the jejunum.[11] Loss of jejunum also means loss of gastrointestinal feedback hormones, which can lead to rapid gastric emptying of liquids, which may then overwhelm the absorptive capacity of the remaining small bowel.

Ileal resection

Under normal physiological conditions most of the 8–9 L of secretions which are secreted by the small intestine are reabsorbed by the ileum. Absorption of vitamin B12 and bile salts occur at the ileum. Bile acids and fats are absorbed and pass directly to the liver via the enterohepatic circulation. If there is less than 100 cm of ileum left in situ the ability to reabsorb secretions is exceeded and there is a net secretory response to food. The loss of enterohepatic circulation will lead to bile salt deficiency and fat malabsorption.[12] Feedback mechanisms usually detect malabsorption, termed the ileal-

ileum usually causes a delay in gastric emptying and intestinal transit times in order to increase gut absorptive capacity.[13] However, ileal resection may lead to loss of these hormonal feedback checks including peptide YY, glucagon-like peptide-I and neurotensin.[14]

Consequences

Increased secretions, reduced absorption of nutrients and fluid and loss of hormonal feedback mechanisms all combine to create diarrhoea with a high osmotic load.[15] Simple carbohydrates which are digested to sugars contribute to the osmotic load and favour small bacterial overgrowth. Products of this overgrowth again contribute to osmotic diarrhoea. Therefore, these patients should have higher protein and fat content in their diet instead of simple carbohydrates.

Adaptation

Following resection of large amounts of small intestine, the gastrointestinal tract undergoes a process of adaption whereby the ileum can increase slightly in length and diameter and adapts functionally to absorb macronutrients. This evolves over a one to two year period. Experimental models show epithelial hyperplasia 24–48 h after resection.[16–18] The length of villi and thus the absorptive area increases. Animal models show that this process is stimulated by enteral nutrition by providing energy for enterocyte reproduction and stimulate the release of trophic factors.[19] Fat-stimulated glucagon-like peptide-II can lead to hyperplasia.[20,21] A number of other growth and trophic factors have been implicated in the process in animal models including enteroglucagon, epidermal growth factor, glutamine, growth hormone, cholecystokinin, gastrin, neurotensin, leptin and insulin-like growth factor.[14,22,23] Few studies have been carried out in humans. Trophic hormone release is stimulated more effectively by fat than either protein or carbohydrate in animal models.[24] In patients with a jejunostomy, limited adaptation occurs and they are less likely to require less nutritional support with time.[25]

The process of adaptation is gradual and can take place over up to two years.[26] Thus those who require parenteral nutrition support may achieve independence as the adaptation process compensates. However, studies have shown that of those who require this support in the home setting only 20% become parenteral nutrition independent in the long-term.[27]

Prognosis

The likelihood of being able to resume a normal oral diet after resection of large amounts of the small bowel can be predicted by certain parameters. Factors favouring the ability to resume oral nutrition include adequate length of the remaining bowel; the presence of colon and intact ileocaecal valve, and co-morbidities. The prognosis may be good where there is an intact duodenum, a jejunal length of greater than 200 cm, and an intact colon. The likelihood of requiring long-term parenteral nutrition increases significantly if there is less than 60 cm of remaining jejunum even if there is colon in continuity.[28] If the colon is not present, the bowel can only adapt if there is at least 100 cm of small intestine remaining. The adaptation process means that up to 70% of those with SBS initially requiring total parenteral nutrition can be successfully weaned off and converted to complete enteral nutrition. However, after two years of parenteral nutrition the probability of intestinal failure is 94%.[28] Intestinal conditions that run counter to successful adaptation include Crohn's disease, radiation enteritis, carcinoma or pseudo-obstruction. These patients do not seem to mount an adequate adaptation response to loss of intestinal function.

Citrulline is a non-protein amino acid produced by intestinal mucosa. Thus plasma levels indicate whether there is functioning mucosa present. Crenn *et al.* used plasma citrulline levels to predict whether patients with short bowel syndrome after two years would go on to develop permanent intestinal failure. In a study of 57 patients, a plasma citrulline level of <20 μmol/L had a positive predictive of 95% and a level greater than this, an 86% negative predictive value for permanent intestinal failure.[29] These results were recently replicated in over 500 patients with intestinal failure conditions.[30]

The reason it is critical to try to wean patients back onto enteral nutrition is due to the high complication rate associated with long-term parenteral nutrition use. In a series of 68 patients with intestinal insufficiency 32.4% died – half due to the consequences of intestinal failure or home parenteral nutrition. Those with lower survival tended to be those on total parenteral nutrition, those with less than 50 cm of intact bowel, those with an end enterostomy or those in whom the aetiology of short bowel syndrome was radiation enteritis or ischaemia. In this series of patients the survival rate was 88% at 3 years and 78% at five years.[27] However, it must be noted that the majority of these patients died from their underlying condition rather than to directly due to complications of parenteral nutrition.

Complications of short bowel syndrome

A: Early

Early complications include dehydration and electrolyte derangements. Intra-venous fluid supplementation (to either enteral or parenteral nutrition) may be required to maintain the patient's hydration status. In particular, magnesium, calcium and potassium may be difficult to control in patients with SBS.

Electrolytes are secreted in high concentrations by the jejunum and ileum and if there is inadequate intestinal length, there may be net electrolyte losses. Knowledge of electrolyte physiology is important to effectively supplement electrolytes. Total body electrolyte levels of magnesium and potassium may be reduced even if serum levels are maintained. Thus, excess electrolyte losses may be diagnosed by reduced urinary electrolyte levels. Oral electrolyte replacement can be problematic as it can cause osmotic diarrhoea necessitating intra-venous supplementation. Replacement

removes the stimulus for active electrolyte uptake in the loop of Henle thus increasing urinary excretion and further depleting body stores. Cellular uptake is slow and therefore repletion requires sustained correction. Electrolyte correction is of particular importance to prevent potentially life-threatening arrhythmias developing.

Hypomagnesaemia is a particular problem with jejunostomies. It is compounded by the hyperaldosteronism which occurs secondary to dehydration. Magnesium salts may worsen diarrhoea and thus parenteral supplementation may be required. Vitamin D supplementation may increase intestinal absorption of magnesium. Hypercalcaemia secondary to hyperparathyroidism in response to low serum magnesium levels should be anticipated and corrected.

Loss of negative feedback to gastric secretions in SBS leads to transient hypergastrinaemia and thus gastric hypersecretion for up to 6 months following resection.[31] The consequence of this may be peptic ulceration and oesophagitis and therefore prophylactic gastric protection is important. Proton pump inhibitors have been shown to improve water absorption.[32]

B: Late

Chronic complications from SBS include TPN- related complications, bacterial overgrowth, micronutrient deficiency and metabolic complications. Parenteral nutrition bypasses first pass liver metabolism and longterm TPN can lead to steatosis, cholestasis and cirrhosis. Recurrent episodes of sepsis from line infections, bacterial overgrowth and biliary stasis all contribute to the development of liver disease.[33] Fifteen percent of patients on TPN for greater than one year develop end-stage cirrhosis which carries with it a 100% two-year mortality rate.[34] More than 50% of those on TPN for more than 5 years develop complicating liver disease. This may be minimised but not eradicated by reducing excess dextrose and lipid feeding. Moreover patients with SBS seem to develop cholestatic liver disease at a greater rate versus other long-term TPN patients. This is postulated to be due to recurrent sepsis from bacterial overgrowth or lack of supplementary enteral nutrition in SBS patients. In one study, liver biopsies demonstrated chronic cholestasis in 65% after 6 months of TPN in patients with a bowel remnant of less than 50 cm.[35] Gallstones and related problems are also more common due to the interrupted enterohepatic circulation, which alters bile composition.[12]

The other major complication of parenteral nutrition is catheter related. Sepsis accounted for one-third of the deaths in a series of SBS patients with a 50% 5-year mortality rate.[28] On average SBS patients on TPN had one hospitalisation per year for infection. Occlusion of the delivery catheter by thrombosis is not an uncommon problem with an incidence of 0.2 episodes per 1000 catheter days. If catheter thrombosis is not due to malpositioning then it is a risk factor for developing superior vena cava thrombosis and mandates warfarin prophylaxis.

Bacterial overgrowth can lead to carbohydrate malabsorption and episodes of sepsis from bacterial translocation. It should be suspected in SBS patients with blind loops or no ileocaecal valve and pyrexia of unknown origin or refractory diarrhoea or weight loss.[36] Bacteria can interfere with chylo-

An inflammatory response may lead to loss of intestinal architecture and further loss of absorptive capacity or may even present as a colitis or ileitis.[37] Prevention is by regular bowel washout using a gastrotomy tube or treatment with short courses of broad spectrum antibiotics. Some patients will require courses of antibiotic every month. The role of probiotics in this setting is unproven. A low carbohydrate diet decreases the nutrient source for intestinal flora.

The greatest risk of developing a micronutrient deficiency is after the transition to enteral feeding. The degree of malabsorption is not easily predictable. In patients with a short length of small intestine serum levels of magnesium, calcium, zinc, selenium and fat soluble vitamins should be measured every 3 months.[38] If there are any concerns about large amounts of enteral losses, urinary excretion of the water soluble electrolytes may give a better indication of total body stores. Since water soluble vitamins are absorbed in the proximal jejunum they are rarely deficient. If there is greater than 60 cm of terminal ileum resected it must be anticipated that B12 supplementation will be required.[39] Resection of the proximal jejunum may lead to folate deficiency. Patients should undergo yearly bone density monitoring.

Lactobacillus, Clostridium perfringens, Streptococcus bovis and other gram positive colonic bacteria ferment non-absorbed carbohydrate to D-lactic acid.[40] This creates an acidic environment, rich in short-chain fatty acids, which supports the proliferation of the intestinal flora. If significant amounts of lactic acid are absorbed, a metabolic acidosis may develop which presents with encephalopathy, headache, ataxia and dysarthria.[41] Broad-spectrum antibiotics against intestinal flora treat the bacterial overgrowth.[40]

Oxalates normally bind to calcium. If fat is malabsorbed, calcium binds to free fatty acids, thus oxalate passes into the colon and is absorbed. This colonic absorption is enhanced by bile acid malabsorption. Higher serum levels and thus increased renal excretion increases the risk of developing nephrolithiasis. Other consequences of the SBS such as metabolic acidosis and a low urinary pH conditions favour nephrolithiasis.[42]

Loss of a large amount of intestine may reduce serum citrulline concentrations to the extent that ammonia cannot be detoxified adequately via the urea cycle. If this is accompanied by renal impairment, the excess ammonia may not be excreted. Arginine administration corrects ammonia levels.[43]

Management strategy

The goal of management of patients with short bowel syndrome is to allow them resume a normal lifestyle. To that end the provision of adequate macro- and micronutrients and sufficient fluid to prevent dehydration are basic pre-requisites. It is important to correct and prevent acid-base disturbances. Steps in the management of SBS are summarised in Fig. 1.

Early goals

Where it is anticipated that a patients is susceptible to short

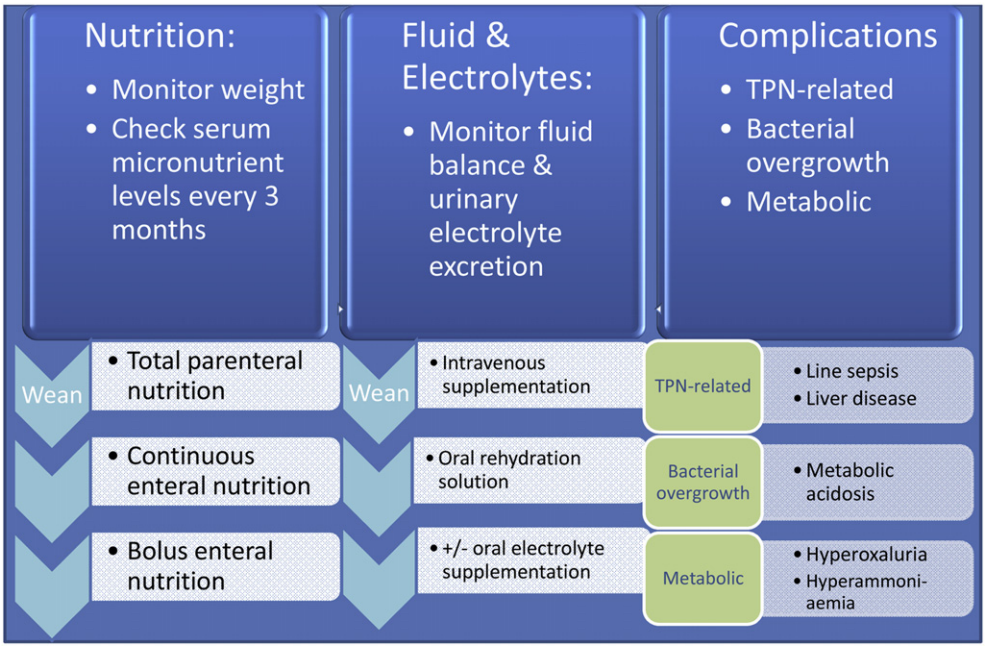
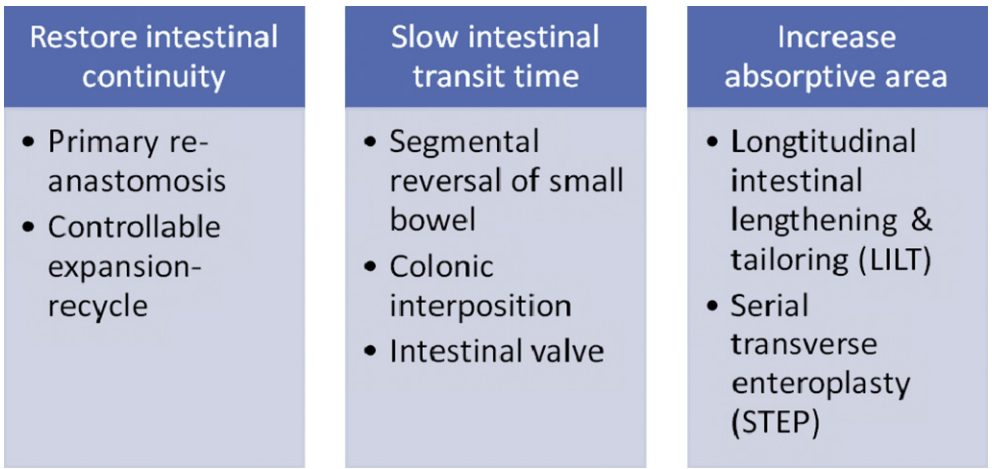


Fig. 1 – Early management of short bowel syndrome.

recommended to begin total parenteral nutrition within the first 24 h (Fig. 2). TPN will usually be required for the first 7–10 days.[44] A plan to measure and replace fluid losses and electrolytes every 2 h should be instituted, thus almost mandating high-dependency level care. Blood glucose levels should be monitored every 4 h and an insulin-sliding scale should be commenced if glucose levels are persistently elevated. Initial TPN requirements should be 25–35 kcal/kg/day, of which 1–1/5 g/kg/day should be provided as protein. Protein absorption is the nutrient which is least affected by reduction in gastrointestinal function, thus there is no requirement for peptide based regimes. If less than 75 cm of jejunum remains the patient is likely to require longterm parenteral nutrition and saline supports. Supplemental fluid will be required parenterally if less than 100 cm of jejunum remains and oral rehydration solution will be necessary if less than 200 cm remains.[25]

Once the patient is stable, enteral nutrition should be slowly introduced – initially at a low rate continuously. The initial rate should be 5% of the patient's daily caloric intake. Enteral feeding rates can then be incrementally advanced every 3–7 days. The diet should be of high protein and fat content (providing 40% of daily caloric intake) to try to minimise osmotic diarrhoeal complications.[45] If the underlying disease process involves inflammation of the intestine leading to reduced enzymmatic secretions, an elemental diet may be considered. If the colon is intact, fibre supplementation can be considered to slow intestinal transit. Parenteral nutrition should be concomitantly weaned as enteral nutrition is advanced. Continuous enteral nutrition via tube stimulates the adaptation process more than isocaloric amounts of nutrition delivered orally.[46] Successfully weaning is indicated by the amount of enteral fluid loss. Enteral fluid loss reflects



DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.