

• REVIEW •

The management of patients with the short bowel syndrome

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Abstract

The surgeon is invariably the primary specialist involved in managing patients with short bowel syndrome. Because of this they will play an important role in co-ordinating the management of these patients. The principal aims at the initial surgery are to preserve life, then to preserve gut length, and maintain its continuity. In the immediate postoperative period, there needs to be a balance between keeping the patient alive through the use of TPN and antisecretory agents and promoting gut adaptation with the use of oral nutrition. If the gut fails to adapt during this period, then the patient may require therapy with more specific agents to promote gut adaptation such as growth factors and glutamine. If following this, the patient still has a short gut syndrome, then the principal options remain either long term TPN, or intestinal transplantation which remains a difficult and challenging procedure with a high mortality and morbidity due to rejection.

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INTRODUCTIONS

A remarkable feature of the gastrointestinal tract is how little of it we require in order to maintain a normal nutritional state. Nonetheless, there is a small group of patients who, following extensive loss of principally the small intestine, are unable to maintain their nutrition by oral intake alone. These patients are defined as having the short bowel syndrome.

The pathophysiological consequences of loss of the bowel is dependent upon two important points. Firstly, the extent and site of the intestinal resection, and secondly, the adaptability of the remaining intestine. In general, we need 50 to 70 cm (i.e. around 1 cm/kg weight) of healthy jejunum or ileum in continuity with a section of the colon in order to avoid developing the short bowel syndrome. This is remarkable considering that the normal human small intestine ranges from about 3 to 5 metres in length. Some have defined short bowel syndrome as the loss of 70% or more of the length of the small intestine^[1]. But length is not everything, and if the remaining bowel is involved with the underlying disease process (e.g. Crohn's disease or ischaemia) then its capacity to adapt will be limited. The minimum amount of small intestinal absorptive area required to sustain life varies from individual

to individual. Survival on an oral diet alone may occur in patients with as little as 15 cm of residual jejunum.

This review addresses the medical and surgical management of patients with short bowel syndrome. Particular emphasis is placed on the conduct of the initial surgical procedure and the therapies that may either constitute definitive methods of treatment or serve as useful adjuncts to other forms of surgery. The latter consisting of autologous gastrointestinal reconstruction and small bowel transplantation.

INITIAL SURGICAL PROCEDURE

The causes of short bowel syndrome differ between adults and children. In adults, it most often results after surgery for Crohn's disease or mesenteric infarction. Whilst in infants, the causes more commonly include necrotizing enterocolitis, gastroschisis, atresia, and volvulus^[2-4].

It goes without saying that it is important to preserve as much of the small and large intestine as possible at the initial surgery. However, the subsequent patient progress will depend on not only the length of gut removed, but on whether the patient has a primary anastomosis or a stoma. Nightingale^[5] has classified patients with short bowel syndrome into two groups: those with a primary jejunocolic anastomosis, and those with a jejunostomy. The latter have major problems with losses of water, sodium, and divalent cations such as magnesium; whereas, patients with a jejunocolic anastomosis rarely have problems with their fluid and electrolyte balance. Maintaining colonic continuity serves to decrease gastric emptying and decreases energy/carbohydrate losses. Nonetheless, if a surgeon is concerned regarding the risk of performing a primary anastomosis for fear of an anastomotic dehiscence, then it is safer to consider a primary stoma with reconstruction delayed for 2-3 mo. Although this can create its own problems of leaving *in situ* a segment of excluded gut. Careful consideration should be given to the siting of stomas. It may be advantageous to have an end stoma in close proximity to a mucus fistula.

Preservation of colonic length is not only important for the absorption of fluid and electrolytes, as has been discussed, but it also has nutritional advantages. Patients with the short bowel syndrome have malabsorption of carbohydrates, even after the ingestion of small amounts of otherwise easily absorbed carbohydrates, and this causes a spill-over of the ingested carbohydrates into the residual colon where it undergoes bacterial fermentation^[6].

Jeppesen and Mortensen^[7] have noted that colonic digestion can salvage up to 3-4 MJ/d⁻¹ in patients with the short bowel syndrome, which is about 50% of the daily requirements. They observed that preservation of more than one-half of colonic function is unusual in patients who require parenteral nutrition and have more than 100 cm of residual small bowel. This data reinforces the concept of the colon as an energy-salvaging organ.

Excluded gut may act as a reservoir for bacterial translocation and recurrent sepsis^[8]. Defunctioned gut is

associated with mucosal atrophy and bacterial overgrowth that predispose to bacterial translocation. Reynolds *et al*^[8], reported a case where a patient with excluded bowel suffered episodes of clinical deterioration, fever and rigors without isolation of bacteria from blood cultures. It is possible that these episodes may have been the result of migration of viable bacteria from the excluded gut lumen into the mesenteric lymph system and peritoneum. In this situation pathogenic organisms cannot be cultured from the blood but may be isolated from the peripheral lymph nodes. Schafer *et al*^[9], reviewed the progress of newborns who had stomas created during surgery for a mechanical ileus or intrauterine perforation of the small bowel. To avoid non-use of the distal bowel, they used a roller pump to pass the effluent from the end enterostomy into the distal bowel through the mucus fistula. They reported that this enabled subsequent re-anastomosis to be performed under optimum bowel conditions. Al-Harbi *et al*^[10], described a similar experience in six neonates (gestational ages of 27-38 wk, birth mass of 533-3400g). Mass gain during refeeding ranged from 5 to 25g·kg⁻¹·d⁻¹ with the refeeding lasting for 16-169 d. It was concluded that this technique lessens the need for parenteral nutrition and electrolyte supplementation prior to reanastomosis.

NATURAL HISTORY OF GUT ADAPTATION

Intestinal failure associated with the short bowel syndrome

may be either transient or permanent. Most patients require nutritional support until their gut has undergone sufficient adaptation to allow survival on an oral diet. Results from animal studies have shown that structural adaptation of the remnant bowel involves both an increase in villous height and mucosal surface area, and an increase in bowel luminal circumference and wall thickness. Functional adaptation is characterised by an increase in rate of absorption of nutrients. This is postulated to be the result of structural change, a slowing of transit rate and/or alterations in intracellular molecular events such as increased transport and/or enzyme activity.

The intestinal mucosa produces several peptides that have a trophic effect upon the intestine (Table 1). Following small bowel resection the rate of secretion of these peptides increases in an attempt to compensate for the missing tissue. Recently, Nightingale^[17] has discussed the role of one of these peptides, glucagon-like peptide-2 (GLP-2), in intestinal adaptation. L cells, located in the ileum and jejunum, secrete GLP-2. Nightingale noted that, in patients without an ileum, intake of a meal does not alter plasma GLP-2 concentration and that remnant jejunum of these patients does not adapt^[18,19]. In contrast, intake of a meal induces an increase in plasma GLP-2 concentrations in ileal resected patients with a retained colon and remnant jejunum of these patients does adapt^[20,21]. Collectively, these pieces of information suggest GLP-2 may be useful in adjunctive therapy for short bowel syndrome.

Table 1 The effect of small bowel resection on intestinal peptides that are known regulate intestinal growth

Factor	Source	Effect of Small Bowel Resection on Factor
Epidermal Growth	Salivary glands and Brunner's glands in the jejunum	EGF levels are increased in saliva and diminished in urine 3 d after resection in mice ^[11] .
Factor (EGF)		
Enteroglucagon	L cells of ileum and colon	12 d after a 75% small bowel resection there was a significant increase in concentration of enteroglucagon in the plasma of rats ^[12] .
Glucagon-like Peptide 2 (GLP-2)	L cells of ileum and colon	There is an increase in expression of GLP-2 mRNA in the ileum of rats after small bowel resection ^[13] . There is a decrease in expression of dipeptidyl peptidase IV mRNA, the enzyme that inactivates GLP-2, in the ileum of rats after small bowel resection ^[14] .
Insulin-like Growth factor-I (IGF-1)	Cells of the small intestine	80% small bowel resection led to a 183% and 249% increase in IGF-1 mRNA in the jejunum and ileum respectively of rats ^[15] .
Peptide tyrosine tyrosine (PYY)	L cells of ileum	After 70% resection in rats the concentration of PYY in plasma was elevated for at least 2 wk and there was a four and six-fold increase in PYY mRNA in ileum and colon at six hours after resection ^[14] .
Neurotensin	Gut mucosal endocrine cells (N cells) in the jejunum and ileum	50% resection of the distal intestine in dogs was associated with a transient increase in neurotensin ^[16] .

INITIAL SUPPORTIVE MANAGEMENT

The aim of supportive care of patients is to maintain nutritional state and promote gut adaptation.

Parenteral nutrition

An important historical use of parenteral nutrition was in keeping patients with short bowel syndrome alive both in the short and long term. The decision to commence parenteral therapy is based on a number of issues. These include, the extensive loss of gut where the clinician believes the patient will be unable to maintain their own nutrition, or where in the post operative period, the patient is unable to maintain their weight and plasma albumin concentration via oral intake alone. Once parenteral nutrition is commenced, for most patient, there follows a period of gradual transition to enteral nutrition and diet therapy.

The use of parenteral nutrition is associated with a number of side effects. Parenteral nutrition has been found to cause intestinal atrophy in humans and animals^[22-24] and long-term parenteral nutrition is associated with complications that

include recurring central venous line sepsis, high costs (Aus \$ 150·d⁻¹), high mortality (20% in children, mainly due to liver dysfunction) and poor quality of life.

In children with short-bowel syndrome receiving long-term parenteral nutrition, hepatic dysfunction is a major problem. Its aetiology is multifactorial and includes alterations in gut motility which lead to intraluminal stasis which is thought to be a major etiologic factor for bacterial overgrowth and subsequent cholestasis, especially when the ileocecal valve is absent. Sondheimer *et al*^[25], reported that 67% of neonates with short bowel syndrome which were nourished by parenteral nutrition developed cholestasis. This progressed to liver failure in 17% of the neonates. As cholestasis developed shortly after the first infection in 90 % of infants^[25] it seems sepsis may sensitize the liver to cholestatic injury. In spite of the problems associated with parenteral nutrition, Suita *et al*^[26], have commented that advances in parenteral nutrition have meant that infants with a small bowel measuring only 20 cm either with or without an ileocecal valve can survive. However, patients do best in the presence of an ileocecal valve and an intact colon^[27].

Medical Therapy

High-volume output from a jejunostomy requires restriction of oral fluids, a high-energy iso-osmolar diet with added salt, and the use of drugs that reduce motility (loperamide, codeine phosphate) and secretions (proton pump inhibitors, octreotide). Nightingale^[5] has stressed that patients who have less than 100 cm of jejunum *in situ* and a stomal output in excess of their oral intake have the most to gain from the use of antisecretory drugs. This is because they usually lose more from the jejunostomy than they take in orally ('secretors') and are more likely to require long-term parenteral therapy. Yet Octreotide reduces nutrient transport in the small intestine, reduces the number of functional nutrient carriers, and is in general detrimental to gut adaptation. Hence its use in all patients with short bowel syndrome is not indicated.

Gastric hyperacidity is a frequently observed change which occurs transiently in the postoperative period following a massive bowel resection. Unless it is controlled with either proton pump inhibitors or H2 receptor blockers, it may result in extensive gastric or duodenal ulceration.

Enteral nutrition

Enteral nutrition is a key element in promoting the intestinal

hyperplasia which is characteristic of gut adaptation. It does this by several mechanisms. Enteral nutrition provides epithelial work and stimulates the release of pancreatico-biliary secretions that are known to maintain the structure and function of the intestine. Food within the intestine also stimulates the release of various regulatory peptides from the intestine and can deliver specific nutrients to the cells of the intestinal mucosa.

There are a number of specific gut nutrients that are important in adaptation (Table 2). These nutrients promote intestinal structure and function by providing cells of the intestinal mucosa with substrates for the synthesis of essential molecules or by providing energy. For example, polyamines, small molecules that are essential for cell growth and regulation of the cell cycle, are synthesised from ornithine. Whereas, fermentable fibres and their products (i.e. short chain fatty acids) are important fuels for enterocytes. Glutamine is another important gut nutrient that promotes intestinal adaptation. This amino acid is the main fuel of enterocytes and also is a substrate for the synthesis of nucleic acids^[34]. The information presented in Table 2 indicate that supplements of glutamine only promote adaptation in parenterally-fed animals. This suggests that supplements of glutamine can only enhance intestinal adaptation in the absence of epithelial work.

Table 2 Nutrients that regulate gut adaptation

Nutrient	Effect on Intestinal Adaptation
Soluble fibre and short chain fatty acids	SCFA-supplemented parenteral nutrition led to an increase in ileal uptake of D-glucose in rats with an 80% small bowel resection ^[28] .
Triglycerides	A 2% pectin-enriched elemental diet led to a significant increase in intestinal weight, mucosal protein content, and mucosal DNA content in rats with an 80% small bowel resection ^[29] . Rats fed with an elemental diet containing 60% long chain triglycerides after a 60% resection had a greater intestinal adaptation than rats fed a diet containing 17% long chain triglycerides ^[30] .
Ornithine α -ketoglutarate	Enteral supplements of ornithine 2g.kg ⁻¹ .d ⁻¹ significantly increased jejunal crypt depth ratio and significantly increased glutamine concentration in anterior tibialis muscle ^[31] . Enteral supplements of ornithine 1g.kg ⁻¹ .d ⁻¹ significantly increased ileal villus height and expression of ornithine decarboxylase mRNA in the ileum ^[32] .
Glutamine	In rats with an 85% small bowel resection, feeding a 2% glutamine-enriched TPN solution, enhanced intestinal adaptation as assessed by mucosal villus height, and mucosal DNA content ^[33] . A glutamine-enriched diet enhanced ileal hyperplasia in rats with an 80% small bowel resection ^[34] . In rats with a 70% small bowel resection, feeding a 5% glutamine-enriched rats chow diet inhibited intestinal adaptation as assessed by duodenal protein content and ileal DNA content ^[35] . A 2% glutamine-enriched elemental diet did not alter markers of intestinal adaptation in rats with a massive small bowel resection ^[36] . A 4% glutamine-enriched oral diet did not significantly alter intestinal adaptation after intestinal resection in rats ^[37] .

There are a number specific gut peptides which mediate the trophic effect of gut nutrients. Glucagon-like peptide-2, which is released by the intestinal L cells, plays a role in the trophic effect of short chain fatty acids (SCFA) on intestinal adaptation. Treatment of rats with SCFA leads to an increase in expression of proglucagon mRNA, a precursor of GLP-2, in the L-cells^[28,39]. Furthermore, Vanderhoof *et al*^[30] speculated that slower absorption of long chain triglycerides allows them to stimulate release of intestinal regulatory peptides, such as GLP-2 and PYY, from L-cells in the ileum. There also may be links between glutamine and PYY as a glutamine-enriched oral diet led to an increase in concentration of PYY in the portal blood after small bowel resection in a rat model^[40].

Epithelial work is important for gut adaptation. Clarke^[41] used a rat model to examine the effect of epithelial work on the structure of the intestine. Isotonic solutions of either glucose, galactose, sodium chloride, *D*-methyl *D*-glucoside, or *D*-mannose were infused into surgically prepared sacs of upper small intestine in rats which fed normally via the gut-in-continuity. Treatment with the glucose, a nutrient and galactose and α -methyl *D*-glucoside, molecules with no nutritional value, led to an increase in villus height. In

addition, treatment with sodium chloride, a molecule that is absorbed by the intestinal mucosa, also led to an increase in villus height.

Age may influence intestinal adaptation as pediatric patients undergo better bowel adaptation than adults. Wasa *et al*^[42] reviewed 12 pediatric and 18 adult patients with short bowel syndrome from Osaka University Hospital. The length of the residual small intestine ranged from 0 to 75 cm (mean 47 cm) in pediatric patients and from 0 to 150 cm (mean 47 cm) in adult patients. Eight pediatric patients (67%) and 4 adult patients (22%) were weaned from TPN. None of the adult patients with residual small intestinal length less than 40 cm could achieve complete intestinal adaptation.

A number of specific oral nutritional regimens have been evaluated to assess their ability to promote gut adaptation. The provision of oral medium-chain triglycerides increases the absorption of energy in patients with short bowel syndrome who have a functioning colon^[43]. Short-chain fatty acids are readily absorbed across the colonic mucosa, whereas long-chain fatty acids are not absorbed by the colon. Hence, patients with a short bowel syndrome and a functioning colon are able to absorb both short-chain and medium-chain C8-C10

triglycerides. Part of their efficacy in this role relates to the fact that both of these types of fat are water-soluble. Manipulation of the dietary fat intake has little appreciable advantage in patients without a functioning colon^[44]. Sales *et al*^[45] reported on four patients, aged 40 - 65 years, with on average 54.5 cm of remaining bowel, who were managed with a progressive step diet. It involved the administration of pectin (Step 1), the use of medium-chain triacylglycerols and complex, nonfermentable sugars (Step 2); coconut oil (47% medium - chain triacylglycerols) and simple sugars (Step 3); and finally long-chain triacylglycerols and lactose (Step 4). Total parenteral nutrition was interrupted at steps 3 or 4 when the energy content of the diet reached 150% of the patient's resting energy expenditure, if serum albumin and weight were stable, or if there were no alterations in frequency, amount and consistency of the stool.

IRREVERSIBLE SMALL BOWEL FAILURE

From studies of patients on long-term parenteral nutrition, it seems that there are between two and three patients per million of population per year who develop irreversible small bowel failure^[46]. Messing *et al*^[47] assessed prognostic factors in 124 consecutive adults with non-malignant short bowel syndrome. Survival and parenteral nutrition-dependence probabilities were 86% and 49% at 2 years, and 75% and 45% at 5 years. In multivariate analysis, survival was related negatively to end-enterostomy, to small bowel length of <50 cm, and to arterial infarction as a cause of short bowel syndrome, but not to parenteral nutrition dependence. The latter was related negatively to post-duodenal small bowel lengths of <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 jejunoileocolic type of anastomosis. In adult short bowel

syndrome patients, small bowel length of <100 cm is highly predictive of permanent intestinal failure. Presence of terminal ileum and/or colon in continuity enhances both weaning off parenteral nutrition and survival probabilities. After 2 years of parenteral nutrition, probability of permanent intestinal failure is 94%. These rates may lead to selection of other treatments, especially intestinal transplantation, instead of parenteral nutrition, for permanent intestinal failure caused by short bowel syndrome.

Gambarara *et al*^[48] have accumulated data that suggests that rather than depending on the length of intestine remaining or the presence of the ileocecal valve, the prognosis of patients with the extreme-short-bowel syndrome depends on recurrent sepsis and early onset liver impairment. In addition, their case review shows that the extreme-short-bowel syndrome is not necessarily an indication for bowel transplantation.

Patients with short bowel syndrome frequently develop other clinical problems which may require therapy. These include, hyperphagia, hyponatremia and hypochloremia, metabolic acidosis, including D-lactic acidosis, cholelithiasis and urolithiasis, gastro-esophageal reflux, dystrophy and symptoms caused by secondary dilatation of the lengthened bowel loops: a protruding abdomen, enteral stasis, leading to constipation or diarrhoea with bacterial overgrowth^[49].

ADAPTATION

The main long term aim of therapy of short bowel syndrome is to promote intestinal adaptation to allow transition to an oral diet. Such management has focused on the use of preferred gut nutrients such as glutamine, and the use of either specific (e.g. intestinal growth factor IGF-1) or general growth factors (e.g. growth hormone). These treatments have followed from the knowledge that both nutrient and growth factor related events drive intestinal adaptation.

Table 3 Molecules that regulate intestinal adaptation

Molecule	Effect on Intestinal Adaptation
Glucagon-Like Peptide 2	Treatment of rats with a 75% mid small bowel resection with twice daily injections of 0.1 µg per gram of bodyweight for 21 d induced led to mucosal hyperplasia in the proximal jejunum but not in the terminal ileum and a significant increase in intestinal absorptive capacity ^[50] .
Interleukin-11	Treatment of rats with a 90% small bowel resection with twice daily injections of 125 mg·g ⁻¹ IL-11 significantly increased villus height and crypt cell mitotic rates ^[51] .
Keratinocyte Growth Factor (KGF)	Treatment of rats with a 75% small bowel resection with 3 mg·kg ⁻¹ ·d ⁻¹ of KGF enhanced intestinal adaptation as assessed by mucosal cellularity, and biochemical activity in duodenal, jejunal and ileal segments ^[52] .
Transforming factor-α	Treatment of mice with a 50% small bowel resection with intraperitoneal TGF-α enhanced intestinal adaptation ^[53] .
Growth Hormone	Treatment of rats with a 75% small intestinal resection with 0.1 mg·kg ⁻¹ ·d ⁻¹ for 28 d enhanced ileal adaptation as assessed by ileal mucosal height. Treatment with growth hormone did not alter ileal mucosal DNA content or ileal mucosal IGF-1 content ^[54] . Treatment of rats with an 80% jejunoileal resection with synthetic rat GH for up to 14 d did not enhance ileal adaptation ^[55] . Treatment of an infant with only 25 cm of jejunum and 2 cm of ileum, with an ileocecal valve, with a 4-week course of 0.5 U/kg of GH allowing weaning from TPN ^[56] . Ten patients with short bowel syndrome were treated with daily subcutaneous doses of recombinant human GH (rhGH) of 0.024 mg·kg ⁻¹ ·d ⁻¹ or a placebo for 8 wk in a crossover clinical trial that included a wash-out period of at least 12 wk. Low-dose rhGH doubled serum levels of IGF-1 and increased body weight and lean body mass; but there were no significant changes in absorptive capacity of water, energy, or protein ^[57] .
Insulin-like Growth Factor-1	Treatment of rats with 70% and 80% jejuno-ileal resection with IGF-1 or analogues significantly attenuated malabsorption of fat and increased weight of stomach and proximal small bowel ^[58] . Gastrostomy-fed rats underwent 80% jejuno-ileal resection followed by infusion of 2.4 mg·kg ⁻¹ ·d ⁻¹ IGF-1 for 7 d. IGF-1 infusion led to a modest increase in ileal but not jejunal growth ^[15] . Treatment of TPN-fed rats for 7 d with IGF-1 after a 60% jejunoileal resection led to an increase in jejunal mass, enterocyte proliferation and migration rates yet had minimal effect on colonic structure ^[59] .
Epidermal Growth Factor (EGF)	Treatment of rabbits with 2/3 proximal resection with oral EGF (40 µg·kg ⁻¹ ·d ⁻¹) for 5 d led to an increase in maltase specific activity and a 3-4 fold increase in glucose transport and phlorizin binding ^[60] . Treatment of rabbits with a 50%-60% small bowel resection with 0.3 µg·kg ⁻¹ ·h ⁻¹ for 7 d led to a fourfold increase in mucosal dryweight at 3 wk post-resection ^[61] . Treatment of rats with a 75% small bowel resection with 6.25 µg·kg ⁻¹ ·h ⁻¹ of EGF increased mucosal thickness at 28 d post-resection ^[62] .
Neurotensin	Treatment of rats with a 75% small bowel resection with 600 µg·kg ⁻¹ ·d ⁻¹ led to an increase in the rate of mucosal proliferation ^[63] .

It makes sense to combine the administration of growth factors with an abundant supply of appropriate nutrients. Such approaches have worked well in animal models. Table 3 presents the results of studies that have evaluated the effect of cytokines and growth factors on intestinal adaptation. Clearly, there are a number of agents that can enhance adaptation. However, the effect of these agents is influenced by factors such as nutrition regimen and type of surgery. For example, Ziegler *et al.*^[15], found that treatment of gastrostomy-fed rats with 2.4mg·kg⁻¹·d⁻¹ IGF-1 for 7 d after 80% jejuno-ileal resection led to a modest increase in ileal but not jejunal growth. In contrast, treatment of TPN-fed rats for 7 d with IGF-1 after a 60% jejunoileal resection and cecectomy did not alter colonic structure^[59]. The effect of treatment with other combinations on intestinal adaptation has yielded less equivocal results. Ziegler *et al.*^[34], used a rat model to examine the effect of glutamine and IGF-1 on intestinal adaptation in rats. Treatment with a glutamine-enriched diet or daily injections of IGF-1 enhanced ileal hyperplasia. More importantly, treatment with glutamine and IGF-1 synergistically increased ileal weight and protein content. Fiore *et al.*^[64], examined the effect of treatment with IL-11 and EGF on intestinal adaptation in rats after 85% small bowel resection. The animals were treated with either 0.10µg·g⁻¹ EGF, 125µg·kg⁻¹

IL-11, or 0.10µg·g⁻¹ EGF and 125µg·kg⁻¹ IL-11 for 8 d. Rats which received EGF and IL-11 had the most number of proliferating cells in the mucosal crypts.

The results in humans have been less convincing. In 1995, Byrne *et al.*^[65], published the results of their investigation of the effect of GH, glutamine and a high complex carbohydrate/low fat diet on 47 patients with short bowel syndrome who had been dependent on TPN for many years. All patients were treated in hospital over a 4 week period. This treatment enabled 40% of patients to be weaned off TPN at one-year follow-up (Table 4). A number of these patients had small bowel length to weight ratios of a little as 0.5cm·kg⁻¹. Subsequent studies have been unable to reproduce these results^[66-68]. The data presented in Table 4 indicates that there was little difference in the type of patients involved in each of the three clinical studies, nor were there large differences in treatment regimens. However, the patients involved in the study by Byrne *et al.*^[65], were treated as inpatients whereas the other patients were all treated as outpatients. It is possible that this may have affected the results as outpatients may have been less compliant. Scolapio *et al.*^[67], considered this issue and believed that the patients involved in their study did comply with the treatment regimen. These conflicting data emphasise the need for further studies to evaluate the effect of trophic agents on intestinal adaptation.

Table 4 The effect of glutamine, growth hormone, and a modified diet on patients with short-bowel syndrome

Authors	Design of Study	Treatment	Number and Type of Patients	Average Length of Remnant Bowel 43	Results
Byrne <i>et al.</i> ^[65]	Uncontrolled study. Patients admitted to hospital and treated for 21d.	GH 0.11mg·kg ⁻¹ ·d ⁻¹ , glutamine 0.16g·kg ⁻¹ ·d ⁻¹ ¹⁸ by the parenteral route with up to 30g·d ⁻¹ by the enteral route, and a diet containing 60% of total calories as carbohydrate, 20% as fat and 20% from protein.	47 patients that were chronically dependent on parenteral nutrition	patients with a colonic remnant had (50±7)cm ^[4] , patients with no colon had (102±24)cm.	At the end of the study 57% of the patients no longer needed TPN, 30% had reduced TPN requirements, and 6% required approximately the same amount of TPN as they did at the start of the study. One year later 40% of the patients no longer needed TPN, 40% had reduced TPN requirements, and 20% required approximately the same amount of TPN as they did at the start of the study.
Scolapio ^[66] Scolapio <i>et al.</i> ^[67]	Double-blind, placebo controlled, randomized crossover study. Patients were treated for 21d as out-patients.	GH 0.14mg·kg ⁻¹ ·d ⁻¹ , glutamine 0.63g·kg ⁻¹ ·d ⁻¹ by oral route, and a diet containing 60% total calories as carbohydrate, 20% as fat and 20% as protein.	8 patients that were dependent on parenteral nutrition for an average of 12.9 years.	71 cm ² patients had colonic continuity.	Treatment led to a significant increase in bodyweight and lean body mass, a significant decrease in percent body fat and induced peripheral edema. All parameters returned to baseline levels within 14 d of stopping treatment. Treatment had no significant effect on intestinal villus height or crypt depth. No significant effect of treatment on absorption of energy, carbohydrate, nitrogen, wet weight, sodium, potassium, calcium or magnesium. Treatment induced adverse effects.
Szkudlarek <i>et al.</i> ^[68]	Double-blind, placebo controlled, randomized crossover study. Patients were treated for 28 d as out-patients.	GH 0.14mg·kg ⁻¹ ·d ⁻¹ , glutamine 30g·d ⁻¹ by oral route and glutamine-enriched parenteral nutrition (17% of nitrogen as glutamine).	8 patients that were dependent on parenteral nutrition for an average of 7 years.	104 cm. 4 patients had colonic continuity.	

SURGICAL MANAGEMENT

Non-Transplant Procedures - Autologous Gastrointestinal Reconstruction

Only a few patients with short bowel syndrome are candidates for non-transplant procedures. Surgery in the form of autologous gastrointestinal reconstruction is designed to redistribute the patient's own residual absorptive bowel to enhance adaptation and, possibly, to increase the absorptive mucosal surface by neomucosal growth. The majority of such reconstructions have been performed on paediatric patients. Intestinal lengthening, as described by Bianchi, is the most commonly used method of gastrointestinal reconstruction for the therapy of short bowel syndrome. It divides the bowel in two longitudinal halves based on the bifurcated mesenteric blood supply, then reconnects the two halves in series with the rest of the small intestine.

Bianchi^[69] has recently reviewed his 16-year experience of longitudinal intestinal lengthening procedures for 20 neonates and infants with short-bowel syndrome that included a dysfunctional dilated jejunum. There was no operative

mortality and the long-term survival was 45%. Survivors had >40 cm residual jejunum and a greater number also retained their ileocaecal valve and a longer colonic length. Death was commonly due to end-stage liver failure. Weber^[54] reviewed the outcome of 16 infants and children who had this procedure performed, with a resultant increase in the length of their bowel by 22%-85% (mean 42%). There were marked improvements in stool counts, intestinal transit time, intestinal clearance of barium, D-xylose absorption, and fat absorption. Fourteen of the 16 patients (88%) no longer required parenteral nutrition.

Small Bowel Transplantation

Intestinal transplantation, either alone or in combination with the liver, may eventually emerge as the preferred therapy for patients with permanent intestinal failure. However, in comparison with solid organ transplantations, such as the kidney and the liver, there has been slower progression from experimentation towards routine clinical practice. The first intestinal transplant was performed in Boston in 1964. It

involved the transfer of an ileal segment from the patients mother, but the recipient died 12 hours after surgery. In New York in 1970, a 170 cm jejunoileal segment was transplanted from an identical sister and the recipient lived for 79 d and was able to eat for 6 wk. At Kiel University in 1988, an intestinal transplant from an identical sister resulted in a survival for 4 years^[70].

The high level of immune surveillance within the small intestine means that large number of 'passenger' immunocytes and dendritic cells are transplanted along with the intestinal tissue. This increases the risk of acute rejection, which leads to the use of high doses of immunosuppressive agents and a greater incidence of side effects. In addition, the immunocompromised recipient is vulnerable to infections such as cytomegalovirus enteritis. In fact, recipients can die of side effects in the presence of a functioning graft^[71]. Improved results are only expected with newer immunosuppressive agents, better antiviral prophylaxis and treatment, and improved preservation and surgical techniques^[72].

Grant^[73] has recently reviewed the world experience in which 33 intestinal transplant programs provided data on 273 transplants in 260 patients. These patients received their transplants before March 1997. Only one-thirds of the recipients were adults and the commonest indication for transplantation was the short bowel syndrome. Many of the transplants involved other organs - intestine plus liver (48%); multi-viscera (11%). The one year graft survival for isolated intestinal transplants performed after early 1995 was 55% (the patient survival was 69%). Overall, 77% of the survivors were being sustained on oral nutrition and had no requirement for parenteral nutrition. The overall three-year survival has been about 40%, which is comparable with the results of lung transplantation.

Organ retrieval from a living donor can be performed safely for small bowel transplantation. However, further study of the management of rejection as well as viral infection is necessary for both living and non-living-related small bowel transplantation^[74]. Endoscopic surveillance may be useful to detect early allograft rejection^[75]. It has been suggested that a lower severity of graft rejection in combined liver-small bowel transplantation improves functional results of intestinal transplantation in children without additional mortality or morbidity^[76].

Goulet *et al*^[77], have stressed that, because parenteral nutrition is generally well tolerated, even for long periods, each indication for transplantation must be weighed carefully in terms of risk and quality of life. In this regard, it is of interest that a T cell lymphoma has been reported in the intestinal graft of a multivisceral organ recipient^[78]. It may have special significance because the lymphoproliferative disorders that are usually observed after transplantation are invariably of B cell origin. Furthermore, Crohn's disease in the recipient can recur in the intestinal transplant^[79].

Kato *et al*^[80], have used a rodent model to demonstrate that EGF augments both the structural and functional adaptation of intestinal grafts. Recipient Lewis rats underwent resection of the distal 80% of the small bowel followed by the insertion of a 20 cm isograft. EGF (30 µg·kg⁻¹·d⁻¹), or a control, was infused intraperitoneally for 3 d immediately after surgery. After 7 d, the graft was isolated for morphologic studies and was used for analysis of glucose and water absorption and the expression of sodium glucose cotransporter 1. These were used as indicators of functional adaptation. After seven days, the EGF-treated group exhibited significantly increased mucosal villous height, crypt cell proliferation, glucose and water absorption, and expression of sodium glucose co-transporter 1 protein

compared to the control group.

Other Surgical Techniques

A variety of surgical techniques have been devised to promote oral absorption of nutrients and delay emptying. These include a reversed intestinal segments, artificial intestinal valves, and recirculating loops. None of these procedures has been associated with significant clinical success. Thompson *et al*^[81], studied 48 adults and 112 children with short-bowel syndrome. The eventual outcome was that 44% adapted and survived on enteral nutrition alone, 28% required long-term parenteral nutrition, and 28% underwent surgery. Thirteen of 15 patients with adequate intestinal length (>120 cm in adults), but dilated dysfunctional bowel, were improved by either stricturoplasty or tapering. However, the patients who received an artificial valve (*n* = 2) or a reversed segment (*n* = 1) did poorly and required further surgery for revision or reversal. In general, success is lowest for procedures designed to prolong intestinal transit time; thus, these procedures should be used only in carefully selected patients^[82].

This is in contrast with the experience of Panis *et al*^[83], who reported their experience with segmental reversal of the small bowel. Eight patients with short bowel syndrome underwent, at the time of intestinal continuity restoration, a segmental reversal of the distal (*n* = 7) or proximal (*n* = 1) small bowel. The median length of the remnant small bowel was 40 cm (range, 25-70cm), including a median length of reversed segment of 12 cm (range, 8-15 cm). Parenteral nutrition cessation was obtained in 3 of 5 patients at 1 years and in 3 of 3 patients at 4 years. Segmental reversal of the small bowel could be proposed as an alternative to intestinal transplantation in patients with short bowel syndrome before the possible occurrence of parenteral nutrition-related complications.

COORDINATED INTERDISCIPLINARY MANAGEMENT

There have been proposals to develop multidisciplinary teams to care for patients with the short bowel syndrome. The key issues are the maintenance of optimum growth and development in infants and children, the promotion of intestinal adaptation, and the safe progression towards an oral diet. Koehler *et al*^[84], evaluated the effect of co-ordinated interdisciplinary team management of children with intestinal failure on nutritional outcome measures. Using an established registry, the authors conducted a comprehensive evaluation of patient data including anthropometric measures, organ system function, and mode of nutrition support. Linear growth velocity of neither pre- nor post-pubescent patients significantly improved during the 2-year study period of interdisciplinary team management.

When innovative, not yet fully proven therapies are introduced, physicians may have neither experience nor sufficient data in the medical literature to assist in their decision. When multiple physicians caring for a single patient have reached different conclusions regarding this new therapy, the potential for disagreement exists that could give rise to ethical issues as well as cause confusion to the patient. To explore these topics, Cooper *et al*^[85], investigated the attitudes of specialists to therapies for short bowel syndrome. A forced choice questionnaire was distributed to clinicians in neonatology and pediatric gastroenterology. Significant differences were noted among specialists as to whom would be involved in discussions of therapeutic options with patients about short bowel syndrome. Differences also were noted in the willingness of specialists to discuss and recommend therapies, in the perceived survival and quality of life by various specialists after transplant and palliative surgery, and in the local availability of various options. The neonatologists

and gastroenterologists at the same institution disagreed on responses in 34% of the questions with only 1 of the 25 pairs in full agreement. There is the potential for much patient confusion when counselling physicians recommend different options. Colleagues as individuals and specialists as groups should talk to each other before individual discussions with families to ensure that there is a clear understanding of differing beliefs.

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