Learning Objectives

- To understand the nature and pathophysiology of the different types of intestinal failure and short bowel syndrome;
- To appreciate the need for restriction of salt-poor fluids in patients with short bowel syndrome;
- To have an understanding of the pharmacological and nutritional therapy of short bowel syndrome;
- To be able to apply this understanding in clinical practice;
- To know the prognosis of short bowel syndrome and have an appreciation of the surgical and other more experimental alternatives to long-term home parenteral nutrition.

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Key Messages

- Short bowel syndrome is a form of intestinal failure, but the definition of intestinal failure also includes those with functional defects who may not have an anatomical short bowel;
- Patients with short bowel syndrome are net secretors and lose fluid and sodium from the intestine;
- Restriction of oral intake of low sodium fluids is a key component of successful fluid management of short bowel syndrome;
- Enteral nutrition should always be encouraged in short bowel syndrome and should continue to be used even when some parenteral support is necessary;
- Careful attention to a number of minerals, vitamins and other micronutrients is important to maintain and improve overall nutrient balance in short bowel patients;
- Judicious use of pharmacotherapy in combination with fluid therapy can maintain nutrition and health in many patients;
- Parenteral nutrition may be required but the needs of some SBS patients are limited to long-term iv therapy with fluids and micronutrients;
- Intestinal transplantation as an alternative to long-term home parenteral nutrition is now a viable option and should be considered while the patient is still sufficiently well for this to be possible.

1. Intestinal Failure and Short Bowel Syndrome – Introduction and Definitions

Intestinal failure (IF) is best considered in functional terms. It exists when there is inadequate functional intestine to allow health to be maintained by ordinary food and drink. It has been defined more formally by several international working groups and is considered to result 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 (1). ESPEN chooses to include in the definition a need for parenteral support for fluid and electrolytes and/or nutrition.
IF is defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" (3).

In clinical terms it can be divided into main 3 types:

Type 1 – usually seen post-operatively or in the intensive care unit. The intestine is generally not functioning because of non-gastrointestinal factors such as drugs, anaesthesia, or acute illness, but this type of intestinal failure is also associated with prolonged post-operative gastrointestinal stasis or ileus. The gut is not otherwise diseased. Type 1 IF is temporary and will resolve spontaneously along with resolution of any external factor(s).

Type 2 – most commonly seen after major GI surgery where the gut anatomy is altered e.g high output entero-cutaneous or entero-atmospheric fistula. There are often other factors involved such as sepsis, short bowel, or severe malnutrition. These patients require a combined multi-disciplinary approach involving intensive and specialist medical, nursing, dietetic and nutritional care. Many of these patients will require further gastrointestinal surgery and around half will go on to require home parenteral nutrition (HPN).

Type 3 – these patients have chronic intestinal failure. Their condition is however relatively stable and it is now usual for them to be managed at home with HPN. Most patients considered as candidates for intestinal transplantation come from this group (3).

These main groups have been further refined in the latest ESPEN reviews and surveys (4).

Short bowel syndrome is a sub-group of intestinal failure. It results from surgical resection, congenital defect, or disease-associated loss of absorption, and is characterised by the general features of IF (inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet) but also by very high stomal or fistula output and special challenges with respect to fluid and electrolyte balance because of net secretor status (1, 2). SBS will often present as a form of Type 2 IF, but with transition to Type 3 IF as the condition comes under control. Current therapeutic options are in line with this.

1.1. Intestinal Failure and Short Bowel Syndrome: the Background

Intestinal failure usually follows major resection, but also occurs when the intact intestine is unable to function because of severe inflammation or disorders of motility (1, 2). In many such patients (eg those with Crohn’s disease) both causes coexist. Severe intestinal failure is rare, with a prevalence of no more than 2.5 in 100,000, and an incidence in the region of 2 in 1,000,000, in most Western nations. It is best managed when anticipated.

The patient with surgical loss is protected from long-term intestinal failure by the process of adaptation, which occurs mostly in the first 6 months after injury, but can take up to 2 years. This process encompasses hyperplasia and hypertrophy at the cellular level within the intestine; the ileum is better at this than the jejunum. It is probable that adaptation is responsive to trophic factors, and related therapeutic opportunities are beginning to emerge. Additionally there is adaptive hyperphagia and changes in dietary choices, which will augment recovery. Intestinal failure should be anticipated in the patient with an ileostomy and <200cm small bowel, in the patient with <100cm with intact colon in continuity, and in the patient with a stoma or fistula output >1.5L/day. Not all such patients will require parenteral nutrition but all will need some degree of nutritional support and monitoring.
The need for intravenous nutrition and/or intravenous fluid support is governed largely by the combination of the anatomy and its pathophysiological consequences (1, 2). If there is a high output (meaning >1.5L) from stoma or fistula, then major electrolyte loss (particularly of sodium and magnesium) is almost certain and a need for daily intravenous fluids is highly likely. If however there is only relative shortening of the small bowel and it remains in continuity with colon, or if there has been no resection, then the intestinal failure will present mainly nutritional problems without major fluid and electrolyte issues. In these patients intravenous nutrition will be the priority and may not be required on a daily basis.

1.1.1. Gastrointestinal Volumes

It is useful to consider normal gastrointestinal volumes in order to place the fluid shifts seen in short bowel syndrome into context. Different authorities order the proportions differently but the totals are always similar.

<table>
<thead>
<tr>
<th>Volume Description</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and drink</td>
<td>1500</td>
</tr>
<tr>
<td>Saliva</td>
<td>750</td>
</tr>
<tr>
<td>Gastric secretion</td>
<td>1250</td>
</tr>
<tr>
<td>Biliary secretion</td>
<td>1000</td>
</tr>
<tr>
<td>Pancreatic secretion</td>
<td>1000</td>
</tr>
<tr>
<td>Jejunal secretion</td>
<td>2500</td>
</tr>
<tr>
<td>Total</td>
<td>8000</td>
</tr>
<tr>
<td>Stool liquid</td>
<td>150</td>
</tr>
</tbody>
</table>

It can thus be appreciated that in intestinal failure from short bowel syndrome (where the distal intestine is lost or out of continuity) the intestinal effluent volume may exceed 5 litres per day even when nil by mouth. As a simple teaching aid one can attribute all of the fluid entering the gut to sites proximal to the junction of the jejunum and ileum, and all of this fluid’s (re-) absorption to the intestine distal to this. The dramatic adverse effects of a distal jejunal stoma or fistula thus become comprehensible.

1.1.2. The Length of the Intestine and Gastrointestinal Losses

It is surprisingly difficult to get an accurate measure of the length of the normal small bowel as radiological, surgical and post-mortem measurements vary, and because the normal range appears wide. Distances of 300 to 600cm from the duodeno-jejunal junction to the ileocaecal valve are recorded in healthy individuals. In general men have a longer small bowel than women but this may just be function of height! The volume of the intestinal effluent (whether from stoma, fistula or from the anus) can be seen to be proportional to the jejunal length. Positive fluid balance requires about 100 cm. It is useful to have the concepts of net absorption and net secretion in mind when considering the patient with a shortened bowel. The normal person is a net absorber, and thus the more he or she drinks the more that is absorbed. Dehydration for any reason leads to thirst, which provokes additional drinking. Because of the net absorption this leads in turn to increased fluid retention and thus to resolution of the problem (any excess being cleared by increased urine flow). However this conceals important components of the site-specific intestinal physiology. Thanks to the combined effects of osmosis and the prevailing sodium
gradient, the proximal intestinal response is secretory, up to a luminal sodium concentration threshold of about 100mmol/L. As almost all drinks commonly consumed are very low in sodium content (typically no more than around 5mmol/L) drinking thus has a proximal secretory effect. In the healthy individual this is not a problem as there is plenty of more distal small bowel and the whole colon for reabsorption of sodium and water. However if substantially less than 150 cm of small intestine exists, this normal proximal secretion is neither reduced nor compensated. Thus the more that is drunk the less that is absorbed. Dehydration, as in the normal individual, provokes thirst and drinking, but this now generates increased fluid secretion into the proximal intestine and therefore increased overall losses: further deterioration in the dehydration therefore follows. The need to introduce restriction of the intake of free fluids to combat this effect is the central challenge of management of the patient with short bowel syndrome (5). The patient, his or her family, and all those involved in the associated healthcare need to learn that thirst requires less drinking. The therapeutic emphasis on this cannot be overstated given the anti-intuitive nature of the observation. Hours of education and support can sometimes be undone by a well-meaning healthcare assistant offering an extra glass of water to the thirsty patient.

1.1.3. Short Bowel, Jejunum, Ileum and the Colon
The majority of fluid reabsorption occurs in the ileum and colon. The ileum can however compensate for the loss of the colon and thus increase fluid absorption as is seen in patients with an end ileostomy but no ileal resection, who rarely have any perceptible problem with fluid balance. The ileum can in addition adapt extremely well to macronutrient absorption and can compensate for a reduced length of functioning jejunum. If the ileocaecal valve is also retained so too is the possible benefit of the physical effect of the valve, but there is a more profound beneficial effect from the so-called ileo-caecal brake in which neurohumoral signalling delays small bowel transit and increases proximal water and nutrient absorption.

In the healthy individual the colon is important but not critical to intestinal fluid balance. The patient who has needed a total colectomy and ileostomy but who has no small bowel disease will not normally require any special nutritional or fluid balance measures. However the colon takes on greater importance in the patient with a shortened small intestine (5, 6). Even short lengths of colon will be able to compensate usefully for some of the fluid handling properties of the ileum. A functional residual colon (meaning half or more of its full length retained in continuity) may be considered, in this respect, equivalent to about 50cm of small intestine. Although its value is mainly in fluid balance, there will also be some nutritional gain from fermentation of unabsorbed carbohydrate.

For these reasons some authorities like to classify patients into one of three anatomical categories, which must not be confused with the three types of intestinal failure described above.

- Type 1 – end jejunostomy (most nutritionally dependent)
- Type 2 – jejunocolic anastomosis
- Type 3 – jejunileo anastomosis (best prognosis for least jejunum)
2. Initial Assessment of the Patient with Short Bowel Syndrome

Most physicians unfamiliar with the short bowel syndrome will select a series of laboratory measurements to assist them in their assessment of the patient. Serum electrolytes, plasma osmolarity, serum urea/creatinine, and a full blood count will usually be requested. All of these are useful in advanced disease, but they are individually very insensitive and will miss key warning signs. Similar issues apply to the various micronutrients.

It is more informative, in the early stages of intestinal failure and in its on-going management, to monitor the body weight serially. Rapid changes in weight will always be a consequence of changes in fluid balance rather than reflections of nutritional status. Examination for postural change in the blood pressure can also provide evidence of inadequate circulatory volume before conventional blood tests become abnormal. Careful fluid balance records can clearly provide important supportive information, but it is difficult for nursing staff to maintain these accurately. Even in the intensive care unit incomplete measurement of losses from fistulas and leaking stomas can confound reliable documentation.

The most helpful laboratory parameter is usually the urine sodium concentration (7). When the patient is becoming dehydrated there is avid sodium retention in order to retain both sodium and water: the urine sodium concentration thus falls. A random urinary sodium concentration below 10mmol/L is effectively diagnostic and a level below 20 mmol/L is highly suggestive. Only in patients with established renal failure and in those (ill-advisedly) on diuretics, is this very useful test confounded, since in those contexts there may be a higher urinary sodium despite dehydration. Random samples are sufficient and there is normally no need for prolonged urine collections.

The serum magnesium will be sought in the patient with tetany (and especially so when the calcium is normal or uncorrectably low), but may be neglected in the apparently asymptomatic patient, not least since it is absent from most hospital panels of “routine” biochemical investigations. As there are substantial losses of magnesium in diarrhoea and high volume stoma or fistula output its blood levels should always be sought.

3. Short Bowel Syndrome: Management

In therapy of short bowel syndrome the aims are to reduce gastrointestinal secretions, to slow the speed of transit, to reverse or prevent malnutrition, and to prevent deficiencies of specific nutrients. The most urgent component however is to identify and to treat elements of dehydration to avoid renal impairment (5). It is also important to avoid precipitating refeeding syndrome in the patient who has been deprived of appropriate nutrition for 1 week or more. Once these early targets have been achieved evolution to a stable longer-term nutritional regimen is then required.

3.1. Management of Dehydration in Short Bowel Syndrome

It is characteristic for patients with short bowel syndrome to present in a seriously dehydrated state, which has often been exacerbated by inexpert management of fluid balance. It is then usual to need intravenous rehydration with a sodium-containing regimen. It has been conventional to refer to the use of intravenous saline for this purpose but this is a suboptimal choice. The primary deficits are of sodium and water and not so much of chloride. Chloride ions are less well cleared from the body even in health and their accumulation in catabolic illness is greater still. It is therefore preferable
to use a chloride-poor alternative to 0.9% sodium chloride (normal saline). A balanced electrolyte solution such as Hartmann’s/Ringer’s Lactate is therefore preferred, the composition of which also more closely parallels the plasma electrolyte profile.

Sodium Chloride 0.9% “Normal Saline”
Sodium 154 mmol/L
Chloride 154 mmol/L

Hartmann’s/Ringer’s Lactate Solution
Sodium 130 mmol/L
Chloride 109 mmol/L
Lactate 28 mmol/L
Potassium 4 mmol/L
Calcium 1.5 mmol/L

Determining the volumes required in very unstable patients will often incorporate assessments guided by the central venous pressure, but as control is achieved it become feasible to use urine volume as a less invasive means. It is obviously important not to allow gastrointestinal volume losses to dictate increases in oral intake as in the short bowel patient this leads to a counterproductive vicious cycle. Once an acceptable urine volume (eg 20 ml/kg per 24 h) has been achieved then a transition to management with oral rehydration solutions (ORS) may be considered (Section 3.3.3). It is important to note however that the final strategy may include a combination of oral/enteral and parenteral approaches to fluid and electrolyte balance.

### 3.2. Refeeding Syndrome

This is not the place for a full account of the refeeding syndrome, which is well covered elsewhere in LLL materials (8). However, its risk is considerable in the early management of SBS as in all malnourished patients. Refeeding syndrome should be considered in patients with intestinal failure even when the initial feeding has not been parenteral, but enteral or even oral. The key diagnostic features, as in other contexts, are rapid changes in plasma electrolytes, and particularly falls in phosphate and magnesium as these move back into cells with the switch back to carbohydrate metabolism and a rapid increase in insulin. Changes in potassium and calcium are less often seen in IF.

### 3.3. Enteral Options in Short Bowel Syndrome

It is important to understand that it is beneficial to employ enteral feeding in patients with short bowel syndrome. The amount of residual functioning small bowel will determine the quantity (and frequency) of parenteral nutrition needed to complete patients’ nutrient requirements. While enteral nutrition may be insufficient to provide all nutritional needs, this does not negate the considerable gains to be accrued from at least a percentage of their nutrition being accessed by the normal route. The benefits to the gastrointestinal tract itself, to hepatic health, and to overall immune integrity are all considered elsewhere in LLL materials.
3.3.1. Food Selection

Firstly it should be emphasised that most patients with SBS can and should be eating. However low the proportion of nutrients that will be absorbed it will generally be greater than zero, and there is evidence that even the smallest amounts of luminal nutrition help to protect against progressive liver disease and other complications. Food selection is therefore an active issue. In most cases the advice can be to eat regular food, preferably of high energy density and high salt content. Most patients find that effluent volumes are minimised by the separation of food from liquid although this has not been verified scientifically. As for general management, there should be avoidance of free fluids for the reasons outlined above. The food strategy should be one of “little and often”.

Enteral fat intake is useful because of its energy density and is of almost unequivocal value in the patients with an end jejunostomy. If the patient has a retained colon fat is less acceptable as it may give steatorrhoea, but also because the opportunity for useful fermentation of carbohydrate may be diminished given that individuals can only manage a certain quantity of food each day (and if this is mainly fat there is necessarily less carbohydrate).

The rare condition of D-lactic acidosis occurs in a small number of patients with a short length of small bowel anastomosed to the colon. In these patients an (excessive) intake of carbohydrates coupled with a change in the colonic bacteria leads, if untreated, to a neurological presentation with marked confusion as the most common feature. The clinical presentation is similar to that of thiamine deficiency and lactic acidosis should be particularly considered in a SBS patient with acidosis and neurological problems where there is no evidence of vitamin deficits. An initial antibacterial regimen followed by a reduction in carbohydrates may be required.

3.3.2. Formula Feeds

Formula feeds and prepared supplements may be helpful in short bowel because of their energy density and convenience, but are certainly not mandatory if food is preferred by the patient. Elemental feeds should be avoided because the combination of high osmolality, low energy density, high volume and relatively poor palatability provides an increase in fluid losses with relatively poor nutrient advantages. There is no evidence that polymeric feeds are inferior to semi-digested ones and there appears no advantage from any of the modified/supplemented feeds. Regular (1kcal/ml) or higher energy (1.3-1.5kcal/ml) feeds can therefore be employed as determined by the patient’s needs and tolerance of osmolality. It may be necessary to add extra salt and this is most easily done by adding high concentration sodium chloride for injection to the feed.

3.3.3. Use of Oral Rehydration Solutions in Short Bowel Syndrome

An ORS-based strategy will naturally and necessarily include a limitation on the intake of free fluids (those with no or little sodium). It will be understood that the aim is not only to reduce the oral intake of free fluid but also to increase sodium intake in general. This can be done effectively by the addition of table salt to food, as well as by the use of high sodium content oral rehydration solutions. The heritage WHO ORS has a sodium content of 90 mmol/L as does the St Mark’s solution, and these remain suitable choices. Proprietary ORSs marketed for acute diarrhoeal illness are less suitable with their recommended recomposition as these generally contain sodium at only 50 to 60 mmol/L. It is however possible to reconstitute
these with less water so that the final sodium concentration equates to 90 to 120 mmol/L without too greatly compromising their palatability.

**Heritage WHO Oral Rehydration Solution**
- Glucose: 111 mmol/L
- Sodium: 90 mmol/L
- Chloride: 80 mmol/L
- Potassium: 20 mmol/L
- Citrate: 10 mmol/L

**St Mark’s Solution (20g glucose, 3.5g NaCl, 2.5g NaHCO$_3$ or 2.5g sodium citrate)**
- Glucose: 111 mmol/L
- Sodium: 90 mmol/L
- Chloride: 60 mmol/L
- HCO$_3$: 30 mmol/L
- or Citrate: 10 mmol/L

The option of bicarbonate or citrate in the St Mark’s solution has little impact on its efficacy but lends very different tastes, thus allowing patients to choose which they prefer. Flavouring with fruit concentrates is also possible.

A fluid and electrolyte “menu” for a patient with mildly to moderately severe SBS might therefore comprise 750 ml WHO solution with a daily limit of 750 ml of all other fluids, combined with generous addition of salt to all meals. It seems helpful also to separate fluid intake from that of solid food. Sodium tablets are generally not helpful, and slow-release, waxed preparations of sodium are (unsurprisingly) almost completely ineffective.

In patients with more severe SBS intravenous support will be necessary on a continuing and often daily basis. In these patients it remains helpful to adopt an oral fluid regimen along the above lines to limit the volume of gastrointestinal effluent, but the approach can be less rigid since the sodium and fluid deficits can be rectified parenterally. In broad terms the patient whose output cannot be readily maintained at less than 1500 mL daily will need intravenous support.

### 3.3.4. Enteral Therapy in Short Bowel Syndrome: Summary

Unless a need for full parenteral support is obvious (as in the patient with total enterectomy) there should always be serious consideration of enteral nutrition therapy, and in almost all patients oral food can be allowed even if its nutritional value is believed to be minimal. The key additional elements of enteral therapy in short bowel syndrome are to limit free fluid intake (to as little as 500mL/day), to add a high sodium oral rehydration solution to a similar volume, and to commence a so-called antisecretory regimen (see below). There should be encouragement of oral feeding, with the addition of standard formula feeds as necessary, potentially using these by overnight tube feeding to maximise the hours available each day. Specific formulae are not obviously justified.

### 3.4. Pharmacological Therapy

#### 3.4.1. Acid Suppression

Proton pump inhibitors (PPIs) have an important role in the management of SBS by reducing the total volume of gastric secretion, since most of this volume is from the secretion of acid. Omeprazole has the advantage in terms of having an increasing effect with increasing dose unlike many other PPIs, most of which have a flatter dose-response
curve. The dose can be adjusted to provide a stoma content pH >5. This typically requires a total daily dose of 80mg or more. Caution is required with very high doses as they can hypothetically lead to liver dysfunction. In patients with an ultra-short bowel and end jejunostomy (<50cms) oral PPIs may not be absorbed. Dissolving the omeprazole capsules in a bicarbonate solution will then aid absorption. In patients where even this is insufficient, it is possible to administer the PPI as an intravenous preparation. These patients will usually be on >3 litres of intravenous fluids daily and will require their PPI infusion after they have completed their PN infusion, unless stability reassurances can be obtained for a PPI to be added to the PN. An alternative in this setting is to use high dose ranitidine which does not usually interfere with the stability of PN admixtures. Some centres consider that the benefit of PPIs in SBS is relatively short-lived and seek to withdraw the drug after 6 to 12 months of HPN. This has not been our experience however and we normally continue omeprazole indefinitely.

3.4.2. Drugs to Delay Transit
Opioid drugs have minimal antisecretory effect but are nonetheless valuable in reducing the speed of intestinal transit. Loperamide is preferred over codeine and combination products containing antimuscarinics, as there is then minimal potential for central side effects such as sedation, and less potential for confusion with dehydration if antimuscarinics cause a dry mouth. A combination of low dose codeine and high dose loperamide may be required for optimal control and patient perception of this. Very high doses of loperamide are sometimes used, but the evidence that greater than 32mg/day is effective is scant, and there are no good controlled trials even for more modest doses.

3.4.3. Somatostatin and its Analogues
Somatostatin and its derivatives have proved disappointing in management of short bowel syndrome and very few patients will continue these agents in the medium- to long-term. It is useful to embark on a 72 hour therapeutic trial (for example with octreotide 100 μg thrice daily) and to continue this only if there is obvious measurable benefit in fluid balance. Their relative lack of value is probably from the fact that their main antisecretory actions in SBS are largely duplicated by the cheaper and less invasive use of sufficient proton pump inhibition. Patients with the unfortunate combination of pancreatic insufficiency and SBS do however appear to gain more from somatostatin analogues. A few patients with disordered motility secondary to surgical complications as well as short bowel are also helped in terms of reducing bloating and other “dumping” type symptoms.

3.4.4. Colestyramine and Colesevelam
The bile salt binding agents are of no value in SBS patients with no colon but when there is retained colon in continuity there can be good symptomatic benefit from their use, as non-absorbed bile is prevented from causing colonic inflammation and secretion. Their tendency to aggravate malabsorption of fat and fat-soluble vitamins will be taken into account.
3.4.5. GLP-2, Teduglutide and Related Drugs

The glucagon family of peptide hormones is of increasing interest in the context of intestinal failure and SBS. Glucagon-like peptide 2 (GLP-2) has so far attracted the most attention. GLP2 is a naturally occurring and largely gut-specific trophic peptide secreted by intestinal L cells in the ileum and colon in response to enteral nutrition. Its levels in blood are depleted in patients with SBS and an end jejunostomy, and although elevated in patients with more distal small bowel and colon in continuity presumably not to a level sufficient to overcome the anatomical defect. Laboratory work indicated that exogenous GLP-2 was able to improve absorption after massive resection via a combination of villous hypertrophy, inhibition of gastric secretion and emptying, and increased mucosal blood flow, but any clinical application was greatly hampered by its very short half-life: GLP-2 is rapidly degraded, mainly by the enzyme dipeptidyl peptidase IV (DPP4).

Teduglutide is a close analogue of GLP-2 and is resistant to DPP4, permitting effective dosing with a single daily subcutaneous injection. Several clinical trials have now been completed in patients with stable Type 3 intestinal failure which demonstrate that a dose of 0.05 mg/kg/day significantly outperforms placebo in a controlled trial setting. The trials have used the objective outcome measure of a sustained reduction in need for PN over a 6 month treatment plan. The drug was responsible for a reduction in PN volumes of at least 20% for the whole of the final month in 45% of treated patients compared to only 6% in controls subjected to the same intensive weaning protocol (p<0.01)(9). There were no major safety concerns, and an extension study taking patients out to 52 weeks reinforced conclusions on both efficacy (68% on the same criteria of 20% below baseline) and safety. A small proportion of patients can be weaned completely from PN (~8%), and a larger proportion (~37%) benefits from a reduction in the number of days on which PN must be given each week (10).

It is probable that unrestricted use of the drug in less intensively monitored SBS patients would see greater benefits but this must remain somewhat conjectural. Unfortunately, despite these results, its first-in-class nature and its formal status as an orphan drug, clinical uptake of teduglutide internationally has been poor. There are several reasons for this. The in-trial assessments of quality of life did not show significant advantages over placebo. There is an important risk of enhancing/accelerating colonic neoplasia in those with or at risk of colonic adenomas necessitating careful colonoscopic surveillance in any patient with retained colon. Additionally the drug is very expensive, its cost being more than 4 times that of the PN it aims (but usually fails) to replace. It is thus unsurprising that at present very few health service funders will authorise its use.

Other GLP-2 analogues are under development and at present clinical trials are furthest advanced with glepaglutide which has similar laboratory effects to teduglutide but with a longer half-life.

GLP-1 is considered of considerable importance in the management of diabetes, and the metabolic consequences of obesity. Several GLP-1 analogues are now in regular use in diabetes clinics. Like GLP-2 it is released from enteroendocrine cells from where GLP-1 acts to modulate the hyperglycaemia that would otherwise follow eating. It increases the secretion of insulin and inhibits the release of (whole) glucagon, and reduces spontaneous food intake. Although these are the main properties of interest to the diabetologist and bariatric physician, it also delays gastric emptying, whilst simultaneously appearing to increase the degree of absorption of food that actually reaches the intestine, perhaps through an effect comparable to that of the ileal brake. Its properties are therefore of potential value in SBS. A pilot study indicates that the
GLP-1 agonist liraglutide may be able to improve fluid and energy balance in short bowel patients (11). As GLP-1 is also degraded by DPP4, several DPP4 inhibitors have been evaluated and are now in use in diabetes/metabolic syndrome patients. There do not yet appear to have been any clinical trials of these orally active agents in short bowel syndrome. GLP-1/GLP-2 co-agonists are however being explored in animal models with a view to use in SBS.

3.4.6. Other Drugs

Human growth hormone (0.05mg/kg/day) has been shown to be effective in improving nutritional and fluid balance in some patients with short bowel syndrome relative to placebo. Unfortunately the modest magnitude of effect, the need to give it by injection and the significant associated toxicity have led most clinicians away from its use. Issues with cost and absence of appropriate regulatory licensing have not helped to change this. Manipulation of the gastrointestinal neuroendocrine axis other than via GLP-2 is also ripe for development as newer peptide analogues and their antagonists become available. To date there are no clinical data but inhibition of vasoactive intestinal peptide or increased expression of peptide YY would be predicted to be helpful. Racecadotril is an oral encephalinase inhibitor which has now been quite thoroughly and positively evaluated in acute diarrhoeal illness. The drug inhibits the degradation of endogenous opioids and as well as influencing motility appears able to reduce the secretion of water and electrolytes into the intestinal lumen. It should work in SBS but remains to be tested, so the magnitude of any effect is unknown. 5-HT3 antagonists have a somewhat ambiguous status in management of irritable bowel but are also widely used as antiemetics. Although intestinal actions useful to the SBS patient might be anticipated there is little clinical support for this premise and specialist centres have not adopted their use for this purpose. There is now quite a body of research looking at agents that affect the chloride channel and the epithelial sodium channel, aiming to realise their potential in cystic fibrosis. Although in general investigators have been seeking actions that would be harmful in the patient with a short bowel some of their findings could indeed be helpful and this may be an area worthy of investigation by IF researchers. Chloride channel blockers also exist. Finally given the seriously disturbed microbiome in the intestine of the short bowel patient and the frequent complication of small bowel bacterial overgrowth there is growing interest in probiotic and prebiotic approaches as well as the use of gut-specific antibiotics such as rifaxamin. Again there are no data specific to SBS as yet.

3.4.7. Pharmacotherapy: Summary

The combination of fluid restriction, oral rehydration therapy and pharmacotherapy is often successful in achieving and maintaining positive fluid and nutrient balance in patients with modest degrees of SBS. This is however very demanding on patients and needs their full and lasting co-operation as well as a prior and detailed personal education programme. Newer approaches with more specific drugs such as teduglutide have changed our collective aspirations. Although at present their efficacy is limited and their availability even more so, a future in which pharmacological options might allow many more patients with SBS to remain well without parenteral nutrition can now be envisaged.
3.5. **Parenteral Therapy – Fluids and Electrolytes**

Patients with very short bowel (eg <50cm) and those who have failed to achieve or are unable to maintain fluid balance with the measures described above will need parenteral therapy. Some of them will only require intravenous fluid and electrolytes (usually the predominant need is for sodium and magnesium) as they have sufficient functioning jejunum to maintain a positive macronutrient balance. The volume and sodium content should be determined by the same criteria outlined in Section 3.1 with the proviso that for longer-term home-based therapy there should be a little more generous provision to allow an “insurance policy” for days on which dietary indiscretion leads to greater losses from the gut or hot weather causes increased sweating. It will be seen that this strategy can pose quite a problem in the more elderly patient with compromised cardiac function in whom the risk of overhydration is also ever present.

If the parenteral fluid requirement is less than 1L/day (which is admittedly quite rare) then the use of subcutaneous fluid is worth considering. This is remarkably well tolerated by many patients, is safer than the intravenous approach, and allows up to 150mmol of sodium, about 8mmol of magnesium and up to a litre of fluid to be given each day. Preferred sites include the abdominal wall and the anterior thighs and it is best to use several different sites to reduce the risk of local fibrosis which then prevents fluid absorption. Patients need to understand that the fluid will form something of a “cushion” during the infusion period that is then gradually assimilated over the next few hours.

3.5.1. Magnesium

In many patients the most challenging electrolyte to correct is magnesium. Many patients complain of tingling or cramps and unless the plasma magnesium is measured the fact that other electrolytes such as calcium, sodium and potassium are normal can lead to confusion. Fortunately frank seizures from hypomagnesaemia are now rare. It is helpful to remember that magnesium absorption, which normally occurs mainly in the proximal intestine, is under the control of vitamin D. Normalisation of vitamin D levels can permit correction of the plasma magnesium without the need for its parenteral delivery.

Oral magnesium supplementation is nonetheless often problematic due to its direct osmotic effect on the distal small bowel and thereby counterproductive laxative actions. Equally intravenous magnesium as a large bolus is generally only temporarily successful and repeat doses are rapidly required. This is because most of a large (20mmol +) dose of intravenous magnesium is rapidly excreted in the urine even in severe magnesium deficiency, and because by the time the plasma level is low the body’s intracellular levels will have been very substantially depleted. Regular smaller (6-12 mmol) doses over many days are more successful. When magnesium administration is the only justification for parenteral therapy it is particularly worthwhile persisting with a subcutaneous approach, perhaps using smaller volumes with higher concentrations, but very few patients will be able to accept more than 16 mmol/L without getting a reaction at the puncture site.

3.6. **Intravenous Nutrition in Short Bowel**

In those with severe short bowel syndrome and also in those with functional intestinal failure in whom all approaches to enteral nutrition have failed it will be necessary to use
intravenous nutrition. The general principles underlying the prescription of parenteral nutrition (PN) outlined in other LLL modules can be followed, but there are a few special considerations for the patient with a short bowel.

The most obvious differences will be in the need for greater quantities of fluid, sodium and magnesium than are usual, for example, in the management of a typical post-operative patient. This substantially limits the possibility of using standard “off-the-shelf” 3-in-1 mixtures as these do not accommodate the volume or amount of sodium needed by the short bowel patient. There are also cautions in respect of the lipid content that are peculiar not so much to short bowel but to the need for very long-term PN, and these are addressed further below.

The prescription for the SBS patient will usually commence with a relatively routine combination of carbohydrate, lipid and amino acids, modified to incorporate the additional sodium, magnesium, and volume needed. All of the vitamins and trace elements will be included.

The amount of energy to be delivered is best determined by calorimetry, but when this is unavailable it is reasonable to follow the simple approach adopted in ESPEN’s advice on nutrition in critical care and to give 25 kcal/kg body weight. In the already malnourished or especially catabolic patient this may be increased to 30 kcal/kg. The amino acid content should be set initially at 1.5 g/kg with the expectation that this is reduced to ~1g/kg as the patient moves into controlled steady-state Type 3 intestinal failure.

There is an expected evolution of the energy to nitrogen ratio from about 15 kcal per gram of amino acids/protein in the acute phase to 25 kcal or more per gram in convalescence and maintenance.

Even from the earliest stages the patient will be taking some nutrition orally, and the nutritional value of this should be included in the calculations, with due regard to the likely rates of absorption. It is usual therefore that the SBS patient on PN will be prescribed a total energy and nitrogen intake well in excess of the calculated needs, as although the PN component of this will surely be delivered, only a proportion of the food eaten will actually be absorbed and available for metabolism.

Once the patient is stable and securely established on intravenous nutrition it will usually be appropriate for discharge from hospital on home parenteral nutrition a process which is fully addressed in the LLL module on HPN.

3.6.1. Avoiding Chronic Cholestasis and Other Long-term Metabolic Problems

The adverse effects of hyperalimentation have long been recognised and avoided in parenteral nutrition practice, but there is an additional factor at play in the management of patients on PN such as those with SBS. It is now clear that there is hazard from long-term provision of more than about 3000kcal of lipid per week, which may also be expressed as a daily limit of <1g lipid per kilogram body weight. Patients who have received consistently higher doses of lipid despite appropriate total energy delivery are found to have a high risk of intestinal failure-related chronic liver disease. The usual presentation is with cholestasis, and the condition can progress to liver failure and death (12). Limiting the dose of long-term lipid reduces this risk substantially (to below 1% in adults). The evidence that this is an effect of soya lipid rather than of lipids in general is increasingly strong. Data from studies of lipid emulsions including medium-chain triglycerides and olive oil are encouraging in this regard, but the best options appear to be those which contain some fish oil (13).

Chronic liver disease is not likely as a result of PN alone, hence the abandoning of the term PN-associated liver disease in favour of intestinal failure-related, and in most
modern adult cases there is underlying chronic sepsis. Nonetheless some other nutritional elements may be important. Manganese is excreted in bile and in excess probably contributes to cholestasis, as a result of which its excretion is further impaired and its circulating levels are driven even higher. As the commercially available trace element sources all have arguably too much manganese even at baseline, the IF clinician is not infrequently in a position where the patient has hypermanganesaemia and perhaps evidence of brainstem deposition on MR scanning and yet is deficient in other micronutrients that are only available in multi-agent vials. Often a compromise must be drawn with high but hopefully not toxic manganese concentrations and mildly subnormal levels of those other trace elements. Fortunately at least zinc and selenium are now increasingly available as singe agents. It has been thought that taurine deficiency might compromise patients with SBS given that standard amino acid solutions have been taurine-free. Anxieties that this might contribute to IF-associated liver disease or other medium-term complications of HPN have not been supported by trial data (14).

4. Short Bowel Syndrome and HPN – the Prognosis
The process of intestinal adaptation extends over at least 6 months to 2 years, and during this time the need for artificial nutritional support will generally fall, allowing some patients to become independent. Risks nonetheless remain and are associated more with the underlying disease process than with any nutritional therapy. HPN itself has been thought to pose an annual mortality rate in excess of 1% in the best centres – predominantly from cathether-associated sepsis. Supplementation with glutamine has been shown to be of no value (15). ESPEN’s recent survey of nearly 500 patients in their first 5 years on HPN revealed a survival rate 88% at one year, falling to 64% at 5 years Crohn’s disease and IF without SBS had a better than average mortality rate in excess of 1% in the best centres – predominantly from cathether-associated sepsis. Supplementation with glutamine has been shown to be of no value (15).

ESPEN’s recent survey of nearly 500 patients in their first 5 years on HPN revealed a survival rate 88% at one year, falling to 64% at 5 years Crohn’s disease and IF without SBS had a better than average outlook and increasing age was detrimental. Moreover a full third of patients were successfully weaned from PN. The ESPEN consensus that the risk of HPN is generally lower than that of intestinal transplantation is thus consolidated along with the recommendation that transplantation should largely be reserved for patients in whom PN has failed (16).

5. Intestinal Transplantation
Intestinal transplantation is being performed more readily in patients with intestinal failure and the results are clearly improving. This evolution reflects experience both at the local level (centres which have performed more than 10 cases have better results) and globally (as more recent cases do better whichever centre is considered). The timing of transplantation has also been shown to make an important difference to outcomes, the overall fitness of the patient pre-transplant being a key prognostic factor; survival is much better if the patient is not hospitalised prior to the procedure. In the 5 years up to 2015 over 850 transplants were performed (about two thirds of them in the USA). Although a shortage of donors is not a problem for isolated intestinal grafts, patients needing multivisceral grafts face a waiting list and associated waiting list mortality. The survival at 1 year proved in excess of 80% in the bigger centres, an improvement attributed to better immunological selection and post-operative immune control. Encouragingly long-term survivors are returning to work and to socio-economic independence. It should however be noted that transplantation rates peaked shortly after these data were obtained, a substantial reduction in operative rates in the USA.
bringing more recent figures from the 2 sides of the Atlantic much closer together and more in keeping with the ESPEN recommendations.

6. Non-transplantational Surgery for Short Bowel

Surgical reconstruction should always be considered in the patient with short bowel syndrome where (for example) emergency surgery for mesenteric ischaemia has left a short length of small bowel terminating in a stoma, and also an intact but defunctioned length of colon. There sometimes seems to be no length of residual bowel too short to offer some gain in nutritional and fluid balance when it is returned to continuity. Reanastomosis of the proximal jejunum to the sigmoid colon will sometimes even be enough to allow weaning from PN without impossible bowel control. Reliance on the rectum and anal canal alone is however generally insufficient if disabling diarrhoea with incontinence is to be avoided. More imaginative reconstructive procedures have also been devised.

6.1. The Bianchi Operation

The Bianchi operation takes advantage of the anatomical distribution of the blood supply to the small intestine, and aims to convert a dilated section of intestine into a narrower segment of double the length (18). Functional results have been good in the small number of patients in whom this has been tried and there have apparently been no deaths.

6.2. The STEP Operation

The STEP operation – or Serial Transverse Enteroplasty Procedure – is a creative development of the common technique of surgical enteroplasty, and also lengthens and narrows the mean calibre of the intestine (19). Results from this operation are also encouraging. Inevitably there must be concern that any operative procedure can make things worse, and informed consent will need to take this into consideration. At present only a small handful of cases are performed each year in the UK, and none in many other developed countries.

6.3. The Spiral Operation

The SILT operation - or Spiral Intestinal Lengthening and Tailoring procedure – was devised with the intention of being as effective as but less invasive and intrinsically safer than the STEP procedure. The first case was performed only in 2014 and the indications are similarly few, so there are to date only a very small number of cases to review and none open to direct comparison with the STEP operation (20).

7. Potential Advances in Management of Short Bowel Syndrome

The use of oral rehydration solutions plays a key part in SBS management but there has been little change in our prescriptions or usage pattern over several decades now despite the clear benefits seen in management of acute diarrhoea from the inclusion of complex polysaccharides rather than glucose alone. This deserves proper evaluation in short bowel. Improvements in long-term PN admixtures, aiming for more physiological regimens, are also desirable. The risk of metabolic complications from PN has fallen over past decades but many patients still have abnormal liver enzymes and it is probable that this poses a real if small risk. Our ability to deliver a balanced composition of trace
elements is still compromised and although relative avoidance of soya lipid is almost certainly advantageous, whether a more physiological balance of amino acids would be helpful is largely untested. New forms of assessment may also help in evaluations of new therapies, and the use of plasma citrulline as a marker of functional small bowel mass is promising (21) and especially so if it proves also to have therapeutic potential. At a practical level it would be helpful to have a range of pre-prepared 3-in-1 options with volume and sodium content suitable for patients with SBS – and better still if they contained the necessary vitamins and trace elements!

The concept of an artificial or bioengineered intestine has existed for some time now and is a reality to a limited degree in the research laboratory. Replication of the intestine is a bigger challenge than that of other organs given the very many distinct and partially competing functions of the normal intestine (such as its role as a barrier but also as a key absorptive surface, or its need to secrete but also absorb, and to be able to provide powerful coordinated motor functions). Even if patients could survive safely without the important immunological actions of the gut it is clear that it is very difficult to combine all of the other functions. Nonetheless work proceeds apace. With the organoid unit approach small intestine epithelial units are seeded onto tubular scaffolds and grown ex vivo before reimplantation, but there is a very high demand on source material (22). Motor function has been replicated in several centres but overall bioengineering of pluripotent stem cells for subsequent transplantation may be the most promising avenue. In one recent such approach decellularised rat intestinal matrix was seeded with human stem cell-derived intestinal epithelium. A monolayer of apparently normal intestinal epithelium could be grown in culture to which human endothelium was then added. “Perfusion” (an analogue here for absorption) of key nutrients including glucose and medium-chain fatty acids from “lumen” to vascular efferents could be demonstrated ex vivo, and subsequent engraftment into rats indicated that genuine absorption occurred and apparently without normal motor function being compromised (23).

It is probable that successful extension of this work to the human situation may still be some way off.

8. Summary

Chronic type 3 intestinal failure and its clinical manifestation as short bowel syndrome are not common, but they pose substantial management problems, which can be overwhelming to medical staff who are unprepared. The tendency for patients with short bowel syndrome to be net secretors, in whom drinking free fluids increases gastrointestinal losses, is particularly challenging. The use of oral rehydration solutions and of restricting free fluids is sometimes sufficient. This will be combined with encouraging solid food to ensure positive nutritional balance. Pharmacological antisecretory approaches should be attempted and along with judicious fluid and enteral food approaches are often successful. The more severely affected patient will generally need long-term intravenous nutrition. The risks of this are lower than in the past, and, with avoidance of purely soy-based lipid formulations, IF-associated chronic liver disease is now rare in adults. Long-term PN should not be exclusive anyway since physical and psychological gain come from eating. New therapeutic options to augment the adaptive process offer the possibility that some of these patients will in future be weaned from long-term PN and that others may never need it. For now however, HPN, or intestinal transplantation in a few highly selected patients, remain the norm for severe short bowel syndrome.
9. References


