Nutritional Support in Gastrointestinal Disease

Module 12.2

Challenges in treating intestinal failure and short bowel syndrome

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Learning objectives

- To understand the nature and pathophysiology of intestinal failure and short bowel syndrome;
- To appreciate the need for restriction of salt-free fluids in patients with short bowel syndrome;
- To have an understanding of the pharmacological and nutritional therapy of intestinal failure and short bowel syndrome;
- To be able to apply this understanding in clinical practice;
- To know the prognosis of intestinal failure and have an appreciation of the surgical and other 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 deficit;
• Patients with short bowel syndrome lose fluid and sodium from the intestine and are net secretors;
• Restriction of sodium-free fluids taken by mouth is a key component of successful therapy of short bowel syndrome;
• Enteral nutrition should always be encouraged in intestinal failure and should continue to be used even when some parenteral support is necessary;
• Intestinal transplantation as an alternative to long-term home parenteral nutrition should be considered while the patient is still sufficiently well for this to be possible.
1. Intestinal failure - introduction and definitions

Intestinal failure 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 an international working group 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).

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 inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet (1).

Current therapeutic options for severe intestinal failure include enteral tube feeding in hospital or at home, intravenous nutrition in hospital or at home, and intestinal transplantation.

1.1 Intestinal failure: 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 (e.g. those with Crohn’s disease) both causes coexist. Severe intestinal failure is rare, with a prevalence of no more than 2 in 100,000, and an incidence in the region of 1.5 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 first 6 months after injury. This encompasses hyperplasia and hypertrophy. The ileum is better at this than the jejunum. It is possible that the process is responsive to trophic factors, which may in the future provide useful therapeutic opportunities.

Intestinal failure should be anticipated in the patient with an ileostomy and <200cm small bowel, in the patient with <150cm with intact colon in continuity, and in the patient with a stoma or fistula output >1.5L/day.

The nature of the need for intravenous nutrition and intravenous fluid support is governed largely by the combination of the anatomy and its pathophysiological consequences. If there is a high output (meaning >1.5L) from stoma or fistula, then major electrolyte loss 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 (not electrolyte) problems. In these patients intravenous nutrition will be the priority and will often not be needed 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>Component</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and drink</td>
<td>1500ml</td>
</tr>
<tr>
<td>Saliva</td>
<td>750ml</td>
</tr>
<tr>
<td>Gastric secretion</td>
<td>1250ml</td>
</tr>
<tr>
<td>Biliary secretion</td>
<td>1000ml</td>
</tr>
<tr>
<td>Pancreatic secretions</td>
<td>1000ml</td>
</tr>
<tr>
<td>Jejunal secretion</td>
<td>2500ml</td>
</tr>
<tr>
<td>Total</td>
<td>8000ml</td>
</tr>
<tr>
<td>Stool liquid</td>
<td>150ml</td>
</tr>
</tbody>
</table>

It is easy to appreciate that in intestinal failure from short bowel syndrome the intestinal effluent volume may exceed 5L/day. As a simple teaching aid to help junior and non-clinical staff and patients, one can ascribe all of the fluid entering the gut to sites proximal to the junction of the...
jejunum and ileum, and all of its (re-)absorption distal to this. A stoma at this point can then be seen to have obvious but also comprehensibly adverse effects.

1.1.2 The length of the intestine and gastrointestinal losses
The volume of the intestinal effluent (whether from stoma, fistula or from the anus) can be seen to be proportional to the remaining jejunal length. Positive fluid balance requires about 1 metre. It is useful to have the concepts of net absorption and net secretion in mind when considering the affected patient. 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. 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 by man 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 fine as there is plenty of more distal small bowel and the whole colon for reabsorption of sodium and water. However, if substantially less than 1.5m of small intestine exists, this normal proximal secretion is not compensated. Thus the more that is drunk the less that is absorbed. Dehydration as in the normal individual provokes thirst and drinking, but this generates increased fluid loss from the bowel and further deterioration. The need to introduce free fluid restriction to combat this effect is the central challenge of management of the short bowel syndrome patient. 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 Intestinal failure and the colon
In the healthy individual the colon is important but not critical to intestinal fluid balance. The patient who has needed total colectomy and ileostomy but who has no small bowel disease, also, will not normally require any special nutritional or fluid balance measures. The colon does however take on greater importance in the patient with a shortened small intestine (3). Even as little as 50% of the colon will be able to compensate usefully for some of the fluid handling properties of the ileum. A functional retained colon (>half) may be considered, in this respect, equivalent to about 50cm of small intestine. Although its value is mainly in fluid balance, there may also be some nutritional gain from fermentation of unabsorbed carbohydrate.

2. Assessment of the patient with short bowel syndrome and intestinal failure
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 osmolality, 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. 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 asymptomatic patient. It is more informative, in the early stages of intestinal failure and in its on-going management, to monitor the body weight serially, and to look for postural change in the blood pressure. The most helpful laboratory parameter is usually the urine sodium concentration (4). 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 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.

3. Short bowel syndrome: management
In therapy of short bowel syndrome the aim is to reduce gut secretions, to slow the speed of transit, and to prevent deficiencies of specific nutrients. The most urgent element however is to identify and to treat elements of dehydration and to avoid precipitating the refeeding syndrome. Once these
have been achieved the process of evolution to a stable long-term nutritional regimen will take priority.

3.1 Management of dehydration in short bowel syndrome
When dehydration is severe it will often be necessary initially to use intravenous saline to render the situation safe, but then, and in those with more moderate dehydration, oral rehydration solutions may be sufficient. Once the fluid balance is corrected it may be enough to limit free fluids (perhaps to 750mL or 1L/day), with no other fluid specific measures.

It will be understood that the aim is not only to reduce the oral intake of hypotonic fluid but also to increase sodium intake in general. This can be done effectively by the addition of table salt to food, by the strategic use of high sodium content oral rehydration solutions, as well as by parenteral sodium administration. Sodium tablets are generally not helpful, and slow-release, waxed preparations of sodium are almost completely ineffective.

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 (5). However, it should be considered seriously, as indeed in all malnourished patients. The possibility should always 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 in intestinal failure 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.

3.3 Enteral options in intestinal failure and short bowel syndrome
Contrary to beliefs held by many non-experts it is beneficial to employ enteral feeding in short bowel syndrome patients and usual that this is possible. It is of course the case that enteral nutrition will generally be insufficient (as is constituent to some definitions of intestinal failure), but this does not negate the considerable gains to be accrued from at least a percentage of nutritional requirements to be accessed by the normal route.

3.3.1 Food selection
Food selection in intestinal failure should be with regular food, preferably of high energy density. 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 in those with short bowel syndrome 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 a terminal 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).

3.3.2 Formula feeds
Formula feeds and prepared supplements may be helpful in intestinal failure because of their energy density and convenience but are certainly not mandatory if food is preferred by the patient. When used in short bowel syndrome they should never be elemental because the combination of high osmolality, low energy density, high volume and relatively poor palatability goes precisely against the main principles of enteral provision in this condition. There is no evidence that polymeric feeds are inferior to semi-digested ones and there is no clear advantage to modified/supplemented feeds. Regular (1kcal/ml) or high energy (1.3-1.5kcal/ml) feeds can therefore be employed as determined by the patient’s needs and tolerance of osmolality.

3.3.3 Use of oral rehydration solutions in short bowel syndrome
A simple electrolyte mix designed to optimise sodium absorption differs little from the original World Health Organisation prescription, and its continued sodium concentration of 90mmol/L is important in management of short bowel syndrome. However, the jejunum maintains a secretory response until the luminal sodium is around 100mmol/L, so even this will do no more than stabilise sodium status in a net secretor.
20g glucose
3.5g sodium chloride
2.5g sodium bicarbonate or sodium citrate

The option of bicarbonate or citrate has little impact on the efficacy of the solution but lends very different tastes thus allowing patients to choose which they prefer. Flavouring with fruit concentrates is also possible. The commercially available rehydration solutions are generally too low in sodium content but can be used successfully when made up to double strength.

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. When there is any doubt enteral therapy should be tried first. The key elements of enteral therapy in short bowel syndrome then are to limit free fluid intake to around 500mL/day, to add 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 The antisecretory regimen

Although there is much reference to antisecretory regimens in intestinal failure, there is little evidence-based support for antisecretory drugs (2). Proton pump inhibitors do however have an important role in reducing the total volume of gastric secretion, since most of this volume is from the secretion of acid. 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. 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 100mcg thrice daily) and to continue this only if there is obvious measurable benefit in fluid balance. In the author’s experience this will apply in fewer than 5% of patients. Newer drugs such as teduglutide - an analogue of the gut hormone glucagon-like peptide-2 (GLP2) - may prove more valuable, but are not yet generally available.

3.5 Parenteral therapy - fluids

In patients with extreme short bowel syndrome and in those who have failed to achieve fluid balance with the measures described above will need parenteral therapy. This will encompass all the components of enterally based regime (but these can be imposed less rigidly). If the parenteral fluid requirement is less than 1L/day the use of subcutaneous fluid is worth considering. This is remarkably well tolerated by many patients, is safer than the intravenous approach, and allows for up to 150mmol of sodium, about 8mmol of magnesium and a litre of fluid to be given each day. Preferred sites include the abdominal wall and the 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.

3.6 Intravenous nutrition in intestinal failure

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. This can be initiated to a routine carbohydrate/lipid/amino acid format modified to incorporate the additional sodium, magnesium, and volume that will be needed in the short bowel patient, as well as normal provision of all the micronutrients. Overall volumes may, conversely, need to be limited in some patients with an intact but non-functional intestine. This is particularly the case in patients with systemic sclerosis (scleroderma) who frequently have impaired cardiovascular reserve and who will not tolerate large volumes.

Once the patient is securely established on intravenous nutrition it will usually be appropriate for discharge from hospital on home parenteral nutrition. In different healthcare settings the responsibilities of patient and carer will differ, but the ambition in the UK is for the weekly or
fortnightly delivery of a complete, pharmacy-prepared feed, which is administered personally by
the patient using full aseptic techniques.

3.6.1 Avoiding chronic cholestasis
Once stable, and once previous lost weight is regained, but no later than 3 months after the
initiation of intravenous nutrition, the prescription should be modified to reduce the provision of
lipid calories. It is now clear that long-term provision of more than about 3000kcal lipid per week is
strongly associated with the later development of intravenous nutrition-related cholestasis and
subsequent liver failure (6). Administration of lower amounts of long-term lipid reduces the lifetime
risk of liver failure to below 1%.

4. Intestinal failure and home parenteral nutrition - the prognosis

Given the option of intestinal transplantation it is important to consider the safety and long-term
prognosis of home parenteral nutrition (HPN). A risk of death exists and is both from the nutritional
therapy and from the underlying disease. The complications of intravenous nutrition are well known
and are addressed in more detail in other LLL modules, but include sepsis, thrombosis and
cholestasis. Each of these occurs in long-term intravenous nutrition and inevitably in home
parenteral nutrition (7). Intestinal transplantation also has its mortality rate and long-term data are
currently more limited. Deaths are from sepsis, rejection and lymphoma as well as from the
underlying disease process as is of course the case also for HPN.

5. Intestinal transplantation

Intestinal transplantation is being performed more readily in patients with intestinal failure and the
results are clearly improving (8). 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. Although there have been important advances in the immunosuppressive regimens
employed these have not individually influenced outcomes tangibly. Outcomes are not influenced
much by the age of patient, or whether the donor is cadaveric or live-related.

6. Potential advances in management of intestinal failure

There is significant research effort being expended on intestinal failure, and several drugs and
possible trophic factors are under investigation.

6.1 Hormones and trophic factors

Work with GLP2 is among the most advanced of these. It is a naturally occurring gut-specific trophic
peptide secreted by intestinal L cells in ileum and colon in response to enteral nutrition. Its longer
acting analogue teduglutide is resistant to dipeptidyl peptase IV and is probably more effective than
the native agent with particular benefit in fluid balance. There was a mean 800mL/day reduction in
faecal effluent in Phase II study (9). A placebo-controlled phase II/III trial has just been completed
and it proved difficult to retain blinding in patients with stomas because of visible stomal
hypertrophy in those (assumed to be) on active therapy. The full results of the study should be
available during 2008, but it seems probable that the drug will permit a reduction in the magnitude
of intravenous support, but that it will not alone replace the need for HPN completely.

Results from the considerable amount of work done with human growth hormone have been
somewhat inconsistent, and are confused by the inclusion, or not, of other agents such as
 glutamine. The most definitive of growth hormone studies (10) yielded positive results. Growth
hormone monotherapy (0.05mg/kg/d) was compared to placebo and increased intestinal absorption
and lean body mass, without major adverse effects, but the advantaged have not been felt of
sufficient magnitude to convince healthcare planners to authorise funding.
6.2 Other new drugs
Better antisecretory regimes may emerge from the introduction of new drugs such as racecadotril (which is a delta opioid receptor), SP-303 (a chloride channel blocker), 5-HT3 antagonists (eg alosetron), and other peptide manipulations (such as VIP antagonists). Gut-specific antibiotics for the common problem of small bowel bacterial overgrowth (eg rifaximin) may also be beneficial.

6.3 Other new approaches
New forms of assessment may also help in evaluations of new therapies, and the use of plasma citrulline as an accurate marker of functional small bowel mass is promising (11,12), and especially so if it proves also to have therapeutic potential.

Improvements in HPN admixtures, aiming for more physiological regimens, are desirable. The advantages of avoiding excess intravenous fat have been described above, but the use of lipid emulsions which more closely match endogenous circulating lipid profiles may yield greater benefits. There is already anecdotal support for protection from soya depleted lipid emulsions (13). Supplementary glutamine appears of no value (14), but other potential “nutriceutical” agents such as taurine, remain to be fully evaluated.

Central catheter complications responsible for infection/thrombosis and therefore the failure of HPN are important and there will always be scope for better intravenous catheter care. The striking data achieved in this regard from simple changes in ICU practice are of only tangential relevance but salutary (15).

7. Non-transplantational surgery for short bowel
Surgical reconstruction will 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 intact but defunctioned colon. More imaginative procedures have also been devised as exemplified by the Bianchi operation, and by serial transverse enteroplasty.

7.1 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 short section of intestine into a narrower segment of double the length (16). Functional results have been good in the small number of patients in whom this has been tried and there have apparently been no deaths.

Figure 1 The Bianchi operation
A) There is blunt dissection between the leaves of the mesentery to expose the vascular pedicles to both sides of the intestine (anterior and posterior as drawn). The intestine is then divided longitudinally between A and B.
B) The intestine is then sutured lengthwise (effectively joining the sites A to the sites B) creating two loops of equivalent length but narrower calibre. These are then anastomosed in an isoperistaltic fashion by joining X to Y.

7.2 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 (17). Early results of 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.

Figure 2 The STEP operation
The intestine is divided and resutured along a “zigzag” which has the effect of lengthening and narrowing. Courtesy of the International Serial Transverse Enteroplasty (STEP) Data Registry
http://www.childrenshospital.org/cfapps/step/index.cfm

8. A future artificial intestine?

The artificial intestine exists already in animal models, the organoid unit approach being the most advanced. Small intestine epithelial units are seeded onto tubular scaffolds, but there is a very high demand on source material, and alternative solutions are needed (18). Intestinal stem cell transplantation employing clusters of allogeneic cells harvested from intestine grown on denuded intestine pose one such approach (19), but in addition to the general problems of stem cell research, there is again a very high demand on source material.

The problems of combining absorptive, secretory, motor/propulsive and other functions in a single organ are clearly formidable but not so as to deter efforts with an artificial tissue engineered intestine. The tissue engineered artificial bladder devised for and now successfully used in microbladder patients provides an intriguing glimpse of this future (20).

9. Summary

Long-term 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 are currently disappointing and the more severely affected patient will generally need intravenous nutrition. This should not be exclusive since physical and psychological gain comes from eating. Additionally the over-provision of lipid must be avoided to minimise chronic liver disease. Intestinal transplantation is no longer experimental and should now be considered in all eligible patients.

References


