Alimentary Pharmacology & Therapeutics

Review article: intestinal failure

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SUMMARY

Intestinal failure is a specific disease entity resulting from intestinal resection or disease-associated malabsorption and characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance. We performed a MEDLINE search (1966–2006) to identify relevant articles, using keywords intestinal failure, parenteral or enteral nutrition, intestinal fistula and short bowel syndrome.

Causes of intestinal failure are varied, with self-limiting or 'Type 1' intestinal failure occurring relatively commonly following abdominal surgery, necessitating short-term fluid or nutritional support. The rarer, 'Type 2' intestinal failure, is associated with septic, metabolic and complex nutritional complications, usually following surgical resection in patients with Crohn's or mesenteric vascular disease. A multidisciplinary approach to the management of patients with Type 2 intestinal failure is crucial: resolution of sepsis is required before adequate nutritional repletion can be achieved, and it is important to optimize nutritional status, not only through enteral or parenteral supplementation, but also by addressing complications of short bowel syndrome, before considering definitive surgical reconstruction.

A structured approach to the management of Type 2 intestinal failure should reduce the likelihood of these complex patients developing 'Type 3' intestinal failure, which is characterized by the need for long-term parenteral nutrition.

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DEFINITION AND CLASSIFICATION

The term 'intestinal failure' was originally defined by Fleming and Remington as 'a reduction in the functioning gut mass below the minimal amount necessary for adequate digestion and absorption of food'.[1] This has often been used synonymously to describe those patients who require parenteral nutrition (PN) to survive, without taking into account the many patients who may simply require fluid and/or electrolyte support; to reflect this, a more recent definition states that intestinal failure occurs 'when there is reduced intestinal absorption so that macronutrient and/or water and electrolyte supplements are needed to maintain health and/or growth'.[2] While it is clear from both of these definitions that post-operative structural loss of intestine may be equally as likely to lead to intestinal failure as disease-related functional loss, neither of the definitions mention disease aetiology. An international consensus group recently attempted to address this issue by proposing that intestinal failure 'results from obstruction, dysmotility, surgical resection, congenital defect or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance'.[3]

It follows from the latter definition that, as potential aetiologies are wide, the resultant intestinal failure can be of varied duration and severity. Fortunately, chronic (or permanent) intestinal failure is much less common than acute (reversible within 6 months) intestinal failure, which occurs often in the post-operative period.[2] A novel classification of intestinal failure was recently devised to reflect this: Type 1 intestinal failure is classified as self-limiting intestinal failure as occurs following abdominal surgery; Type 2 is intestinal failure in severely ill patients with major resections of the bowel and septic, metabolic and nutritional complications requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery; Type 3 is chronic intestinal failure requiring long-term nutritional support.[4] The majority of patients with Type 1 intestinal failure are managed in non-specialist units and receive fluid, electrolyte, enteral and/or parenteral nutritional support for a limited period of time, before making a full recovery without complication. There have been a number of recent articles (e.g. Howard and Ashley[5] and Buchman *et al.*[6]) delineating the management of patients with established short bowel syndrome (SBS) and those requiring long-term PN (Type 3 intestinal failure). The main focus of this paper will be the management of patients with Type 2 intestinal failure, based largely on the experience of one of the two national intestinal failure units (IFUs) in the UK.

TYPE 2 INTESTINAL FAILURE

In 1980, Prof. Miles Irving established the first IFU in the UK in Hope Hospital, Salford, as a four-bedded unit for patients with complex intestinal disorders, requiring control of abdominal sepsis, intensive nutritional support and often major surgery.[7] This IFU expanded to a 13-bedded unit in the late 1990s and, together with its sister unit at St Mark's Hospital, London, received funding in 1997 from the Department of Health to act as national referral centres for the management of patients with severe intestinal failure.

AETIOLOGY

Type 2 intestinal failure can result from a variety of conditions affecting the gastro-intestinal tract (Figure 1). Intestinal volvulus, strangulated hernia, mesenteric thrombosis and abdominal TB were principal causes in the earlier part of the last century.[8] While patients with mesenteric vascular disease still form a major component of all admissions to the two national IFUs, Crohn's disease has been the most common underlying condition responsible for intestinal failure since the units were founded in the early 1980s.[7, 9] Indeed, there has been very little change at this insti-

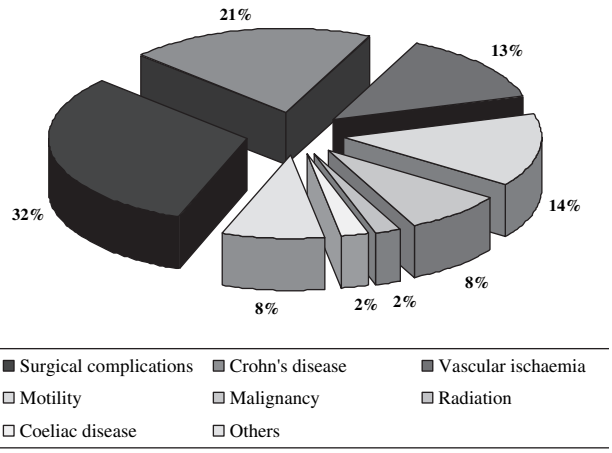

Figure 1. Disease spectrum of patients with Type 2 intestinal failure admitted to Hope Hospital intestinal failure unit (2002–2005; $n = 134$).

tution in disease aetiology since the unit was founded 25 years ago.[9] Patients with underlying malignancy are rarely referred for intestinal failure management and cancer patients rarely receive home parenteral nutrition (HPN) in the UK.[10] By contrast, cancer was reported as the second commonest underlying condition in patients on HPN in one large American series;[11] the exact reason for this discrepancy in trans-Atlantic practice is unclear, although cancer is certainly a major indication for home enteral nutrition in the UK.[10]

In broad terms, intestinal failure can result from intestinal resection, inflammation or fistulization, from mechanical or functional intestinal obstruction, or indirectly from the effects of sepsis on the gastrointestinal tract (see later).[12] These processes may act alone or – as occurs more commonly in clinical practice – together to cause intestinal failure; it is not uncommon, for example, for a patient to present with Type 2 intestinal failure following massive resection of infarcted small bowel with subsequent sepsis secondary to intra-abdominal abscess formation with fistulization after anastamotic leakage. It is certainly more common for patients with Crohn's disease to suffer intestinal failure following complications of surgical treatment than as a consequence of extensive primary disease.[13] A recent audit at our unit, for example, revealed that 16 of the 26 patients (62%) admitted over the last 3 years with Crohn's disease had undergone surgery in the 12 months prior to admission.

As interplay between a number of factors can lead to the development of intestinal failure, patients can present with a variety of complex and challenging problems, and a set of criteria has been devised to clarify the indications for referring such patients to a specialist unit (Table 1). Although the threshold for referral will depend on the expertise and facilities available in the referring hospital, there does seem to be geographic variation in referral rate to the specialist units in the UK (Figure 2). In 2004, for example, 8.1/million of the Northwest population required admission to Hope Hospital IFU, whereas only 1.7/million of the West Midlands population were referred for specialist management. Whether this reflects a lower prevalence of Type 2 intestinal failure in the latter region or, more likely, reduced referral of such patients, remains to be determined.

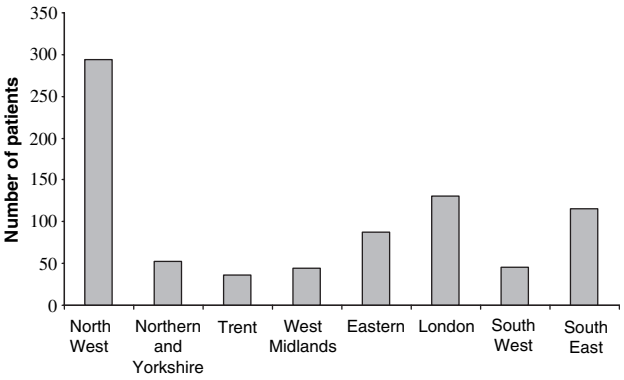

Figure 2. Residence of all new referrals to two National intestinal failure units (1999–2005).

MANAGEMENT OF TYPE 2 INTESTINAL FAILURE

The multifaceted aetiology of Type 2 intestinal failure calls for a structured approach to its management. A patient malnourished following intestinal resection, for example, who develops intestinal fistula and abdominal sepsis secondary to anastamotic breakdown, will

Table 1. Criteria for referring patients with Type 2 intestinal failure to a specialist unit

Persistence of intestinal failure beyond 6 weeks and complicated by venous access problems
Multiple intestinal fistulae in a totally dehisced abdominal wound
Total or near total small bowel enterectomy (<30 cm of residual small intestine)
Recurrent venous access problems in patients needing sustained parenteral nutrition
Persistent abdominal sepsis, not responding to radiological and surgical drainage
Persistent nutritional or metabolic complications relating to high-output fistulae and stomas, and/or to prolonged intravenous feeding
Any patient with a persisting intestinal fistula beyond the expertise of the referring hospital

Adapted from Irving.[93]

require therapy for infection, as well as nutritional and metabolic support, and surgical repair. Intestinal failure in such a patient will not only result from a short bowel secondary to resection and fistula formation, but also from the indirect effect of sepsis on gastro-intestinal function. There is a clear temporal sequence in managing the various facets of intestinal failure in these patients; resolution of sepsis is of prime importance before intestinal function and nutritional status can be restored, and nutritional repletion is vital before considering further reconstructive surgery. A therapeutic strategy that can be adopted, termed the 'Sepsis-Nutrition-Anatomy-Plan' or 'SNAP' approach, serves as a useful guide to managing Type 2 intestinal failure (Table 2; Williams *et al.*[14]).

SEPSIS

Localized abscess collections occur commonly in patients with intestinal failure of a variety of causes, particularly in association with intestinal fistulas.[12] Sepsis was identified as the principal cause of death in patients with intestinal failure over 25 years ago[15] and, despite advances in therapy, the same is true today. Of the 15 patients with Type 2 intestinal failure who have died on the IFU at Hope Hospital over the last 3 years, sepsis was the immediate cause in 10.

This detrimental effect of sepsis on survival is multifactorial. Active infection, for example, leads to impairment of a number gastro-intestinal functions, such as nutrient transport,[16] intestinal motility,[17] enterocyte proliferation and apoptosis,[18] and mucosal barrier function[19]. Furthermore, spontaneous healing of intestinal fistulas is less likely in the presence of ongoing sepsis.[20, 21] Not only does it compromise intestinal function and healing, sepsis is also associated with increased metabolic demand and impaired fuel utilization, particularly as a consequence of loss of the anabolic effect of insulin (insulin resistance).[12, 22] The clinical impact of this process is demonstrated by the finding that insulin resistance adversely influences surgical recovery,[23] and that tight glycaemic control with insulin infusion improves post-operative outcome.[24]

Impaired intestinal function and increased metabolic demand in the septic patient leads to progressive weight loss,[12] which means that aggressive nutritional support is unlikely to be successful until the sepsis is investigated and treated;[25] this concept is fundamental to the 'SNAP' approach of managing Type 2 intestinal failure.

Table 2. The 'Sepsis-Nutrition-Anatomy-Plan' approach to the management of intestinal failure

Sepsis
Cultures and swabs
Abdominal imaging
Other sources of infection: e.g. respiratory tract infection, bacterial endocarditis
Nutrition
Dietetic assessment
Supplemental feeding and route: enteral vs. parenteral (peripheral vs. central)
Anatomy
Contrast studies for intestinal length and fistulae definition
Plan
Multidisciplinary approach
Timing of surgery if indicated (early to resolve uncontrolled sepsis vs. elective)
Metabolic and nutritional optimization
Wound/stoma care
Management of short bowel syndrome
Management of underlying disease and complications related to therapy
Training and support if home enteral or parenteral nutrition required

Investigation of sepsis

Sepsis should be sought in all patients with intestinal failure who fail to thrive. It is, however, crucial to recognize that classical signs such as pyrexia or leucocytosis may be absent in patients with intra-abdominal abscesses contained within a wall of fibrin and collagen.[26] Nearly all of the 134 patients with Type 2 intestinal failure admitted to Hope Hospital IFU over the last 3 years were eventually found to harbour infection, but <50% displayed direct evidence of this in the form of abnormal physical findings, leucocytosis or elevated inflammatory markers at presentation. Indeed, more subtle features such as cachexia, hypoalbuminaemia, hyponatraemia and abnormalities in liver function will often indicate occult intra-abdominal sepsis.[27, 28] Standard investigations in the form of blood cultures (from both peripheral veins and any indwelling central lines), urine cultures, wound swabs (including screening for methicillin-resistant *Staphylococcus aureus*) and chest X-rays are performed on all patients admitted to the IFU as routine (Table 2).

Radiological imaging of the abdomen forms a key part in the diagnostic assessment of all patients with Type 2 intestinal failure. Computerized tomography (CT) is the modality of choice to identify abdominal or pelvic abscesses and has a diagnostic accuracy of >95%.[27] Intestinal and intravenous contrast can be used to enhance definition of a cavity wall, but differentiation between sterile and infected fluid collections may require CT-guided sampling of the fluid.[28] Abdominal ultrasound has the advantages of cost-effectiveness, lack of radiation and increased mobility; the latter being particularly beneficial for the critically ill patient on the intensive care unit. However, the diagnostic accuracy and inter-observer agreement of ultrasonography is inferior to that of CT in investigating post-operative intra-abdominal sepsis,[29] and its use in this setting may also be limited by the presence of surgical wounds, drains and by the presence of an ileus.[28] Radionuclide studies may play a role in those patients in whom the results of anatomic imaging are negative or at odds with the clinical impression, but false-positive results can occur because granulating wounds can manifest as areas of increased activity on leucocyte scans even in the absence of infection.[30] Magnetic resonance imaging is useful for assessing peri-anal disease,[31] but, unlike CT, does not allow for drainage of abdominal collections while the patient is in the scanner. Although the development of cross-sectional imaging techniques has meant that CT has replaced fluoroscopic studies in the initial radiological evaluation for possible intestinal fistulas, radiological contrast studies, including fistulography, still play a crucial complementary role in delineating post-operative intestinal anatomy and anomalous connections.[32]

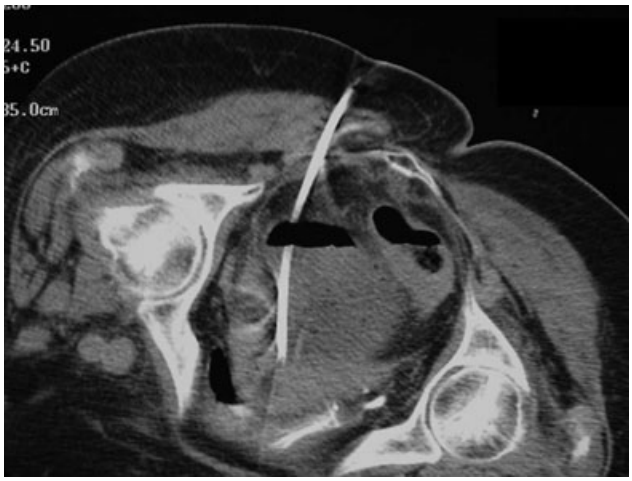

Figure 3. Management of an intra-abdominal abscess with computerized tomography-guided percutaneous drainage.

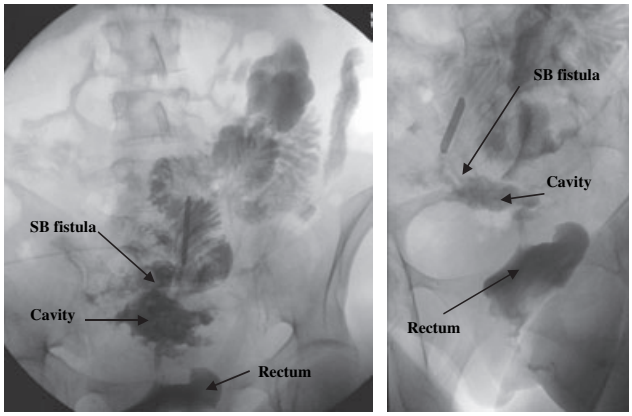

Figure 4. Contrast study demonstrating an enterocavitary fistula between the small intestine and rectum.

Treatment of intra-abdominal sepsis

The finding of an intra-abdominal collection necessitates immediate drainage.[33] Percutaneous insertion of one or more drains under CT guidance is now the standard first-line approach in the management of abdominal or pelvic abscess cavities (Figure 3).[28] Inaccessibility of the cavity rarely precludes CT-guided drainage, as trans-gastric, trans-gluteal, trans-vaginal, trans-rectal or even trans-hepatic approaches can be used as an alternative to the direct percutaneous route to facilitate drainage of deep-seated collections.[34] Antibiotic therapy, guided by results of aspirate culture, plays a complementary role, particularly if there are systemic features of infection such as pyrexia or leucocytosis; however, antibiotics alone will not lead to complete resolution of the cavity unless combined with a drainage procedure.[33] Persistently high-volume drainage from the abscess should lead to the suspicion of an associated enterocavitary fistula, which is said to complicate 15–44% of all intra-abdominal abscesses and may only be demonstrated on follow-up contrast studies (Figure 4).[35] Thus, the drain(s) should be kept *in situ* and irrigated with saline on a daily basis. Complete resolution of the abscess and closure of any associated fistula may take weeks, and many patients can be discharged from hospital and taught to care for and irrigate their drains at home. Removal of the drain

should not be considered until drainage from the catheter ceases and, importantly, follow-up contrast study through the catheter demonstrates complete cavity collapse. CT-guided drainage will lead to resolution of most of intra-abdominal or pelvic abscess cavities; those associated with low-output enteric fistulas have been shown to resolve in 84% of cases.[36]

Surgical intervention will occasionally be required for complete resolution of the abscess cavity; this is more likely with the associated presence of multiple interloop abscesses, a high-output enteric fistula feeding the cavity, marked lack of intestinal continuity or obstruction distally, extensive anastamotic breakdown or high-fluid viscosity.[35] Attempted radiological drainage still has a role in these settings by assisting in the control of sepsis, allowing nutritional support and allowing careful definition of intestinal anatomy before operation (Table 2).

A number of surgical strategies may be adopted in the management of abdominal sepsis associated with intestinal fistulas (for review see Carlson[33]), but a cardinal feature of all should be to avoid primary anastamosis in the presence of sepsis. If a fistulating segment of intestine is resected, the ends should be exteriorized as stomas; alternatively drainage and proximal diversion of the gastro-intestinal tract may be appropriate. In certain intractable circumstances, the abdomen may be left open, to allow drainage of the fistulating segments, and allowed to heal by granulation (Figure 5).[37] Whatever the initial surgical approach, subsequent restoration of intestinal continuity should not be considered until the sepsis has completely resolved and the patient's nutritional status has been optimized – a process which may take many months.

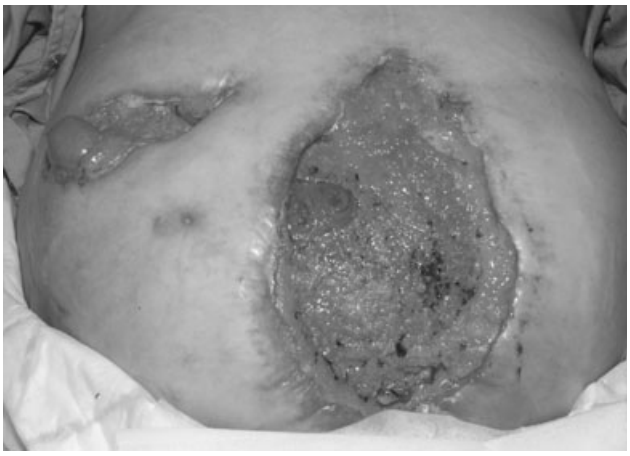

Figure 5. Laparostomy wound.

NUTRITION

The aim of nutritional support is twofold. First, it is important to replenish nutrients in the often malnourished patient with Type 2 intestinal failure. For example, two-thirds of patients admitted to Hope hospital IFU between April 2004 and March 2005 had a Body Mass Index (BMI) of <18.5. Secondly, as malnutrition is associated with impaired immune response [38] and wound healing,[39] it is crucial to maintain adequate basal requirements of energy and nitrogen while the patient recovers from the precipitant of his/her intestinal failure.[12] However, it is worth reiterating that resolution of sepsis is a fundamental requirement for replenishing and maintaining adequate nutritional status. It has been shown that despite the provision of adequate nitrogen and caloric requirement in excess of metabolic expenditure, septic patients will remain catabolic and continue to lose substantial amounts of protein.[40]

Assessment of nutritional status

There is no universally agreed, single measurement of nutritional status and so a variety of parameters are taken into account when assessing the nutritional status of a patient. Weight and BMI provide simple and objective measures, but caution is required in patients with precarious fluid balance, such as those with high-output stomas, oedema or severely malnourished patients undergoing initial refeeding, as rapid fluctuations in weight are likely to reflect changes in hydration, rather than lean body mass. Recent weight loss is a crude yet useful predictor of outcome.[41] Body composition (fat and muscle status) should be estimated from bedside techniques such as triceps skin-fold thickness and mid-arm muscle circumference.[42] A point of note in such anthropometric assessment is that the same, experienced individual should perform all the measurements to reduce inter-observer variability.[43] Biochemical measurements are not routinely used to assess nutritional status; indeed, it is important to recognize that serum albumin is an inappropriate marker of nutritional status,[44] not least because (i) inflammatory disorders *per se* are associated with a reduced level,[45, 46]; (ii) the serum albumin can be normal in cases of severe malnutrition, such as anorexia

nervosa;[47] and (iii) hypoalbuminaemia may result from excessive administration of intravenous saline.[48]

Fluid balance studies are also crucial to the assessment of patients with Type 2 intestinal failure. Careful records of daily input against urine output, stoma and fistula output are necessary in all patients with Type 2 intestinal failure, while weekly assessment of urinary electrolytes will provide essential information regarding an individual's fluid status. Nutritional and fluid status assessment is a continual process that should occur on a day-to-day and week-to-week basis by nursing, medical and dietetic staff, gauging the patient's ability to manage oral supplements, enteral feeding and/or parenteral feeding, with appropriate adjustments if requirements are not met.

Mode of nutrition

The route and quantity of nutritional supplementation in patients with Type 2 intestinal failure should be tailored to the individual's needs. Detailed discussion of the refeeding syndrome is beyond the realm of this study, but, suffice it to say, when instituting nutritional support in any patient, initial electrolyte and vitamin replenishment and subsequent monitoring of fluid, glucose, sodium, potassium, magnesium, calcium and phosphate levels is vital to avoid the potentially life-threatening complications of this syndrome (for review see Stroud *et al.*[49]).

There has been a long-standing debate as regards the pros and cons of enteral vs. PN.[50] Proponents of enteral nutrition would argue that its benefits lie in a reduction in infective risk,[51] principally by promoting gut-barrier function.[52, 53] However, there is little evidence that enteral nutrition reduces bacterial translocation or enhances gut-barrier function in humans.[54] Moreover, the greater infective risk said to be associated with the parenteral when compared with enteral route may have been as a consequence of poor catheter care leading to line infections or as a result of parenteral overfeeding and hyperglycaemia, which itself may predispose to sepsis.[50]

Enteral nutrition is certainly the modality of choice in patients with a functional gastro-intestinal tract. Mucosal disease, intestinal obstruction, short bowel and intestinal fistulas will limit its use in intestinal failure to variable degrees. While there is no evidence that enteral nutrition will be detrimental to post-operative anastamotic integrity or hinder the spontaneous closure of intestinal fistulas,[12] it may be detrimental if the fistula is feeding a blind-ending, non-draining abscess cavity. Enteral feeding will be of limited nutritional benefit in patients with very proximal small intestinal fistulas, and may also exacerbate their (already high) output. In such patients, insertion of a gastrostomy feeding tube into the intestine distal to the fistula (fistuloclysis) has proven a successful means of providing enteral nutrition, and this can obviate the need for – or, at least, reduce the energy and/or fluid requirements of – parenteral feeding prior to reconstructive surgery.[55]

Experience in PN has gathered apace over the latter part of the last century, and the survival of patients on long-term PN is now determined principally by the underlying disease rather than by complications of feeding.[5] Improved catheter care, and in particular the use of dedicated central venous catheters for nutrition alone through single lumen catheters has certainly led to a reduction in PN-associated infective complications.[56] Indeed, optimal aseptic care of intravenous feeding catheters of all patients, whatever the severity or duration of intestinal failure, should be the rule, in order to reduce later problems with venous access should the patient require long-term PN. The short-term use of peripheral venous cannulas or peripherally inserted central venous catheters (PICC lines) provides a safe alternative means of providing PN in Type 1 intestinal failure, although their use may be limited in patients with Type 2 intestinal failure, who will often have high energy and/or fluid requirements secondary to their hypercatabolic state and/or high-output enterocutaneous fistula respectively.[57] Insertion of a tunnelled, cuffed central line should be confined to those patients likely to require long-term PN.

A pragmatic approach is necessary when considering the optimum mode of nutritional support in intestinal failure; patients may require a varied combination of both enteral and PN according to the degree of dysfunction of their intestinal tract.[58] The most important factor is that patients receive adequate nutritional intake by whatever means, so that their clinical condition is optimized as they recover from sepsis and plans are made for the definitive management of their intestinal failure. This process can take several months, and patients may require parenteral and/or enteral nutrition at home.

ANATOMY

A detailed knowledge of intestinal anatomy is required before definitive treatment of intestinal failure, of

whatever cause, can be planned. In the absence of a specific marker of functional epithelial mass, the residual small intestinal length provides a surrogate prediction of nutritional deficiencies arising as a result of SBS. This can be measured using an opisometer in a small bowel contrast study if the length was not measured at the time of surgery.[59] Anatomical information may also be gleaned from contrast studies that may have been performed to investigate fistulating intestinal segments associated with abdominal or pelvic abscesses. However, complete assessment of the entire length of small and large intestine is required before planning reconstructive surgery, not least to rule out any strictured segments, which may predispose to future dehiscence of an anastamosis sited proximal to the stricture.[33]

Thus, all patients with Type 2 intestinal failure should undergo detailed anatomical assessment with oral and enema contrast studies, as well as fistulography, if appropriate (Figure 4). The timing of contrast studies is important as enteric contrast agents may produce artefacts on cross-sectional images, such that patients should undergo a CT scan first. Water-soluble iodinated contrast agents are preferred to barium when perforation or dehiscence is suspected, as there is a risk that extravasated barium may induce an inflammatory reaction in the peritoneum; this must be balanced against the greater sensitivity of barium studies for demonstrating gastro-intestinal fistulas, as barium yields greater radiographic opacity than water-soluble agents because it has a lower tendency to dilute.[35] Extra-intestinal internal fistulas may warrant additional evaluation by urography, vaginography or cholangiography if sufficient information is not obtained from the primary bowel study, and full assessment of such fistulas needs simultaneous assessment of cross-sectional images such as CT or magnetic resonance scans.[32]

PLAN

Making a long-term plan for a patient with Type 2 intestinal failure can only take place once progress is made towards resolving infections and improving nutritional status, as persistence of sepsis and malnutrition will prove the major cause of morbidity and mortality. Furthermore, reconstructive surgery cannot take place until a detailed knowledge of the patients residual intestinal anatomy has been acquired, which will also help predict, and therefore hopefully prevent, metabolic and nutritional complications of SBS.

A multidisciplinary team comprising dieticians, pharmacists, biochemists, enterostomal therapists, nurses, microbiologists, radiologists, pain specialists, surgeons and physicians should combine to provide appropriate input into the patient's care from the onset of intestinal failure, and the team will interact ultimately to guide definitive management. Depending on the nature of the patient's disease, particularly the presence of fistulizing disease, involvement of urologists, gynaecologists and/or plastic surgeons may be necessary. Support from a trained psychologist is essential throughout and following the patient's hospital stay. In this regard, it is perhaps important to realize that coping strategies may be different for patients with chronic diseases such as Crohn's or intestinal pseudo-obstruction who develop intestinal failure more gradually over a period of time, when compared with patients with massive intestinal infarction who can develop intestinal failure overnight.

Medical management

Underlying disease

A member of the multidisciplinary team not already mentioned is the pathologist. He or she plays a critical role in assessing the histological specimens of all patients with intestinal failure as a means of reviewing and, very occasionally, revising the primary diagnosis of all patients, particularly those referred for specialist management from other hospitals. A therapeutic strategy for controlling the primary underlying disease can then be devised. Patients with mesenteric vascular disease, for example, should be investigated with a thrombophilia screen and considered for long-term anticoagulation.[60] The use of corticosteroids or other immunomodulators, such as infliximab, in patients with Type 2 intestinal failure secondary to Crohn's disease may be unsafe given the likely presence of sepsis. The benefit of long-term treatments, such as azathioprine or methotrexate, in Crohn's patients with Type 3 intestinal failure who are dependent on PN, should, in the author's opinion, be balanced against the risk of these drugs predisposing to recurrent central venous catheter infections: in the absence of published guidance, decisions to institute immunomodulating therapy should be made on a case-to-case basis. Furthermore, it is also important to consider conditions co-existing

with the primary disease as potential causes of persistent weight loss, diarrhoea or failure to thrive in patients with intestinal failure. Examples of such diagnoses include celiac disease occurring in patients with inflammatory bowel disease [61] or small bowel bacterial overgrowth in patients with intestinal dysmotility.[62]

Short bowel syndrome

Short bowel syndrome is commonly associated with Type 2 intestinal failure and is said to occur when <200 cm of small intestine remains following resection.[6] To define SBS by specific length in this way may be somewhat arbitrary, first, because the 'normal' length of the adult human small intestine ranges from 275 to 850 cm[63] and, secondly, because the function of the remnant intestine is not taken into account. In order to address this, an international consensus group have recently proposed a new definition of 'SBS-associated intestinal failure' as a clinical entity occurring secondary to 'surgical resection, congenital defect or disease-associated loss of absorption and characterized by the inability to maintain protein energy, fluid, electrolyte or micronutrient balances when (the patient is) on a conventionally accepted, normal diet'.[3]

The degree of intestinal dysfunction in SBS is difficult to quantify objectively. Plasma citrulline concentration has been proposed as a measure of enterocyte function, that may also predict dependence on PN, although its use in clinical practice requires further validation.[64] For the time being, the degree and nature of nutrient, fluid or electrolyte imbalance secondary to SBS may be predicted by the length and also by the anatomical site of the intestinal segment diseased or resected. Very little water or sodium absorption takes place in the proximal 100 cm of jejunum and secretory loss into the lumen is characteristic.[65, 66] Jejunal mucosa has more porous intercellular junctions than the ileum so that osmotic water fluxes are greater in the jejunum, allowing its contents to become isoosmolar.[67] The colon also has a vital role in fluid and electrolyte re-absorption, with the capacity to absorb up to 6 L of fluid daily.[68] Thus, patients with SBS can be divided into two broad groups, largely based on these physiological absorptive or secretory functions:

1 Those with an end-jejunostomy. Patients with more than 100 cm of residual jejunum are usually able to absorb more sodium and water from an oral diet and attain a positive balance; those with <100 cm are less able to do so and from balance studies will be net 'secretors', usually necessitating parenteral fluid supplementation.[69]

2 Those with a jejunocolonic anastamosis. Colonic absorption of electrolytes and water means that patients with this type of anastamosis can be independent of supplemental parenteral fluids.[70]

Patients with a jejuno-ileal anastamosis have classically been categorized as a third group of SBS patients.[71] In practice, however, such patients are uncommon, not only because Crohn's disease, a common cause of intestinal failure, is more likely to affect the terminal ileum, but also because, if the jejunum is resected, the remnant ileum may adapt both structurally (through lengthening and hypertrophy) and functionally to increase nutrient absorption.[72] The jejunum can also adapt functionally to enhance its absorptive capacity if the colon is in continuity, and this process, termed 'intestinal adaptation', may account for the ability of some patients with SBS to reduce their PN requirements after many months.[73] A number of local and systemic, nutrient and non-nutrient factors have been proposed to promote intestinal adaptation[74] and, of these, factors such as growth hormone[75] and glucagon-like peptide-2[76] have received recent attention through attempts to develop their pharmacological role in promoting intestinal adaptation in SBS.

Excessive secretory losses from intestinal stomas and/or enterocutaneous fistulas are common problems encountered in Type 2 intestinal failure. A variety of nutritional and pharmacological measures can be adopted to limit such losses in an attempt to maintain protein-energy, fluid, electrolyte and micronutrient balances (for detailed review see Buchman *et al.*[6]). For example, it is important to restrict the oral intake of hypotonic fluids (500–1000 mL/day) in patients with a high-output jejunostomy, while encouraging the use of an oral glucose-electrolyte solution (with a sodium content of 120 mmol/L) to replenish sodium losses and maintain hydration.[77] Such measures should be used in tandem with high-dose antimotility agents, such as codeine phosphate and loperamide[78] and antisecretory agents, such as omeprazole[79] or octreotide,[80] although the benefit derived from the latter is often limited. Moreover, it is crucial to continue these measures should the patient require PN, not only to limit the amount of parenteral support required (and therefore reduce any associated complications), but also to limit painful wound irritation secondary to corrosive stomal and/or fistula contents.

Complications of therapy

It is not only important to consider the underlying disease, but also complications of therapy as potential causes of morbidity in patients with Type 2 intestinal failure. For example, prior corticosteroid therapy in patients with inflammatory bowel disease may place them at increased risk of Addison's disease, and presenting features of this disease in patients with intestinal failure may be atypical given that the administration of PN may mask any associated electrolyte abnormalities.

Similarly, hepatobiliary problems are not uncommon in patients with Type 2 intestinal failure, and again, these may result from the underlying condition itself or from complications of therapy. For example, sepsis can induce hepatic dysfunction,[81] as can the antibiotics that may be used to treat it.[82] Rapid weight loss, particularly protein-calorie malnutrition is associated with steatosis,[83] and conversely, hepatic dysfunction is also a well-recognized complication of PN (for review see Buchman[84]). A transient rise in serum transaminase concentrations occurs commonly within 1–2 weeks of starting PN[85] and persistently abnormal hepatic function has been reported to occur in up to 39–52% of patients on long-term PN,[86, 87] particularly in patients with a shorter bowel [86] or who have associated small intestinal bacterial overgrowth.[88]The predominant histological finding in adult patients with PN-associated liver disease is steatosis, although signs of intrahepatic cholestasis are also usually evident.[84] Clinical presentation with long-term PN can vary from incidental, stable mildly abnormal liver function tests,[86] to decompensated liver disease with evidence of portal hypertension.[87]

It is often difficult to determine the degree to which hepatocellular dysfunction in Type 2 intestinal failure is a consequence of the underlying disease, nutritional support or drug therapy. Identification of potential pharmacological causes, such as high-dose proton pump inhibitors that may be used in the management of SBS, is clearly important, as is the recognition and resolution of any on-going sepsis. From a nutritional standpoint, there is evidence that calorie restriction, not only avoiding dextrose overfeeding,[84] but also limiting intravenous fat to 1 g/kg/day,[87] may be helpful in reversing PN-associated liver disease, while the use of ursodeoxycholic acid[89] may also prove beneficial in this setting.

Surgical management

Spontaneous closure of intestinal fistulas may occur within 6 weeks of their first appearance, but is less likely in the presence of continuing sepsis or malnutrition;[12] hence, again, the critical importance of resolving sepsis and optimizing nutritional status before considering surgical repair of persistent fistulas or considering restoration of intestinal continuity in patients who have previously undergone an intestinal diversion procedure. It may take several months for sepsis resolution before such definitive surgery can be considered and this may necessitate a prolonged period of home nutritional support, via the enteral (e.g. fistuloclysis[55]) and/or parenteral route.[90] Early definition of the patient's intestinal anatomy is equally important, not only in planning reconstructive surgery, but also in predicting fistula closure, as the latter will be impaired if there is mucocutaneous continuity, distal bowel obstruction, discontinuity of bowel ends or internal (e.g. vesico-colic) fistulization.

The optimal surgical approach to managing SBS is the restoration of intestinal continuity, since, as mentioned earlier, colonic re-anastamosis will promote jejunal adaptation.[73] A variety of other surgical procedures, aimed at increasing intestinal length and/or slowing transit to enhance nutrient absorption, have been tried with varying degrees of efficacy in reducing the PN requirements of patients with SBS associated with Type 3 intestinal failure.[33, 91] Intestinal transplantation is generally reserved for patients with intestinal failure who cannot be managed on long-term PN due to life-threatening complications,[92] although, in the UK, there have been very few adult intestinal transplants, largely due to the success of the HPN service offered.

OUTCOME OF TYPE 2 INTESTINAL FAILURE

The varied aetiology of Type 2 intestinal failure makes prognostic generalizations difficult. Furthermore, there are limited data available on the outcome (or aetiologies) of patients with Type 2 intestinal failure, who are managed at their local hospital. However, 1-year representative 'snapshot' of the outcome of patients treated at our unit may be most informative; of the 54 patients admitted with Type 2 intestinal failure to Hope Hospital IFU between April 2003 and March 2004, four died following surgery undertaken for intra-abdominal sepsis unresponsive to interventional

radiology and medical management. Fifty patients were discharged after a median in-patient stay of 69 days (range 3–410). Of these, 30 (60%) were solely dependent on PN, five (10%) received a combination of parenteral and distal enteral (fistuloclysis) feeding, four (8%) received gastrostomy or jejunostomy feeding and 11 (22%) were discharged tolerating a full oral diet. In this series, nine patients who had required HPN on discharge were independent of it 1-year later, and eight of these underwent reconstructive surgery during the course of that year.

CONCLUSION

Whilst Type 1 intestinal failure is quite common, fortunately, Type 2 (and Type 3) intestinal failure is relatively rare. Once Type 2 intestinal failure has developed, a structured, multidisciplinary approach – resolving sepsis, optimizing nutritional status, defining intestinal anatomy and then formulating a definitive management plan – is crucial in reducing the morbidity and mortality associated with this complex condition. Perhaps the optimum management strategy for Type 2 intestinal failure is to avoid its occurrence wherever possible; for example, by making an early diagnosis of a potentially ischaemic intestine or by adopting a careful surgical approach aiming to prevent adhesions and avoid technical errors that may lead to intra-abdominal sepsis or fistula development. Once intestinal failure has developed, careful timing of any further surgical procedures, in particular deferring definitive surgery if there is ongoing sepsis or the patient is malnourished, should serve to minimize further intestinal loss and, hopefully, obviate the need for long-term PN.

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