# Complications of Enterocutaneous Fistulas and Their Management

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**ABSTRACT**

Complications related to enterocutaneous fistulas are common and include sepsis, malnutrition, and fluid or electrolyte abnormalities. Intestinal failure is one of the most feared complications of enterocutaneous fistula management and results in significant patient morbidity and mortality. The authors review emerging trends in the medical and surgical management of patients with intestinal failure.

**KEYWORDS:** Enterocutaneous fistula, intestinal failure, short bowel syndrome, intestinal transplantation

**Objectives:** Upon completion of this article, the reader should: (1) be familiar with the etiology and pathophysiology of intestinal failure in patients with enterocutaneous fistulas; (2) be able to summarize the current and emerging medical treatment options for patients with intestinal failure; and (3) be able to summarize the surgical treatment options and results of small bowel transplantation for intestinal failure.

Enterocutaneous fistulas (ECFs) are associated with considerable morbidity and mortality. Recent case series suggest a mortality rate of 6 to 33%, with sepsis and concomitant malnutrition being the most common causes of death.[1] Increased mortality has been shown to be associated with high fistula output and the presence of infectious complications.[2] Edmunds et al identified the classic triad of complications of enterocutaneous fistulas as sepsis, malnutrition, and fluid or electrolyte abnormalities.[3]

Septic complications related to ECFs include localized abscess, soft tissue infection, generalized peritonitis, or frank sepsis. Early control of fistula output, drainage of localized collections, and appropriate antibiotic therapy are the keys to early management of these patients.

Postoperative ileus, sepsis, loss of bowel integrity and absorptive surface area, and the external loss of protein-rich enteric contents all contribute to the malnutrition and fluid and electrolyte abnormalities seen in patients with enterocutaneous fistulas.[4] Early correction of fluid and electrolyte abnormalities and the provision of nutrition (parenteral or enteral) are of paramount importance in minimizing or avoiding these complications altogether. In a significant number of patients with enterocutaneous fistulas, however, intestinal failure can ensue as a consequence of the natural history of the disease or as a consequence of attempted surgical management. The focus of this review is to summarize the diagnosis and management of intestinal failure in patients with ECFs.

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## INTESTINAL FAILURE AND SHORT BOWEL SYNDROME

### Definitions and Etiology

Intestinal failure has been defined as a reduction in functioning gut mass below the minimal amount necessary for adequate digestion and absorption of the nutrient and fluid requirements for maintenance in adults or growth in childen.[5] The severity of intestinal failure is usually determined by the nutrient and fluid requirements of the patient. In general, intestinal failure is severe when parenteral, moderate when enteral, and mild when oral nutritional supplements are needed.[6] Failure of the intestinal tract to maintain life in the absence of artificial nutritional support may arise from a variety of disease processes, but it typically manifests in the form of two separate clinical syndromes: acute and chronic intestinal failure.[7]

Acute or type 1 intestinal failure is common and frequently reversible. It may develop as a result of several underlying conditions including mechanical bowel obstruction, postoperative ileus, pseudoobstruction, massive enteric resection, inflammatory bowel disease, enteritis (infectious, radiation, chemotherapy-related), internal or external enteric fistulas, and intraabdominal sepsis. Most cases of acute intestinal failure are transient in nature and resolve spontaneously or with minimal nutritional support. In a subset of patients, however, the clinical course is complicated and often necessitates referral to a specialized intestinal failure unit where the majority of patients (>60%) will require surgical intervention.[8] In specialized centers, ~50% of acute intestinal failure is associated with intestinal fistulas and, in approximately half, this condition arises as part of the natural history or complicating treatment of Crohn's disease.[7]

Chronic (type 2) intestinal failure is much less common, usually irreversible, and frequently arises as a consequence of complications of surgical treatment. The most common cause of chronic intestinal failure is short bowel syndrome secondary to extensive small bowel resection. Other causes include chronic intestinal pseudoobstruction, enteritis (radiation-induced, Crohn's), refractory sprue, and congenital villous atrophy.[9,10]

The definition of short bowel syndrome is controversial; however, it is generally accepted to be a subtype of intestinal failure which follows massive small bowel resection and usually occurs when less than 200 cm of residual small bowel remains.[11] The severity of short bowel syndrome depends more on the functional quality of the remaining small bowel and whether or not the colon is preserved than the absolute length remaining. Mesenteric ischemia, volvulus, and malrotation account for a significant proportion of cases, whereas serial resections for recurrent Crohn's disease or attempted surgical repair of complex enterocutaneous fistulas can lead to the development of short bowel syndrome over time. Less commonly, short bowel syndrome occurs as a result of massive enterectomy for tumors involving the base of the small bowel mesentery, such as desmoids or angiomas.[12]

Not all patients with ECFs are doomed to develop chronic intestinal failure. The patient's ability to undergo further surgery to repair the fistula and restore gastrointestinal (GI) continuity, the remaining length of small bowel, the anatomy of the fistula, and the patient's ability to maintain a safe nutritional balance in the absence of nutritional supplementation are all important determinants of outcome.[13]

### Clinical Presentation and Diagnosis

Intestinal failure typically presents as malabsorption leading to intractable diarrhea and dehydration (secondary to high output losses from either an ECF, jejunostomy, or through the rectum), malnutrition, and weight loss. The specific clinical manifestations of short bowel syndrome are dependent on the type and extent of intestinal resection. There are three main types of patients with short bowel syndrome: those who have had a jejunoileal resection and a jejunocolic anastomosis ("jejunum-colon"); those who have had a predominantly jejunal resection and have greater than 10 cm of terminal ileum and colon remaining ("jejunum-ileum"); and those who have had a jejunoileal resection, colectomy, and creation of an end jejunostomy ("jejunostomy").[10,14]

Patients with the jejunum-colon subtype will often appear well after their resection except for diarrhea and steatorrhea, but over time, will lose weight and become severely malnourished. The jejunum-ileum patient rarely develops significant problems with absorption, but if they do, their clinical presentation will be similar to that of the jejunum-colon patient. Patients with a jejunostomy will experience dehydration almost immediately secondary to large stomal water and electrolyte losses. Patients with a high-output proximal ECF behave in a similar fashion to patients with a jejunostomy and, in effect, have a "functional" short bowel syndrome, as small bowel distal to the fistula is defunctioned.

The clinical assessment of a patient with intestinal failure should include an assessment of water, sodium, magnesium, and nutritional status.[10] Water and sodium deficiencies, most commonly seen in jejunostomy patients, may result in thirst, hypotension, and acute renal failure. It is essential to document daily body weight and fluid balance (including stomal and/or fistula output) to accurately replace these losses. Nutritional status may be predicted by recording body mass index, percentage weight loss, or serum albumin.

The diagnosis of short bowel syndrome is rarely in question, but a variety of methods can be employed to

quantify the predicted severity of disease. At the time of intestinal resection, the surgeon should make an effort to estimate the length of residual small bowel. Postoperatively, the length of residual small bowel can be determined with a small bowel radiograph using an opisometer, an instrument designed to measure the length of curved lines.[15] The functional residual intestinal length can also be measured using citrulline.[16,17] Citrulline is a nonessential amino acid produced almost exclusively by small intestinal enterocytes and is a reliable marker of intestinal enterocyte mass. In a study by Crenn et al, a serum citrulline level of less than 20 μmol/L (normal range 30 to 50 μmol/L) classified short bowel syndrome patients with permanent intestinal failure with high sensitivity (92%), specificity (90%), positive predictive value (95%), and negative predictive value (86%).[16] Furthermore, plasma citrulline level was a more reliable indicator than anatomic measurement in distinguishing transient from permanent intestinal failure 2 years after resection.

## Pathophysiology

The major consequence of intestinal failure is the extensive loss of absorptive surface area of the small bowel. The ability of the small intestine to maintain nutrition after a massive resection is related to the extent and site of resection, the presence of the ileocecal valve and colon, adaptation of the intestinal remnant, and the nature of the underlying disease.[18]

There are several important physiologic changes associated with extensive small bowel resection. Temporary hypergastrinemia and increased gastric acid secretion occurs in up to 50% of patients after intestinal resection.[19,20] The mechanism for this is largely unknown, but appears to be limited to the first few weeks following resection.

Rapid gastric emptying and decreased intestinal transit time are common in patients with a jejunostomy, while patients with the colon in continuity tend to have preserved gastric motility. Loss of inhibition of gastric emptying appears to be related to the absence of normal ileal and colonic "braking" mechanisms mediated by the release of GI hormones (such as peptide YY, glucagon-like peptides, and neurotensin) from the terminal ileum and colon.[21] In short bowel syndrome patients, rapid gastric emptying may compromise the gastric phase of digestion and lead to inadequate mixing of gastric juices with pancreatobiliary secretions, resulting in incomplete nutrient absorption. Furthermore, the majority of GI secretions are reabsorbed in the proximal jejunum, but patients with less than 100 cm of jejunum proximal to a jejunostomy are unable to absorb these secretions in addition to food and fluid taken orally, resulting in large volume diarrhea on the order of 3.2 to 8.3 L per day.[22] In the jejunum-colon patients, the colon becomes an important absorptive organ, thereby abrogating fluid and electrolyte losses. The colon can also salvage unabsorbed carbohydrates that are degraded by colonic bacteria to short-chain fatty acids and absorbed across the colonic mucosa.[18]

Magnesium deficiency is common in patients who have undergone jejunal resection and is related to large-volume diarrhea and severe fat malabsorption, leading to sodium depletion and secondary hyperaldosteronism.[23]

Deficiencies in fat-soluble vitamins are common in short bowel syndrome—deficiencies in water-soluble vitamins are uncommon, except in patients with a proximal jejunostomy.[24] However, vitamin B12 deficiency is common after resection of 50 to 60 cm of terminal ileum as this is the only site of absorption.[25] Similarly, terminal ileal resection leads to fat malabsorption due to loss of the enterohepatic circulation of bile acids.[26] In jejunum-colon patients, the presence of unabsorbed bile salts and long-chain fatty acids in the colon reduces transit time and aggravates diarrhea.[27] In addition, unabsorbed long-chain fatty acids are toxic to colonic bacteria involved in carbohydrate fermentation and they bind calcium and magnesium, thereby increasing stool losses of these minerals and contributing to hyperoxaluria and nephrolithiasis.[28,29]

Gallstone formation is common in short bowel syndrome and occurs in up to 45% of patients, regardless of type of intestinal resection.[30] It is likely a consequence of biliary stasis leading to biliary sludge formation and is related to multiple factors, including abdominal surgery, rapid weight loss, ileal resection, changes in GI transit and flora, and disturbed cholesterol and bilirubin metabolism.

Dysmotility and/or the loss of the ileocecal valve after intestinal resection may predispose to bacterial overgrowth, which will lead to impaired absorption as bacteria compete with enterocytes for nutrients.[31]

## Intestinal Adaptation

Intestinal adaptation is the process that attempts to restore the total gut absorption of macronutrients, macrominerals, and water to that prior to intestinal resection.[32] *Structural adaptation* is the process of increasing the absorptive area of the remnant bowel; *functional adaptation* attempts to improve nutrient absorption by slowing GI transit. This process is thought to occur over a period of 1 to 2 years, but may continue for several years.[9]

Patients with short bowel syndrome initially adapt to reduced energy absorption through hyperphagia, the spontaneous oral intake of 1.5 times the patient's normal resting energy expenditure.[33] In general, a diet that provides 120 to 200% of the usual energy and protein requirements will compensate for the malabsorption that occurs.

In animal models, the remaining small bowel undergoes an adaptive reaction characterized by epithelial hyperplasia, usually within 24 to 48 hours of small bowel resection.[34] In humans, the remnant intestine hypertrophies to become more efficient in nutrient absorption and the predominant changes are in the diameter and villous height of the bowel, with minimal bowel lengthening.[35,36] Several growth factors synthesized by ileal L cells, including glucagon-like peptide 2 (GLP-2), peptide YY, insulin-like growth factor 1, and enteroglucagon, have been shown to play a role in the intestinal structural and functional adaptive response.[9]

The amount of remaining small bowel is the main predictor of adaptive potential.[18] Patients with a retained colon have a better long-term prognosis as they display the ability to undergo adaptation, likely due to high circulating levels of the aforementioned growth factors.[10] Patients with a high jejunostomy, however, show no evidence of either structural or functional adaptation and, therefore, their nutritional and fluid requirements are unlikely to change over time.[37] Other factors may have a negative impact on intestinal adaptation including fat malabsorption secondary to an interruption in the normal enterohepatic circulation of bile acids.[9]

The postoperative adaptation process is comprised of three main phases.[38] The acute phase begins immediately after intestinal resection and lasts for a period of up to 4 weeks, representing initial patient stabilization. The adaptation phase lasts for 1 to 2 years and during this time patients will usually require nutritional support (parenteral or enteral) until sufficient adaptation has occurred. The last phase is the maintenance phase and nutritional support during this period should be individualized based on the extent and quality of persistent nutritional deficits.

## MEDICAL MANAGEMENT OF INTESTINAL FAILURE

Intestinal failure, especially secondary to short bowel syndrome, remains one of the most challenging GI conditions to manage and requires the involvement of a multidisciplinary team capable of providing appropriate medical, nursing, dietetic, and psychological care. Medical therapies in intestinal failure are directed toward maintaining the nutritional status of the patient as well as improving adaptation to help patients achieve a higher plateau of intestinal function (hyperadaptation), reduce the time required to reach the plateau (accelerated adaptation), or both.[39]

### Parenteral Nutrition

Parenteral nutrition is the mainstay of therapy for patients with intestinal failure, providing the essential nutrients and fluid to sustain life in addition to providing the energy requirements to promote intestinal repair and adaptation. In some patients, parenteral nutrition will be a lifelong requirement and can lead to life-threatening complications. As such, efforts must be made to maintain the critical balance between meeting the metabolic needs of the patient and limiting complications of therapy.[12]

Initially, total parenteral nutrition should be administered at a target of 25 to 30 kcal/kg/day, with dextrose being the most commonly used monohydrate and protein supplied in the form of amino acids. Lipids should account for 20 to 30% of energy requirements. The type and amount of lipid emulsion should be selected on the basis of age, disease, and presence of underlying liver disease. Long-term use of intravenous (IV) soy-based lipid emulsions has been associated with the development of parenteral nutrition-related liver disease.[40] Recently, fish-oil based lipid emulsions (Omegaven and SMOFlipid; Fresnius Kabi, Bad Homberg, Germany) have been reported to improve liver function and even reverse parenteral nutrition-related liver disease, however studies evaluating long-term safety are lacking.[41,42]

In patients who receive little or no enteral nutrition, micronutrients (such as selenium and zinc) need to be provided via the parenteral route. The micronutrient composition should be directed by the underlying disease as well as comorbidities, such as renal or liver dysfunction. In metabolically stable patients, parenteral nutrition should be administered in a cyclic infusion to reduce the risk of hyperinsulinism and liver steatosis.[40]

During the adaptation phase, attempts should be made to gradually wean patients from parenteral nutrition, given that they have sufficient bowel length and function to tolerate adequate oral or enteral nutrition. Negative predictors of weaning from parenteral nutrition include short remnant bowel length (<50 cm) and absence of an ileocecal valve.[43] In those patients who will continue to need some form of parenteral nutrition indefinitely, home parenteral nutrition is more cost effective than in hospital parenteral nutrition, but it has serious complications and requires the close supervision of a multidisciplinary team.[44]

#### COMPLICATIONS OF LONG-TERM PARENTERAL NUTRITION

The long-term complications of parenteral nutrition are listed in Table 1 and can lead to mortality in up to 30% of patients with chronic intestinal failure.[45]

Biliary complications are common in patients with short bowel syndrome and include acalculous cholecystitis, biliary sludge, and cholelithiasis.[46,47] These complications are likely a consequence of decreased oral intake and stimulating gallbladder contraction by either enteral feeds or injection of cholecystokinin

**Table 1 Long-Term Complications of Parenteral Nutrition***

| | |
|---|---|
| Liver disease | |
| | Abnormal liver function tests |
| | Steatosis |
| | Cholestasis |
| | Fibrosis |
| | Cirrhosis |
| | Liver failure |
| | Cholelithiasis, cholecystitis, acalculous cholecystitis |
| | Biliary sludge |
| | Hepatocellular carcinoma |
| Sepsis | |
| Loss of vascular access | |
| | Thrombosis |
| | Line dislodgment |
| Metabolic complications | |
| | Fluid/electrolyte abnormalities |
| | Micronutrient deficiencies/ toxicities |
| | Acidosis |
| Metabolic bone disease | |
| | Osteomalacia |
| | Osteopenia |
| | Osteoporosis |
| Renal dysfunction | |
| | Hyperoxaluria |
| | Nephrolithiasis |
| | Chronic renal insufficiency |
| Neurologic | |
| Psychosocial | |

*Adapted from Bines et al.[12]

(CCK) has been shown to reduce gallstone and biliary sludge formation.[48]

Several hepatic abnormalities are observed in patients on parenteral nutrition, including steatosis, hepatitis, cholestasis, fibrosis, and cirrhosis.[49] End-stage liver disease is the most severe long-term complication of parenteral nutrition and patients with the shortest residual bowel length are at the greatest risk for its development.[50] The liver failure in these patients is likely caused by malabsorption rather than a direct toxic effect of parenteral nutrition.[51] In one U.S. study, it is suggested that 15% of patients receiving parenteral nutrition for more than one year will develop end-stage liver disease, which is associated with a 100% mortality at 2 years.[52] According to a French study, more than 50% of adults on parenteral nutrition for greater than 5 years will develop complicated liver disease.[53]

Catheter-related complications are a common cause of morbidity in patients dependent on parenteral nutrition. According to the Oley Foundation Registry, patients are hospitalized at least once per year for catheter-related infections.[54] In a study by Messing et al, 31% of deaths in patients on permanent parenteral nutrition were attributable to sepsis, and the central venous catheter was cited as the source of sepsis in 50% of these cases.[55] Mortality from line-related sepsis has decreased with proper line care, but patients with ECFs and skin colonization by multidrug resistant organisms remain at high risk of morbidity.[47] Long-term central venous catheterization also predisposes to thrombus formation and subsequent venous occlusion. Other complications associated with progressive loss of venous access include superior vena cava (SVC) syndrome, pulmonary embolus, and septic thrombi.[56,57]

## Enteral Nutrition

The enteral route is the preferred method of nutritional support for patients with intestinal failure as it is safer, cheaper, easier to administer, and has both metabolic and physiologic advantages over parenteral nutrition.[12] All patients with intestinal failure should be provided with some luminal source of nutrition to maintain enterocyte mass and prevent mucosal atrophy.[58] In choosing an enteral nutrition strategy, one must take into consideration the time interval from surgery, the site of resection, the extent of residual disease, and presence of coexisting medical or surgical problems.

In the acute phase, continuous enteral nutrition via a nasogastric, gastrostomy, or jejunostomy tube may be better tolerated than bolus feeds, although there are lifestyle advantages to bolus feeds once patients have stabilized. In patients with severe short bowel syndrome, small volume enteral feeds with a glucose-electrolyte solution should be utilized. Currently, there are a large range of commercially available enteral formulas that provide flexibility in balancing individual nutrition needs with the capacity of the intestine to digest and absorb the nutrients available.

There is some controversy surrounding the optimal enteral diet in patients with a high jejunostomy. In general, an elemental diet provides nutrients that require little or no digestion so that absorption within a limited length of intestine may be maximized, but these formulas tend to be hyperosmolar and can aggravate diarrhea. Limited data suggest that a polymeric diet is as useful as a peptide-based diet in this patient population.[59] In a French study, however, the use of a small peptide-based diet was associated with improvement in protein absorption compared with a polymeric diet.[60]

For patients with a retained colon, diets high in carbohydrates and low in fat compared with high fat, low carbohydrate diets provide a 20% increase in energy absorption.[61] On rare occasions, however, a diet rich in carbohydrates (especially mono- or oligosaccharides) can lead to D-lactic acidosis, a result of abnormal colonic

bacterial colonization.[62] The resultant syndrome of ataxia, ophthalmoplegia, and nystagmus can be treated by changing to a diet high in polysaccharides and administering broad-spectrum antibiotics.[63] Medium-chain triglycerides can be absorbed by the colon and provide a considerable source of energy.[64] There is, however, controversy surrounding the proportion of long-chain fatty acids that should be included as they can aggravate diarrhea early in the illness. Experimental evidence suggests that long-chain fatty acids are the most efficient stimulators of intestinal adaptation when compared with medium-chain fats or carbohydrates.[65] Most experts advocate using medium-chain triglycerides early in the acute phase and gradually increasing the proportion of long-chain triglycerides in the adaptation phase. Overall, it is recommended that patients with an intact colon receive a diet that is high in polysaccharides, normal in fats (i.e., not restricted), and low in oxalate to prevent renal stone formation.[10]

Fistuloclysis is a relatively novel procedure in which enteral nutrition is provided via a feeding tube placed directly into the distal limb of a high-output fistula. It is especially useful in cases where there is mucocutaneous continuity at the site of fistulization and sufficient bowel length distal to the fistula (>75 cm).[66] Fistuloclysis has been shown to increase weight and serum albumin in patients with ECFs, even in the absence of refeeding chyme through the distal limb of a fistula, facilitating successful weaning from parenteral nutrition until definitive reconstructive surgery can take place.[67]

An important goal in the management of patients with intestinal failure, if possible, should involve a transition to oral nutrition with gradually increasing nutrient loads. Oral nutrition should contain free fatty acids, small amounts of medium-chain fats in patients with preserved colons, carbohydrates, pectins, and adequate amounts of vitamins and trace elements distributed in small, frequent meals.[68] If oral intake is not sufficient, enteral nutrition can be used as a supplement during either the adaptation or maintenance phase.

## Pharmacologic Agents

Several pharmacologic agents have been employed in patients with intestinal failure in an attempt to influence fluid and electrolyte absorption.

Antisecretory agents, such as H2 blockers or proton pump inhibitors, have been shown to reduce stoma output in patients with short bowel syndrome, but they do not appear to affect the absorption of nutrients or reduce the severity of intestinal failure.[69,70] Similarly, octreotide has shown benefit in reducing intestinal secretions for patients with a high-output jejunostomy, but it has been associated with a negative impact on nutrient absorption and adaptation.[71,72]

Clonidine, an α-2 adrenergic agonist, has been previously shown to be an effective treatment for diarrhea caused by cholera. Recently, however, it has been used in patients with high-output stomas and has been shown to reduce stoma output and sodium losses.[73,74] It may prove to be a useful adjunct in patients with a high-output ECF and short bowel syndrome; however, further studies are needed.

Antimotility agents, such as loperamide and codeine phosphate, are postulated to improve absorption by slowing intestinal transit and studies have shown that their administration decreases water and sodium output from a stoma by 20 to 30%.[75] It is important to note that loperamide acts via the enterohepatic circulation, which is disrupted in patients with short bowel syndrome, therefore extremely high doses may be required in these patients (12 to 24 mg per dose).[10]

The use of conjugated bile acid replacement therapy in patients with short bowel syndrome has been investigated recently.[76–78] The rationale for replacement is that patients with short bowel syndrome have an interruption in the enterohepatic circulation of bile acids, leading to decreased bile acid secretion and fat malabsorption, which has a negative impact on intestinal adaptation and the nutritional status of the patient. Cholylsarcosine, a synthetic conjugated bile acid, has been shown to improve fat and calcium absorption in these patients.[77,78] Ursodeoxycholic acid has been used in patients with parenteral nutrition-related liver disease to improve bile flow and reduce cholestasis.[79]

## Novel Medical Therapies

In recent years, there has been growing interest in the potential therapeutic benefit of growth factor supplementation in patients with intestinal failure. Several hormonal mediators and peptide growth factors are postulated to play a role in intestinal adaptation (Table 2). There are now experimental and clinical studies evaluating the efficacy of several of these mediators in treating intestinal failure.

**Table 2 Hormonal Mediators of Intestinal Adaptation**

| |
|---|
| Growth hormone |
| Glucagon-like peptide 2 (GLP-2) |
| Peptide YY |
| Insulin-like growth factor 1 (IGF-1) |
| Insulin-like growth factor 2 (IGF-2) |
| Keratinocyte growth factor |
| Epidermal growth factor |
| Transforming growth factor-alpha (TGF-alpha) |
| Transforming growth factor-beta (TGF-beta) |
| Neurotensin |
| Interleukin 11 |

#### GROWTH HORMONE

There is no general consensus regarding the potential benefit of growth hormone in patients with short bowel syndrome. Byrne et al, at the Nutritional Restart Center, were able to show dramatic improvements in tolerance of enteral nutrition; however, their findings have not been confirmed by other groups.[80] Since this initial study, four randomized placebo-controlled trials have been performed using growth hormone to stimulate mucosal growth, but only one of these studies has shown a small improvement in nutrient absorption.[81–84]

#### GLUCAGON-LIKE PEPTIDE 2

GLP-2 and its synthetic analogue, teduglutide, have received considerable attention recently and they are the strongest intestinotrophic candidates to date. GLP-2 is a natural peptide that is synthesized and secreted by the enteroendocrine L cells of the ileum and colon and is released in response to enteral nutrition. Receptors for GLP-2 are found throughout the intestine, but the highest concentrations are found in the jejunum.[12] Patients with short bowel syndrome and an end jejunostomy have a minimal adaptive response and they have been shown to have markedly decreased postprandial GLP-2 profiles compared with either healthy controls or short bowel syndrome patients with retained colon.[85] In small uncontrolled open-label pilot studies of short bowel syndrome patients, native GLP-2 and its long-acting analogue, teduglutide, caused significant improvements in fluid absorption and adaptive morphologic changes in the intestinal mucosa of these patients.[86,87] Results were similar for patients with and without a retained colon, suggesting that supraphysiologic doses may exert additional benefit. A phase 3 multicenter study of teduglutide has recently been presented at international meetings and published in abstract form.[88] A significant reduction in parenteral nutrition-dependence has been demonstrated in patients randomized to receive teduglutide compared with placebo. Further studies are underway to examine the long-term efficacy and safety of teduglutide in patients with intestinal failure.

#### OTHER GROWTH FACTORS

Several other growth factors have been investigated in preclinical models of intestinal failure. Transforming growth factor-α (TGF-α) administration in mice 3 days after intestinal resection stimulated enterocyte and intestinal adaptation in one study.[89] In another experimental rat model of short bowel syndrome, high doses of TGF-α stimulated increased villous height and crypt depth resulting in increased enterocyte mass.[90] Insulin-like growth factor 1 (IGF-1) infusion in gastrostomy-fed rats after extensive small bowel resection has been shown to increase ileal mucosal growth.[91] In other similar experimental studies, infusion of epidermal growth factor and keratinocyte growth factor have been shown to increase mucosal growth and biochemical activity within the small bowel mucosa.[92,93] These growth factors have yet to be evaluated in patients with short bowel syndrome, but they may prove to have therapeutic benefit.

## SURGICAL MANAGEMENT OF INTESTINAL FAILURE

Surgical management of intestinal failure ranges from the treatment of intraabdominal sepsis, to restoration of intestinal continuity, to delaying intestinal transit time, to lengthening intestine, and finally, in cases of complicated chronic intestinal failure, to replacement of the small bowel through transplantation. The overall goals of surgery are to improve nutrient and fluid absorption and reduce the severity of intestinal failure or its complications.

### Nontransplant Surgery

The value of nontransplant surgery in patients with intestinal failure has likely been underestimated and underutilized.[12] When possible, repair of ECFs and restoration of intestinal continuity should be performed, as this will improve fluid, electrolyte, and nutrient absorption and it is associated with successful weaning from parenteral nutrition.[11,94]

In patients with adequate small bowel length but not responding to medical therapy, several techniques to slow intestinal transit in an effort to improve absorption have been described. Reversal of segments of small bowel,[95] construction of artificial valves,[96] interposition of colonic segments,[97] and implantation of reversed electrical pacing devices have all been employed.[98] Experience and associated results vary considerably in the literature; however, reversal of small bowel segments seems to be the most effective of these techniques. The therapeutic benefit of this technique appears to be limited to patients with at least 90 cm of residual bowel remnant in whom adaptation is complete.[7]

Dilatation of residual small bowel may be associated with bacterial overgrowth that impairs absorptive function and, as such, tapering of dilated segments has been said to be of benefit in these cases, especially in children.[12] Intestinal lengthening procedures, such as the Bianchi procedure and the serial transverse enteroplasty procedure (STEP), have traditionally been reserved for patients with an extremely short residual bowel length and most of the experience is in pediatric populations.[99,100] A recent single institution series by Sudan et al, comparing the Bianchi and STEP procedures in both adults and children, showed that 58% of patients were able to wean from parenteral nutrition following either

procedure with a trend toward higher rates of weaning in patients undergoing a STEP procedure.[101]

### Intestinal Transplantation

Intestinal transplantation initially emerged as a means to manage end-stage intestinal failure; however, outcomes have been hampered by high rates of morbidity and mortality owing to rejection, graft loss, and septic complications. Over the past two decades, development of new immunosuppressants and the refinement of surgical technique and critical care have led to an extraordinary improvement in short-term patient and graft survival. Data from specialized U.S. centers report 1-year patient and graft survival of 84% and 72%, respectively, while 5-year patient survival is approaching 60%[45,102,103] In comparison, patients with chronic intestinal failure have a survival of 87% after 1 year, 77% after 2 years, and 44 to 75% after 5 years.[43,55] However, patients who develop cirrhosis secondary to parenteral nutrition-related liver disease have a 1-year survival of only 20 to 30%.[104]

The indications for transplantation and the choice of organs to include are dependent on the baseline disorder, existence and grade of liver disease, and the functional quality of other organs. Isolated small bowel transplant is the graft of choice for patients with intestinal failure and preserved liver function, whereas combined liver and small intestine transplant is reserved for patients with intestinal failure and irreversible liver disease. Multivisceral transplantation (which may include liver, stomach, duodenum, colon, pancreas, spleen, kidney, and/or abdominal wall) is performed in some centers for complex abdominal disorders related to intestinal failure, but graft survival is slightly inferior compared with isolated small intestinal transplant.[105] The current U.S. Medicare-approved indications for intestinal transplantation include impending or overt liver failure due to parenteral nutrition-induced liver injury, thrombosis of two major venous access sites in patients with intestinal failure, frequent development of catheter-related infection and sepsis, and frequent episodes of severe dehydration despite IV fluid replacement and provision of parenteral nutrition.[106]

In the United States, mortality on the waiting list for intestinal transplant approaches 25% and is much higher than for any other solid abdominal organ.[107] For patients who undergo intestinal transplantation, post-transplant complications are common (50%) and the top three causes of death are sepsis, rejection, and respiratory failure.[47] However, more than 90% of patients can be weaned from parenteral nutrition after successful intestinal transplantation.[108] Intestinal transplantation has proved to be a cost-effective treatment for parental nutrition-dependent patients with intestinal failure, reaching parity with home parenteral nutrition after 2 to 3 years and becoming more cost effective thereafter.[106]

Intestinal transplantation is not currently an alternative for patients with intestinal failure doing well on parenteral nutrition as survival in these patients is still better than for those undergoing transplantation. However, patients failing parenteral nutrition have a very poor prognosis and intestinal transplantation in this select group of patients offers a clear survival benefit. It is imperative that patients failing parenteral nutrition therapy be referred early for evaluation of intestinal transplantation to increase the likelihood of a successful outcome.[47]

### Future Directions

A shortage of organ donors has led to the development of the field of tissue engineering. Recently, several groups have described normal histology and function in short segments of tissue-engineered small intestine (TESI) in animal models.[109–111] These segments show normal structure and include neuronal elements that appear functional, although motility has yet to be demonstrated. In the future, tissue engineering may obviate the need for all other nontransplant procedures and perhaps even replace intestinal transplantation as a treatment for intestinal failure.

## PROGNOSIS

Patients with intestinal failure have a higher mortality than age-matched controls from the general population.[112] Factors that are negatively associated with patient survival include the development of parenteral nutrition-related liver disease, remnant bowel length of less than 40 cm, and inability to wean from parenteral nutrition. The majority of adult patients with intestinal failure, however, can successfully wean from parenteral nutrition. Studies from France show that 75% of patients with short bowel syndrome eventually achieve home parenteral nutrition independence and this usually occurs within the first 2 years.[113] Long-term users, therefore, represent only 15 to 20% of those patients initially started on a home parenteral nutrition program.

Quality of life in patients with intestinal failure has only been sporadically addressed. In general, however, quality of life is reduced in patients with intestinal failure receiving home parenteral nutrition compared with patients not receiving home parenteral nutrition and is comparable with that reported for patients with chronic renal failure treated by dialysis.[114] Furthermore, there is some evidence to show that overall quality of life improves after intestinal transplantation.[47]

Despite many recent advances in medical and surgical management, some patients will ultimately succumb to their underlying primary disease or to complications related to the treatment of intestinal failure. In terminal patients, defined as persons who will die in

three months or less from their debilitating fatal illness, decisions regarding end-of-life care should be undertaken as early as possible. Important considerations include whether to discontinue active treatments, such as parenteral nutrition, and when to involve palliation specialists in patient care. Patients should be encouraged to complete advanced directives and discuss their wishes with their family, friends, and health care personnel. Again, the early involvement of a multidisciplinary team with expertise in recognizing and addressing these important, and often controversial, end-of-life issues is essential.

## SUMMARY

Intestinal failure is a feared complication of ECF management, but it is no longer a death sentence. Many patients with this condition can go on to live productive and lengthy lives if they are educated and managed appropriately. Involvement of a multidisciplinary team that has expertise in all aspects of treatment for intestinal failure, including parenteral nutrition, reconstructive surgery, and transplantation, is paramount to achieving good outcomes. Over the coming years, the management of patients with intestinal failure will continue to evolve as advances are made in the understanding of intestinal adaptive mechanisms.

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