ORIGINAL CONTRIBUTION

The Management of Enterocutaneous Fistula in a Regional Unit in the United Kingdom: A Prospective Study

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BACKGROUND: Enterocutaneous fistula associated with type 2 intestinal failure is a challenging condition that involves a multidisciplinary approach to management. It is suggested that complex cases should only be managed in select national centers in the United Kingdom.

METHODS: Over an 18-month period, we prospectively studied all patients referred to us with established enterocutaneous fistulas. Patients followed standardized protocols. Eradication of sepsis, appropriate wound management, establishment of nutritional support, and restoration of normal physiology were attempted. Definitive surgical management was deferred for at least 6 months after the last abdominal surgical intervention. Follow-up was for a minimum of 6 months.

RESULTS: Of 55 patients, 10 were internal referrals and 45 were from institutions elsewhere. The mean age was 50 years. Nine patients had colonic fistulas. Forty-six had small bowel fistulas; 19 of these (35%) were associated with inflammatory bowel disease. Patients had undergone a median of 3 previous operations. Four fistulas (7%) healed spontaneously. Thirty-five patients (63%) underwent definitive surgery. Recurrent fistula occurred in 4 patients (13%); 1 required further surgery, and 3 healed spontaneously. The overall mortality rate was 7% (4/55 patients), with 3 patients dying before definitive surgery and 1 patient dying postoperatively.

CONCLUSIONS: Our results compare favorably with data from designated national centers (overall mortality, 9.5%–10.8%; operative mortality, 3%–3.5%), suggesting that these patients can be effectively managed in regional units that have sufficient expertise, interest, and volume of patients. Rationalization of funding and referral of patients with type 2 intestinal failure to regional centers may allow national centers to conserve their scarce resources.

KEY WORDS: Enterocutaneous fistula; Intestinal failure.

Enterocutaneous fistulas are abnormal communications between the gastrointestinal tract and the skin. In severe cases, they can result in intestinal failure. The majority of fistula formations occur following abdominal surgery for malignancies or inflammatory bowel disease, or with attempted division of dense adhesions during relaparotomy.[1] In the remaining instances (15%–25%), enterocutaneous fistulas form spontaneously secondary to underlying pathology. Inflammatory bowel disease (Crohn disease, in particular) is the most common cause of spontaneous enterocutaneous fistulation.[2] Other causes include radiation enteritis, diverticular disease, malignancy, intra-abdominal sepsis, and trauma.[3–6]

Enterocutaneous fistulas are associated with considerable morbidity and mortality. Their treatment continues to be a significant medical and surgical challenge. For this reason, it has been suggested that these patients should be treated in supraregional nationally-designated units (of which there are only 2 in the United Kingdom (UK)). Patients have frequently undergone several previous operative procedures, leaving their physiological, nutritional, and psychological reserves severely compromised. In several retrospective studies, improvements in outcome have been observed where attention has been focused on the eradication of sepsis, appropriate wound management and skin protection, good nutritional support (enteral and

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parenteral), control of fistula output, and appropriate timing of surgical intervention. Reported mortality rates have fallen from 65% to between 10% and 11%, with surgical mortality rates falling to between 3% and 3.5%.[2,7–11]

To date, no publications have shown results of following a standardized protocol for the management of patients presenting with enterocutaneous fistula in the UK. Our prospective study includes patients presenting to a regional unit over an 18-month period.

METHODS

We collected prospective data on all patients with enterocutaneous fistulas treated in our unit from October 2005 to April 2007. Patients with enteroenteric, enterovesical, enterovaginal, and peristomal fistulas were excluded. Patients in whom there was a pancreatic component to the fistulous disease were also excluded.

Patients were managed in a standardized manner by a combined intestinal failure team comprised of medical staff, surgical and specialist nursing staff, dieticians, pharmacists, and social workers, although there were minor variations for each patient. On initial presentation, oral intake was kept to a minimum while estimations of fistula, urine, and stomal output were recorded. This fluid volume was replaced intravenously with crystalloid solution. Serum electrolyte imbalances of sodium, potassium, magnesium, zinc, and the trace elements were corrected intravenously, and anemia was corrected by infusing folate or iron when appropriate. Blood transfusions were given only in those patients whose anemia did not respond to folate or iron. Patients were weighed, body mass index was calculated, and premorbid body mass index was also determined. When parenteral nutrition was required, a balanced regimen was used that included glucose and lipid calories, amino acids (without glutamine), trace elements, fat-soluble vitamins, and water-soluble vitamins. In patients who presented having undergone prolonged prior periods of starvation ($>$7 d), nutrition was introduced in phases over several days, commencing at 25% of the predicted requirements. In most cases, energy need was determined by the Schofield equation, and nitrogen was administered at a ratio of 1 gN to every 150 kcal. If weight loss had been substantial, if there were major difficulties weighing the patient, or if substantial fluid retention was suspected, indirect calorimetry was performed to provide resting energy expenditure.

Oral intake was quickly reintroduced at the earliest opportunity. This was always intended to be based on hospital food, but included supplementation with high-calorie nutritional drinks and feeding through a nasoenteric tube if these were necessary to meet predicted requirements; we thus recognized that the amounts to be delivered would normally be greater than the amounts needed, given the inevitable malabsorption in most of the patients. If the combined fistula and stomal/fecal output was high, an attempt was made to reduce the loss to a level at which supplementary intravenous fluid or parenteral nutrition was not required (normally where daily intestinal losses were less than 1.5 L). This was achieved by limiting the intake of low-sodium fluids (free fluids) to 500 mL per day and encouraging the patient to drink an electrolyte solution containing high concentrations of sodium and glucose (up to 1000 mL per d). A choice was offered according to the patient's preference between the St. Mark's solution (sodium 90 mmol/L) and Dioralyte (Sanofi-Aventis, Guilford, UK) made up of twice the manufacturer's recommended concentration (sodium 120 mmol/L). Small quantities of cordial concentrate were permitted to flavor the electrolyte solutions, which were kept at refrigerator temperature. Drinking large volumes with food was discouraged. High doses of the antimotility drugs loperamide (up to 36 mg daily) and codeine phosphate (up to 240 mg daily) were given, as well as a proton pump inhibitor to reduce gastric secretions. Patients were advised to avoid food preparations containing sorbitol and similar agents. Parenteral nutrition (PN) was introduced only in cases of proximal fistulas, persistently high stomal or fistula output, distal obstruction, failure to tolerate an adequate oral intake and maintain weight, or failure of the overtly malnourished to gain weight. To accomplish this, a dedicated tunneled central line was inserted under radiological guidance, with particular care paid to continuing aseptic technique to avoid central line sepsis. Line handling was performed only by those trained specifically in the use of central catheters for PN, and aseptic technique with sterile gloves was used for all manipulations. Lines were not used for venesection or for the administration of drugs or blood, except in patients in whom peripheral venous access was exceptionally poor and for whom double-lumen lines were used (one lumen reserved for PN and one for other purposes).

In previous studies, sepsis has been shown to be the most common cause of mortality in patients with enterocutaneous fistulas.[2,12,13] Therefore, all cases of sepsis were managed aggressively. Patients with fevers, raised inflammatory markers, failure to respond to nutrition, and persistently low serum albumin levels underwent contrast-enhanced CT scans of the abdomen and pelvis. Intra-abdominal collections were drained percutaneously, using either ultrasound or CT imaging guidance. If this was unsuccessful, formal surgical drainage by laparotomy was performed and a defunctioning proximal stoma was brought out. In cases of suspected central line sepsis, parenteral feeding was discontinued, and the blood cultures were obtained from the line and peripherally. Broad-spectrum antibiotics were commenced via the central catheter with "line-locking," and the choice of antibiotic was modified according to subsequent bacterial sensitivities. Central venous lines were removed only in nonresolving

sepsis and in patients in whom fungal infection was identified.

Effective wound management and skin care was achieved using a variety of barriers, adhesives, and wound drainage bags. These allowed containment, drainage, and accurate measurement of effluent (thereby assisting fluid and electrolyte replacement), as well as improvement of patient mobility and comfort. Large wound defects were managed with a vacuum-assisted closure (VAC) device, principally as a means of managing the wound rather than treating the fistula. Wounds considered suitable for VAC were those which were deep and had no exposed bowel loops or bowel mucosa. Although its use and outcomes in treatment of enterocutaneous fistulas is still controversial, recent advances in the technology have allowed application in enterocutaneous fistula wounds, where the bowel is protected against direct suction.[14–17]

The anatomy of the enterocutaneous fistula was delineated by a combination of clinical observation (small bowel or large bowel effluent) and radiological investigation. In particular, contrast studies (eg, fistulogram, computed tomography, and MRI) were used. Magnetic resonance imaging of the small bowel allows visualization proximally and distally from the fistula, along with visualization of structural abnormalities such as strictures.

Surgical closure of the persistent enterocutaneous fistula was planned for at least 6 months after the fistula had arisen, or 6 months after the most recent laparotomy, and only when the patient's nutritional condition had returned as closely as possible to the premorbid state. These 2 factors have been shown to be important prognostic indices with respect to morbidity, mortality, and recurrent fistula formation after surgery.[2,18]

Definitive surgery was comprised of laparotomy and careful adhesiolysis (in particular, avoiding further enterotomies), en bloc resection of the involved bowel and overlying skin, and anastomosis. All diseased bowel was resected, and reanastomosis was only performed between healthy ends, irrespective of the amount of bowel lost. The remaining small and large bowel was measured to assess whether long-term nutritional support would be necessary during recovery. In the presence of unexpected persistent active sepsis, Crohn disease, serum albumin level of less than 25 g/l, or if multiple anastomoses were required, a temporary defunctioning stoma was fashioned. Patients with significant abdominal wall defects (in particular those with laparostomy wounds) were managed with the insertion of absorbable mesh (with or without component separation, depending on the size of defect) to facilitate abdominal wall closure during definitive surgery. Nonabsorbable mesh was not used at the time of definitive fistula surgery due to the high risk of infection of the prosthesis. All patients were followed up for a minimum of 6 months after surgery or hospital discharge (in the event of spontaneous closure of fistula). A schematic summary of our treatment algorithm is shown in Figure 1.

The end point of our study was patient status at 6 months after follow-up (whether postsurgery or postdischarge). Outcome variables included spontaneous closure, successful surgical closure, persisting fistula, recurrent fistula, or death.

RESULTS

Fifty-five patients with established enterocutaneous fistulas were treated in our unit over the 18-month period. Ten patients were internal referrals within our institution, and 45 came from other institutions. The median time from the last surgery to referral to our service was 3 (range, 1–7) months. Patient demographics are summarized in Table 1. Nine fistulas involved the large bowel, 46 involved the small bowel, and 19 (35%) were associated with Crohn disease. Only 2 of 55 patients had fistulas that did not result from previous abdominal surgery. Both of these patients developed spontaneous fistulation secondary to Crohn disease. Other associated diseases in our group of patients included diverticular disease, endometriosis, Ehlers-Danlos syndrome, and abdominal tuberculosis. The median age was 50 (range, 21–84) years, with a median of 3 (range, 1–23) previous abdominal operations. Thirty-three of 55 patients (60%) had high-output fistulas (>500 mls/d) at the time of referral to our unit.

The majority of patients had passed the acute sepsis phase following fistula development before referral to our unit. After assessment, however, 47 patients underwent CT scans to delineate whether they had ongoing or new sepsis. Imaging revealed that 24 patients had multiple loops of bowels involved in fistula tracts, 23 of whom had an associated intra-abdominal abscess. The majority of these were successfully drained using percutaneous imaging-guided techniques. Two patients needed premature laparotomy and defunctioning with a proximal stoma to drain their intra-abdominal sepsis.

Twenty of 55 (36%) patients were receiving parenteral nutrition at the time of referral, and its short-term use was considered necessary in 12 additional patients during the initial period of evaluation and stabilization. The principal novel intervention for most patients was the restriction of sodium-poor fluids, but in the majority of cases the dose of opioids needed to be increased. Octreotide (100 mcg three times daily) was used in all patients in whom the fistulous output nonetheless remained greater than 1 L per day. In no case did it make a clinically meaningful difference, and it was therefore discontinued after a 72-hour trial period. All patients were encouraged to eat as much as was comfortable and consistent with acceptable management of stoma/fistula/laparotomy outputs. After initial assessment and stabilization, only 12 (22%) continued to be dependent on parenteral nutrition.

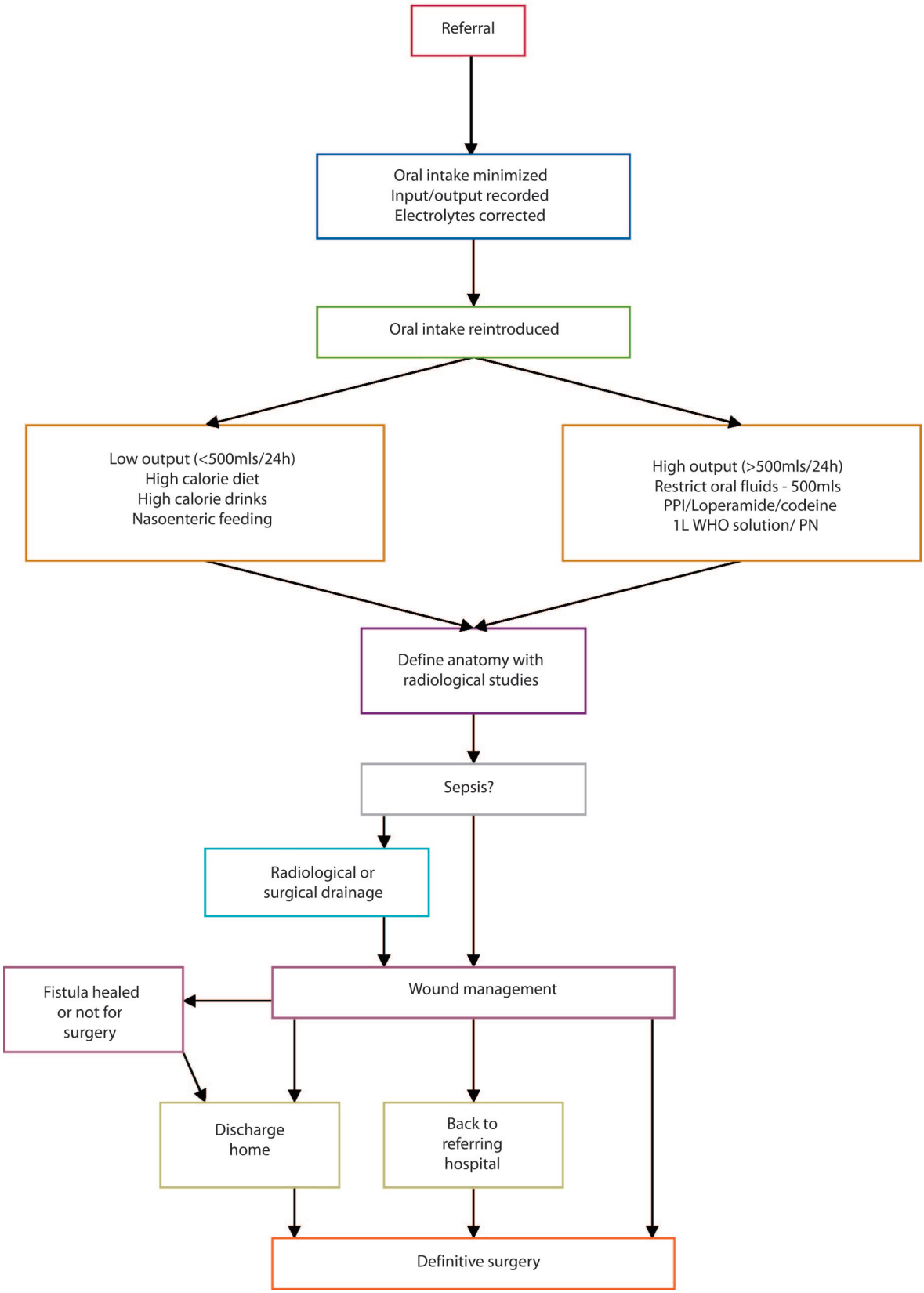

FIGURE 1. Treatment algorithm for patients with enterocutaneous fistulas.

TABLE 1. Patient demographics

	Number	*Percentage*
Mean age	50 y	Range, 21–84
Source of referral		
Internal	10	18
External	45	82
Postoperative		
Yes	53	96
Spontaneous	2	4
Mean number of previous operations	3	Range, 1–23
Etiology		
Crohn disease	19	35
Ulcerative colitis	2	4
Diverticular disease	9	16
Intra-abdominal malignancy	11	20
Radiotherapy	8	15
Other[a]	6	10
Fistula origin		
Small bowel	46	84
Colonic	9	16
Fistula complexity		
Simple	31	56
Complex	24	44
Fistula output		
Low (<500 mL/24h)	22	40
High (>500 mL/24h)	33	60
Presence of laparostomy		
Yes	26	47
No	29	53
Mortality		
Preoperative	3	7
Postoperative	1	3

[a]Includes desmoid disease, endometriosis, tuberculosis, and Ehlers-Danlos syndrome.

Thirty-eight patients (including 12 of those on PN) required supplementary nasoenteric feeding at some time, while 37 patients were given high-calorific oral supplementation drinks. In most cases, it was possible to wean the patient from tube feeding. No patient was left without some form of artificial nutritional support, but in the great majority of patients (n = 33), more than 50% of required nutrients were delivered in the form of normal food.

Thirty-five patients underwent definitive surgery to repair the enterocutaneous fistula. Four fistulas (7%) healed spontaneously. Three patients died before definitive surgery could be performed (see below). The remaining 13 patients were treated without an operation and had persistent fistulas. Of these 13 patients, 5 were considered unsuitable for surgical treatment due to multiple comorbidities and high anesthetic risk, 5 had metastatic malignant disease, and 3 did not want surgery as their fistulas had low outputs and were easily managed after initial assessment. Definitive surgery in the 35 patients was delayed for a median of 9 (range, 6–48) months after previous major surgery or the occurrence of a fistula. Ten patients were defunctioned with a loop stoma proximal to their site of fistula resection. Seven patients needed absorbable mesh to facilitate abdominal wall closure, and all unfortunately developed incisional hernias after surgery.

The overall mortality of our series was 7% (4/55 patients). Three of the 4 deaths occurred before definitive surgery. One patient died from overwhelming uncontrollable sepsis, and the second died from mesenteric infarction. The final patient, who was severely malnourished with type IV Ehlers-Danlos syndrome, developed a spontaneous splenic rupture on a background of severe sepsis and died despite emergency splenectomy. There was 1 (3%) postoperative death from a combination of generalized sepsis and chest sepsis with respiratory failure following pneumothorax from central line insertion, but we had no fistula-related deaths. In total, 35 patients had successful fistula healing. Four patients healed spontaneously and 31 patients healed after surgery (including the 10 patients who had reversals of defunctioning stomas after definitive surgery). Four patients (11%) developed a recurrent fistula at the site of anastomosis after surgery. Only one of these patients required further surgery, whereas the other 3 healed spontaneously. No patients were left dependent on parenteral nutrition after definitive surgery.

DISCUSSION

Intestinal failure (IF) constitutes a wide spectrum of clinical situations, from short-lived, spontaneously-resolving disease to chronic, complex cases requiring prolonged parenteral nutrition. Various classifications have been suggested based on anatomical, physiological, or etiological characteristics of IF. A recent classification by Shaffer[19] takes into account the different duration and severity of IF: type 1—self-limiting IF as occurs following abdominal surgery; type 2—IF in severely ill patients with major resections of the bowel and septic, and metabolic and nutritional complications requiring multidisciplinary intervention with metabolic and nutritional support to permit recovery; type 3—chronic IF requiring long-term nutritional support.

All cases in this series (and the majority of referrals to our unit) are type 2 IF as a result of fistulous disease. It is recognized that many cases of type 2 IF are seen in surgical units throughout the country, and the less severe cases may be safely managed without referral to a specialist unit. There are, however, substantial numbers of more severe cases that require a combined approach from a larger specialist unit. Such an approach involves appropriate input from related specialties such as nutritional gastroenterology and radiology, as well as specialized nursing in wound care, stoma management, and intravenous nutrition. These cases merit timely referral to a regional center where a rapid, comprehensive assessment can be performed before deciding on a treatment plan. In some cases, assessment in a regional center for a few weeks may be followed by either the return of the patient to the referring hospital

or a discharge home. In such cases, appropriate support from nursing and medical staff would be necessary for several months before definitive surgery is performed. Our unit prefers that, before definitive surgery is performed, a period of 6 months will have elapsed since the most recent surgical intervention, and active inflammation will have been resolved.

At present there are 2 national centers (Hope Hospital, Salford and St. Mark's Hospital, Harrow) for the management of complex IF in the UK. These centers' funding comes from the Department of Health via the National Specialist Commissioning Advisory Group, which designates and funds specialist services nationally rather than allowing the financial burden to lie with the primary care trusts.[20] We suspect that the incidence of patients with acute and catastrophic cases of IF is much higher than the proportion of patients needing long-term home PN; however, there is no robust data to support this. The majority of these patients could be appropriately treated in regional centers, and it may be appropriate to rationalize both funding and referral of the majority of patients with type 2 IF to regional centers, which are able to manage them successfully. This would allow national centers to conserve their scarce resources (recent reports suggest that in 2007, approximately 870 adults required home parenteral nutrition[21]). It is probable that, because of the organizational structure of IF services in the UK, many of the catastrophic cases of type 2 IF are currently not receiving timely specialist care; however, there is currently no robust data on this matter.

The chronic, debilitating nature of IF leads to a rapid sapping of psychological reserves in most patients. The proximity of support networks of family and friends becomes increasingly important in helping reduce these patients' sense of isolation over many months, or even years, of treatment. The provision of regional units would improve access to this vital supply of morale.

This study shows that early recognition and control of sepsis, management of fluid and electrolyte imbalances, meticulous wound care, and nutritional support have resulted in significant reductions in morbidity and mortality.[2,6–9] The low levels of morbidity and mortality in our study (overall mortality, 7%; operative mortality, 3%) compare favorably with those achieved in designated national centers for the management of enterocutaneous fistulas (overall mortality, 9.5%–10.8%; operative mortality, 3%–3.5%). This study has again shown uncontrollable sepsis to be the most common cause of death. The low levels of spontaneous closure are probably explained by the fact that the majority of patients were referred to our institution from elsewhere. In the majority of cases, there was a delay between the onset of the fistula and the referral, suggesting that many fistulas may have spontaneously closed before a decision was made to transfer to our unit.

TABLE 2. Factors that influence spontaneous closure of enterocutaneous fistulas

Favorable	*Unfavorable*
• Long fistulous tract	• Short/wide fistulous tract
• Intestinal continuity	• Discontinuity
• Absence of distal obstruction	• Distal obstruction
• No sepsis	• Sepsis
• Low fistula output (<500 mL/24 h)	• High fistula output (>500 mL/24 h; although absolute volume uncertain)
• No malnutrition	• Malnutrition
• Anastomotic leakage	• Disease at the fistula origin (eg, inflammatory bowel disease, malignancy, radiation enteritis)
• Absence of inflammatory bowel disease	

The factors that determine spontaneous fistula closure are shown in Table 2. Our policy to delay definitive surgery for at least 6 months is based on previous retrospective studies that have demonstrated a significant reduction in operative complications if surgery is deferred.[2,7,10,11] This allows for fistula maturation, resolution of inflammation within the peritoneal cavity, optimization of the patient's nutritional state, and resolution of residual sepsis. Signs that enough time has elapsed are the return of a "soft" abdomen, as well as prolapse of the fistulating bowel. These indicate the formation of neoperitoneum, with any residual skin induration being limited to the perifistula region.

We did not have a large enough sample to determine which factors determine good outcomes for enterocutaneous fistulas. However, several studies from other centers have looked at this. Using multiple logistic regression analysis, Visschers et al[22] found that intact abdominal walls and administration of parenteral nutrition were independent predictors of spontaneous closure of enterocutaneous fistulas. The study also found that surgical closure was negatively associated with male gender, high output abdominal wall defects, presence of sepsis, and preoperative albumin levels of lower than 25 g/l. Mawdsley et al[23] conducted multivariate analysis and concluded that successful surgical enterocutaneous fistula closure related to the complexity of the fistula (multiple fistulas or presence of internal abscess cavity), and that fistula-related mortality was related only to the presence of a comorbidity. This is consistent with our study's finding that the 4 recurrent fistula patients had complex fistulas or abscess cavities at the time of definitive surgery.

Thirteen of our 55 patients (37%) did not undergo definitive surgery for their enterocutaneous fistulas. As previously mentioned, 10 were considered unsuitable for surgical treatment due to multiple comorbidities or metastatic malignant disease, and 3 did not want surgery because their fistulas were low-output and easily manageable after initial assessment. Operating on these patients, although technically feasible, would certainly have increased

our mortality rate. Despite this, good results were achieved that compare favorably with the best reports in the literature.

One significant finding from our study was that 12 patients were dependent on parenteral nutritional support when referred, but no patients remained dependent on total parenteral nutrition after reassessment, stabilization, and definitive surgery. This finding contrasts with previous retrospective studies showing that between 5% and 9% of patients remained dependent on long-term parenteral nutrition.[2,5,7] This suggests that it should not be a prerequisite that enterocutaneous fistula management units be able to offer home parenteral nutrition services. This has implications in terms of resources and costs.

There is ongoing discussion about the best route of nutrition. Linked to this debate is whether periods of "bowel rest" are beneficial or detrimental in patients with fistulas. It has been suggested that parenteral nutrition may decrease small bowel secretions and so not only decrease fistula output but also possibly increase the likelihood of spontaneous closure. However, there have been no randomized trials comparing enteral to parenteral nutrition, and in the absence of reliable data it is our policy to introduce enteral nutrition as early as possible for a few different reasons. First, enteral feeding has a trophic and activating effect on the bowel that may prevent mucosal atrophy and play an important role in the prevention of bacterial translocation.[24] Second, enteral feeding facilitates more rapid healing; it also maintains immune function and helps prevent sepsis, especially in the setting of prolonged nonoperative management.[25] However, there are scenarios (such as proximal fistula, distal obstruction, and ongoing intra-abdominal sepsis) where enteral feeding is impossible and the introduction of parenteral nutrition is inevitable. Additionally, the complications of feeding a patient intravenously through a central line should not be underestimated, as significant morbidity and mortality is associated with line sepsis, venous thrombosis, and pneumothorax. The use of octreotide to manipulate fistula output was attempted in a few selected patients, but it failed in all cases. This should not be surprising, as previous studies have shown minimal effect in its ability to either reduce output or encourage spontaneous closure.[26,27] It also has a deleterious side effect of mucosal atrophy.[23] We therefore do not use it as part of our routine practice.

CONCLUSION

This study has demonstrated that patients with enterocutaneous fistulas can be successfully managed in a regional unit with sufficient expertise, interest, and volume of patients. It may be appropriate to rationalize funding and referral of the majority of patients with type 2 IF to regional centers that are able to manage them successfully, thereby allowing the national centers to conserve their scarce resources.

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