Metabolic Support of the Enterocutaneous Fistula Patient

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ABSTRACT

Enterocutaneous fistula (ECF) is a challenging clinical problem with many etiologies; however, the most common cause is iatrogenic, complicating abdominal surgery. Advances in the overall care of the ECF patient have resulted in dramatic reductions in morbidity and mortality over the last five decades. A structured approach to the management of ECF has been shown to result in improved outcomes. Initial physiologic stabilization of the postoperative patient, focused on hemodynamic and fluid support as well as aggressive sepsis control are the critical initial maneuvers. Subsequent optimization of nutrition and wound care allows the patient to regain a positive nitrogen balance, and allow for healing. Judicious use of antimotility agents as well as advanced wound care techniques helps to maximize healing as well as quality of life, and prepare patients for subsequent definitive surgery.

KEYWORDS: Enterocutaneous fistula, nutrition, parenteral, metabolic support

Objectives: Upon completion of this article the reader should be able to understand the unique issues related to the metabolic support of the enterocutaneous fistula patient as well as their associated treatment applications.

The enterocutaneous fistula (ECF) is a devastating complication for both surgeons and patients alike. Prior to the advent of sophisticated critical care support and parenteral nutrition, the development of an ECF nearly equated to a death sentence. In the current era, the mortality rate has been reduced to 5 to 20%.^{1,2} However, the development and management of an ECF remains a chronic, debilitating condition³ associated with prolonged intensive care unit and hospital length of stay, and hospital costs of over \$500,000.⁴ The ECF arises from a myriad of conditions including Crohn's disease, malignancy, trauma, and diverticular disease. However, the most common etiology is iatrogenic injury following abdominal surgery, accounting for 75% of ECF.²

The management of the ECF patient can globally be organized into three principal phases. The first phase entails acute stabilization of the patient from a metabolic and sepsis standpoint in the first hours to days of presentation. The second phase includes the development of an interim plan for wound care and nutrition. The third and final phase of treatment is the definitive management or closure of the fistula. The initial metabolic support of the ECF patient during the first and second phase of treatment is the focus of this review.

CONTROL OF SEPSIS

Depending on the volume of fistula output, patients present along a continuum of physiologic severity.

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Presentations range from a localized skin infection with a small underlying low-output fistula to septic shock with profound dehydration in patients with a proximal high-output fistula. Treatment of the ECF patient must be customized accordingly. The septic patient requires aggressive critical care support with initial therapy targeted at volume resuscitation and electrolyte correction. It is the early management in controlling intraabdominal sepsis that is most closely linked to mortality. Patients with high-output fistulas are often severely hypokalemic upon presentation, requiring aggressive replacement to prevent cardiac disturbance. Early goal-directed therapy⁵ should be initiated in the critically ill septic patient with aggressive resuscitation; fistula output should be replaced cc for cc with the appropriate replacement fluid (Table 1) every 4 to 6 hours. Measurement and laboratory evaluation of the fluid composition may aid in replacement fluid selection. Resuscitation should be correlated with physiologic parameters including urine output (≥ 0.5 mL/kg/h), central venous pressure of 8 to 12 mm Hg, mean arterial pressure ≥ 65 mm Hg, and mixed venous oxygen saturation $\geq 65\%$ when appropriate.⁶ Vasopressor support may be necessary if the patient remains hypotensive after adequate resuscitation.

Broad-spectrum antibiotics must be initiated without delay in the infected patient (within 1 to 3 hours from presentation for the sepsis).⁶ Blood cultures and cultures from any coexisting intraabdominal fluid collections should be taken prior to antibiotic administration if possible. Recent guidelines suggest that cultures of an intraabdominal abscess in the patient with a community-acquired intraabdominal infection are optional.⁷ However, the majority of ECFs are iatrogenic, and thus represent nosocomial infections.⁸ In these cases, cultures may prove useful in identification of resistant pathogens or yeast. The empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative and anaerobic organisms is recommended. Though antibiotic choice remains widely variable across institutions, acceptable regimens include meropenem, imipenem-cilastatin, doripenem, and piperacillin-tazobactam as single agents or ceftazidime or cefepime in combination with metronidazole.⁷

Escherichia coli resistance to quinolones and ampicillin-sulbactam is common. Therefore, these agents

should not be empirically administered in patients with severe intraabdominal infections unless hospital antibiograms indicate $>90\%$ susceptibility to these agents. Additionally, *Bacteroides fragilis* species are increasingly resistant to cefotetan and clindamycin.⁷ Treatment with fluconazole is warranted for patients with *Candida albicans* isolated from intraabdominal cultures. Empiric antimicrobial coverage directed against methicillin-resistant *Staphylococcus aureus* should be provided to patients with health care-associated intraabdominal infection who are known carriers of the organism or who have had prior treatment failures and significant antibiotic exposure.⁷

Guidelines recommend limiting the duration of antibiotic therapy to 4 to 7 days, unless source control cannot be achieved.⁷ Longer duration of therapy has been associated with worse outcomes in patients with intraabdominal infections, presumably because of inadequate source control or inappropriate antibiotic selection.⁹ Patients that continue to demonstrate evidence of infection following a 7-day treatment course should be reevaluated for an ongoing source of infection such as line sepsis, an abscess, or resistant microorganisms rather than simply continuing antibiotics. There are no data to support antimicrobial therapy in the patient with a stable ECF once source control has been established and an adequate 4 to 7 day treatment course has been completed.⁷

Source control is imperative to manage intraabdominal sepsis. All patients who are suspected to have an abdominal source of sepsis should undergo computed tomography scanning. These patients do not always manifest the usual signs of infection. Rather, they may present with weight loss, hypoalbuminemia, or jaundice.¹⁰ Therefore, practitioners should have a low threshold for repeat scanning of a recurrent or persistent abscess if suspected. Any intraabdominal fluid collections must be adequately drained either percutaneously or surgically. Reports in the literature demonstrate that 10% of patients presenting to a tertiary referral center for management of an ECF require percutaneous drainage of an abscess.³ Subsequent manipulation or upsizing of the initial catheter may be required to ensure adequate drainage. Contrast injected into the cavity can give information regarding the size of the cavity and identify a fistulous communication.¹⁰ Although many associated

Table 1 Gastrointestinal Tract Secretions, Electrolyte Composition, and Suggested Replacement

	Volume (mL/d)	Na	K	Cl	HCO ₃	Replacement
Gastric	2,000	60	10	90	0	0.45NS + 10K
Small bowel	3,500	120	15	120	30	NS + 10K
Pancreatic	1,000	140	5	50	100	NS + 10K + HCO ₃
Diarrhea	1,000–4,000	50	30	50	50	0.45NS + 20K

Adapted from Grant JP. Handbook of Total Parenteral Nutrition. 2nd ed. Philadelphia: Saunders; 1992:174. All electrolyte values are mEq/L.

intraabdominal abscesses are amenable to surgical drainage, operative intervention is commonly required. ECF representing anastomotic leak may require proximal diversion if possible to facilitate closure. Any prosthetic mesh must be removed and the underlying infection irrigated and debrided adequately.

WOUND CARE

The effluent from an ECF poses a challenging dilemma for wound management. This is particularly true in the enteroatmospheric fistula, which is positioned within an open abdominal wound.¹¹ The fistula must be isolated from surrounding tissue to allow for nursing care, protection of the skin or healing of the surrounding open wound. Additionally, quantification of the effluent is critical in the early stages of presentation for adequate replacement of the calculated volume loss. A stoma appliance can be fashioned to fit most fistulas surrounded by intact skin. However, the enteroatmospheric fistula is extremely challenging to isolate. A multidisciplinary team consisting of wound care specialists, enterostomal therapists, and physicians is required to establish an effective wound care system. Various strategies include wound care managers, similar to very large stoma appliances that encompass the entire wound bed. The fistula effluent is isolated with closed suction drains and the surrounding wound is managed with a wet to dry dressing (Fig. 1).

Experience with vacuum-assisted wound management in other open wounds has led to its application in the ECF patient.^{12–14} The vacuum suction wound management system can be utilized to isolate the fistula within the open wound, allowing for pouching of the

fistula. Alternatively, the vacuum sponge can be directly applied to the fistula in an attempt to facilitate closure. Wainstein et al¹⁵ reported a 46% closure rate with a type of vacuum-assisted device in Argentina. However, this was a different system from the typical Vacuum-Assisted Closure system (V.A.C.; Kinetic Concepts, Inc., San Antonio, TX) that is commonly employed in the United States. Whereas the V.A.C. system currently available in the United States can generate up to 125 mm Hg of negative pressure suction, the suction used by Wainstein and colleagues generated negative pressures ranging from 350 to 600 mm Hg.

Currently, there are no prospective trials evaluating vacuum-assisted therapy in the management of the ECF and the system has not been approved for this use. Ironically, there have been increasing reports of iatrogenic ECF development that have surfaced in association with the use of vacuum-assisted therapy on open wounds of exposed bowel.¹⁶ A prospective randomized trial of 51 patients with an open abdomen, comparing vacuum-assisted closure to polyglactin mesh was associated with the development of an ECF in 21% of the V.A.C. group versus 5% in the mesh group, although this trend did not reach statistical significance.¹⁷ If vacuum-assisted therapy is utilized within an open intraabdominal wound, caution is advised and precautions should be taken to protect the underlying bowel. Nonadherent barrier dressings (e.g., petroleum-coated gauze) should be considered for use directly over the exposed bowel and the hydrophilic white foam as opposed to the standard black foam should be applied over bowel.

Regardless of the interim wound management scheme, once the adjacent tissue within the surrounding open wound is granulated, it may be skin grafted to allow

Figure 1 (A) Enterogatmospheric fistula opening into the midline wound. (B) Vacuum-assisted dressing isolating fistula and enabling pouching with a stoma appliance and drain in place.

for placement of a stoma appliance. This technique thereby converts the fistula into a stoma that can be pouched and cared for by the patient. This is an excellent bridge for the patient to definitive surgery, which should be delayed for several months.

NUTRITION MANAGEMENT

Time and experience have borne out that a standardized approach to initial management of ECF results in improved outcomes, decreased morbidity and mortality, and increased closure rates. These guidelines¹⁸ indicate that once initial sepsis has been managed, efforts should next be directed toward optimization of the nutritional state.

Caloric Goals

Nutritional and caloric goals are determined by many factors, and cannot be approached with a “cookie-cutter” method. The most common clinical scenario is a post-operative ECF from the small bowel. The patient has likely suffered from multiple metabolic and physiologic stressors including dehydration from bowel preparation, third-spacing of fluids from operative intervention, sepsis and additional loss of nutrients through the fistula. Such a patient is likely acutely malnourished. Consideration must be given to the nutritional needs and tolerances of a patient in such a fragile state. They have likely shifted to starvation mode metabolism, and are experiencing the hypercatabolic state of sepsis. Prompt initiation of caloric support is essential. In a seminal publication in 1964, Chapman and others reported on a dramatic decrease in mortality from 58% to 16% in patients with ECF who received more than 1500 kcal/d. The majority of these patients received enteral feedings. Those who were able to maintain optimal nutrition (defined as >3000 kcal/d) had a mortality rate of 12%, and a fistula closure rate approaching 90%. Those patients unable to maintain this intake continued to have a high mortality rate and low fistula closure rate (55% and 37%, respectively).^{19,20}

An initial assessment of the metabolic needs of the patient can be estimated via the use of the Harris-Benedict equations (Table 2), taking into account appropriate modifiers for sepsis and postoperative states. Additionally, the rate of output from the fistula can greatly affect nutritional needs.

Baseline nutritional requirements are 20 kcal/kg/d of carbohydrate and fat and 0.8 to 1 g/kg/d of protein.¹¹ No more than 30% of the daily caloric needs should be provided as lipid. Requirements for low-output fistulas increase to 25 to 30 kcal/kg/d with a protein need of 1.5 to 2 g/kg/d of protein. High-output fistulas may require up to 2 times the overall caloric daily requirement and 2 to 2.5 × baseline protein requirements to achieve a pos-

Table 2 Harris-Benedict Equation (with Modifiers)

Men: $66.5 + (13.75 \times \text{kg}) + (5.003 \times \text{cm}) - (6.775 \times \text{age}) \times$ modifier
Women: $655.1 + (9.563 \times \text{kg}) + (1.850 \times \text{cm}) - (4.676 \times \text{age}) \times$ modifier
= Basal energy expenditure/d (kcal)
Modifiers:
Infection, mild (10%)
Infection, moderate (25%)
Infection, severe (45%)
Infection, peritonitis (15%)
Operation, minor (10%)
Operation, major (15%)
Postop (5%)
Burns, < 20% (50%)
Burns, 20–40% (70%)
Burns, 40% (100%)
Trauma, multiple (30%)
Trauma, blunt (40%)
Trauma, skeletal (20%)
Trauma, long-bone fracture (25%)
Cancer (15%)

itive nitrogen balance; daily small bowel secretions may contain up to 75 g of protein, material that would ordinarily be reabsorbed.¹⁹

The optimal route of administration of caloric needs continues to remain controversial; however, several tenets continue to apply. During initial management of ECF, after sepsis control, establishment of positive nitrogen balance and minimizing fistula output are critical. This often mandates an initial trial of complete bowel rest, and thus, the use of total parenteral nutrition is often initiated.

Total Parenteral Nutrition

Total parenteral nutrition (TPN) allows clinicians to both resuscitate and begin nutritional repletion of the ECF patient.

The advent of TPN coincided with a dramatic improvement in morbidity and mortality related to ECF management. Initial reports showed significant improvement in mortality and fistula closure rates in patients who were receiving TPN. There is some controversy in attributing these dramatic improvements solely to TPN, rather than as an overall shift in the focus toward establishing methods and protocols for management of the issues related to ECF, including optimizing nutrition. There is data to support the fact that TPN does decrease fistula volume, but no class I data exists to show that TPN increases the rate of fistula closure.²¹ Initial infusion is aimed at both satisfying fluid requirements as well as beginning to address caloric needs and restoration of nitrogen balance. As a result,

initiation of parenteral nutrition must be ramped up to goal over the course of 1 to 2 days.

Complications of Total Parenteral Nutrition

Too-rapid initiation of TPN may result in *refeeding syndrome*. Refeeding syndrome is characterized by metabolic and electrolyte abnormalities induced by rapid repletion of elements that the body has adapted to being scarce; *hypokalemia* may result as glucose and amino acids are rapidly moved into cells in exchange for potassium; *hypophosphatemia* may result as glucose and other newly available substrate are phosphorylated; *thiamine depletion* can occur resulting in Wernicke encephalopathy. Enteral intolerance of rapid refeeding will be covered below. Slower initiation of caloric delivery and judicious use of vitamins, minerals, and trace elements will help minimize the risk of this potentially devastating complication.²²

Additionally, because the hypertonicity of TPN requires central venous administration, patients are at risk for all of the complications of central venous access. Placement of temporary central lines runs the risk, albeit low, of pneumothorax and inadvertent vascular injury. Even with elective, image-guided peripherally inserted central catheter (PICC) lines, some degree of venous thrombosis occurs in almost 40% of patients who are not prophylaxed with blood thinners.²³ Though the clinical consequence of thrombosis varies, this highlights the not insignificant risk associated with this common procedure.

Longer-term use of hyperalimentation requires chronic central venous access, and the risk of catheter-based sepsis is much more significant. In one study, over 80% of patients requiring central venous access for TPN developed bloodstream infections (BSI), and almost 80% had more than one episode.²⁴ In addition, chronic TPN dependence can result in cirrhosis and liver failure.²⁵

Enteral Nutrition

"If the gut works, use it." This age-old surgical adage is well known, and bespeaks a fundamental principle that a functioning gastrointestinal (GI) tract is critically important to a patient's overall health. The critical care literature is replete with data showing that enteral feeding maintains GI mucosal immunity, and elemental diets may also minimize or even decrease fistula output. Supplementation with immunonutrition, i.e., enteral formulas supplemented with additives such as fish oil, arginine, glutamine or omega-3 fatty acids appears to reduce infections in critically ill patients,^{26,27} but larger systematic reviews and meta-analyses fail to show any translation into improvement in mortality.^{28,29}

Although initial bowel rest may be useful for early control and minimization of fistula output, once sepsis is controlled and the patient is stabilized, many advocate early initiation of enteral feeds. Dudrick states that with

at least 4 feet of functioning small bowel between the ligament of Treitz and the ECF, adequate nutritive absorption may be possible.¹⁹

Initiation of enteral feeds must be approached cautiously. Continuous, low volume feeds are ideally delivered via soft postpyloric feeding tube. Gradual increases toward target volume and concentration are limited by patient tolerance and site of feeding, and TPN is often needed to bridge the 4- to 5-day gap needed to achieve full enteral caloric delivery. For gastric feeding, osmolality is increased slowly to hyperosmolar targets, followed by volume targets, whereas in small bowel feeding, volume tolerance needs to be achieved first.¹⁹ This may be difficult in the high-output proximal fistula, as enteral feeds can increase the volume of fistula output. However, in a seminal work published in 1989, Levy and his group from Paris studied a cohort of 335 high-output ECF patients, and though many received initial stabilization with TPN, 85% of patients ultimately were maintained exclusively on enteral feeds. The majority (234 of 335) of patients was able to be managed conservatively, and almost 40% of patients experienced spontaneous fistula closure; mortality was only 19%.³⁰ The use of fistuloclysis, or refeeding into the efferent limb of a fistula was used in many patients, either with enteral formulas or chyme output from the proximal fistula. This method has been supported with modern experience as well.³¹

There remains no clear consensus as to the absolute superiority of parenteral versus enteral feeding; however, it is clear that maintaining a positive nitrogen balance is important in this period, as patients have usually not been fed orally for many days, and are in the catabolic states of sepsis and postoperative recovery. The authors advocate the general guideline of regular initial use of TPN during the period of sepsis control and postoperative resuscitation, with the use of enteral feeds as soon as the gut is capable of tolerating it, provided this does not make ECF control unfeasible. Use of elemental feeds and fistuloclysis is advocated in attempts to maintain use of the GI tract for nutrition.

ANTIMOTILITY AGENTS AND OCTREOTIDE

The data for the use of octreotide, a synthetic analog of somatostatin, in the setting of patients with an ECF are scarce. Three small prospective, randomized trials ranging from 14 to 31 patients were identified in the literature.³²⁻³⁴ One study demonstrated a significant reduction in the volume of the effluent with octreotide therapy.³² However, none of the studies demonstrated any effect on rate of fistula closure. Two additional retrospective studies demonstrated a greater than 50% reduction in the fistula volume with octreotide therapy.^{35,36} However, similar to the prospective trials, neither study demonstrated efficacy in fistula closure.

Table 3 Antimotility Agents Used for High-Output Fistulas

Agent	Dose
Loperamide	up to 4 mg 4 × daily
Diphenoxylate	2.5–5 mg up to 4 × daily
Tincture of opium	0.3–1.0 mL up to 4 × daily
Codeine	15–100 mg up to 4 × daily
Paregoric	5–10 mL 2–4 × daily
Proton pump inhibitors	Dosage varies by agent
Octreotide	50–500 µg subcutaneously up to 3 × daily

Based on these limited data, octreotide may be useful as an antimotility adjunct for volume and electrolyte management when other agents have failed.¹⁰ However, there are no reliable data to suggest that subsequent reduction in the volume of effluent effects closure of the fistula.

Although volume reduction of effluent is not likely to facilitate spontaneous closure of the fistula, it does provide other significant advantages. Patients with low volume (<200 cc/d) fistulas suffer minimal electrolyte imbalance and volume depletion. Wound care is simplified greatly by effluent volume reduction. Additionally, the majority of patients with low-output fistulas can tolerate enteral nutrition.¹⁰ Therefore, significant effort should focus on antimotility and antisecretory therapy including treatment with loperamide, diphenoxylate, tincture of opium, codeine, and proton pump inhibitors to combat gastric hypersecretion (Table 3).

Drugs aimed at slowing intestinal transit are the mainstay of reducing fistula output. The least potent and best tolerated of these medications is loperamide, which is available over the counter. If the patient is eating, it should be taken 30 minutes prior to meals. It can be titrated up to 16 mg over a 24-hour period. If it is not effective in reducing the volume of effluent, other prescription medications may be added. Diphenoxylate and opiates are effective but have dosage-limiting anticholinergic and sedating side effects, respectively. However, for refractory cases, these agents may prove necessary. Disturbances in the CCK and secretin feedback mechanism associated with an ECF may result in gastric hypersecretion through regulation of gastrin secretion. This leads to the release of a highly acidic effluent with subsequent increased volume. Treatment with acid suppression by way of proton pump inhibitors can effectively reduce the disadvantageous effect of gastric hypersecretion. The dosage of proton pump inhibitor should be increased to achieve a pH greater than 6 in the fistula effluent and a volume less than 1 L per day.

CONCLUSION

The physiologic, financial, and emotional tolls of the development of an ECF are overwhelming. Given that

Figure 2 Algorithm for metabolic support in the management of the enterocutaneous fistula patient.

most are iatrogenic, the most effective means of treatment is prevention with sound surgical judgment and meticulous technique. However, when faced with the development of an ECF, early recognition and correction of initial metabolic disarrangement and sepsis is imperative for long-term success. Subsequent comprehensive care requires a multidisciplinary team specialized in treatment of these challenging patients. The use of a standardized approach with initial sepsis and fistula control followed by appropriate nutritional support are key components in the initial management and stabilization of the ECF patient (Fig. 2).

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