Postoperative Enterocutaneous Fistula: When to Reoperate and How to Succeed

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ABSTRACT

An enterocutaneous fistula (ECF) is a potentially catastrophic postoperative complication. Although the morbidity and mortality associated with ECF have decreased over the past 50 years with modern medical and surgical care, the overall mortality is still surprisingly high, up to 39% in recent literature. It seems prudent, then, for every surgeon to have a thorough grasp of optimal treatment strategies for ECF to minimize their patients' mortality. Ultimately, the algorithm must begin with prevention. Once an ECF is diagnosed, the first step is to resuscitate and treat sepsis. The second is to control fistula output. The third step is to optimize the patient medically and nutritionally. The last step is definitive restoration of gastrointestinal continuity when necessary. Special mention is given in this article to exceptionally refractory fistulas such as those arising in the presence of inflammatory bowel disease and irradiated bowel. This plan gives a framework for the difficult task of successfully treating the postoperative ECF with a multidisciplinary approach.

KEYWORDS: Enterocutaneous fistula, nutritional support, sepsis, radiation enteritis

Objectives: Upon completion of this article, the reader should be able to summarize the management of postoperative enterocutaneous fistulas.

The development of an enterocutaneous fistula (ECF) is a potentially catastrophic postoperative complication. Virtually any intra-abdominal procedure can result in an ECF, with procedures that intentionally or unintentionally damage the bowel wall carrying the greatest risk.¹ Most surgeons have seen previously healthy patients undergoing routine, low-risk operative procedures have their lives decimated by a postoperative ECF. Although the morbidity and mortality associated with ECF have decreased over the past 50 years with the advent of novel antibiotics, improvements in resuscitation, intensive care unit care, nutritional support, wound care, and new diagnostic and treatment modalities, the

overall mortality is still surprisingly high. Mortality rates in the recent literature vary from 6.5 to 39%.²⁻⁶

It seems prudent, then, for every surgeon to have a thorough grasp of optimal treatment strategies for ECF to minimize their patients' mortality. Ultimately, the algorithm must begin with prevention. Strategies to prevent the formation of ECF are discussed in the following. Once an ECF is diagnosed, the first step is to resuscitate and treat sepsis. The second is to control fistula output. The third step is to optimize the patient medically and nutritionally. The last step, when necessary, is definitive restoration of gastrointestinal continuity, after extensive preoperative planning.¹

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Reoperative Surgery; Guest Editor, Michael J. Stamos, M.D.

Clin Colon Rectal Surg 2006;19:237-246. Copyright © 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI 10.1055/s-2006-956446. ISSN 1531-0043.

DEFINITION

A fistula is defined as an abnormal connection between two epithelialized surfaces. An ECF is defined as an abnormal connection between the gastrointestinal (GI) tract and the skin. Under the strictest definition, this includes fistulas from the esophagus, stomach, biliary tree, and pancreas as well as the small bowel, colon, and anus. More commonly, the term ECF means an abnormal connection between the small bowel and skin only. It is this definition we use throughout this discussion.

CLASSIFICATION

Classification of fistulas is by no means standard. There are three usual classification systems, and most fistulas benefit from being described using all of them at once. The anatomic classification names the fistula using the organs involved. By convention, the highest pressure system is named first, for example, a gastrocutaneous fistula or an aortoenteric fistula. The anatomic classification may also include a description of the fistula tract, such as complex versus simple, or long versus short, and a description of the bowel defect, usually measured as greater or less than 1 cm. The physiologic classification uses output as the defining characteristic. A high-output ECF is defined as one that produces more than 500 mL/day. A low-output fistula has been variously defined as producing less than 500 mL/day^{1,4} by some authors or less than 200 mL/day by others.⁷ In the latter case, there is an additional designation of a moderate-output fistula that secretes 200 to 500 mL/day. The etiologic classification names fistulas by their associated disease processes, for example, a diverticular fistula or a neoplastic fistula. These classification systems can be used to estimate the mortality and the chance of spontaneous closure of a fistula.⁷ Mortality is five times greater for high-output fistulas than low-output fistulas.⁵ Table 1 gives examples of fistula characteristics that predict the likelihood of the fistula closing spontaneously.

Table 1 Effect of Fistula Characteristics on Likelihood of Spontaneous Closure

	More Likely to Close	Less Likely to Close
Anatomic	Jejunal	Ileal
	Tract < 2 cm	Tract > 2 cm
	Bowel defect < 1 cm ²	Bowel defect > 1 cm ²
		Epithelialized tract
Etiologic		Distal obstruction
	Appendicitis	Neoplastic
	Diverticulitis	Inflammatory bowel disease
		Radiation
	Postoperative	Foreign body

ETIOLOGY, RISK FACTORS

Most (75 to 90%) ECFs are iatrogenic or, to be more specific, postoperative or postprocedural.^{1,2,4,7} Approximately half of these are thought to be caused by anastomotic leak or dehiscence and about half by inadvertent enterotomy.⁷ The other 10 to 25% of ECFs are spontaneous. These include fistulas from inflammatory bowel disease, neoplasia, vascular insufficiency such as radiation enteritis or mesenteric ischemia, diverticulitis, appendicitis, pancreatitis, tuberculosis, or other intra-abdominal infections, abscesses, or inflammatory processes such as malakoplakia.⁸ Penetrating traumatic fistulas are included in the spontaneous category.⁴

The first step in fighting fistulas is prevention. Understanding the risk factors that predispose a patient to postoperative fistulas can allow surgeons to take steps to decrease a patient's risk and can allow increased vigilance and earlier diagnosis of fistulas if they do occur. Risk factors for postoperative fistulas include both technical and patient-related factors. The same technical principles that guide surgeons in reducing postoperative infection and anastomotic leak rates are those that reduce fistula formation. Preoperative skin preparation and perioperative systemic antibiotics reduce the incidence of infection and thus ECF. Intraoperatively, the surgeon should focus on creating a tension-free anastomosis and ensuring that the bowel is well perfused. Stapling devices or sutures, or both, should be placed carefully and accurately to create an intact anastomosis. Surgeons should insist on meticulous hemostasis and avoid leaving hematomas as possible niduses of infection. Performing careful, sharp dissection to avoid unintended enterotomies and securely repairing any enterotomies or serosal injuries are paramount. Resection and anastomosis of defects greater than half of the small bowel circumference rather than simple oversewing or wedge resection result in lower fistula rates. Operative time greater than 2 hours and intraoperative contamination of the field have been shown to increase anastomotic leak rates; thus, the surgeon should be efficient and take steps to reduce contamination. Drains should not be left immediately adjacent to anastomoses; they can act as foreign bodies and erode into the anastomosis. If possible, placing omentum between the abdominal wall and the repair can reduce fistula formation, although wrapping the anastomosis in omentum (omentoplasty) has not been consistently shown to reduce anastomotic leaks. The final step is a secure abdominal closure with care taken to avoid inadvertent small bowel inclusion. Postoperatively, the main focus should be on maximizing the patient's oxygen-carrying capacity by ensuring adequate volume status and avoiding hypotension, anemia, and hypothermia.^{1,7,9-11}

When possible, patient-related risk factors for fistula formation should be optimized or treated preoperatively. Patient factors such as malnutrition, low serum

albumin, cardiovascular disease, advanced age, chronic obstructive pulmonary disease, corticosteroid use, prior abdominopelvic radiation therapy, alcohol abuse, smoking, two or more systemic diseases, high American Society of Anesthesiologists status, intra-abdominal abscess, peritonitis, and sepsis all increase the risk of developing a postoperative ECF.¹¹ Medical optimization of comorbidities such as diabetes, coronary vascular disease, and inflammatory bowel disease should be attempted preoperatively. Nutritional status should be optimized for elective procedures. Smoking and alcohol cessation programs can be initiated preoperatively. Assuring normovolemia, normotension, and adequate hemoglobin prior to the induction of anesthesia optimizes tissue perfusion. Intraoperative or postoperative transfusion of more than two units of packed red blood cells increases anastomotic leak rate and therefore fistula rate.¹¹ Taking all of these risk factors into consideration, it is evident that patients undergoing an emergent surgery have a higher rate of fistula formation; it may be impossible to alter many of these factors in emergent situations. Operations performed for adhesions, bowel obstruction, cancer, radiation enteritis, or inflammatory bowel disease have the highest rates of fistula formation. It is in these cases that the meticulous surgical technique described previously and proper postoperative care are the mainstays of fistula prevention.

DIAGNOSIS

The definitive diagnosis of an ECF is usually made by visualizing the drainage of succus from the operative incision or from a drain site. This usually occurs between postoperative days 5 and 10.¹ Alternatively, the fistula may arise with an overt wound infection; upon opening the surgical wound, enteric contents are found. Commonly, in the days preceding the fistula's external presentation, the patient shows a persistent ileus, leukocytosis, abdominal pain, fever, or otherwise unexplained signs of sepsis. Rarely, a patient may show sudden, severe septic shock with peritonitis, requiring urgent reoperation and the discovery of the fistula.

STABILIZATION

Primary treatment is resuscitation. Attention should first be paid to restoring intravascular volume with crystalloid solutions. Patients are in general hypovolemic because of bowel losses from the fistula as well as intra-abdominal third spacing related to inflammation induced by succus in the peritoneal cavity. Correction of electrolytes with intravenous replacement should be immediately initiated. Anemia should be corrected with transfusion if needed. Septic patients are at risk for capillary leak secondary to systemic inflammatory response syndrome and progression to multiple organ

dysfunction syndrome; thus, these patients should be closely monitored, with adequate venous access and a central venous pressure monitor or pulmonary artery catheter if necessary.

TREATMENT OF SEPSIS

Untreated sepsis is the primary cause of mortality in ECF. The control of any septic foci should begin when the patient is sufficiently stable to undergo diagnostic and therapeutic intervention. Computed tomography (CT) is the best test for elucidation of intraperitoneal abscesses, which can then be drained. In a stabilized patient, these collections are preferentially drained percutaneously by an experienced interventional radiology team. Alternately, the abscess can be drained through the fistula tract with a sump drain, with the tip of the drain placed near the enteric opening. Again, this should be done by an experienced interventional radiology team under fluoroscopic guidance with fistulography.¹² While draining the abscess collection, cultures should be sent. If the patient is septic, broad-spectrum antibiotics should be started with the intent to narrow antibiotic coverage as culture results permit. A patient with an ECF without fevers, tachycardia, or signs of local infection such as cellulitis does not need antibiotics.

A patient with severe sepsis unresponsive to resuscitation or with an abscess unable to be percutaneously drained may need an urgent return to the operating room for washout of the abdominal cavity and control of the fistula. In this case, the best management is often a diverting proximal stoma.¹³ In most patients who are hemodynamically stable after resuscitation, the optimal treatment is to delay a return trip to the operating room and control sepsis through antibiotics, drainage, and supportive care. The postsurgical abdomen 1 week after laparotomy is an inhospitable arena where dense adhesions and friable, edematous bowel make reoperation difficult and increase the chance of further complications. Avoidance of reoperation at this time, when possible, is imperative.

SKIN PROTECTION

Protection of the skin around the fistula is a vital early step. The fistula effluent can be acidic or alkaline, depending on its origin, but at high volume or with stasis on the skin excoriation can occur within 3 hours. Once the skin is raw, painful, and weeping, stoma appliances and other output control methods are much more difficult to use. Enzymes in the succus can digest the abdominal wall and result in a large wound with a fistula at its center. In cases where the fistula is discovered upon opening a midline wound for presumed wound infection, the fistula is already situated in a large, open abdominal wound. This can greatly complicate

management of the fistula effluent. Thus, it is important to control effluent early in the course of the fistula and to prevent skin damage when possible. It is also important to involve an experienced enterostomal therapy team to manage the fistula output.

To protect the skin, an ostomy appliance may be attached to the skin, with a custom fit for the exterior opening of the fistula. The ostomy nurse can contribute various pastes and powders to compensate for moist skin and uneven fistula edges. Rapidly draining wounds may require a sump tube through the appliance to control output further. Fistulas in large wounds may benefit from sump drains and a large Eakin stoma appliance to protect the tissue around the fistula.¹⁴

A newer approach is the application of a negative-pressure dressing, such as the vacuum-assisted closure device (VAC, KCI International, San Antonio, TX.) In the late 1990s the VAC system was thought to promote or at least potentiate fistulas and was not used for this indication; however, there has been a resurgence of interest and use in this device for fistulas. The VAC system can be tailored in many ways to divert fistula effluent. As described by Goverman et al,¹⁵ the VAC also treats the wound bed around the fistula with negative-pressure dressing, resulting in increased granulation tissue and wound contracture. The device also functions as a bolster to grafted skin around the fistula while diverting the enteral contents from the graft.¹⁵ Other studies have shown that the VAC does not prevent spontaneous fistula closure.^{16,17} The concept of negative-pressure dressing is not limited to the VAC; a simple drain with an occlusive balloon inserted into a fistula tract and set to negative pressure has been shown to be effective in controlling effluent and allows spontaneous closure as well.¹⁸

NUTRITION

After sepsis, other significant causes of mortality from ECF include fluid and electrolyte disturbances and malnutrition.⁴ These are managed with nutritional support. The introduction of total parenteral nutrition (TPN) by Dudrick et al in 1968 revolutionized the treatment of patients with ECFs. Fistulas may result in massive daily fluid and electrolyte losses. Common complications of high-output fistulas can include dehydration, hyponatremia, and hypokalemia as well as metabolic acidosis. Rehydration and electrolyte replacement are performed intravenously during the stabilization phase but, once replete, can often be taken orally. Nutritional supplementation should begin as soon as the patient's volume and electrolyte status is stabilized.⁴

Malnutrition in ECF is due mainly to GI losses, hypercatabolic state secondary to sepsis, and inadequate caloric intake. Malnourished patients show weight loss and hypoproteinemia; hypoproteinemia is independently

associated with a higher mortality in ECF.⁴ The initial evaluation of a patient's nutritional status is customarily done with a baseline laboratory evaluation including transferrin, albumin, and prealbumin but can include a metabolic cart analysis and multiple-frequency bioelectrical impedance analysis.¹⁹ The Harris-Benedict equation multiplied by a stress factor for sepsis can be calculated to approximate the patient's caloric needs. Patients with ECF generally require from 25 to 32 kcal/kg/day and 1.0 to 2.5 g/kg/day of protein, depending on the fistula output.^{4,9} Continuing evaluation of the patient's nutritional status is necessary and facilitates fine adjustments of the nutritional supplementation.

The route of nutritional supplementation should be enteral when possible. Enteral nutrition is associated with fewer complications than TPN, such as line infections and central venous thrombosis.^{4,20} Enteral feeding also improves gut absorptive function and may decrease bacterial translocation,²¹ and it may improve the immunologic and hormonal function of the intestine and increase hepatic protein synthesis. When given enterally, as little as 20% of caloric needs are beneficial.⁹ Eating per os is the preferred form of enteral nutrition, but some patients may need nasogastric, nasojejunal, gastrostomy, or enterostomy feedings to maintain caloric intake. Patients with proximal jejunal fistulas may benefit from fistuloclysis or feeding the distal limb of a fistula. This requires adequate distal bowel for absorption and lack of distal obstruction. A feeding catheter with balloon tip is placed into the distal limb of intestine under fluoroscopic guidance and used to infuse enteral feeding solution. Benefits of this approach include adequate nutrition, decreased use of TPN in patients with proximal fistulas, decreased cost, and improvement in bowel quality distal to the fistula, making subsequent definitive surgery easier.²² Fistuloclysis catheters should be tightly secured; they have been drawn completely into the distal small bowel by peristalsis in two patients, one of whom required reoperation for obstruction.²³

Not all patients are candidates for enteral nutrition. TPN-dependent patients are those who cannot obtain enteral access, who have fistulas with outputs too high to replace enterally, or who cannot tolerate enteral feedings because of nausea, abdominal distention, or pain. Patients with inadequate length of small bowel to allow absorption of needed calories and nutrients are also TPN dependent. Most patients are started on enteral and parenteral nutrition simultaneously, and TPN is weaned as enteral feedings are increased to goal.

Patients who are dependent on TPN usually need to supplement their vitamins and trace minerals as well. ECF patients should receive twice the recommended daily allowance for trace minerals and vitamins and up to 10 times the recommended daily allowance for vitamin C, selenium, and zinc.⁴

TPN is best administered with the assistance of a multidisciplinary team. These teams usually consist of physicians, pharmacists, nurses, nutritionists, infusion therapists, social workers, and home health providers as necessary. The team approach reduces line-associated complications such as infection, air embolism, venous thromboembolism, line placement complications, and electrolyte and fluid imbalances and can also reduce cost.^{2,20} Home administration of TPN is ideal for patients who require long-term TPN and has been shown to be safe and effective. It assists patients in tolerating their period of nutritional optimization longer, during which time a proportion of fistulas close spontaneously with medical management, decreasing the need for definitive surgery.²⁰

REDUCTION IN FISTULA OUTPUT

Reduction in fistula output alone would seem intuitively to increase the rate of spontaneous closure of a fistula, as less volume traversing the fistula should allow easier closure. However, the association of decreased fistula output with increased rate of spontaneous closure has not been proved. Reduction of fistula output, however, does allow patients to maintain their volume, electrolyte status, and nutrition more easily and decreases the amount of effluent on the skin, making fistula care easier. Several strategies for reducing fistula output have been studied.

Bowel rest with TPN decreases fistula output but, as discussed earlier, does not outweigh the benefits of enteral feeding. Acid suppression with H₂ blockers or proton pump inhibitors can decrease fistula output as well as reduce gastric acidity, prevent stress ulceration, and reduce electrolyte losses, although it has not been shown to increase the rate of fistula closure.^{4,9,24}

Somatostatin is a tetradecapeptide found throughout the body that inhibits multiple GI hormones, such as secretin, gastrin, glucagon, vasoactive intestinal peptide, cholecystokinin, and insulin. It decreases GI tract output by decreasing pancreatic, gastric, enteric, and biliary secretions and also decreases motility of the intestine.^{4,9} Somatostatin has an extremely short half-life of 2 to 3 minutes and is degraded by digestive enzymes; thus, it must be administered by continuous intravenous (IV) infusion. Complications of somatostatin infusion include frequent hyperglycemia and rebound hypersecretion of insulin, glucagon, and growth hormone on cessation of use.⁴

Octreotide is a synthetic analog of somatostatin that has a longer half-life and thus more convenient dosing. It lasts 1.5 to 2 hours after either IV or subcutaneous injection. Complications of hyperglycemia and rebound effects are decreased compared with somatostatin; however, both somatostatin and octreotide cause

an increased incidence of gallbladder sludge and cholelithiasis as well as pain at the site of administration.^{4,9,25}

Somatostatin and octreotide have both been studied in randomized, controlled trials to determine the effect of these drugs on fistula output, fistula closure rate, and time to fistula closure. The only randomized, controlled trial using somatostatin that addressed fistula output showed a significant decrease in output compared with placebo; however, pancreatic fistulas were included in the study.²⁶ Randomized, controlled trials using octreotide have not consistently shown a decrease in fistula output.²⁴ No study has shown an increased rate of fistula closure with use of either somatostatin or octreotide.²⁷ In several studies, somatostatin has been shown to reduce the time to fistula closure, although pancreatic fistulas were not considered separately in the series with the largest number of patients.²⁴⁻²⁷ Results of trials using octreotide with time to closure as an endpoint have been divergent and inconclusive.^{3,24,27} It should be noted that neither somatostatin nor octreotide can be expected to assist in the closure of a fistula kept open by mechanical means, such as distal obstruction. Thus, treatment with either should only follow adequate delineation of fistula and bowel anatomy.²⁸ Although the evidence is stronger for the use of somatostatin, current literature shows no clear improvement in outcome with the use of either octreotide or somatostatin for ECF. Although outcome may not be improved, management of the fistula effluent, fluid and electrolyte management, and skin protection may be easier with somatostatin or octreotide treatment if, in a particular patient, it results in reduction in fistula output.²⁸ At this time, not enough data exist to support using either somatostatin or octreotide in the routine treatment of ECFs.

ELUCIDATION OF THE FISTULA ANATOMY

Fistulas that have not spontaneously closed despite control of sepsis, skin protection, medical management, and nutritional support need further evaluation. Complicating factors such as foreign bodies in or near the fistula tract, radiation enteritis or inflammatory bowel disease in the associated bowel, untreated infection, epithelialization of the tract or mucocutaneous continuity, neoplasm in the fistula tract, and distal obstruction can prevent spontaneous closure. At this point, a full evaluation of the fistula tract and bowel must be performed.

If there is doubt about the existence of a fistula, the initial test often recommended is oral administration of methylene blue.⁴ This is inexpensive and relatively risk free and may be performed in the diagnostic phase of fistula management. If the fistula effluent takes on a blue color, the existence of a fistula is confirmed, as is its origin from a portion of the bowel in continuity with the rest of the digestive tract rather than from a

defunctionalized limb, such as a Roux limb. Oral charcoal has also been used in this manner.

As previously discussed, early CT is the study of choice in patients with signs of sepsis, as it may delineate areas of undrained abscess. Repeating the CT as needed after percutaneous drainage to ensure complete drainage is recommended.¹² These scans, when performed with oral contrast material, may also demonstrate the fistula tract and provide anatomic information about the orientation and length of the tract and its "feeding bowel."

The "gold standard" for examining a fistula is a fistulogram performed with water-soluble contrast material. This should be performed later in the management of the fistula, after stabilization and treatment of sepsis. A fistulogram can show the configuration of the tract, the source of the fistula, and any abscess cavity that communicates with the fistula. It can show underlying disease of the bowel at the origin of the fistula such as inflammatory bowel disease. Distal bowel obstruction, such as a stricture, can be diagnosed. Lastly, the fistulogram allows an estimate of the size of the bowel defect at the origin of the fistula.⁹ This information is combined to assess the chance of spontaneous closure of the fistula with supportive care. Upper GI series and Gastrografin enemas may also be useful in the evaluation of the fistula and its anatomic relation to the bowel as well as of the bowel quality and presence or abscess of distal obstruction.

Ultrasonography can demonstrate involved bowel, abscess cavities, and areas of possible stenosis but does not adequately evaluate the fistula tract. Ultrasonography supplemented with hydrogen peroxide fistulography has been shown to be at least as accurate as barium enema and static x-ray fistulography in characterizing the fistula tract and involved bowel and as effective as CT scan in identifying undrained abscess.²⁹ This study is particularly operator and interpreter dependent.

Endoscopy can be used in the accumulation of data regarding the characteristics of a fistula and surrounding bowel. Therapeutic endoscopic maneuvers can also be attempted which may assist in fistula closure. Uncommonly, the first presenting sign of Crohn's disease may be an ECF. In this case, endoscopy can be used to make a new diagnosis in patients with inflammatory bowel disease who present in this manner. Endoscopy can also be used to evaluate for neoplasm associated with the origin of the tract or distally. Strictures can be identified and treated endoscopically with dilation.³⁰ Further endoscopic treatments are discussed subsequently. Fistuloscopy (endoscopic evaluation of the fistula tract through the external fistula opening) can be used for identification and removal of foreign bodies, débridement of the tract, diagnosis and biopsy of neoplasm in the tract, and treatment in selected cases.³¹

NONSURGICAL FISTULA CLOSURE

Several methods of nonsurgical fistula closure have been attempted but none has been proved in a randomized, prospective trial.

The injection of fibrin glue into the fistula tract has been described in many case reports. In some instances, the fistula is located endoscopically and its internal opening injected with fibrin glue, a mixture of bovine thrombin and human fibrinogen.³² In other cases, the fibrin glue is injected from the external opening, with or without guidance by fistuloscopy.³¹ Many fistulas require multiple applications. Results have been encouraging, although most fistulas described in these series are internal, pancreatic, biliary, gastric, esophageal, rectal, or colonic. In general, the fistulas treated successfully with this method have been low output, short, uncomplicated, and uninfected, without evidence of neoplasia or inflammatory bowel disease.³⁰ A large randomized, controlled trial is needed to determine the true efficacy of this intervention.

Because of the bovine proteins in fibrin glue, there is a risk of allergic reaction and, theoretically, of prion contamination.³³ As recombinant human thrombin becomes available, this risk should decline. Fistuloscopy can lead to air embolism through increased pressure in the fistula tract. It can also lead to sepsis if the tract connects to an undiagnosed abscess cavity or the tract is infected.³⁰ As an alternative to surgery, fibrin glue application is safer and much less invasive and may save selected patients the mortality associated with operative intervention.

Other injectable treatments include histoacryl glue, which is not derived from animal products and thus has no risk of transmitting infection or causing allergic reactions related to bovine protein. Histoacryl glue also has the benefit of resisting enzymatic breakdown by fistula effluent as it is not a protein; thus, it may be more suited to high-output fistulas. Dalton and Woods reported a case of a recurrent, high-output duodenocutaneous fistula treated successfully with one application of histoacryl glue after failure of standard conservative therapy.³³ As with fibrin glue, a randomized, controlled trial is needed to evaluate this technique.

Porcine small intestinal submucosa (Oasis, Cook Biotech, West Lafayette, IN) is a naturally derived, extracellular matrix material that acts as a scaffold for host tissue ingrowth. It has been used most commonly in the treatment of abdominal wall defects but has been recently used to treat perianal fistulas and, less commonly, in small bowel fistulas.^{34,35} Schultz et al reported treating two patients with ECF resistant to conservative therapy by inserting a tightly rolled piece of small intestinal submucosa into the external fistula opening. The first patient's fistula closed immediately, and the second patient's fistula closed after removal and reapplication of the product the next day. The risk of

application of this product is minimal; infectious risk is low as the product is acellular and sterilized. Again, a randomized, controlled trial is needed to evaluate this technique in ECFs.

TIMING

The best time to abandon conservative management alone and attempt nonoperative fistula closure or definitive surgical closure has not been proved definitively in the literature. In the absence of complicating factors such as foreign bodies in or near the fistula tract, radiation enteritis or inflammatory bowel disease in the associated bowel, untreated infection, epithelialization of the tract or mucocutaneous continuity, neoplasm in the fistula tract, and distal obstruction, up to 74% of ECFs heal spontaneously with maximum conservative therapy.^{4,6,14} Of these spontaneously closing ECFs, 91% close by 4 weeks and the remaining 9% close by 12 weeks.^{1,4,9} Characteristics of fistulas that decrease their likelihood of closing spontaneously were discussed earlier in the section on classification of fistulas. If, after appropriate eradication of sepsis and medical management, 6 weeks has passed and the fistula has not closed or shown marked decrease in output, planning for definitive surgical closure should begin.

Surgical intervention should be delayed until intra-abdominal and systemic conditions are optimal. The abdomen after laparotomy complicated by ECF and sepsis shows a dense fibroadhesive reaction from ~10 days to 6 weeks or longer. There is no definitive way to tell when this dense reaction has subsided, but there are indications on careful clinical examination. The abdomen should be soft and nontender and the prior scar should be pliable. The abdominal wall should have healed as much as possible around the fistula and be free of inflammation.¹ Fistulas with mucocutaneous continuity should begin to prolapse when the intra-abdominal adhesions have softened and a neoperitoneum has developed.^{14,36} Until these clinical signs occur, the abdomen should be considered hostile. During this time of adhesion remodeling the bowel is edematous, hyperemic, and friable. Division of adhesions can cause significant blood loss from continuous oozing of cut surfaces. Operating too early can result in further enterotomies, recurrent fistulas, and may even necessitate the excision of large amounts of small bowel, resulting in short gut syndrome.

Systemically, the patient must be optimized medically and nutritionally prior to elective fistula repair. All abscesses should be drained and any infections adequately treated. The patient should have adequate serum albumin and normal serum electrolytes. Any comorbidities such as hypertension and diabetes should be well controlled, and patients should stop smoking.

In general, the longer the patient and surgical team can wait to undertake the elective operation, the

easier and safer it will be and the lower the fistula recurrence rate. These preoperative requirements may take up to 6 months to fulfill, and it is not unreasonable to wait that long to progress to definitive surgical intervention.¹⁴ Recommendations vary but usually specify waiting 3 to 6 months or longer after the original operation.^{9,10,14,36} In determining when to reoperate to close an ECF, there is no substitute for good clinical judgment and patience.

SURGICAL TECHNIQUES

Reoperation for ECF is technically challenging and time consuming. The case should be booked for the entire day to resist the urge to rush through the likely tedious dissection. The abdomen should be reopened away from any areas of possible contamination. If an old laparotomy incision will be used, the surgeon should enter the abdomen above or below the surgical scar to reduce the chance of encountering dense adhesions to the midline and creating an enterotomy. Once inside the abdominal cavity, gentle traction and sharp dissection should be used to divide adhesions. Many surgeons advocate adhesiolysis with a knife blade.^{1,9} Patient, meticulous dissection is crucial. Any serosal injuries should be repaired with Lembert sutures and enterotomies securely closed transversely in two layers. The bowel should be separated from the abdominal wall and fully freed of adhesions from the ligament of Treitz to the cecum. This facilitates examination of the entire bowel, resection of the area containing the fistula, and reconstruction of the bowel without tension; rules out distal pathology; and releases any bands of adhesion that may compromise postoperative bowel function and put the anastomosis at risk. Simply freeing the bowel near the fistula enough for resection and reanastomosis is not adequate.^{1,9,14}

When the fistula has been identified, the method least likely to result in recurrent fistula is resection and primary anastomosis of the area of bowel involved in the fistula. This should be performed in an area of bowel free of edema and friability, such that the anastomosis is positioned outside of any abscess cavity and away from the prior fistula site. Oversewing the fistula defect and performing a wedge resection of the involved bowel are associated with higher incidence of recurrence (32.7%) than resection and reanastomosis (18.4%).¹⁰ Diversion of the loop of bowel containing the fistula by exclusion of that segment of bowel without excision can be performed in the case of palliative operations for unresectable malignancy.³⁷ In nonneoplastic circumstances, diversion in this fashion should be reserved as a last resort, as it rarely results in fistula closure.²⁸

After resection and anastomosis, the entire bowel should be run to identify any further serosal or full-thickness injuries. These should be repaired as described earlier. The abdomen should be copiously

irrigated and any bleeding controlled. The omentum, if available, should be placed between the bowel and the midline wound. Seprafilm can be used under the midline wound to decrease adhesion formation but should not be placed directly over the anastomosis. The abdominal wall should be closed securely. In the case of a large abdominal wall defect, consultation with a plastic and reconstructive surgeon can facilitate abdominal wall closure with separation of components or a myocutaneous flap.⁹

Postoperatively, maintenance of the patient's oxygen-carrying capacity by assuring adequate volume status and avoiding hypotension, anemia, and hypothermia allows the new anastomosis to heal correctly. Avoiding infection and breakdown of the midline wound also helps prevent recurrent fistulas. Nutritional support should be continued.

Recurrence of ECF is a disheartening complication, which occurred in 21% of cases in one large series.¹⁰ The treatment of recurrent ECF is identical to that of an initial ECF. The fistula closure rate was not influenced by a previous attempt at operative fistula closure in the previously mentioned study or by the number of prior intra-abdominal surgeries. This supports the view that with persistence, even recurrent fistulas close.

UNDERLYING DISEASE

The presence of Crohn's disease, cancer, or radiation enteritis in the segment of bowel related to the ECF is a poor prognostic factor. Fistulas associated with these underlying diseases deserve special mention and case-by-case consideration in their management.

Crohn's disease is an immune-mediated disease of unknown cause that primarily affects the GI tract. An inflammatory process in the intestine causes micro-perforations and can lead to fistulas in one out of three cases. Most ECFs in Crohn's disease are spontaneous, arising from the site of a flare of the disease, or occur after percutaneous drainage of a spontaneous abscess. Unlike that with common postoperative ECFs, the associated bowel in this case is abnormal (affected with Crohn's.) This results in a lower incidence of spontaneous closure with conservative treatment. If fistulas do close spontaneously, they are more likely to reopen.³⁸ Postoperative ECFs in patients with Crohn's disease usually arise from bowel uninvolved with Crohn's (or an anastomosis would not have been fashioned there) and act like common postoperative ECFs in non-Crohn's patients.

Treatment of spontaneous or postdrainage ECFs in Crohn's follows the same algorithm as for non-Crohn's fistulas, with the addition of medical management for the treatment of Crohn's disease. Steroids and 5-aminosalicylic acid (5-ASA) have not been shown to effect healing of Crohn's ECF. 6-Mercaptopurine has

been used with some success, but response is slow and complications of neutropenia and pancreatitis limit its use. Cyclosporine has also been used, but the dose necessary for response is high and associated with frequent complications. Relapse occurred with switching to oral cyclosporine.³⁸

The most promising medical treatment for ECF in Crohn's is infliximab. Infliximab is an immunoglobulin G1 murine-human chimeric monoclonal antibody to tumor necrosis factor α . It has been shown to effectively treat moderate to severe Crohn's disease and was noticed to cause closure of enterocutaneous fistulas in this population. Present et al developed a multicenter, randomized, placebo-controlled study to assess the effect of infliximab on fistulas. This study showed a significant reduction in draining fistulas and a significant higher and faster rate of complete response in the patients in the infliximab groups compared with placebo.³⁹ A high proportion of the patients had perianal fistulas, which responded better to infliximab than ileocutaneous fistulas.

The ACCENT II study was a multicenter, double-blind, randomized, placebo-controlled trial to evaluate infliximab maintenance therapy on fistulas in Crohn's disease.⁴⁰ This study found that responders after induction therapy showed a significantly longer time until the loss of response, which was defined as the reduction of at least 50% of the draining fistulas, and a higher rate of fistula closure as compared with placebo after 1 year maintenance therapy with infliximab. The rate of adverse events, especially infection, is high. Because of the immune modulation of infliximab, there is a concern for infliximab-induced cancer and a risk of development of antinuclear antibodies, which may arise as an overt lupus-like syndrome. This also has not been definitively proved in the ACCENT II trial. This trial also had a high percentage of perianal fistulas as compared with abdominal fistulas; thus, its results may not be as meaningful for abdominal ECF in Crohn's.

In a retrospective chart review, Poritz et al treated 26 patients with varying fistula types with an induction dose of infliximab and then followed their surgical course to evaluate the impact of infliximab treatment on the need for surgery.⁴¹ They found that more than half of these patients still required surgical intervention but that the timing, indications, and difficulty were altered. More patients underwent operations for stricture than for fistula excision; this may attest to scarring from rapid fistula healing with infliximab. Intraoperatively, they also found less inflammation around the fistula tract and technically easier procedures in the patients treated with infliximab. As with the Present and ACCENT II trials, patients with perianal disease responded better to infliximab. Poritz et al found that no patients with ECF had complete closure with induction doses of infliximab.⁴¹

Infliximab has also been used efficaciously as a treatment for non-Crohn's disease ECF in three cases.⁴² The authors postulated that infliximab decreased the persistent inflammation that was causing these ECF to fail to close spontaneously despite maximal conservative treatment. Infliximab in Crohn's ECF and non-Crohn's ECF patients certainly deserves further investigation. Current literature regarding infliximab's role in closing Crohn's fistulas is promising.

ECFs associated with neoplasm are also resistant to spontaneous closure and may be resistant to operative closure. The presence of a malignancy increases the mortality associated with ECF. Among patients with postoperative ECF, 48% had prior radiation therapy and 48% had prior chemotherapy, which suggests that these factors increase the risk of postoperative ECF in patients with cancer. Chamberlain et al found that the presence of an ECF may delay or prevent the pursuit of adjuvant treatments for cure or palliation in 63% of cases.⁴³

Radiation damage to the bowel may cause complications weeks to years after the insult. The longest reported interval between radiation treatment and fistula development is 27 years.⁴⁴ Late injury usually occurs from progressive vasculitis, collagen deposition, and fibrosis. This causes tissue hypoxia, which can result in ulceration, necrosis, and perforation, ultimately leading to fistulization. ECFs associated with radiation enteritis are resistant to spontaneous closure and frequently require operative closure. The technique recommended at operation is variable. When possible, resection and reanastomosis is the preferred treatment, although the anastomosis must be made from healthy bowel.⁴⁵ If this cannot be accomplished because of the risk of short gut syndrome, a proximal defunctionalizing stoma should be considered in healthy bowel proximal to the fistula resection.¹⁰ Using healthy bowel to bypass the fistula in situ obviates the need to dissect radiation-damaged bowel, although the anastomotic dehiscence rate at the bypass can equal that of a resection.⁴⁶ Fistulas caused by radiation enteritis are often kept open by a distal stricture; in this case, stricturoplasty is the treatment of choice. Consulting with a plastic or reconstructive surgeon for a muscle or myocutaneous flap to buttress the fistula repair may decrease leak and improve healing by moving healthy tissue into the area.⁴⁷ Unfortunately, recurrence of fistulas from radiation is high.

CONCLUSION

An ECF is a devastating postoperative complication. Prevention cannot be stressed enough and is much more effective than the best treatments available for ECF. Once an ECF is diagnosed, the best outcomes come from early implementation of a treatment algorithm. The first priority is to resuscitate and to treat any sepsis; the second is to protect the skin. The third step is to

optimize the patient medically and nutritionally, which may allow spontaneous fistula closure. The last step is definitive operative treatment when necessary. The key to successful operative intervention is patience—first, patience in delaying the definitive operation until conditions are optimal, and second, performing a patient and technically precise procedure. Lastly, persistence is needed in the case of recurrent fistulas. With early implementation of a management plan, the patience to delay operative intervention until most likely to succeed, and persistence, nearly all fistulas close.

DISCLOSURE

The authors have no conflicts to disclose relative to this article.

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