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Review

Redefining "bowel regimen": Pharmacologic strategies and nutritional considerations in the management of small bowel fistulas

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ABSTRACT

Enterocutaneous fistulae (ECF) and enteroatmospheric fistulae (EAF) are difficult complications that primarily arise after abdominal surgical procedures. Development of an ECF or EAF carries significant mortality and morbidity. Effective management of patients with these disease states requires a multidisciplinary approach, which includes surgical, pharmacotherapeutic, and nutritional interventions. This review focuses on the medical and nutritional management of ECF/EAF, providing background on drug agents and nutritional strategies that may be helpful in reducing effluent volume, optimizing fistula healing, and maintaining nutritional health.

1. Introduction

The management of an enterocutaneous fistula (ECF) or enteroatmospheric fistula (EAF) is complex and resource intensive. These complicated disease processes require a multidisciplinary approach that should include a surgeon, dietitian, wound care nurse experts, and pharmacist. The fundamentals of ECF/EAF management consist of sepsis control, intravascular volume repletion, correction of electrolyte derangements, wound care, control of effluent, and provision of nutrition. Wound care and sepsis control are beyond the scope of this review. This review will discuss the pathophysiology of ECF/EAF as well as appropriate pharmacotherapeutic and pharmaconutrition-based multidisciplinary care of patients with this disease process.

2. Pathophysiology

A fistula is an abnormal connection between epithelialized structures.[1] An ECF is a communication between the lumen of the intestinal viscous and the skin; an EAF is a subset of ECF where a communication exists between the lumen of an intestinal viscous and the atmosphere. An EAF is not a true fistula because it lacks a tract as well as vascularized soft tissue coverage; therefore, spontaneous closure of an EAF is unlikely.[2,3] The processes that lead to ECF and EAF are most often a result of surgical and/or procedural complications; however an ECF can occur as the result of malignant process or inflammatory bowel disease (e.g., Crohn's or ulcerative colitis).[4]

The intestinal tract has different physiologic makeup and volume of output depending on the region (Table 1). Subsequently the viscous where the ECF/EAF originates can have varying pathophysiology that may alter the approach to management. ECFs are defined based on their anatomy, etiology, and/or pathophysiology.[5] The effluent nature and output probability are highly correlated to the anatomic region. Low, moderate, and high output fistulae are generally defined as <200 mL/day, 200–500 mL/day, and >500 mL/day, respectively.[1] Fortunately, up to one third of all ECFs will close spontaneously, whereas most EAFs will require surgery for definitive closure.[6,7]

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Table 1
Electrolyte composition of the gastrointestinal tract.[9]

Source	Sodium (mEq/L)	Potassium (mEq/L)	Bicarbonate (mEq/L)	Chloride (mEq/L)	Volume (mL/d)
Gastric	60	10	0	90	2000–2500
Pancreatic	140	5	90–110	30–45	1000
Bile	140	5	35	100	1500
Small bowel	100–130	15	25–35	100–140	3500

2.1. Gastrocutaneous fistulae

The majority of gastric ECFs (gECFs) are iatrogenic as a result of a surgery or a procedure. Other causes include radiation, malignancy, ischemia, or chronic inflammation. Management of a gECF must be approached based on the make-up of the gastric contents, volume of output, and the anatomy. The stomach can produce 2000–2,500 mL of gastric fluid in 24 h.[8] The gastric fluid is acidic and contains sodium, potassium, and chloride (content breakdown and volume amount seen in Table 1);[9] therefore, poor control of effluent can quickly lead to volume depletion as well as metabolic derangements including hypochloremic hypokalemic metabolic alkalosis. The acidic nature of the gastric fluid will quickly destroy skin and surrounding soft tissue.

Initial management includes volume resuscitation to restore intravascular volume and correct electrolyte abnormalities, making the patient nil per os (NPO) to control effluent, as well as decompression of the stomach with a nasogastric tube. Failure of the output to decrease significantly after 24–48 h should warrant investigation of the anatomy to assess for causes of persistent high output, which may include distal obstruction, an enterogastric fistula, or uncontrolled sepsis.

2.2. Duodenal fistulae

Duodenal fistulas are very difficult to manage, have a poor spontaneous closure rate, and often have very high output. These fistulas are often the result of surgery for various disease processes, such as peptic ulcer disease, trauma, and malignancy. Duodenal fistulas can be lethal secondary to uncontrolled sepsis and complex volume, electrolyte, and nutritional losses. The duodenum receives drainage from the pancreas, biliary tree, and stomach as well as reflux from the distal small bowel; therefore, duodenal fistulas may lose multiple liters of gastric, pancreatic, and biliary fluid per day.[9] End duodenal fistulas have a higher spontaneous closure rate (85%) when compared to lateral duodenal fistulas, which have only a 30–40% spontaneous closure rate.[5]

2.3. Small bowel and colonic fistulae

Small bowel fistulas can vary widely depending on the region of the small bowel involved. In general, the ability to control fistula output is more predictable for fistulas of the distal small bowel (ileum) compared to those more proximal (jejunum). Although the effluent volume from jejunal ECF/EAF can be very difficult to manage, enteral nutrition is possible in many cases. In some scenarios, the fistula may be used as a stomal aperture for placement of a feeding tube to feed the distal intestine, which will be discussed in more detail in later sections. A multidisciplinary approach with surgeons, dietitians, wound/stomal experts, and pharmacists makes this much more seamless.

Colocutaneous fistulas are often of low output and typically lack complex electrolyte abnormalities. The effluent is often easier to control and is more readily modifiable with pharmacotherapy.

2.4. Enteroatmospheric fistulae

The EAF is defined as superficial or deep. Deep EAFs are often seen in the presence of uncontrolled sepsis. The providers' goals are control of sepsis – in the operating room or by interventional radiological techniques – and resuscitation. The ideal means of source control is to remove the infected area; however, this is often not plausible secondary to the hostile nature of the abdomen due to obliterative peritonitis and/or frozen abdomen. If effective source control is not possible, the goal becomes proximal diversion as long as there is adequate bowel mobility. The attempt to control effluent, especially if the EAF is deep to any surrounding structures, can be futile. EAFs often must have an initial period of total bowel rest with administration of parenteral nutrition (PN), gastric decompression, and restoration of all volume and electrolyte abnormalities. Once this has been achieved, aggressive multifaceted wound management to control effluent is necessary. When effluent control has been achieved, most patients should be given consideration for enteral feeding. A number of pharmacologic strategies to achieve effluent control are available, which are discussed in the remainder of the review along with nutrition support strategies.

3. Opioids

Opioids decrease gastric motility and prolong gastric emptying time via mu receptor activation on parietal cells which leads to increased secretion of somatostatin and increased release of acetylcholine.

3.1. Loperamide

Loperamide is a phenylpiperadine opioid first synthesized in 1969. It was designed to maximize the antimotility effects of opioids while minimizing the euphoric effects by combining chemical features of neuroleptics with anticholinergics. Loperamide has low oral bioavailability (0.3%) due to significant first-pass metabolism. Absorbed drug is highly protein bound (97%) and has minimal central nervous system (CNS) penetration, leading to minimal CNS side-effects at standard doses.[10]

Loperamide is substantially more potent than morphine as a mu-receptor agonist, has a longer duration of action, and is only partially reversible with administration of naloxone.[11] Animal data suggest loperamide is a more potent antimotility agent than diphenoxylate, morphine, and codeine.[12] Additionally loperamide may reduce both pancreatic and colonic secretions,[13,14] further contributing to its effectiveness for approved indications.

In 1975 Tytgat and Huibregte published a placebo-controlled crossover study of 20 patients with well-established ileostomies showing administration of loperamide 8–12 mg per day in divided doses was associated with a statistically significant reduction in daily fecal weight as compared to placebo with minimal adverse reactions.[15] The same group conducted a second crossover study of 14 patients (7 with well-established ileostomy and 7 with ileorectal anastomosis) 2 years later which showed significant reductions in

fecal wet weight, mean daily stool volume, and fecal excretion rate.[16] A subsequent double-blind crossover study compared loperamide 4 mg three times daily to codeine phosphate 60 mg three times daily in 10 patients with high output ileostomy and found that, while both medications significantly decreased stool output and weight, loperamide significantly improved sodium and potassium balance and was associated with less adverse reactions.[17]

A recent case series suggested high-dose loperamide (up to 400 mg per day in divided doses for up to 2 years) is safe and efficacious for management of high-output ileostomies that do not respond to more conventional measures.[18] Additional reports suggest doses less than 12–24 mg per dose are unlikely to be effective in high output states, possibly related to decreased transit time of the medication.[19] However these reports should be interpreted with caution given the potential for dependence[20] and adverse reactions, specifically ventricular arrhythmias,[21,22] with high dose therapy. Further, high dose therapy requires specially-compounded dosage forms, as loperamide is only commercially available as 2 mg tablets/capsules and a 1mg/5 mL and 1mg/7.5 mL solution. These authors recommend that loperamide should be considered first-line pharmacologic therapy for the management of ECF/EAF; however caution is advised with doses higher than 16 mg per day, and individual doses higher than 24 mg should be reserved for investigational environments. Liquid loperamide should be avoided due to propylene glycol content which may increase fistula output.

3.2. Diphenoxylate/atropine

Diphenoxylate, structurally related to meperidine, is a more potent antidiarrheal than morphine, with an active metabolite, difenoxin, producing additional antidiarrheal effects by binding to mu receptors in the gastrointestinal (GI) tract. Diphenoxylate is well absorbed following oral administration with peak effect at about 1–2 h which may result in more adverse drug reactions such as euphoria.[23]

In 1977, Kramer evaluated the effect of diphenoxylate on ileostomy output using a dose of 5 mg four times daily for three day versus a preceding three day control. Overall mean differences in volume of ileostomy output over 72 h was unexpectedly increased with diphenoxylate use; however, only 3 patients were evaluated.[24] The following year, Newton reported findings of five patients who received five days of diphenoxylate 5 mg three times daily that reduced ileostomy sodium and potassium content compared to preceding five-day control period. Four of the patients showed a decrease in total ileostomy output; however, it did not reach statistical significance.[25]

Because CNS effects are seen at higher doses of 40–60 mg/day, the maximum recommended daily dose is 20 mg in four divided doses. Diphenoxylate is commercially available in 2.5 mg tablets, combined with small doses of atropine (brand name Lomotil) to discourage potential abuse due to euphoric effects seen at high doses of diphenoxylate.[23] Although there is limited available literature, diphenoxylate/atropine is used for fistula management and should be initiated at 2.5mg/0.025 mg (1 tablet) four times daily and titrated to the lowest effective dose. Liquid diphenoxylate/atropine should be avoided due to sorbitol content which may result in increased fistula output.

3.3. Codeine & morphine

Due to adverse effects including somnolence, nausea, and abdominal pain, morphine is less commonly used to decrease ECF/EAF output unless significant analgesia is also desired.[23]

Codeine is about 60% orally bioavailable due to extensive first pass metabolism, with a small amount metabolized by the liver via CYP2D6 to morphine. This conversion lends codeine its analgesic effect since the parent drug alone displays low affinity for opioid receptors.[23] Kanaghinis et al. reported the use of codeine for control of ileostomy effluent in two cases, resulting in decreased weight of fluid output and decreased loss of sodium and potassium. One case described the use of codeine 240 mg/day divided in four doses for 10 days, with discontinuation of codeine causing marked dehydration and wasting of sodium and potassium.[26]

In 1977, Kramer studied a lower codeine dosing regimen of 15 mg four times daily, which resulted in a 26% and 22% decrease in ileostomy effluent in two of three patients from control. The use of codeine was also associated with a decrease in sodium excretion of more than 15 mEq/day.[24] The following year, Newton published a study evaluating the effect of codeine use on ileostomy function. Five patients serving as their own controls were given codeine 60 mg three times daily, 30 min prior to meals. Patients collected ileostomy output for 3 days prior to treatment and 3 days during treatment. Codeine reduced ileostomy output of water, sodium, and potassium; however, two patients stopped early due to intestinal obstruction, which was self-limiting after discontinuation of codeine.[25] King et al. reported on their double blind crossover study comparing codeine to loperamide with results previously described in this paper.[17]

Due to its lower affinity for opioid receptors, codeine results in fewer side effects than those seen with morphine and other orally bioavailable opioids; however, caution should still be taken to monitor for these effects. Codeine therapy to reduce fistula output should be reserved for patients who have failed other treatments and should be initiated at 15 mg four times daily and titrated to the lowest effective dose.[23]

Based on current available literature and clinical practice, loperamide has become the initial opioid agent of choice for the management of high output ECF due to data and tolerability of the drug. Lomotil has become the second line agent if loperamide at maximum dosing does not achieve goal control. Codeine and morphine are not commonly used because of CNS adverse reactions.

4. Anti-secretory agents

4.1. Somatostatin analogues

Somatostatin is a naturally occurring peptide hormone that reduces the secretion of various GI hormones, including gastrin and cholecystokinin, leading to decreased gastric and pancreatic secretions, reduced splanchnic blood flow, and prolonged gastric emptying.[27] The plasma half-life of somatostatin is only 1–2 min, which requires administration of a drug via continuous infusion to maintain adequate serum levels. Due to this pharmacokinetic disadvantage, synthetic analogues of somatostatin have been developed with longer half-lives which allow for intermittent dosing.[27]

Octreotide is an octapeptide analogue of native somatostatin with similar anti-secretory and intestinal musculature relaxing actions; the end result is decreased GI motility and increased water and electrolyte absorption in patients with ECF/EAF. These actions lower fluid and nutrient losses and may promote fistula healing. The prolonged elimination half-life of approximately 90 min allows for intermittent subcutaneous administration, with the most common initial dose of 100mcg three times daily.[28] Another synthetic somatostatin analogue, lanreotide, is available as a prolonged-release microparticle intramuscular injection, allowing for administration every 10 days.[29]

Possible adverse effects of somatostatin and analogues include transient GI symptoms, such as nausea, vomiting, cramping, and bloating. Administration as late as possible after meals may minimize these effects in patients receiving EN. Somatostatin also affects insulin secretion, which may cause mild hyperglycemia. This effect is less pronounced with octreotide due to slight differences in receptor specificities. Steatorrhea may result from fat malabsorption due to decreased pancreatic exocrine secretion, and gallstones have been reported in up to 50% of patients treated with long term somatostatin analogue therapy.[28]

Several small randomized controlled trials (RCTs) and case series have compared somatostatin and somatostatin analogues to standard medical therapy or placebo in patients with ECF. An early trial evaluating the effect of octreotide on small-bowel fistula output was published by Nubiola-Calonge et al., in 1987. Fourteen patients with persistent post-operative small bowel fistulas were randomized to receive octreotide 75-100mcg subcutaneously every eight hours or placebo during a four day randomized, single-blind crossover phase, after which all patients were transitioned to open-label octreotide. In patients initially given placebo and transitioned to octreotide, mean fistula output decreased from 698 mL per 24 h to 246 mL per 24 h after 2 days of octreotide therapy ($P < 0.01$).[30] The promising outcomes of this study were followed by multiple small RCTs with varying results.[31,32] A multicenter RCT evaluating somatostatin analogues in ECF patients by Sancho and colleagues in 1995 reported no improvement in the rate of spontaneous fistula closure in the group treated with octreotide compared to standard care.[33]

Due to conflicting results, small sample sizes, and failure to meet power in studies evaluating somatostatin and somatostatin analogues, multiple systematic reviews and meta-analyses have been published on the subject.[27,31,32] In 2012, Coughlin and colleagues assessed eight studies comparing somatostatin or its analogues to standard therapy in patients with established post-surgical ECF anywhere along the GI tract. Outcomes assessed included mortality, time to and incidence of fistula closure, duration of hospital stay, and need for reoperation. Overall, the analysis found that somatostatin analogues appeared superior to control based on outcomes including time to fistula closure (mean 6.37 fewer days, 95% CI -8.33 to −4.42), hospital length of stay (mean 4.53 fewer days, 95% CI -8.29 to −0.77), and need for reoperation (RR 0.41, 95% CI 0.20 to 0.82). No treatment effect of somatostatin analogues on incidence of fistula closure or mortality was found, and no high quality evidence suggested superiority of one somatostatin analogue to another.[31]

Later in 2012, Rahbour et al. published another systematic review and meta-analysis evaluating the use of somatostatin and somatostatin analogues for ECF management. Nine RCTs were included, eight of which were the same studies assessed in the meta-analysis by Coughlin et al. Overall results were similar, however the authors did report a significant increase in rate of ECF closure between the somatostatin analogue group vs. control groups (100/152 vs. 77/155 fistulae closed, $p = 0.002$). The authors attributed this statistical difference to a single study by Gayral et al. evaluating lanreotide.[27] Interestingly, in their original publication, Gayral et al. do not report a difference in fistula closure rate but instead describe a statistically significant increase in the number of "responders" to lanreotide therapy, defined as a 50% reduction in fistula output within 72 h of the first intramuscular injection.[29] Therefore, these results do not support the conclusion of the Rahbour meta-analysis that somatostatin analogues increase the likelihood of fistula closure.

Overall, the available evidence suggests that somatostatin analogues may be helpful in decreasing ECF output and shortening time to fistula closure, but evidence to support any effect on mortality or improved fistula closure rates is lacking. It is the opinion of the authors to only trial the use of somatostatin analogues, preferably octreotide, after optimizing use of other available agents first.

4.2. Histamine H2-receptor antagonists and proton pump inhibitors

Both Histamine H2-receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) may be useful in the management of high output fistulas due to their effects on gastric acid secretion. H2RAs, such as cimetidine, famotidine, and ranitidine, exert their effect by competitively antagonizing histamine at the parietal cell Histamine-2 receptor, thus reducing gastric acid secretion.[34] Proton pump inhibitors decrease gastric acid secretion through covalent binding to membrane-bound hydrogen/potassium-ATPase molecules of the parietal cell, decreasing hydrogen ion secretion into the gastric lumen. After oral administration, most PPI absorption occurs in the proximal small intestine after degradation of the protective delayed release coating in the stomach.[35]

In patients with little remaining small bowel, enteral absorption of both H2RAs and PPIs can be impaired due to decreased drug contact with the intestinal mucosa. Intravenous drug administration may result in improved response compared to oral administration.[34,36] PPI preparations containing intact granules in a liquid may clog feeding tubes; therefore, immediate release omeprazole or lansoprazole suspensions are preferred for enteral tube administration.[35]

As the prototypical H2RA, cimetidine was the first acid-reducing agent to be assessed in patients with short bowel syndrome. A 1986 report describes decreased stool mass and sodium loss in short-bowel patients with jejunostomies receiving cimetidine 400 mg four times daily.[37]

In 1991, Nightingale and colleagues described the effect of oral omeprazole on intestinal output of eleven patients with short bowel syndrome. Seven patients described as "secretors" (displaying higher intestinal output than oral intake) were given 40 mg of oral omeprazole twice daily which produced a mean daily reduction in intestinal output of 0.66 kg/24 h (output during control period ranged from 1.48 to 8.25 kg/24 h) while also reducing mean sodium loss and improving potassium balance.[36] A subsequent double blind, randomized crossover trial by Jeppesen et al. evaluated the effects of intravenous omeprazole 40 mg twice daily versus intravenous ranitidine 150 mg twice daily on the absorption of water, electrolytes, nutrients, and energy in thirteen patients with short bowel disease. Ranitidine failed to show a significant treatment effect, but omeprazole was found to increase water absorption in the patients with higher fecal outputs. Neither ranitidine nor omeprazole significantly affected absorption of electrolytes/macronutrients or allowed discontinuation of parenteral fluid supplementation.[34]

Despite potential utility in decreasing intestinal output leading to reduction of electrolyte losses, H2RAs and PPIs have not been shown to increase the rate of fistula closure.[38–40] It is the opinion of the authors that when used, intravenous therapy is preferred over enteral administration initially due to questionable and possibly erratic absorption.

5. Miscellaneous

5.1. Clonidine

Limited data suggests that the alpha-2 agonist clonidine may be an effective means to decrease stool output in a variety of patient populations. The administration of clonidine up to 0.6 mg orally twice daily was associated with a statistically significant reduction

in diarrhea volume in 3 patients with insulin-dependent diabetes mellitus; upon withdrawal of the drug, diarrhea returned which was treatable with resumption of clonidine therapy.[41] No significant hemodynamic effects were noted. The proposed mechanism of action for clonidine is increased mucosal absorption of fluids and electrolytes via alpha-2 agonism at the enterocyte, which is supported by improved electrolyte balance in the aforementioned case series.[41]

An additional case series of 2 patients with high-output short bowel syndrome showed dramatic reductions in ostomy output (from 4 L per day to 1 L per day in the first patient, and from 4 L per day to 1.5 L per day in the second patient) with addition of clonidine 0.1–0.2 mg orally twice daily.[42] Finally, a controlled study of 8 patients with high output jejunostomies showed a reduction in fecal weight and improved sodium balance with addition of clonidine 0.3 mg transdermal patch to their current antidiarrheal regimen.[43] No hemodynamic adverse events were reported.

While clonidine should not be considered first-line therapy, its addition to a current antidiarrheal regimen may decrease output in patients not controlled with conventional therapy based on very limited evidence. If used, transdermal clonidine at a dose of 0.3 mg per day is recommended; however this formulation is substantially more expensive than enteral. Enteral clonidine at a dose of 0.1–0.6 mg twice daily, may be considered in patients unable to afford transdermal therapy.

5.2. General medication considerations

Medications requiring delayed release or extended release formulations should be avoided. Immediate release formulations should be utilized for patients with fistulas to optimize potential for absorption. Laxatives and bowel stimulants—including sorbitol flavorings or propylene glycol solvents in liquid medications—should also be avoided. Table 2 lists pharmacotherapy options discussed for decreasing fistula output with recommended starting doses and titration when appropriate as well as relative cost comparison.

6. Nutritional considerations

Nutrition support plays a critical role in the management and successful closure of ECF/EAF. Patients with ECF/EAF often present with or develop malnutrition during their medical/surgical course. Correcting and preventing further malnutrition becomes a clinical challenge for both the patient and the multidisciplinary healthcare team. With the introduction of PN in the 1970s, fistula patients realized improved nutritional status, closure rates, and survival.[44] Bowel rest and PN provided a cornerstone of therapy for nutrition support for the past four decades. However, EN contributes to maintaining the functional and structural integrity of the intestinal epithelium, stimulates intestinal contractility and blood flow, prompts the release of GI hormones and enzymes, and modulates the gut-associated lymphoid system (GALT).[45]

Nutrition support should be promptly initiated following the treatment of any intra-abdominal infection or sepsis and establishment of hemodynamic stability with fluid resuscitation. Knowing the exact fistula location in the GI tract is critical when choosing between PN and EN. A minimum length of approximately 60–100 cm of small bowel with an intact ileocecal valve and colon is needed to maintain adequate absorption, provided the remaining bowel is healthy and non-obstructive. This length alone does not guarantee optimal and immediate absorption.[46] A proximal fistula with insufficient or non-healthy remaining bowel necessitates prompt PN initiation to avoid further calorie, protein, vitamin, and trace element malnutrition.[47] Patients with a distal fistula may never require PN and may adapt and tolerate EN or an oral diet. The volume of fistula output will also determine the success of tolerating EN as the sole source of nutrition support. High output fistulas may require PN until edema decreases with increasing albumin levels, and fluid and electrolyte absorption can support EN tolerance. Due to its functional and immune benefits over PN, EN should be initiated as soon possible or reattempted frequently, even with low doses of 10–20ml/hr. EN can be initiated once the bowel is in continuity and/or the drainage can be controlled. Vigilant replacement of electrolytes and thiamine when initiating EN/PN may reduce the effects of refeeding syndrome in patients who have had a prolonged NPO status.[48]

Nutritional requirements should be individualized to account for any ongoing disease states such as Crohn's disease, acute injuries, surgical procedures, along with any degree of malnutrition or wounds present prior to the development of the fistula. Basal energy expenditure can be calculated using one of several predictive equations such as the Harris Benedict Equation multiplied by an appropriate "stress/activity factor" to estimate caloric requirements.[49] Caloric needs often range between 25 and 32 kcal/kg if the patient is not extremely underweight or obese. The World Health Organization (WHO) established the Recommended Dietary Allowance (RDA) for protein for a healthy person as 0.8 g/kg/day.[50] When determining protein requirements for patients with a fistula, the provider must take into account several additional aspects including current nutritional status, albumin levels, wound healing, and volume of fistula output. Measurement of urinary nitrogen balance is likely inaccurate due to the potential for significant nitrogen and fluid loss through the fistula. Cheatham et al. reported

Table 2
Pharmacologic therapies.

Drug	Initial Dose	Route	Frequency	Titration	Max Dose	Cost	Special considerations
Loperamide	4 mg	PO	TID w/meals or q6h w/EN	By 2 mg	16 mg/day	$	Avoid liquid due to propylene glycol content
Diphenoxylate/ Atropine	2.5mg/0.025 mg (1 tablet)	PO	TID w/meals or q6h w/EN	By 1 tablet	2 tablets QID (20 mg diphenoxylate)	$$	Avoid liquid formulation due to sorbitol content
Pantoprazole	40 mg	IV	BID	None	40 mg BID	$$$	Discontinue as soon as feasible
Codeine	15 mg	PO	TID w/meals, up to QID	By 15 mg	45 mg QID	$$	Monitor for CNS effects
Octreotide	100mcg	subQ	TID	None	None	$$$	Discontinue if output not decreased after 3–5 days
Clonidine	0.3 mg	Transdermal	q7d	None	0.3 mg q7d	$$$$	Monitor HR and BP

Mg = milligrams, mcg = micrograms, PO = oral, IV = intravenous, subQ = subcutaneous, TID = three times daily, q6h = every 6 h, EN = enteral nutrition, BID = twice daily, QID = four times daily, q7d = every 7 days, $ = less than $1 per day, $$ = more than $1 per day; $$$ = more than $5 per day, $$$$ = more than $10 per day (prices estimated based on approximate inpatient acquisition cost), CNS = central nervous system, HR = heart rate, BP = blood pressure.

an estimate of 2 g of nitrogen per liter of abdominal fluid output should be included in the nitrogen balance calculations of any patients with an open abdomen.[51] Most patients will require at least 1.5 g/kg/day of protein as an initial dose which should be adjusted according to monitoring parameters, wound healing, and renal function.[39] High output fistulas may require up to 1.5–2.5 g/kg/day to replenish protein stores, maintain a positive nitrogen balance, and stimulate wound healing.[52] Ongoing nutrition assessment and monitoring is critical to avoid protein and calorie malnutrition, further wound breakdown, or impairment of fistula closure. Prealbumin and albumin levels should be monitored weekly and micronutrients assessed monthly, as vitamin C and zinc deficiency frequently occur due to excess losses.[39]

6.1. Enteral nutrition

Adequate absorption of fluids, electrolytes, EN, and oral medications depends on the location of the fistula and integrity of the remaining bowel. Patients with a distal fistula may be able to avoid PN and protein calorie malnutrition with a specialized modified oral diet. Nutrition counseling with a registered dietitian is paramount to avoid macro- or micronutrient deficiencies in these scenarios. Adherence to a short bowel syndrome diet of 4–6 small meals daily, high protein liquid nutritional supplements, no concentrated sugars or hyper-osmotic liquids or medications, and supplementing fiber as tolerated is prudent. Chewable or gummy vitamins and mineral supplements are critical if EN or PN are not utilized.[53] If EN is necessary, establishing enteral access may also pose a challenge with an altered GI tract. A gastric or duodenal feeding access is likely adequate with a distal fistula, but a proximal duodenal or jejunal fistula will require passage of a tube beyond the fistula via a percutaneous endoscopic gastric tube placement with jejunostomy or a surgically or radiologically placed jejunostomy.

Fistuloclysis is a technique of providing enteral nutrients directly through the fistula opening. A polymeric formula without fiber should be initiated at 10–20ml/hr and advanced slowly towards the goal rate as tolerated. Teuber et al. reported 11 of 12 patients successfully weaned off of PN using polymeric EN via fistuloclysis, with no associated complications.[54] Wright et al. published a case report of successfully feeding a high-calorie polymeric formula via fistuloclysis.[55] If the polymeric formula is not tolerated, a trial of a semi-elemental formula would be the next step as was successfully reported in a case study by Ham et al.[56] Yin et al. recently reported 9 patients successfully transitioned from PN to a semi-elemental EN with an EAF. The median timing of initiation and achievement of full strength EN after the occurrence of EAF was 9^{3-22} and 27^{22-43} days, respectively. PN was discontinued when one-half to two-thirds of full-strength EN was reached.[57] Yuan retrospectively reviewed outcomes of 82 patients with an open abdomen and GI fistula with severe sepsis. In patients fed within 14 days, abdominal closure was accomplished more rapidly (142.8 vs 184.5 days, $P = 0.017$), and mortality was significantly decreased (11.1% vs 47.8%, $P < .001$) compared to those fed after 14 days.[58] Succus entericus reinfusion (SER)[33] protocol was performed for 41 (50%) of the 82 patients with proximal small bowel fistula with high-output volume (>500 ml) or multiple fistulae.[58] The SER method collects the output from the proximal stoma and reinfuses it back in the distal limb to help maintain fluid and electrolyte balance; however the necessity of this therapy has been questioned and patients find it difficult and unpleasant.[59]

6.2. Immunonutrition

Glutamine is the primary nitrogen and energy source for enterocytes and has a wide range of effects on immune function. Novak et al. aggregated 14 randomized trials evaluating the use of glutamine supplementation in surgical and critically ill patients.[60] In surgical patients, glutamine supplementation may be associated with a reduction in infectious complication rates and shorter hospital stay without any adverse effect on mortality. In critically ill patients, glutamine supplementation may be associated with a reduction in complication and mortality rates. The authors concluded that patients receiving high-dose, parenteral glutamine had the greatest benefit.[60] De Agular Nascimento et al. concluded that oral glutamine accelerated healing and reduced mortality rates in a series of patients with post-operative high-output intestinal fistula receiving PN.[61] Controversy exists regarding supplementing glutamine since the authors of the REDOX trial reported that early provision of glutamine or antioxidants did not improve clinical outcomes, and glutamine was associated with an increase in mortality among critically ill patients with multi-organ failure.[62] As glutamine is renally eliminated, excessive supplementation should be avoided in patients with renal failure.[63] No prospective randomized controlled studies to date have been published with a combination immunonutrition formula evaluating outcomes specifically for ECF/EAF.

6.3. Parenteral nutrition

Despite the theoretical benefits of EN, PN remains a vital therapy for patients with an ECF/EAF. Indications for PN include insufficient healthy bowel (<60–75 cm), prolonged high dose vasopressor therapy, inability to establish enteral access, and high volume fistula output exacerbated by EN.[1,40] Electrolyte and fluid management is simpler with PN due to the lack of GI irritation associated with EN, fluids, and enteral medications. Patients receiving only PN should have enteral or oral nutrition reintroduced at routine intervals to stimulate the GI tract, minimize cholestasis, and reduce PN-associated liver disease.[64] Meticulous central line care and frequent laboratory monitoring is critical to avoid complications such as catheter associated infections as well as electrolyte, glucose or lipids disturbances. Most patients prefer to cycle PN over 12–18 h daily to allow for 6–12 h disconnected from PN.

7. Electrolyte considerations

Upon initial diagnosis of ECF, the patient may require several liters of intravenous crystalloid fluid and electrolyte replacement to correct dehydration and electrolyte abnormalities.[40]

The content of the 4–7 L of losses in high output ECF may be predictable depending on ECF location; however, losses may include secretions both proximal and distal to the ECF such as those from the mouth, esophagus, stomach, small bowel, pancreas, and biliary tree.[39,40]

Ongoing loss of electrolyte-rich intestinal fluid via ECF should be avoided with interventions previously described in this review if possible. Fluid and electrolyte disturbances commonly seen in patients with ECF include dehydration, metabolic acidosis or alkalosis, hyponatremia, and hypokalemia.[40] Magnesium, phosphorus, bicarbonate, and calcium levels may also be affected.[39] A major concern includes sodium loss with the associated fluid loss that follows. This more likely occurs from the jejunum than the ileum, as the distal small bowel and colon typically reabsorbs this secreted sodium from the jejunum.[65] This sodium loss is exacerbated by fluid intake with low sodium content or large volumes of free water; thus, patients should only consume small amounts of water between meals. Preferably patients should consume oral replacement solutions containing glucose and at least 90 mmol/L of sodium to prevent further sodium loss.[65]

Depending on factors described above, patients may receive

nutrition support via PN or EN with adequate provision of fluid and electrolytes.[39] Serum electrolyte levels including potassium, ionized calcium, magnesium, and phosphorus should be monitored daily in the acute setting and weekly in the outpatient setting.[53] Patients receiving EN or PN may require additional intravenous replacement of fluid and electrolytes, while patients receiving EN or with volitional intake may receive oral or per tube electrolyte replacement. Potassium, magnesium, and phosphate should be cautiously replaced via the enteral route due to their potential osmotic laxative effects and subsequent exacerbation of electrolyte losses. Patients should be advised to present to the emergency department if their fistula output suddenly increases or persists at a high rate as electrolytes may require immediate replacement.

8. Conclusions

The management of ECF and EAF can be quite complex. Effective management requires a multi-disciplinary team approach to optimize the patient and provide the best outcomes. The team should comprise of surgeons, nutritional support dietitians, pharmacists (for both pharmacotherapy and pharmaconutrition), and wound care/enterostomal experts who collectively consider the patient's condition and derive a plan. Initial diagnosis of an ECF/EAF is followed by fundamental management that includes: control of sepsis, intravascular volume repletion, correction of electrolyte derangements, wound care, control of effluent, and provision of nutrition. Once the patient is stabilized, providers must consider and appropriately use pharmacotherapy to decrease effluent flow and improve retention of EN. EN must be considered at the forefront of management on all ECF/EAF patients; it is safe and feasible with time and education to feed almost all of these cases with EN. Reliance on PN for most ECF/EAF cases places the patient at higher risk of many complications, particularly infectious in nature, and is significantly more expensive. Utilization of select medications, particularly loperamide and octreotide, as well as avoidance of potentially harmful medications such as laxatives and liquids, may allow for additional provision of EN and subsequent fistula closure.

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Appendix A. Supplementary data

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