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Review article

Evolution in Management of Enterocutaneous Fistulas: An Historic Perspective and Updates

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Abstract
Enterocutaneous fistulae (ECF) are a pathological entity that has increased in frequency since the advent of the open abdomen and damage control surgery, since in up to 85% of cases its origin is iatrogenic. The principles in the management of this nosological entity have been stipulated for more than 50 years [1], however evidence-based medicine and advances in some areas such as nutritional support and negative pressure systems have allowed us refine its management algorithm, discarding some ideas that were held as dogmas and establish less invasive therapies with better results for the patient.

Keywords: ***Enterocutaneous fistula, parenteral nutrition, general surgery, gastrointestinal surgery.***

Introduction

An enterocutaneous fistula (ECF) management represents a great challenge for the general surgeon, regardless of his or her experience, since it requires careful nutritional and medical management, as well as surgical intervention, with an often-uncertain prognosis. From the last 60 years to the present, new therapies have been introduced with the aim of improving the evolution of patients with this pathology, among the most relevant are the use of parenteral nutrition by Dudrick et al., focused on reversing the catabolism established by the proinflammatory state and malnutrition secondary to fasting [2], the use of better spectrum antibiotics and the constant drainage of abscesses that is a characteristic of patients with ECFs, thus improving mortality from sepsis, which is the main cause of death in patients with this pathology in the early phase of disease [1,3-5], we must also consider negative pressure systems, which have improved the outlook in these patients.

Materials and Methods
"Not applicable".

Results and Discussion

Classification
FECs can be classified according to their output: High output > 500 mL/24 hours, Moderate 500 - 200 mL/24 hours and Low output <200 mL/24 hours; by location [1]: Type I - Esophageal, gastric and duodenal, Type II - Small intestine, Type III - Colon and Type IV any location with drainage to a large abdominal wall defect (enteroatmospheric fistulas); by its etiology: Iatrogenic (injury during a surgical procedure, trauma, foreign body, associated with an anastomosis), by inflammatory bowel disease, by infectious diseases (tuberculosis, actinomycosis), associated with neoplasms [6]. An additional type of ECF is the enteroatmospheric fistula (EAF), which is an intestinal fistula that occurs in the setting of an open abdomen, creating a communication between the gastrointestinal tract and the external atmosphere [7], both of which have increased in its frequency after the use of the open abdomen as an alternative in complex surgical scenarios [8-11]. Fistula closure without the need for surgical management has greatly improved after the introduction of measures such as parenteral nutrition and wound management with negative pressure systems, providing better skin care and an anabolic state that improves prognosis in spontaneous closure of the fistula.

Chapman's work
Chapman first listed a standardized sequence of steps for the management of patients with enterocutaneous fistula in a series of 56 cases, published in the American Journal of Surgery in 1964 [1]. The steps that he initially proposed were indicated as "Priorities in the treatment of intestinal fistulas" (**Table 1**), in them he established two key aspects for the management of patients with ECFs: time and order.

Nutrition in patients with intestinal fistula
Nutrition plays a primary role in the management and reduction of morbidity and mortality in patients with ECF, and although it has

been described for more than 3 decades, it remains one of the main problems in the management of these patients in our country [10], either due to lack of resources or knowledge in the administration of nutritional support. This situation is exacerbated in patients with infectious complications, which represent the main cause of death in patients with ECF, who also increase catabolism in the septic state and require aggressive protein and caloric replacement [8].

Early nutritional support is crucial for the successful management of the ECP patient. Immediately after diagnosis, resuscitation and correction of fluid and electrolyte imbalances are essential to reverse shock, restore acid-base balance, and stop the progression of the inflammatory process to instances such as shock and organ failure.

In addition, according to location in the gastrointestinal tract from the fistula ionic alterations may vary, becoming more relevant in proximal fistulae, where the output may be rich in potassium and bicarbonate. A high-output fistula can be replaced with 0.9% saline solution and potassium supplementation (KCl at 10 mEq/L), meanwhile in special circumstances, replacement could be guided by taking a biochemical study of the fistula output and according to the serum deficit [6], so it is important to know the normal hydroelectrolytic composition of the fluids in each segment of the gastrointestinal tract (**Table 2**) [9].

To meet these nutritional requirements during the earliest phase of management, parenteral nutrition (PNT) strategies have been established in conjunction with the restriction of oral intake, which seek to maintain the patient's fluid and electrolyte balance and reduce the cost of ECF, thus improving the metabolic conditions to achieve its spontaneous closure. Although TPN is a great alternative to provide nutritional support to patients with ECF, in the long term and in selected patients, enteral access and even the oral route can be used to maintain appropriate nutrition in search of inducing spontaneous closure of the fistula or in view of performing a surgical closure [12]. There are some recommendations on caloric needs in patients with ECF [3,12-14], regarding total calories, protein, vitamins and trace elements.

Antibiotic Treatment

The specific antimicrobial treatment for the management of patients with ECF is not established, however it is possible guide it by the patient's clinical status and the conditions in which it is received. The Surviving sepsis campaign guidelines [15] recommends to start management with a broad-spectrum antibiotic during the first hour in patients with septic shock, after taking cultures; Likewise, it is important to identify at what level of the digestive tract the origin of the fistula is located, in order to guide management towards these pathogens, whether we are dealing with a fistula of the small intestine or the colon [16]. Another important factor to consider is that the etiology of enterocutaneous fistulas is associated with a previous surgical procedure, even in up to 95% of cases in some series [17], so the pathogens that are commonly involved were acquired within the hospital and there is a latent risk of multi-resistance to antibiotics, so that the indication is to start with an extended-spectrum antibiotic when dealing with a patient at risk. Some authors argue that in a stable patient, antimicrobial treatment could be delayed until the abdominal infection site is swabbed for culture, in order to optimize targeted therapy [15-18]. Despite this, knowledge of local and regional resistance is a fundamental piece for the appropriate selection of empirical antibiotic therapy [19].

Conservative management vs surgical management

Drugs to decrease fistula effluent

Reducing the fistula effluent is one of key steps in the stabilization of the patient with ECF, since it minimizes water and electrolytic losses it is also easier to protect the skin from damage caused by gastrointestinal fluids and is an essential requirement to be able to restart the diet either enterally or parenterally [12]. Within the arsenal of drugs we have gastric secretion inhibitors (PPIs and anti-H2), intestinal motility inhibitors with activity on the opioid receptor: Loperamide (the most used in our country), codeine and opium tincture and the somatostatin and analogs (octreotide, lanreotide and sandostatin).

Hypergastrinemia is a pathophysiological consequence of intestinal resection [20-21] and PPIs (proton pump inhibitors) are the drugs of choice to reduce gastric acid secretion and are usually used for high-output fistulas, increasing their doses to achieve a fistula output of less than 1 liter/day and achieve a pH of the same > 6 [22] without having a direct relationship with spontaneous closure [15], however it is with the decrease in effluent and the characteristics of the same.

Of the drugs that have been used as cathartics in the management of high-output fistulas, loperamide is the most widely used in our country due to its easy accessibility and cost. It has a known effect on the opioid receptor, causing a delay in intestinal transit by inhibiting the myenteric plexus [23], with doses of up to 16 mg per day, however, in some specialized centers doses higher than 40 mg/day have been used, as reported in their work Hollington et al [4]. Due to its pharmacokinetic characteristics, it is recommended to take it 30-60 minutes before meals. One study showed that loperamide and codeine have similar efficacy in reducing high-output fistula or stoma effluent, with fewer adverse effects associated to use of loperamide [24].

Somatostatin is a cyclic peptide of 14 amino acids, with multiple functions at the systemic level. Its use in the management of enterocutaneous fistulas is based on its effects at the level of the pancreas, where it is capable of inhibiting almost all of its exocrine secretion, as well as promoting the absorption of water and electrolytes [25]. Both somatostatin and its analogs (octreotide, lanreotide and sandostatin) have shown no effect on the decrease in intestinal effluent and FEC in some studies, however they have shown benefits in many others [26-30]. A meta-analysis by Rahbour et al showed that somatostatin improved the number of fistulas with spontaneous closure [n=61/82 vs control 30/85, RR 2.79, 95% CI (1.03,7.56) z=2.02, P=0.04)] and time to closure [(n=85 vs controls 82 [SMD -0.79, 95% CI (-1.11, -0.47), z= 4.86], P <0.00001)], in the same way the analogs (octreotide/lanreotide) [n=100/152 vs control 77/155, RR 1.36, 95% CI (1.12,1.63) z=3.17, P=0.002 // n=141 vs control 147 [SMD -0.51, 95% CI (-0.75, 1.56), z= 0.41], P 0.68)], with no impact on mortality [31].

Table 1: Priorities in the management of intestinal fistulas (Chapman, 1964).

First priority: (0-12 hours)
A. Correct blood volume deficit
B. Obvious and easily accessible abscess drainage
C. Fistula control, protect skin
1. Place a buffer or a bag
Second priority: (0-48 hours)
A. Correction of fluid and electrolyte imbalance
B. Daily fluid replacement and electrolyte losses
C. Start a plan for intravenous nutrition
Third priority (1-6 days)
A. Passage of a catheter distal to the fistula
B. Feeding Jejunostomy
C. Continued search and drainage of obvious abscesses if they appear
Fourth priority: (After 5 to 14 days)
Major surgical intervention:
A. Find hidden foci of sepsis
B. Closure or bypass of the fistula

It has been described that the use of somatostatin or its analogs should be reflected clinically in the reduction of expenditure during the first 72 hours of its administration [4].

Conservative vs surgical management

As we have previously mentioned, it is vitally important to carry out an appropriate support treatment to achieve spontaneous closure of the ECF. But when can we think about surgical closure of the fistula? The evidence shows that spontaneous closure of the fistula is unlikely to be achieved after 4 weeks of supportive treatment [4,32-33].

A topic that has gained great interest is the most appropriate time to resolve the fistula through surgery. The largest series with a good success rate have established a cut-off point of at least 6 months [4,19,33,34,46] with the appropriate conditions, despite this there is a recurrence of 13 to 34% [3]. In most cases, the surgery performed is a resection of the segment in which the fistula is located with primary anastomosis, although reinforcement or wedge closure of the fistula have been described, a recurrence of 32% vs 18% has been identified. Compared to resection versus anastomosis [36], a technique with which successful closure rates of up to 80-95% have been achieved [14,36-38]. Despite these encouraging results, surgical management is technically and physically demanding and a successful surgery will be related both to the intraoperative judgment of the surgeon in charge, and to achieving the best pre- and postoperative conditions [33].

There are innovative techniques that seek to minimize invasive treatment in patients with ECF, such as fibrin sealants, endoscopic treatment using clips, covered stents or tissue patches, which have limitations in their use and require more extensive studies.

Local treatment

Topical treatment is part of the comprehensive care plan to promote the closure of the ECF, this includes the containment of effluents and the protection of the peri-fistula tissue. Isolation of the opening of the ECF and prevention of contamination of the rest of the wound by the fistula effluent are important factors in the management of this entity [39-41].

Negative pressure wound therapy (NPWT) is a safe means of achieving spontaneous closure of ECPs, especially those of distal location and low output, or to facilitate the transition to surgical closure, because it creates favorable conditions for outflow of intestinal content, improves granulation of the wound bed and decreases local inflammation. In addition, it protects the surrounding skin from maceration and irritation from the effluents, however, a rate of new fistula formation of up to 7% associated with its use has been reported [39].

Image 1: Fistulogram of a patient with enterocutaneous fistula.

Image 2: An example of vacuum assisted closure device used to close an open abdomen with entero-atmospheric fistula.

Recommendations for its use continue to be based on expert opinion and clinical observations, so it cannot be recommended as a definitive means of achieving ECP closure. The choice of NPWT intervention should be based on clinician skill and resource availability.

Isolation of the fistula is achieved by surrounding it with NPWT foam dressing and applying pressures between -75 mm Hg and -125 mm Hg, with dressing changes every 2-5 days, depending on the capacity of the selected products [40,42].

Another method is fistula intubation by inserting a Jackson Pratt (JP) 16 drain or Foley catheter into the fistula orifice, to which negative pressure of -125 mm Hg is applied, is used as a means to achieve spontaneous closure and for the management of the effluent until surgical closure. For the protection of the perifistula tissue, the products used include ostomy paste and hydrocolloid rings [40].

As has been described, local control of ECF is a challenge due to the enormous variability of this entity: the size of the wound, the position and number of fistulous orifices, the affected intestinal segments and the volume of effluent, to date There is no single device or solution that can be used to ensure adequate local control in this heterogeneous complication, which is why the creation of a personalized device made of polycaprolactone (PCL) by 3D printing has recently been proposed, which is capable of isolate the fistulous orifice from the NPWT and favors wound granulation, reducing the need for dressings, improving patient comfort and avoiding complications derived from the discharge of intestinal effluent into the surgical area. This personalized device adjusted to the characteristics of the patient's wound is feasible and offers promising results in the management of ECF [41].

There are also hybrid techniques such as the one reported in Mexico by Cuendis et al, this technique consists of four steps to control the drainage of the fistula, protect the wound and the surrounding skin while creating a stoma ("ostomization of the fistula"), which facilitates subsequent handling of the effluent, prevents septic complications from persistent intestinal contamination, allows formation of granulation tissue, protects the skin, increases the speed of wound healing, transforms a difficult-to-treat fistula orifice into a well-controlled orifice that simulates an ostomy and facilitates future restoration of intestinal continuity and construction of the abdominal wall. It includes the following steps: (1) Condom-FEC anastomosis with continuous 4-0 non-absorbable suture (polypropylene); (2) Creation of the fistula isolation ring with NPWT black foam dressing cut in a circle; (3) Placement of NPWT

Table 2: Electrolyte composition (mEq) in gastrointestinal fluids.

	Na+	K+	Cl-	HCO_3-
Stomach	60-80	15	100	0
Bile	140	5-10	100	40
Small bowel	140	20	100	25-50
Colon	75	30	30	0

black foam dressing wrapped with white sponge (polyvinyl alcohol) on the rest of the wound with continuous negative pressure from 125 mm Hg to 150 mm Hg; (4) Placement of ostomy bag for drainage collection. The advantages of this technique are that it is quick and easy, low cost, accessible materials, applicable with sepsis or peritonitis, provides effective diversion of fistula effluent and easy quantification, has a good seal, is useful for any size of FEC hole (especially with large protruding mucosa), allows progressive closure of the abdominal wall and is feasible in cases of multiple fistulae. This confirms that it is feasible, safe and effective for patients with ECF with good functional results [42].

Table 3: Nutritional requirements in a patient with ECF.

	Caloric demand (kcal/kg/d)*	**Protein requirements (g/kg/d)**	**Vitamin C**	**Another vitamins**	**Trace elements (Zn, Cu, Se)**
Low output fistula	20-30	1-1.5	5-10 times of daily requirement	At least the daily requirement	At least the daily requirement
High output fistula	25-35 **	1.5-2.5***	10 times of daily requirement	Double the daily requirement	Double the daily requirement

*Lipids should represent 20-30% of the total.
**Depending on the volume you spend, it can be increased up to 1.5-2 times the requirement of a healthy adult.
***In relation to losses from the fistula (up to 75 g of protein), the requirement may be higher.

Conclusions

Despite the great scientific advances that have been introduced in medicine, in surgery and specifically in the treatment of patients with ECF, the etiology of enterocutaneous fistulas remains the same, exacerbating with the raise of damage control surgery. Another point to correlate is that the current series report a spontaneous closure of the fistulas similar to that achieved by Chapman and his team in 1964.

However, surgical conduct has become more relevant in the resolution of this pathology in our time, since one of the the final assertions in his work states the following sic. “Our review indicates that the majority of fistulae will close spontaneously with an adequate conservative regimen”, meanwhile the most recent studies have shown that, despite adequate comprehensive management, surgery will be necessary to achieve closure of more than half of the ECF. Despite this, surgical management has not modified mortality or long-term complications in the patients in whom it is performed. It is possible to conclude that actually the surgeons achieved to increase the percentage of fistulas with spontaneous closure by improving support measures, however, it must be considered that this ranges from 15 to 75%, due to the heterogeneity of the populations compared, however some gaps remain in the management of patients with ECF and it is necessary to analyze the new options for non-surgical closure of fistulas, which offers a wide field of research and work for the surgeon and the multiple disciplines that are involved in the management of this complex pathology.

Table 4: Factors related to spontaneous closure of ECF [3,13,14,31].

Favorables	**Unfavorables**
Postsurgical etiology	Ileal or jejunal location, non-surgical etiology
Appendicitis and diverticulitis	IBD, cancer, radiation
Transferrin > 140 mg/dL	Transferrin < 140 mg/dL
No obstruction, bowel in continuity, no infection or inflammation of the bowel	Distal obstruction, bowel discontinuity, adjacent infection, adjacent active inflammation
Length > 2 cm, terminal fistula	Length < 2 cm, lateral fistula, multiple fistulas
Output < 200 mL/24 hours	Output > 500 mL in 24 hours
No sepsis or electrolyte imbalance	Sepsis or electrolyte imbalance
Initial referral to a specialized center	Delay in referral to a specialized center

Ethics approval and consent to participate

“Not applicable”.

List of abbreviations

ECF: Enterocutaneous fistula, EAF: Entero-atmospheric fistula.

Conflicts of Interest

“The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.”

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Authors' contributions

All authors read and approved the final manuscript.

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