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Management of fistulas in the upper gastrointestinal tract

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ABSTRACT

Fistulas in the upper gastrointestinal (GI) tract are complex conditions associated with elevated morbidity and mortality. They may arise as a result of inflammatory or malignant processes or following medical procedures, including endoscopic and surgical interventions. The management of upper GI is often challenging and requires a multidisciplinary approach. Accurate diagnosis, including endoscopic and radiological evaluations, is crucial to build a proper and personalized therapeutic plan, that should take into account patient's clinical conditions, time of onset, size, and anatomical characteristics of the defect. In recent years, several endoscopic techniques have been introduced for the minimally invasive management of upper GI fistulas, including through-the-scope and over-the-scope clips, stents, endoscopic suturing, endoluminal vacuum therapy (EVT), tissue adhesives, endoscopic internal drainage. This review aims to discuss and detail the current available endoscopic techniques for the treatment of upper GI fistulas.

1. Introduction

A fistula is defined as a pathologic communication between two epithelialized surfaces. Upper gastrointestinal (GI) fistulas can originate from any epithelialized surface of the upper GI [1]. Fistulas are classified as internal when the connection is between two internal organs, and as external when the connection is between an internal organ and the external body surface [2]. Fistulas determine aberrant drainage of the gastrointestinal contents resulting in a wide range of pathophysiological events. They can occur spontaneously as a result of inflammatory or malignant processes, or following medical procedures, including endoscopic treatment, radiation therapy, and oncologic or bariatric surgery [3]. Indeed, a fistula may also originate from the persistence of an anastomotic wall defect, namely a leak, resulting in an abnormal connection between the gastrointestinal tract and other organs or abscess cavities [4].

Regardless of the mechanism responsible for fistula formation or its location, the management of these patients aims to reestablish digestive tract continuity. Currently, there are no specific guidelines on this topic. As the anatomy of each fistula is unique, a multidisciplinary and personalized approach is required that should take into account the characteristics of the wall defect (location, length, characteristics of the tissue around the orifice) and also the patient's general status and associated comorbidities [5]. However, treatment of fistulas is intrinsically challenging due to their chronic nature. Traditional therapeutic strategies relied on conservative measures and surgery. However, surgery for fistulas is usually complex and characterized by elevated morbidity [6]. Recent advances in the field of endoscopy led to the development of endoluminal techniques for the management of GI fistulas, providing further minimally invasive options before referring patients to surgery. This narrative review aims to discuss and detail the current status of the endoscopic management of fistulas in the upper GI tract.

2. Diagnosis and basic principles of upper GI fistulae

A proper diagnosis requires a high level of clinical suspicion as the clinical presentation is often atypical. The first step for diagnosis is the collection of medical history and physical examination. Clinical manifestations include pain, fever, or sepsis and signs or symptoms related to

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the sites involved, including cough, dyspnea, diarrhea, and purulent/enteric material draining cutaneous orifices [1]. However, some patients can be asymptomatic. To diagnose a suspected upper GI fistula, imaging studies are necessary after initial clinical assessment, including cross-sectional imaging with computed tomography (CT), fistulogram, and digestive tract X-rays with a water-soluble contrast medium [1,3]. Eventually, upper endoscopy can confirm the site of the fistulous orifice in the GI tract. Definitive diagnosis and definition of the fistula's origin and route are mandatory to plan a proper therapeutic strategy.

The management of upper GI fistulas includes some essential therapeutic steps. First, the administration of intravenous fluid is crucial to correct the hypovolemic status and electrolyte imbalances related to gastrointestinal losses through the fistula tracts. In the case of sepsis, appropriate antibiotics administration and image-guided drainage of associated collections are necessary [3]. Further, the maintenance of adequate nutrition by enteral or parenteral feeding is crucial to reduce mortality and increase the chances of fistula healing. The route of nutritional support is influenced by the feasibility of enteral nutrition, as data suggest it is safer compared with parenteral nutrition [7].

3. Endoscopic clips

Endoscopic clips are largely used to close defects of the GI wall. Two kinds of clips are available: the through-the-scope (TTS) clips and the over-the-scope (OTS) clips. The TTS clips are introduced and fired through the operative channel of the scope. Despite the low cost and ease of use, the employment of TTS clips for the closure of fistulas is limited by their small aperture and weak closing force, particularly on large defects or fibrotic and inflammatory tissue on the edges [8]. As such, their use is limited to small defects (<10 mm). Further, the TTS clips spontaneously dislodge within a few weeks, and this may lead to the recidivism of the wall defect, especially in case of chronic epithelized fistulas [9].

The OTS clip is characterized by a wider aperture and a greater closure force compared with the TTS clip, enabling the engagement of more tissue [10]. As such, the OTS clip allows for full-thickness closure of upper GI defects up 1–2 cm [11]. The most used OTS clip is the OTSC® (Ovesco Endoscopy AG, Tübingen, Germany), a bear-trap-shaped clip made of Nitinol, a biocompatible super-elastic shape-memory material [12]. The system is assembled to the scope and the clip is deployed similarly to a variceal band ligator. The margins of the defect are approximated by aspirating the target area into a cap and/or by using two twin graspers, the clip mounted on the cap is fired by turning the hand wheel attached to the endoscope. The main limitation is the challenging removal of the OTSC in case of failure to defect closure, requiring devices using monopolar or bipolar currents to break the clip, or cold saline injection to enhance its malleability [13–15].

Most of the evidence is limited to small single-arm studies, case series, and case reports, with limited data on the long-term efficacy.

In a meta-analysis by Weiland T et al. including small studies and case series on both upper and lower GI fistulas treated with OTSC, the mean procedural success was 84.6 %, and the clinical success in terms of durable healing was 69 %, respectively [12]. A subsequent study by Law et al. reported the use of the OTSC in 47 patients with chronic GI fistulas (28 lower GI, 19 upper GI) [16]. The initial technical success occurred in 89 % of patients, but 46 % of them had fistula recurrence after a median of 39 days, despite clip retention [16].

In a multicenter study including 188 patients with upper or lower GI wall defects (108 fistulae, 48 perforations, 32 leaks) undergoing OTSC therapy, long-term success was observed in 60.2 % of patients (median follow-up of 146 days) [17]. However, the rate of successful closure was significantly higher for perforations (90 %) and leaks (73.3 %) compared with fistulae (42.9 %) [17].

In a systematic review and meta-analysis of 10 studies including 195 patients with post-laparoscopic sleeve gastrectomy (LSG) leaks/fistula treated with OTSC, the overall success rate was 86.3 %, with 56.8 % having solo OTSC procedure [18]. However, most of the studies had small sample size, short-term follow-up, and mixed data of concomitant endoscopic procedures.

Donatelli et al. reported the use of the OTSC in 30 patients with post-surgical fistulas (29 upper GI, 1 lower GI) after a median time of 146.6 days following primary surgery [19]. The technical success rate was achieved in 15/30 (50 %) of cases. However, 4/15 patients had a fistula recurrence, leading to an overall OTSC clinical success of 36.6 %. On the other hand, the success rate of the OTSC used in 15 patients with acute perforation was 100 %.

Based on these data, the long-term clinical efficacy of the OTSC for managing fistulae is questionable and no conclusions can be drawn. Fistulas, especially if long-standing, are often characterized by fibrotic and retracted edges, leading to a challenging approximation of the rims and an increased risk of failure. This may explain the different success rates reported for chronic fistulae and acute defects.

4. Endoscopic stents

Endoscopic stents are widely employed in the management of upper GI defects with excellent technical and clinical outcomes. An endoscopic stent is aimed at covering the defect, thus sealing the fistula and diverting the luminal contents. This treatment has proved to induce an early restart of oral intake, shorten hospitalization, and reduce mortality compared with conservative management [20].

Stent placement should be conducted with double endoscopic and fluoroscopic guidance, with the patient under general anesthesia or conscious sedation. After the insertion of a guidewire under an endoscopic view, the stent is deployed. The procedure can be performed either with or without fluoroscopic control [21].

Stents are usually removed 4–5 weeks after insertion, in order to avoid complications [22].

Different types of stents are available, namely self-expandable plastic stents (SEPS), self-expandable metal stents (SEMS), and biodegradable stents.

A SEPS is made of polyester completely covered with silicon, allowing for easy repositioning and removal [23]. However, its deployment requires a specific delivery system, in contrast with SEMS which is ready for use [23]. Moreover, SEPS insertion is associated with a high rate of migration (about 50 %) [9].

Indeed, one of the main limitations of endoscopic stenting is the stent migration. Currently, SEMSs are the most used stents for the management of upper GI defects. A SEMS has a core made of a metallic alloy (Elgiloy or Nitinol) covered by a plastic or silicone rubber coating along

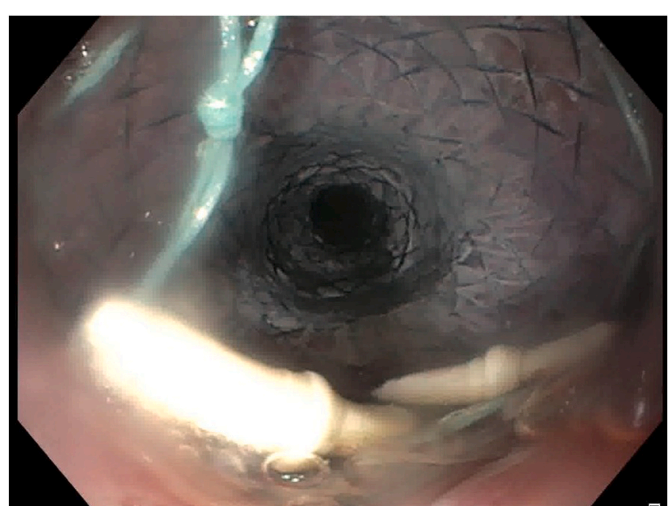

Fig. 1. FCSEMS sutured at the proximal extremity.

its full length (fully covered - FCSEMS) (Fig. 1) or with uncovered distal and proximal ends (partially covered - PCSEMS) to reduce stent migration [23].

Uncovered SEMS are not indicated for GI defects as they cannot seal the fistula and divert the luminal flow [3]. FCSEMS placement is associated with a 30 % migration rate, which can be reduced to 15.9 % by endoscopic suturing of the extremities [24,25] (Fig. 1).

Recently, the use of an over-the-scope clip device for stent fixation (Stentfix OTSC; Ovesco Endoscopy, Tuebingen, Germany) has been described. This fixation technique was associated with a significantly lower migration rate than other techniques (8.3 % vs 35.4 %, P < 00.001), indicating a relative risk reduction of 76.5 % associated with stentfix OTSC application [26].

The reported migration rate after PCSEMS placement is 10.6 % [27]. However, the mucosal in-growth at the extremities of a PCSEMS may make the removal challenging, increasing the risk of bleeding and perforation. A stent-in-stent technique has been proposed to improve the removal of PCSEMS [28,29]. A SEPS is introduced within the PCSEMS for 6–10 weeks, thus causing pressure necrosis of the ingrown tissue and making the stent retrieval procedure easier [28,29].

Most of the data describe the use of endoscopic stenting in patients with upper GI acute defects, such as perforations and leaks. For instance, a large meta-analysis, including 1752 patients with upper GI leaks/perforation, showed complete healing of the wall defect in 87 % of patients undergoing plastic or metallic stent placement, with plastic stents showing significantly higher migration rates (24 % vs 16 %, p = 0.001), and lower technical success (91 % vs 95 %, p = 0.032) compared with metallic stents [30].

In a case series by Buscaglia et al. the temporary FCSEMS placement was associated with an 80 % success rate in 15 patients with esophageal fistula or leak [31]. Suzuki et al. reported a success rate of 71.4 % in 14 patients with benign esophageal fistula who underwent patients fully or partially covered SEMS placement [32]. In a retrospective study by El Hajj et al., 54 patients with esophageal leaks (n = 29), fistulae (n = 15), and perforations (n = 10) underwent esophageal stenting [33]. The procedural technical success was 100 %, with an overall primary closure rate (i.e. after a single SEMS placement) of 74 %, and a secondary closure rate (i.e. after repeated stent placement) of 83 %. In the cohort with benign or malignant esophageal fistulae, stenting resulted in 73 % successful fistula closure. The authors reported that a shorter time between diagnosis of esophageal and stent insertion and a smaller defect opening size were the only factors associated with successful primary closure. No differences were found between FCSEMS and PCSEMS.

Freeman et al. reported that leak/fistula location at the proximal cervical esophagus, stent crossing the gastroesophageal junction, a defect longer than 6 cm, or an anastomotic leak associated with a more distal conduit leak were associated with a higher risk of stent failure [34].

Endoscopic stenting has also been evaluated for the management of post-bariatric surgery leaks/fistulas. El Mourad et al. reported the use of PCSEMS in 47 patients with acute leak/fistula (diagnosis 1–31 days) after bariatric surgery, fistula healing was obtained in 87 % of cases [35]. In another study by Eisendrath et al., 21 patients with post-bariatric surgery fistulas underwent SEMS treatment that resulted in 62 % (13/21) primary closures [36]. Complementary endoscopic treatment, including surgical tissue adhesive, bioprosthetic plug, or clipping, resulted in 4 secondary closures, with a total success rate of 81 % (17/21). Gastro-cutaneous fistulas on sleeve sutures had a lower healing rate (60 % vs 100 % of fistulas after other bariatric surgeries), probably due to the more challenging achievement of watertight sealing of the fistula by the stent in these cases.

In a retrospective multicenter study including 110 patients with post-LSG fistulas treated with several endoscopic techniques including SEMS and OTSC, the authors reported that no previous history of gastric banding, small leak/fistula (≤1 cm), a short time between LSG and fistula development (≤3 days), and a short interval between fistula diagnosis and the first endoscopy (≤21 days) are associated with better outcomes [37].

Recently, customized bariatric stents (CBS) have been developed to treat post-LSG leak/fistula, to ensure complete sealing of the defect. These stents are characterized by a longer length and larger diameter along with an anti-migration system, to ensure a complete sealing of the defect and to reduce the risk of migration. In a meta-analysis comparing CBS and conventional esophageal stents, CBS showed a similar technical success rate, but a lower clinical success rate (82 % vs 93 %) compared with conventional stents. In successfully treated patients, CBS was associated with a lower mean number of stent insertions and a shorter healing time compared stents. However, the overall quality of evidence was very low [38].

Though stent migration is the most common adverse event, endoscopic stenting is associated with other adverse events including stent rupture, reflux, food impaction, mucosal ulceration, perforation, massive bleeding, and tissue ingrowth [30].

Biodegradable stents are made of an absorbable material (polydioxanone) which degrades within 3–4 months in a low pH ambient. Stent integrity and radial force are maintained for 6–8 weeks after implantation [39]. Currently, there is only one biodegradable stent available on the European market - SX-ELLA (Milady Horakrove, Hradc Kralove, Czech Republic). In a small case series, five patients with post-operative leak/perforation underwent biodegradable stent placement, showing technical and clinical success of 100 % and 80 %, respectively, with stent migration in three cases (60 %) [40]. Further studies are needed to assess its efficacy in fistula closure.

5. Endoscopic suturing

Endoscopic full-thickness suturing can be used to close GI luminal defects. The OverStitch device (Apollo Endosurgery, TX, United States) consists of a disposable suturing device mounted on a double-channel gastroscope allowing the placement of full-thickness stitches (Fig. 2). The newer version OverStitch Sx can be used with every single-channel gastroscope. Compared with other techniques, endoscopic suturing is technically more challenging and requires a higher level of training and expertise [3].

Hold of sutures is closely related to the characteristics of tissues approximated, with healthy and robust mucosa being associated with better results [41].

A multicenter retrospective study, including 122 subjects treated with endoscopic suturing for stent anchorage (n = 47), fistulas (n = 40), leaks (n = 15), and perforations (n = 20), showed a clinical success rate of 91.4 % for stent anchorage, 93 % for perforations, 80 % for fistulas, and 27 % in anastomotic leak closure. The only predictor of success was early treatment, namely within 30 days of diagnosis [42].

A prospective European registry of 137 patients with GI defects undergoing OverStitch-based endoscopic suturing reported a technical success rate of 99.3 % [43]. The clinical success rate was 64.7 % for leaks/fistula, 94.7 % for perforations, and 85 % for stent fixation. The correlation analysis did not show a significant association between success and location, number, or pattern of sutures; however, fistulas <1 cm sutured using a continuous pattern were most likely to be successfully treated.

A recent meta-analysis of 5 studies (149 patients) evaluating endoscopic suturing with OverStitch for GI defects, confirmed a higher clinical success for perforations compared with leaks/fistulae (89.5 % [73.8–96.3] vs. 60.4 % [50.1–69.9], respectively) [44].

6. Tissue adhesives

Fibrin glue and cyanoacrylate have been employed for the closure of surgical anastomotic leaks and low-output fistulas. In a retrospective study including 52 subjects with GI fistulas (32 upper GI and 20 lower GI), the application of fibrin glue was successful in 55.7 % of cases [45].

Fig. 2. A) Esophageal fistula; B) Endoscopic full-thickness suturing with OverStitich; C) Final result of fistula closure after suturing.

In a small retrospective study including 15 patients with post-operative GI fistula undergoing fibrin glue injection, complete sealing of the fistula was obtained in 86.6 % of cases, with 87.5 % in case of the low-output fistulae and only 55 % in case of the high-output fistulae [46]. Based on these data, low-output fistulae are more like to respond to fibrin adhesive therapy. A prospective study showed 88 % successful closure after alpha-cyanoacrylate monomer injection in 25 patients with intractable esophageal fistulas, with no recurrences [47]. A meta-analysis of 14 studies (203 patients) evaluating the efficacy of cyanoacrylate in the healing of fistulae showed a cumulative success rate of 81 %, with the studies evaluating upper GI fistulas showing a success rate between 46 and 100 % [48]. However, these studies are heterogeneous in terms of indications, resulting in difficult interpretation and generalization of outcomes.

7. endoscopic vacuum therapy

Endoscopic Vacuum Therapy (EVT), also known as endoscopic negative pressure therapy, has become an important tool for the treatment of GI transmural defects. It consists of applying negative pressure on non-healing wounds to favor mural edges apposition and closure of the defect. The healing effect of this technique occurs through multiple mechanisms, including changes in perfusion, microdeformation, macrodeformation, exudate control, and bacterial control [49]. EVT can be used throughout the upper GI tract for esophageal, gastric, small bowel, and biliopancreatic defects. It has additional benefits for critically ill patients in need of infectious source control by removing necrotic tissue and purulent material while promoting tissue healing [50].

Endoscopic and radiologic evaluations are always required before treatment in order to identify the wall defect, characterize the fistulous tract, and evaluate the contaminated cavity. The device consists of an open-pore polyurethane sponge linked to a nasogastric tube connected to a vacuum pump generating negative continuous or intermittent pressure, from - 125 mmHg to −175 mmHg [51,52] (Fig. 3).

EVT can be placed either transmurally into the cavity (defects >10 mm) or intraluminally (defects <10 mm) and can be customized to fit different size defects [53].

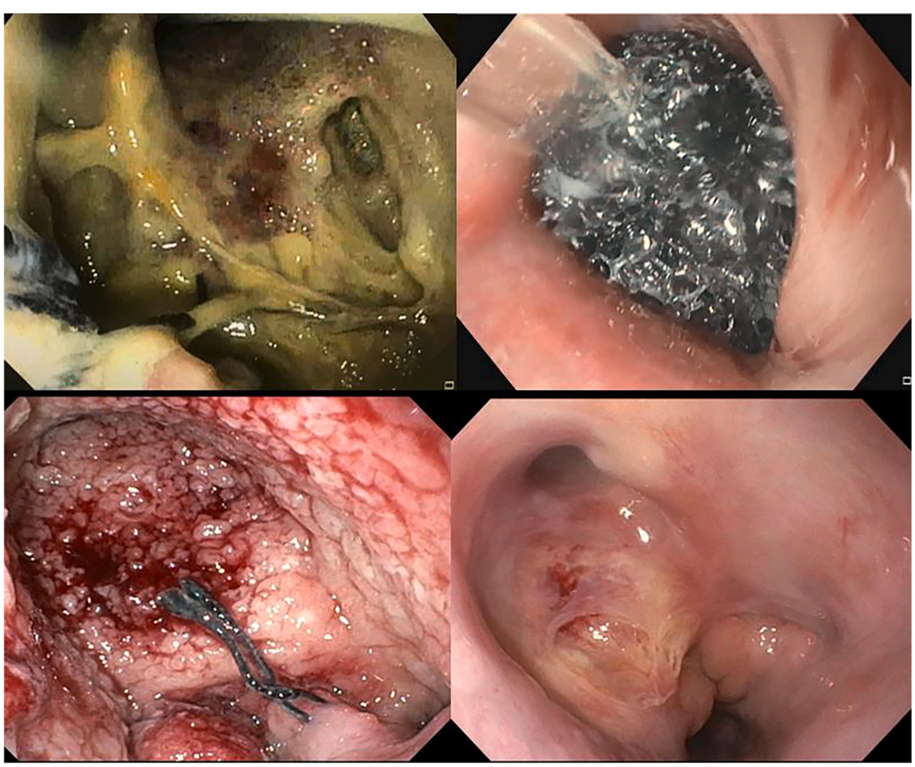

Fig. 3. A) Large esophageal defect; B) Open-pore polyurethane sponge (Esosponge) placed into the defect; C) Granulation tissue after sponge removal (9 changes); D) Endoscopic follow-up at 6 months after treatment.

The sponge-drainage system is endoscopically replaced every 3–5 days, to avoid the ingrowth of granulation tissue and until the cavity appears to be clean and closed (Fig. 3). However, some authors suggest a shorter interval of 2–3 days to prevent excessive tissue ingrowth, while others prefer a 7-day interval to reduce the number of necessary procedures [54–57].

The main indications of EVT are large defects (i.e. perforations, leaks, and fistulas), typically associated with fluid collections, for which this technique proved high rates of success [58,59].

In a meta-analysis of 29 studies including 498 subjects with upper GI perforations, leak, and fistulas, the pooled estimated rate of defects closure with EVT was 0.85 (95 % confidence interval [CI]: 0.81–0.88), with rates for mortality, complications, and post-EVT strictures of 0.11, 0.10, and 0.14, respectively [4]. A subgroup analysis based on the etiology of the transmural defect (perforation vs. leak and fistula) showed no differences in terms of efficacy or safety.

The main drawbacks of EVT are the need for repeated endoscopic procedures, discomfort caused by the nasogastric tube, and the risk for sponge displacement.

One major concern regarding EVT in the upper GI tract is the risk of major bleeding, therefore it is recommended to be avoided in the proximity of major vessels or in patients on anticoagulant therapy. Two deaths were reported because of massive hemorrhage related to EVT [60]. Two other major bleeding were reported during EVT that underwent immediate surgery for aortic stenting [56]. Another review performed by Pines et al. reported some major, but rare massive bleedings during sponge exchange – one from an aorto-esophageal fistula and the other from an atrio-esophageal fistula, other complications being represented by late strictures, bronchopleural fistula and sepsis [61]. In conclusion, EVT is a new, effective option in the management of transmural defects, nonetheless it should be performed in experienced centers, under close monitoring.

8. Endoscopic internal drainage

Endoscopic internal drainage (EID) has been recently introduced for the treatment of leaks or fistulas following bariatric surgery. It involves placing several double pigtail stents through the fistulous tract in order to allow the pathologic cavity fluids to drain into the digestive tract and to guide reepithelization [62] (Fig. 4).

A retrospective study of 617 patients who underwent EID for the management of leak, fistula and collection after sleeve gastrectomy showed an overall clinical success was 84.7 % whereas 15.3 % of cases required revisional surgery after EID failure [63].

However, EID can be used in the management of GI tract defects after other types of digestive surgery. Donatelli et al. also prospectively enrolled 11 patients with duodenal fistulas, colic fistulas and esophagogastric-jejunal fistulas that achieved 100 % technique success rate after first endoscopic procedure [64]. Overall, they obtained a clinical success rate of 82 % after an average of 44 days of treatment.

When comparing EID with other fistula closure techniques, Jung et al. showed a 100 % success rate for EID versus 85.2 % for EVT [65]. Another study comparing other "closure" management (SEMS, clips, drains, glue) with EID for postgastrectomy fistulas found a significantly higher success rate for the EID group (86 % versus 63 %) [66]. In this study, the authors also concluded that in case of a collection larger than 5 cm, an internal drainage has to be proposed first. EID is associated with few adverse events, including ulcerations, bleeding, and stent migration [63].

Spota et al. reported the treatment of 339 fistulas post-bariatric surgery mostly treated with EID (90.9 %) with a clinical success rate of 77.2 % [67]. Interestingly, the authors propose an algorithm for the management of fistula that takes into account the time of onset. In more detail, they suggest managing early fistulas (<4 weeks) by EID with one/multiple double pigtail stents and simultaneous nasojejunal feeding tube placement; chronic fistulas (>4 weeks) should be treated with multiple EID (every 4 weeks) that can be associated with an endoscopic septotomy to promote emptying of the associated collection.

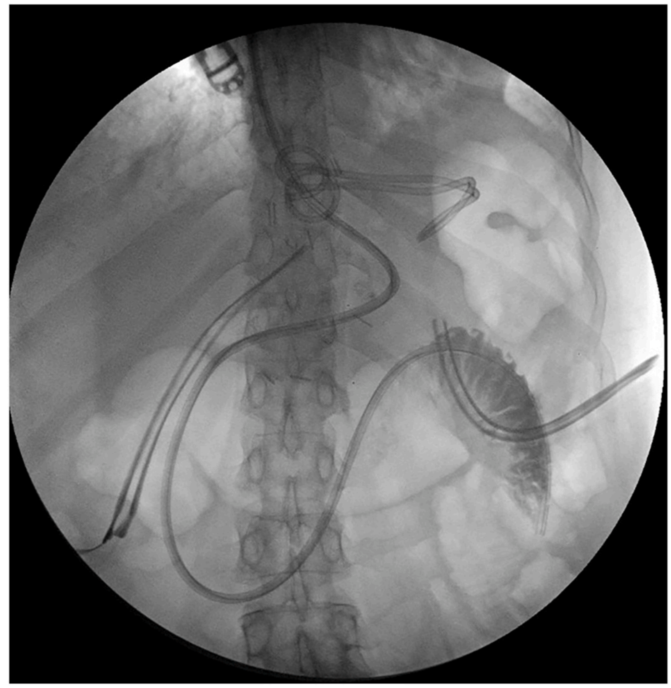

Fig. 4. Endoscopic internal drainage with double pig tails for the treatment of post-sleeve gastrectomy fistula.

9. Innovations and future prospectives

A novel approach based on the submucosal injection of the stromal vascular fraction obtained by the mechanical emulsification of autologous adipose tissue (tSVFem) has been described by Nachira et al. for the treatment of five patients with esophageal fistulas refractory or not suitable for conventional treatment, either endoscopic or surgical [68]. The tSVFem is obtained by mechanical emulsification of fat harvested from the subcutaneous tissue and then is endoscopically injected by a 22G needle in the 4 quadrants of the fistula edges. The tSVFem is characterized by anti-inflammatory and regenerative properties that may safely promote rapid and effective tissue healing. Complete closure of the fistula was obtained in all five treated patients after 7 days following the procedure, and endoscopic follow-up at 6–12 months confirmed complete healing with no complications.

Recently, the off-label use of cardiac septal occluder has been described in a few case reports for the treatment of persistent upper GI fistulas of several etiologies, with promising results [69–71].

However, the outcomes of these novel approaches should be validated in future larger prospective studies.

10. Conclusions

Upper GI fistulas are challenging conditions to manage, as the continuous exposure to GI secretions and the reiterated inflammation hinder the healing process. Early diagnosis, proper antibiotic therapy, and drainage of associated fluid collections are crucial for a successful treatment. Currently, multiple endoscopic techniques are available. However, no guidelines for the endoscopic management of these conditions are available, and high-quality studies comparing different techniques are lacking. Although endoscopic stents have been shown to be effective, their use in clinical practice is limited due to the non-negligible rate of adverse events and migration risk. For early and small fistulas, clips or endoscopic suturing may be an acceptable first-step approach; however, these techniques are likely to fail in large and/or chronic fistulas. When the fistula is associated with a collection requiring drainage, the strategy can involve EID with double pigtail stents or EVT for small and large defects, respectively. In cases where traditional approaches have failed, rescue therapy with novel techniques, such as injection of tSVFem or placement of cardiac septal occlude, can be considered. However, the selection of the best treatment strategy should be tailored to each patient in the setting of multidisciplinary management and should take into account the time of onset, size, and anatomical characteristics of the defect, and cannot be prescind from treatment of sepsis and adequate nutritional support.

11. Practice point

- Fistulas of the upper gastrointestinal tract are complex clinical conditions that can occur as a result of inflammatory or neoplastic processes as well as endoscopic or surgical procedures.
- The clinical presentation is often atypical and a high level of clinical suspicion, based on medical history and physical examination, is crucial for a proper diagnosis. After initial clinical assessment, imaging studies and upper GI endoscopy are mandatory for diagnosis and definition of the fistula's origin and route to plan a proper therapeutic strategy.
- Several endoscopic techniques are currently available, including clipping, stenting full-thickness suturing, endoscopic vacuum therapy, tissue adhesives, and internal drainage that proved promising results in the treatment of upper GI fistulas.
- The therapeutic strategy should be tailored to each patient, taking into account clinical conditions, time of onset, size, and anatomical characteristics of the fistula, as well as local expertise and availability of devices.

12. Research agenda

- Currently, no guidelines on the management of fistulas of the upper GI tract are available.
- Most of the evidence on current techniques comes from case series and retrospective single and multicenter studies with limited follow-up.
- Among the innovations, endoscopic injection of mechanical emulsification of autologous adipose tissue characterized by anti-inflammatory and regenerative properties is a promising technique for the management of refractory fistulas.
- Larger prospective comparative studies are necessary to further evaluate the efficacy and safety of the current endoscopic treatments for upper GI fistulas.

CRediT authorship contribution statement

Maria Valeria Matteo: Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization. **Maria Mihaela Birligea:** Writing – original draft, Methodology, Data curation, Conceptualization. **Vincenzo Bove:** Writing – original draft, Data curation, Conceptualization. **Valerio Pontecorvi:** Writing – original draft, Data curation, Conceptualization. **Martina De Siena:** Writing – original draft, Data curation. **Loredana Gualtieri:** Writing – original draft, Methodology, Data curation. **Federico Barbaro:** Validation, Writing – review & editing. **Cristiano Spada:** Writing – review & editing, Methodology, Conceptualization. **Ivo Boškoski:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization.

Declaration of competing interest

Ivo Boskoski is a consultant for Apollo Endosurgery, Boston Scientific, Nitinotes, Pentax, Cook Medical, Microtech, ERBE, and Endo Tools Therapeutics S.A.

Federico Barbaro is consultant for Olympus.

Cristiano Spada is a consultant for Medtronic and AnX Robotics and received speaker's fees from Olympus and Pentax.

All the other authors have nothing to declare.

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