gastrointestinal disorders

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Review

Endoscopic Salvage of Gastrointestinal Anastomosis Leaks—Past, Present, and Future—A Narrated Review

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Abstract: Background: Anastomotic leakage, which is defined as a defect in the integrity of a surgical join between two hollow viscera leading to communication between the intraluminal and extraluminal compartments, continues to be of high incidence and one of the most feared complications following gastrointestinal surgery, with a significant potential for a fatal outcome. Surgical options for management are limited and carry a high risk of morbidity and mortality; thus, surgeons are urged to look for alternative options which are minimally invasive, repeatable, non-operative, and do not require general anesthesia. Methods: A narrative review of the international literature took place, including PubMed, Scopus, and Google Scholar, utilizing specific search terms such as "Digestive Surgery AND Anastomotic Leakage OR leak OR dehiscence". Results: In the present review, we try to describe and analyze the pros and cons of the various endoscopic techniques: from the very first (and still available), fibrin gluing, to endoclip and over-the-scope clip positioning, stent insertion, and the latest suturing and endoluminal vacuum devices. Finally, alongside efforts to improve the existing techniques, we consider stem cell application as well as non-endoscopic, and even endoscopic, attempts at intraluminal microbiome modification, which should ultimately intervene pre-emptively, rather than therapeutically, to prevent leaks. Conclusions: In the last three decades, this search for an ideal device for closure, which must be safe, easy to deploy, inexpensive, robust, effect rapid and stable closure of even large defects, and have a low complication rate, has led to the proposal and application of a number of different endoscopic devices and techniques. However, to date, there is no consensus as to the best. The literature contains reports of only small studies and no randomized trials, failing to take into account both the heterogeneity of leaks and their different anatomical sites.

Keywords: anastomotic leakage; tissue sealants; clips; stents; endoscopic vacuum therapy; endoscopic internal drainage

Citation: Menni, A.; Stavrou, G.; Tzikos, G.; Shrewsbury, A.D.; Kotzampassi, K. Endoscopic Salvage of Gastrointestinal Anastomosis Leaks—Past, Present, and Future—A Narrated Review. *Gastrointest. Disord.* **2023**, *5*, 383–407. https://doi.org/10.3390/gidisord5030032

Received: 29 July 2023
Revised: 6 September 2023
Accepted: 13 September 2023
Published: 15 September 2023

1. Introduction

Anastomotic leakage is a dreaded complication after major surgery in hollow viscera of the gastrointestinal tract (GI), which is associated with prolonged stay in the intensive care unit and increased mortality [1]. It is defined as a pathological communication between intra- and extra-luminal compartments as a result of the dehiscence of the anastomotic suture line, which can occur in near proximity to surgery, usually on post-operative days 3 to 5 or in the later part of the first 3 weeks [1,2]. This anastomotic "full-thickness" defect often leads to leakage of the luminal contents into the peritoneal cavity or the mediastinum, possibly leading to sepsis and death, occurring in up to 60% of cases if treatment is delayed [1,3], and is thus responsible for the preponderance of surgical mortality [4–6].

Despite the advances in surgical techniques and the significant decrease in surgery-related mortality and morbidity of whatever etiology, anastomotic leakage still occurs

in a significant number of patients [7]; the percentage varies depending on the type of oncological surgery. It occurs in 8% to 26% of patients after esophagectomy [5,8–11] and in 3% to 12% after gastrectomy [5,8,12,13], while in colon surgery the case occurrence is 5% to 15% following colorectal anastomosis [14,15], rising to 15% to 28% after low anterior resection in large cohorts [2,16–19].

In bariatric surgery, on the other hand, related leaks have been reported in only 0.6% to 5.25% of cases after a Roux-en-Y gastric bypass [20,21] and in 1% to 3.9% following sleeve gastrectomy [22–26].

Intra-abdominal or intrathoracic leaks are generally the most complex in relation to the extraperitoneal ones, with treatment options varying from the conservative to open surgery re-operation, depending on the patient's clinical condition and their hemodynamic stability, the leak size, the anatomical site of leakage, the presence of a pus-filled cavity near the dehiscence, and the time elapsed since surgery [27,28].

Over the last 30 years, interventional endoscopy has evolved as an effective and less invasive alternative to surgery, progressively changing the management model for anastomotic leaks. Presently, a variety of techniques are available to reestablish the continuity of the hollow viscera in a less invasive manner, thus minimizing patient morbidity related to re-operation.

Although there is a plethora of publications on the different endoscopic devices and techniques available, there is no consensus as to the best, due to both the heterogeneity of leaks and their different anatomical sites. In the present review we try to describe and analyze the pros and cons of the various endoscopic techniques from the very first (and still available), fibrin gluing, to the latest suturing devices and endoluminal vacuum stents. We do not extend our analysis to the varying reported success or failure rates in previous publications or systematic reviews and meta-analyses since there are so many, some of which have only very recently been published. Moreover, we do not try to construct an algorithm of what is the correct escalation of treatment with respect to the defect size, time elapsed, or other parameters, since there is a plethora of publications supporting this option; we are performing this analysis mainly because we believe that best treatment lies with the informed judgement of an experienced endoscopist.

2. Results

2.1. History of Endoscopic Sealing

The Cuffed Stent

Historically, the first successful endoscopic attempt to seal an esophago-tracheal defect was performed by Lux et al. [29] in the University of Erlangen in 1987 using a modification of the typical Wilson–Cook Medical esophageal silicone tube, a cuffed stent. This commercially available esophageal cuffed tube comprises a silicone shaft with a metal spiral wire embedded in its wall to strengthen it. The proximal and the distal ends, constructed from softer silicone rubber, are funnel shaped to prevent tube displacement. This tube is a standard silicone rubber Wilson–Cook medical tube with an internal diameter of 12 mm and length varying between 4.4 cm and 16.4 cm.

The modification consists of a balloon-type addition around the tube shaft. Indeed, the shaft is surrounded by a polyurethane foam, tightly air-sealed with a silicone rubber sheath, forming a cuff for the prosthesis. The foam shrinks when a vacuum is created in the cuffed portion by means of a syringe connected to a plastic fine-suction catheter, the end of which is impacted into the foam. When the cuff has totally shrunk, the tube's outer diameter is only 2.6 cm. After insertion of the tube, by means of a suitable introducer, into the pre-measured position in the esophagus, which is the center of the cuff strictly against the center of the wall defect, the suction-induced vacuum is released; the self-inflating cuff fills with air through the fine catheter, allowing the foam rubber to expand to a final diameter of 4 cm, this being adequate to seal the anastomosis opening. The natural elasticity of the polyurethane foam allows its shape to conform to that of the esophagus without

excessive pressure risking tissue necrosis. To further ensure that the cuff is fully expanded, it is possible to inject additional air with the syringe until pressure resistance is felt.

This modified tube cuffed stent has only been reported four times in the literature, in a total of 28 cases with malignant esophagogastric communication, since its production was officially discontinued in 1990 [29–32]. One such tube, from our laboratory museum, is illustrated in Figure 1.

Figure 1. The Wilson–Cook cuffed stent.

In our department, we have personal, unpublished experience of its use in four cases of benign esophageal–tracheal fistulas from tracheal cuff pressure in long-intubated multi-trauma patients.

2.2. Current Technology

2.2.1. Tissue Adhesives

One of the initial techniques used to cope with anastomotic leaks, usually less than 5 mm in length, was the use of adhesives, namely fibrin glue and cyanoacrylates.

The commercially available fibrin glue (Tisseel VH Fibrin sealant, Baxter AG, Vienna, Austria) consists of two frozen components: fibronectin, reconstituted with aprotinin, and thrombin, reconstituted with calcium chloride. They are delivered via a dual-barrel syringe and combined at the site of the anastomotic defect through a specially designed long double-lumen catheter inserted through the biopsy channel of the endoscope [33]; upon contact of the two components, thrombin converts fibronectin into fibrin, forming a stable clot within 10–60 s in a manner similar to that of the coagulation cascade. This fibrin clot initially acts like an acellular clot, the aprotinin component increasing its resistance to degradation in a fibrinolytic environment, while, within the next two weeks of application, it is fully reabsorbed progressively by macrophages and fibroblasts [33,34]. It is advised that fibrin glue be applied after a thorough debridement of the area and coating with normal saline [33,35], while others consider the fibrin clot to be most effective when applied to dry areas [3].

N-butyl-2-cyanoacrylate (Histoacryl; B. Braun, Melsungen, Germany) is a synthetic adhesive which is polymerized upon contact with damp surfaces [3]. This is why it is advised that, just before injection, both the catheter and the delivery syringe be flushed with 5% dextrose solution and that the catheter be as short as possible in order to avoid the premature polymerization of the glue within the catheter. For the same reason, both the biopsy channel and the distal part of the endoscope must be lubricated with silicon oil to prevent the permanent attachment of glue [33]. When cyanoacrylate comes in contact with the tissue, it initially generates a localized foreign body reaction, leading to an inflammatory response which promotes angiogenesis and, finally, tissue healing while the glue itself sloughs off spontaneously within the next five to ten days [33,34].

In cases of larger anastomotic defects, there are few reports of Vicryl meshes being used to create a backbone to keep the fibrin glue in place at the leak edges [36]. Fiber adhesives are also generally applied as a combination of adjunctive treatment after endosponge placement, before temporary stent placement, or as a complementary treatment after leak repair with clip placement [37].

2.2.2. Endoclips and Over-the-Scope Clips

Endoscopic clips, originally used in the context of an emergency hemostasis or for mucosal marking, were first used in 1990 in an effort to close gastric and colonic perforations, mainly iatrogenic ones [38]. However, their small size opening makes them incapable of successfully treating large mucosal defects since they grasp only the mucosal layer margins and exhibit weak closing force and limited mucosal tissue apposition [34,39]. Today, the newly available endoclips, also called through-the-scope clips (TTS), are fully rotatable and have a wingspan of 11 mm; thus, a success rate of 60 to 80% is reported [3,40], mainly in cases of upper GI tract perforations and esophageal defects, while in cases of inflammation and fibrosis of tissue around the perforation, their placement is a struggle due to their limited closure potential [28].

On the other hand, large clips that are loaded over the endoscope, over-the-scope clips (OTSC—Ovesco Endoscopy, AG, Tubingen, Germany), have become particularly popular for the closure of larger, full-thickness GI tract defects since their first appearance in 2007 [15,41] (Figure 2). OTSCs are full-thickness suturing devices, designed precisely for flexible endoscopes and made of biocompatible elastic shape-memory nitinol alloy; the clip, with its four prongs, allows continuous pressure to be applied to the grasped area so that even in cases of swelling and sinking of the grasped tissue, there is sufficient pressure to maintain tissue apposition. On the other hand, blood flow is maintained through the interprong space of the clip, thus enabling the OTSC to prevent tissue necrosis and allowing unimpeded wound healing.

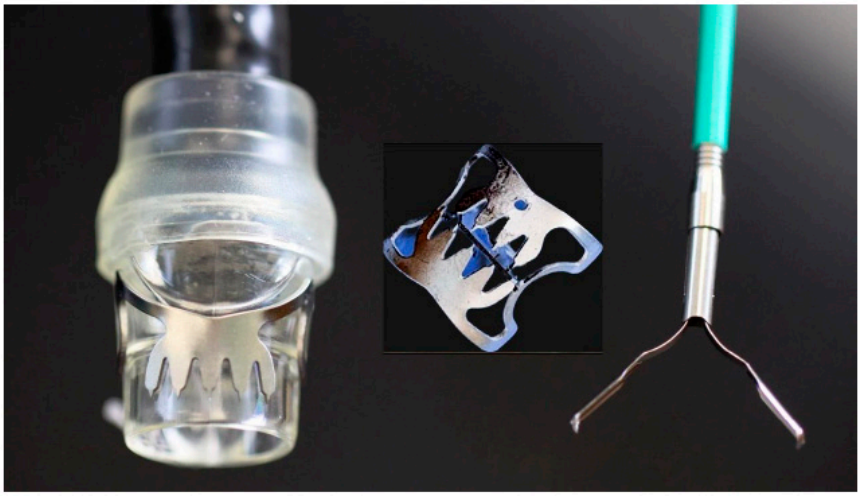

Figure 2. The TTS and OTSC clips.

The OTSC system consists of an applicator cap with a mounted nitinol clip, a hand wheel, and a thread retriever. The cap, which is attached to the tip of the endoscope in a manner similar to that of a band-ligation cap, comes in three sizes with respect to diameter, 11 mm, 12 mm, and 14 mm, to ensure proper attachment to the tip of endoscopes of different diameters. Caps are also available in two depths, 3 mm or 6 mm, related to the tissue grasping capacity appropriate to the thickness of the tissue to which they will be applied. In addition, there are three different clip shapes: pointed, which is used for perforation and fistula closure, as is ideal for inflammatory and fibrotic tissues; round, which facilitates tissue compression and is used for hemostasis, especially in the esophagus and colon; and

a longer pointed clip, mainly used for the thicker stomach wall [42]. Of similar philosophy is the more recent hexagonal-shaped padlock clip (Steris, Mentor, OH, USA) with a full circumferential closing system [3,43].

There are also three additional devices facilitating clip application: (i) the three-pronged tissue anchor, which has three stretchable needles opening simultaneously to grasp a lesion, as in the cases of difficult chronic ulcers and fistulas [44]; (ii) the twin grasper, which grasps both sides of a lesion through the separate and alternative opening of its blades, thus facilitating tissue apposition; and (iii) the reloader, in case more than one clip is needed to close the gap [42]. An endoscope with a 3.2 mm working channel is recommended, while a double channel one may better facilitate the handling of additional devices [45].

For OTSC positioning, when the endoscope, having loaded the cup with the clip, is against and in touch with the defect, the surrounding tissue can be sufficiently aspirated within the cap and, by turning the hand wheel, the clip is deployed. If the entire defect can't be suctioned within the cup, the tissue anchor or the twin grasper is also used [34,41].

2.2.3. Stents

The rationale for placing a temporary stent over a GI anastomotic leakage is to "seal" the defect and divert the contents of the lumen, thus enabling the defect to heal. Although there are many reported "side-effects" after a stent placement in cases of anastomotic leaks—the main being stent migration—these devices still remain an effective, safe, and easily applied therapeutic option, even when applied by an inexperienced endoscopist [46–49].

Although plastic stents were the first introduced in the 1990s for the repair of esophageal perforations [50], today they have been successfully replaced with the more flexible and more easily handled metal self-expandable stents. These are placed endoscopically over a guidewire, preferably under fluoroscopic control to ensure proper positioning, while frequent imaging monitoring is advised due to the high migration rate [49].

Metal stents are made of either Elgiloy, an alloy of cobalt, nickel, and chromium, or of Nitinol, an alloy of nickel and titanium [3]. Those stents, used for sealing defects, are either fully or partially covered by a polyurethane, polyethylene, or silicone rubber membrane, either along their full length or leaving uncovered the distal and proximal ends [3,34,49]. It is well understood that the use of a totally non-covered stent, although having the advantage of not migrating, is not finally a wise decision, since it is unable to seal the leakage and, additionally, the tissue overgrowth through the stent metal grid results in it rapidly becoming impacted in the mucosa and thus totally impossible to remove.

When totally covered stents are used, they must be secured in place, either by clips in at least two, diametrically opposite sites or by sutures [49,51] due to the high probability of migration [49]. On the other hand, partially covered stents embed in the mucosa at their proximal and distal ends, making migration difficult/less likely (Figure 3) but stent removal a little more difficult. Thus, in no case should such a stent be placed over an Endo-Vac sponge, as a prerequisite of this treatment is frequent (twice a week) stent removal to change the sponge.

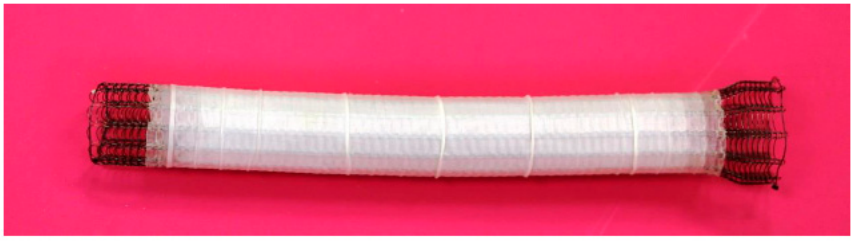

Figure 3. A self-expandable metal stent.

Physicians should also always keep in mind that the digestive tract is not a geometric cylinder, so no matter how well the stent is placed, there will almost always be

microleakages from the peripheral part, at least in the first few days [52]. Regarding colon anastomoses dehiscence, stents may be used only in end-to-end anastomoses; while in the case of an anastomosis after low anterior resection of the rectum, it is generally contra-indicated, since its peripheral end must be terminated at least 1 cm above the dentate line [53]. Additionally, prior drainage of any nearby collection is mandatory and, should sepsis occur, stent placement is strictly prohibited [54].

The use of stents has also proved to be particularly effective in bariatric surgery-related leakages. Specially designed stents are now available, such as the Mega Stent (Taewoong Medical, Seoul, Republic of Korea)—a fully covered stent of large diameter and length (18 cm to 24 cm) with a special design to avoid migration and increased elasticity. The Niti-S-Beta stent (Taewoong Medical, Seoul, Republic of Korea) is also a fully covered stent with a proximal flange and a double-bump in the proximal third to reduce the likelihood of migration [3].

2.2.4. Endoscopic Vacuum Therapy (EVT)

The technological knowledge and experience gained from the successful application of negative pressure therapy to treat open abdominal wounds and/or entero-atmospheric fistulas over the last 20 years, known as the vacuum-assisted closure technique [49,55], is easily transferred for the restoration of anastomotic dehiscence after GI surgery. This technique was first described by Nagell and Holte [56] in 2006 as vacuum-assisted closure for the treatment of anastomotic leakage after rectal resection by means of digitally inserting the sponge into the rectum and, through the defect of the anastomosis, into the presacral space (Figure 4). Two years later, Weidenhagen et al. presented their experience with 29 patients with anastomotic leakage after anterior resection of the rectum, and, in 2010, the first small series of six patients after esophageal resection [57,58].

Figure 4. A custom-made endo-vac.

In order to insert the Endo-Vac sponge—an open-pored polyurethane foam—into the peri-anastomotic cavity, an introducer "sleeve" is first advanced under endoscopic control until the entrance of the cavity. The introducer sleeve is fixed in this position, the endoscope is withdrawn, and the sponge attached to the evacuation tube—having already been cut to exactly fit the geometry of the cavity—is compressed and inserted into the introducer sleeve. A pusher is then used to advance and totally insert the sponge into the peri-anastomotic cavity; then, the introducer sleeve is finally withdrawn, leaving the sponge fully deployed in the cavity, with the peripheral end of the 14Fr evacuation tube exiting from the mouth and connected to the vacuum wound drainage system under a negative pressure of approximately 125–150 mmHg [34,57–59].

It is strongly advised, prior to starting treatment, that the cavity and the anastomosis defect orifice be thoroughly irrigated and debrided using every available instrument, from standard biopsy forceps to an over-the-scope grasper and a cytology brush [59]. Continuous negative pressure reduces tissue swelling, promoting microcirculation and leading to the formation of granulation tissue and bacterial clearance [60], but frequent sponge changes, every two to three days, are strictly required [61].

Finally, the use of a self-expandable metal stent placed over an Endo-Vac sponge—named "the stent-over-sponge [SOS] approach"—seems to be another suitable therapeutic option for treating leaks [62]. The stent optimizes the vacuum force by sealing the sponge toward the GI lumen, thus maximizing the suction efficacy while avoiding dislodgement from the correct position [63,64]. However, the sponge should be replaced with a new one every three to five days in order to prevent the ingrowth of granulation tissue, and thus the stent also needs to be removed and replaced, significantly affecting the cost of treatment [64].

2.2.5. Endoscopic Internal Drainage (EID)

Fluid or pus collection outside the anastomosis defect remains a serious problem for uneventful healing, leading sometimes to peritonitis or mediastinitis or even sepsis, especially when there is insufficient drainage of this "cavity" through an external drainage tube placed at the time of operation. Although this cavity is a closed space among the surrounding viscera, formed mainly by granulomatous inflammatory tissues and pseudomembranes and communicating only with the lumen of the GI tract through the existing leakage orifice [34], it must be emptied, since its occlusion may result in pus formation and possible sepsis. Pequignot et al. [65], in 2012, were the first to attempt the insertion of a double pigtail stent, or a naso-biliary drain, through the leak orifice into the "cavity" in order to drain fluid/purulent contents into the gut lumen. (Figure 5).

Figure 5. A pig-tail stent.

Whatever the technique used for dehiscence, this extra-luminal cavity must be inspected carefully, washed-out as far as possible, and every effort must be made to drain internally, towards the lumen, or externally, through the existing drainage tube fistulus tract. According to the endoscopic internal drainage technique, the cavity is catheterized with a straight catheter and a guidewire over which one or more final single- or double-pigtail catheters—depending on the cavity size—are placed [28], changes of which need to be carried out every three weeks [66]. By such means, tissue granulation and re-epithelialization occurs [28,67], progressively closing this dead space. Additionally, a naso-duodenal feeding tube may be inserted into the third part of the duodenum to ensure adequate intestinal feeding for at least the first four weeks, while, in the case of a heavily purulent collection, a

nasobiliary tube should be inserted into the cavity to ensure the interchange of irrigation and drainage procedures.

In cases of large defects, the pigtail catheter should be combined with a simultaneous stent placement. In this way, the anastomosis opening is sealed with the stent while at the same time the collection is drained towards the lumen by the use of the pigtail.

2.2.6. Vac-Stent Technique

The Vac-Stent technique is a relatively new one (2019), combining the advantages of the self-expandable covered metal stent, for the coverage of the anastomotic defect, with those of improving wound healing through the endoscopic vacuum technique (EVT) in one medical device, thus optimizing the suction efficacy for sealing the leak and keeping the stent in position while maintaining intestinal passage.

It would be considered a transformation or an evolution of the previous described technique of "SOS" (stent-over-sponge) [63,64] but for the significant difference that the vacuum sponge—the Endo-Vac device—applied in the former is placed within the peri-anastomotic cavity while the present device—the Vac-stent—remains within the GI lumen, making application much easier.

The VACStent® (VAC Stent Medtec AG, Steinhausen, Switzerland) is 7 mm long with a diameter of 14 mm in the center and 30 mm at the flare ends. The device consists of a self-expandable stent (Micro-Tech Co. Ltd. Nanjing, Republic of China) covered with a 50 mm long open-pore cylindrical polyurethane foam (10 mm thick) fixed to the outer layer of the stent and connected via a catheter to a vacuum source (Möller Medical GmbH Fulda, Germany). The VACStent® is made of nitinol wire and is fully covered with a silicone–parylene layer to prevent tissue ingrowth and seal the sponge toward the esophageal lumen [68].

At present, the Vac-Stent is indicated only for the treatment of esophageal leaks which can be reached endoscopically. Using the vacuum stent enables drainage of inflammatory wound secretions by means of negative-pressure wound therapy and sealing of the leak through the liquid-tight coated stent, taking preservation of the passage into account.

A continuous suction of between 40 and a maximum of 125 mmHg is applied to the sponge, keeping it in place due to suction, even in difficult sites of the GI tract, while it allows for the direct passage of endoscopic instruments, enteral nutrition, and intestinal contents [28,68,69].

The Vac-Stent device is placed over a guidewire inserted through the working channel of the endoscope under fluoroscopic or endoscopic guidance in order to center the body of the stent and, subsequently, the sponge on the defect, which is then deployed via a distal release system. Finally, the suction catheter attached to the sponge is guided through the nose and connected to the vacuum negative-pressure system, which should be flushed with water three times per day in order to keep the suction catheter open. Depending on the size of the contact with the wound, the manufacturers recommend removing the vacuum stent after two to seven days and replacing it with a new system. If the wound contact covers a large area, the system should be changed after a maximum of 72 h [70]. Removal is facilitated by a tapered hood distal attachment cap, or simply by means of endoscopic foreign body grasping forceps. To prevent the edge of the wound from tearing open again, it is recommended that the stent be rinsed prior to extraction in order to more effectively remove any adhering dressing (see instructions for use, 2023, on www.vac-stent.com, accessed on 1 May 2023).

The Vac-Stent and similar devices are indicated for defects of approximately 30 mm, with definite contraindications being defects with diameters of more than 50 mm, leaks within a distance of less than 20 mm from the upper esophageal sphincter, and a contaminated extraluminal cavity. However, further studies are required to establish it in the armamentarium of devices for the salvage of anastomotic leaks.

2.2.7. The Suturing System

The idea of designing a suture machine small enough to be loaded onto the tip of an endoscope is at least 20 years old. Perhaps the first successful attempt was that of the BARD EndoCinch-I endoscopic suturing system, used for endoluminal gastroplication as an alternative to surgical fundoplication in patients with gastroesophageal reflux disease [71], which was quickly replaced with the newly designed ESD [72], both devices being able to perform plications involving only gastric mucosa. Following these, several other attempts were made, focusing on full-thickness suturing; the majority of these, however, have revealed major limitations mitigating against their widespread clinical use.

The OverStitch system (Apollo Endosurgery, Austin, TX, USA) was first developed in 2009 and is currently the most common endoscopic suturing device [73,74]. The first version of this device could only be loaded onto an Olympus dual-channel therapeutic endoscope; however, the next generation, the newly introduced Over-Stitch SX, can be mounted on any channel endoscope, enabling single-operator surgical suturing.

The main components of this suturing platform are: the needle driver handle, attached to the endoscope controls, the cap with the metallic needle, mounted on tip of the endoscope, and an anchor exchange catheter. Grasping forceps and a tissue retracting helix device may be used to help tissue apposition, while a specially designed non-absorbable suture accompanying the device is used for full-thickness uninterrupted or continuous suturing [3,28,75,76].

However, its relatively large size and its reduced maneuverability have made its use challenging in the narrow or angulated GI areas such as the gastric fundus, the duodenum, and the sigmoid colon. To date, it has been effectively used mainly for closure of mucosal defects after endoscopic resections, transoral outlet reduction after bariatric surgery, and in stent fixation in order to prevent migration. However, there are few studies explicitly evaluating the role/use of OverStitch in primary closure of GI leaks and fistula, mainly in stapler line leaks after bariatric surgery. Therefore, no conclusions or recommendations can be drawn for this indication [77–79].

It is of great importance to emphasize that robust and healthy mucosa is essential to hold the sutures when tissues are approximated and that before attempting an endoscopic closure it is paramount that the involving tissues be de-epithelialized in order to guarantee a reliable closure. Thus, various techniques such as coagulation of the defect perimeter, mechanical abrasion of the fistula tract, modified endoscopic submucosal dissection to completely ablate the mucosa, or multiple endoscopic mucosal resections around the fistula opening have been reported as a "must" [80,81].

Although the results from the OverStitch device seem encouraging, it remains a complex procedure and a high level of expertise and proper training is required for its operation, limiting its use to a few tertiary centers.

2.3. The Possible Future

2.3.1. Stem Cells

Just two years ago, the Costamagna group in collaboration with thoracic surgeons [82] presented a case series of successfully treated difficult esophageal fistulas after initial failures to respond to other endoscopic or surgical treatments. A stromal vascular fraction obtained after mechanical emulsification of autologous adipose tissue, known as tSVFem, was endoscopically injected with the objective of exploiting its regenerative capacity for fistula closure—a technique being widely used in other medical fields, mainly plastic surgery.

The tSVFem comprises mesenchymal stromal cells and fragments of the extracellular matrix obtained after proper harvesting of fat obtained from the superficial layer of subcutaneous tissue as well as from oil released after the mechanical disruption of mature adipocytes. By means of endoscopy, 10 mL of fat was initially injected to completely fill the fistula and, thereafter, 1–2 mL of tSVFem was injected into the submucosa of the 4 quad-

rants of the fistula borders to obliterate it completely. Seven days later, endoscopy revealed complete healing of the fistula [82,83].

The same technique has also been applied for successful closure of a gastro-bronchial fistula after a 25 mm leak at a laparoscopic sleeve gastrectomy suture line, followed by a huge fluid collection in the left subphrenic area, communicated with another intrapulmonary collection [84].

These initial references to using autologous stem cell transplantation seem promising, since there is already knowledge and experience of the technique, even in other fields of reconstructive and regenerative medicine.

2.3.2. Modification of Luminal Microbiome

Over the last decade, Alverdy's laboratory group have undertaken in-depth research on the mechanisms of low anterior anastomosis dehiscence beyond the broadly believed etiologies of tissue ischemia, anastomotic tension, malnutrition, hypo-albuminaemia, etc. There have been multiple confirmations, experimentally and clinically, that a low microbial diversity within the gut lumen allows the overgrowth of mucin-degrading members of the Bacteroidaceae and Lachnospiraceae families. Pathogens such as Pseudomonas aeruginosa, Enterococcus faecalis, and Serratia marcescens, with their capacity to proliferate when the microbiota become depleted, can produce collagenase and elicit intestinal inflammation, leading to anastomotic leaks [85,86]. It has also been found experimentally that anastomotic dehiscence develops when Pseudomonas aeruginosa, normally colonizing anastomotic sites, becomes transformed in vivo after a single nucleotide polymorphism (SNP) mutation to express a tissue-destroying, more virulent phenotype [86]. Similarly, they demonstrate that anastomotic dehiscence sites in rats were colonized by Enterococcus faecalis strains, which exhibited an increased collagen-degrading activity and an increased ability to activate host MMP9 through the expression of the gelE and sprE genes, both of which contributed to anastomotic leakage; elimination of E. faecalis strains through topical application of proper antibiotics or pharmacological suppression of intestinal MMP9 activation prevents anastomotic leaks in rats [85].

Although recent work has revealed that, in humans, the presence of collagenolytic bacteria is the most deterministic cause, alone it is not sufficient to cause anastomotic leakage [87].

However, taken together, various other interventions performed in colon surgery-subjected humans, such as mechanical bowel preparation, oral and intravenous antibiotics, inotropes, opioid analgesics, and even the presence of diabetes mellitus, could have a negative influence on the microbiome [88].

On the other hand, looking at the beneficial effects of probiotics in enhancing epithelial barrier function, preventing systematic infections, reducing surgical site infections and all surgery-related complications, and in improving wound healing [88–93], a promising approach might be the "dietary" manipulation of patients prior to surgery by means of boosting their gut with beneficial probiotic species whose immune-modulatory, anti-inflammatory, and healing properties are well-documented [94,95].

3. Materials and Methods

A literature search was conducted using PubMed, Google Scholar, and Scopus. The search terms applied were "Digestive Surgery AND Anastomotic Leakage OR leak OR dehiscence". No ethical approval is required for this study, as it is a narrative review of the existing literature (Figure 6).

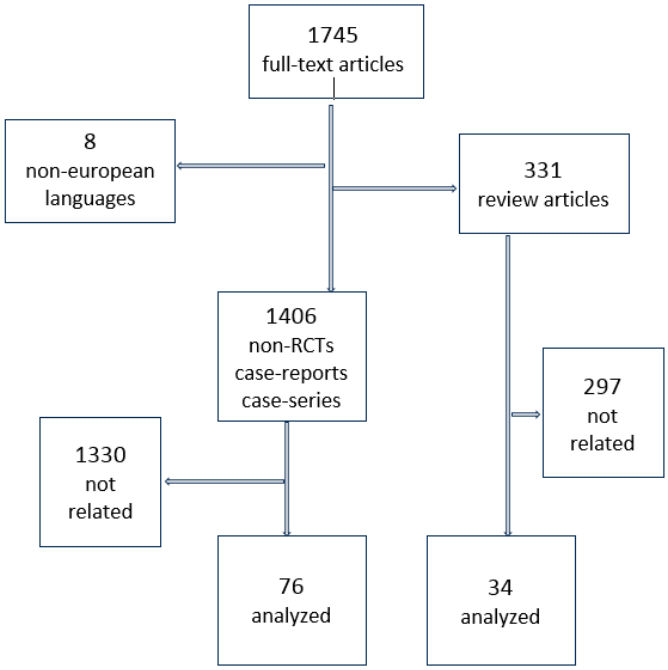

Figure 6. Flow Chart.

4. Discussion

GI anastomotic leakage is an unintended communication between the viscera lumen and an extra-luminal space that, most commonly, is the peritoneal cavity or the mediastinum; it occurs suddenly, after a dehiscence of the anastomotic suture-line caused by many known reasons and many others that still remain largely unclear [96]. Despite advances in surgical techniques and technological means, the prevalence of GI leaks is still high and has increased in recent years, most probably due to the increased complexity of GI surgery [3,97].

Over the last 30 years, therapeutic endoscopy has earned a pivotal role in the management of anastomotic leaks as well as the management of fistulas, mainly occurring in oncological patients, the technological advancements having established it as a first line approach over surgery and not only as a rescue treatment [98–100].

Although a variety of endoscopic techniques are currently available for successful management of anastomotic leaks, neither a definite consensus exists nor even a standardized evidence-based algorithm for the appropriate therapeutic approach since each treatment requires a complex decision-making process that is totally patient- and procedure-specific [3,101,102].

Each treatment should be tailored according to the clinical and patient's general status, the size and location of the opening, the presence of healthy surrounding tissues, the onset time from surgery and from anastomosis rupture, the endoscopic accessibility, the presence of an extra-lumen cavity/collection and the degree of contamination, the ability to drain, and, mainly, the local expertise and availability of devices [3,101–103]. In the same way, comparison between different approaches is extremely difficult due to the largely heterogeneous population and the complete lack of prospective trials and of retrospective large series; thus, there is only limited evidence based on retrospective case series and expert experience [1,3]. Last but not least, it should not be forgotten that the potential delay of commencement of adjuvant chemotherapy due to the prolongation of anastomotic defect treatment may increase the risk of both local recurrence and mortality [104].

In this review, we make an effort to analyze the pros and cons of the available endoscopic techniques as presented over time, from the very first cuffed-stents to the very recent Vac-Stents, and even to stem cell submucosal injections and to local intraluminal microbiome modification. Regarding the most appropriate closure technique, parameters

such as the anatomy of the patient's anastomotic defect, the availability of specialized equipment, and the ability to tolerate possible failure of treatment must be taken into account; however, the overall criterion is the endoscopist's expertise and the procedure s/he is most familiar with [15].

4.1. Tissue Adhesives

The first successful application of fibrin glue for sealing four cases of anastomotic leakage was performed in the University of Erlangen by Groitl and Scheele in 1987 [105]. Soon after, Eleftheriadis et al., from the University of Thessaloniki, reported seven cases of high-volume enterocutaneous fistulas after gastric surgery [106], after which other cases following bariatric surgery were published [107–109].

Fibrin sealant compounds are extracted from pooled human blood but are carefully screened and therefore have only a minute risk of infectious transmission [110]. They are applied by the use of a 180-cm long double lumen catheter passed through the endoscope; high injection volume does pose some difficulties with handling, since the catheter-end plugs when in contact with the mucosal tissue and thus a quantity of the product remains unused within the catheter [33]. Furthermore, Kahler has suggested that the fibrin glue should be injected into the tissue and not just into the lumen of the fistula [1], while abrasion of the fistulous tract should also prove helpful, facilitating plugging and, thus, tissue approximation. It is important to note that the mechanism of action of fibrin glue is absolutely biological and not mechanical, as Nordentoft et al. conclude after a systematic review of only experimental studies [111].

The sealing mechanism is partially unclear and may be related to a combination of the physical barrier created by the fibrin clot, the facilitation of tissue tight approximation, the promotion of tissue healing by the glue components, and the creation of adhesions with surrounding tissues. The tensile strength of the fibrin clot is mainly proportional to the fibrinogen concentration, while the concentration of thrombin may also influence the mechanical strength and also speed-up the completeness of clotting [33,110].

The success rate of this technique is highly variable in the literature, ranging from 55.7% to 96.8%, a difference most likely due to treatment discontinuation; it is well known that successful closure requires repeated sessions and large volumes of sealants [33,103,110,112].

Regarding non-bioabsorbable cyanoacrylate glue, it is well known that its internal use is associated with inflammation, tissue necrosis, and infection, and so it should be used only with caution [110]. However, there is a short series of eight cases with in situ drainage tube insertion at the time of the operation in very close approximation to the anastomosis opening so that the transcutaneously inserted endoscope could approximate the serosal surface of the organ. By inserting an endoscope from the external stoma through this fistulous track, the authors applied cyanoacrylate glue to the serosal opening of the anastomosis to form a backbone, after which an endoscope was inserted into the gut lumen and the fibrin glue was injected, with the cyanoacrylate preventing its spillage and thus facilitating mucosal healing [33].

It is well understood that with the development of technology there are now more sophisticated methods for closing ruptured anastomoses, so there are some authors who recommend the use of glue only for small defects and for low-volume enterocutaneous fistulas [15]. Nevertheless, the application of fibrin glue is still a valuable technique of low cost compared to the newer ones and, more importantly, it is easily applied even by less experienced endoscopists.

4.2. Through-the-Scope (TTSC) and Over-the-Scope Clips (OTSC)

As a general rule, for the application of all clip types, good strength of the GI tissue around the ruptured anastomosis is a prerequisite, as the clip needs to grasp the tissue without tearing it, as will happen when mucosa suffers inflammation and tissue edema and/or ischemia. Additionally, sufficient drainage of the cavity outside the lumen is mandatory [1,101].

The over-the-scope clip has bigger and stronger arms, can grasp more tissue, and finally exerts a powerful sealing force for closure of anastomosis defects. It can be used for defects up to 30 mm since additional forceps can be inserted though the clip to properly grasp the wound edges and pull them into the clip [1]. To facilitate healing of the defect, most experts suggest epithelial ablation of defect edges prior to OTSC placement [101].

Based on a nine-year review of 1517 cases, Kobara et al. [45] suggested the application of OTSC within one week of dehiscence, when the wound edges still have a low level of fibrosis and an opening of up to 30 mm, as a favorable factor for success; then, the average clinical success rate climbs to 78%. However, the general rate relating to anastomotic dehiscence is only 66%, which is probably related to the need for pliable tissue for successful placement [113]. Despite the somewhat poor performance of the OTSC system for anastomosis defects, the results are more than satisfactory when considered as the only available method in a given situation for patients for whom transfer to a tertiary hospital is not possible [45].

Notably, despite their advantages over TTS clips, OTSC clips show increased rates of fistula recurrence after initial therapeutic success [114]. Moreover, some cases of mucosal lacerations have been reported following the advancement of the bulk cap through the upper esophageal sphincter [115]. Although the overall complication rate is low, at only 1.7%, the incidence rate of severe complications requiring surgery is referred to as being only 0.59% [45].

Encouraging evidence exists for the use of OSTC clips in closing iatrogenic perforations, predominantly in the upper gastro-intestinal lumen, possibly due to the restricted vision via the endoscope when the cup with the clip is placed at the tip of the endoscope around its objective lens [101].

However, the user must be familiar with the technique through ex vivo tissue training as well in in vivo cases; once a clip is falsely fixed on the target lesion, it is very difficult to remove and replace it.

Finally, we have to mention a trick applied in some cases after endoscopic full thickness resection, known as loop closure, which should be used on a recently broken anastomosis. The TTS clips are placed on a detachable snare at the edges of the defect. After satisfactory placement of the clips, the detachable snare is tightened to close the defect [103].

4.3. Stents

The self-expandable metal stent (SEMS) remains the easiest to apply and thus the most used technique to cover an anastomotic defect, seal the fistula, and achieve diversion of the contents. Nevertheless, due to the non-tubular geometry of the majority of anastomoses, especially those involving the stomach, the proximal end of the stents perfectly "impact" and cover the circumference of the esophagus or of the gut but then do not completely follow the curvatures of the organ, so that their distal end is not in touch with the entire perimeter of the lumen, meaning that fluids can flow back between the stent and the organ wall towards the anastomotic defect [1,97]. Nitinol-made stents have the property of thermal shape memory and increased radial resistive force and are thus better at keeping continual contact with the organ wall than those made from Elgiloy [3]. They also exhibit greater elasticity and thus avoid excessive tissue pressure [116,117].

The majority of metal stents used for tightening the defects are covered stents; since there is no stricture at the anastomotic site, the fully covered stents are prone to migrate at a rate of up to 30% [118,119] while the partially covered ones, due to the tissue overgrowth through their uncovered portion, result in a more effective sealing at the top of the stent (proximal) and thus minimize the migration rate [15,103,120]. However, removing these stents once the leak has healed is more difficult [120]. A posterior stricture available in the near future has also been reported. In a survey conducted among international multicenter experts, 56% of the participants reported fully covered self-expandable metal stents as their usual first option, while 80% of those use additional techniques to minimize migration [101].

To prevent stent migration, most centers apply endoclips or sutures to secure the stent in place—these should be applied at least on two opposite sides of the proximal part of the stent to achieve optimal effect [103,121], while to prevent leakages between the stent and the organ wall, stents with wide diameters from 23 mm to 35 mm are used [1]. Particularly in the case of colorectal anastomosis, there is an increased failure rate due to the geometry of the gut lumen, due either to the proximal end not being well impacted into the gut circumference to avoid leakage or due to stent migration, as it is often too narrow for a typical colorectal anastomosis [34].

Bleeding, erosion, ulceration, perforation, circumferential anastomotic breakdown, tracheal pressure, fistula, and reflux are among the complications generally described [15,34,103,122].

Low rectal anastomoses are not amenable to stents, as the distal end of the stent must lie 5 cm above the anal verge. Stents placed lower than this lower limit have the risk of rectal pain and foreign body sensation below the dentate line, as well as concerns for stent migration [123,124]. This is why Cliffort, et al., after a retrospective review, support the use of stents only for esophageal defects, and only in those involving less than 30% of the esophageal circumference or without extensive necrosis [15].

All stents must be removed or replaced after six to eight weeks, generally presenting a leak resolution rate of 87.8% [28,120,125].

4.4. Endoscopic Vacuum Therapy (EVT)

An alternative technique for the restoration of anastomotic dehiscence after GI surgery is the use of the endoscopic application of an endo-sponge. This is a technique similar to the vacuum-assisted closure technique, applied in ruptured abdominal wounds [39], which is based on multiple mechanisms, including changes in perfusion, micro- and macro-deformation, control of exudates, and bacterial control [126]. This method must only be applied in patients in a stable hemodynamic condition and without symptoms of generalized peritonitis [127]. Its effectiveness comes from continuous suction by means of continuous negative pressure applied, enabling drainage of fluid or pus collections out of the lumen even in the case of moderate defects [128].

The sponge should be as small as possible, but its diameter should guarantee that all parts of the cavity are equally drained after the application of negative pressure. However, there is no consensus regarding the optimal pressure and the frequency of changing the sponge. Most authors recommend an exchange every three days and a negative pressure of 125 mmHg [1].

Success rates range from 81–85% for cases of upper digestive leaks, and up to 90% for bariatric complications [28]. However, it is well understood that in order to achieve high rates of success, a high level of competence in interventional flexible endoscopy is mandatory. This is why the long-proven training system for flexible endoscopy at Tuebingen University has already been modified to include a two-stage process of special training for EVT [129].

Its early placement after anastomotic leakage increases success rates, while the overall healing time varies from 20 to 244 days [130]. Furthermore, it does not affect any subsequent adjuvant radiotherapy or chemotherapy, although the EVT duration was found to be significantly longer in patients subjected to neo-adjuvant therapy and significantly more interventions were also needed [131,132].

Continuous negative pressure reduces tissue swelling, promoting microcirculation and leading to the formation of granulation tissue and bacterial clearance [60]. The minor disadvantage of the endoscopic vac is the possible exposure of the sponge to large vessels through negative pressure aspiration, resulting in bleeding. For this reason, it should be avoided in patients receiving anti-coagulants [103]. Furthermore, pelvic abscess formation with or without strictures and the frequent changes required—once every 48–72 h—to avoid sponge ingrowth, which usually, at least for the initial treatments, requires anaesthesia or sedation, make the method difficult to apply due to the multiple endoscopies required [2,61].

Nevertheless, it remains a promising method, especially for patients unsuitable for surgical intervention.

Aiming to tailor the optimal therapy for each situation, new methods and materials have recently been employed as helpful alternatives to the classical polyurethan foam, such as other, softer sponge materials ('white sponge') and open pore film drainage. The latter is a great improvement that allows the treatment of smaller leakages, and both can be left in situ for longer intervals due to their limited likelihood of ingrowth into the granulation tissue [7,133–135].

Despite most of the studies reporting fewer complications in EVT treatment in relation to stent placements, a meta-analysis failed to show a significant difference, underlining the possibility of esophago-tracheal or -bronchial fistula and esophageal stenosis development after healing of the leakage in both therapies [7].

Regarding the effectiveness of endo-vac sponges with stents or stent placement alone, the former technique seems to generally have a shorter duration of treatment, with the exception of two studies that showed a shorter, but not significant, treatment time in the stent group. However, we must remember that the endo-vac sponge plus stent option needs significantly more frequent changes of the sponge and subsequent stent removal and placement (3.57 times more frequent than with stents alone), a practice that increases both the cost of treatment and the patient's quality of life [7]. On the other hand, the disadvantage of the higher number of endoscopic interventions is also an advantage, since this procedure allows a better monitoring of local inflammation as well as repeated endoscopic lavage and debridement [7].

Finally, it needs to be emphasized that significant EVT-related complications, such as severe hemorrhage due to eroded blood vessels [70] or dislodgement of the sponge into the pharynx, compromising respiration, have been reported. In addition to this, physicians need to be aware that repeated sponge replacements can lead to considerable psychological distress in affected patients. An extreme case is that of a patient who, having undergone 16 sponge replacements over a period of 89 days, developed an adjustment disorder that made psychiatric counseling necessary. Additionally, recurrent sedation may also result in complications. In this regard, recent studies suggest the use of a naso-mediastinal drainage system to drain the mediastinal abscess, similar to EVT, eventually reducing the number of endoscopic interventions necessary to change the sponge [7,58,136].

One more reason for EVT and stents not being comparable is the fact that the expandable stent procedure is standardized and reproducible, whereas EVT has many variables which may present differences between institutions: (i) extent of negative pressure, (ii) extra- or intraluminal placement of the sponge, (iii) time interval between sponge changes, and (iv) size of the sponge and material [7].

Last but not least, quality of life is much worse with EVT due to the necessity of a permanent nasogastric tube, to the degree that Giraldo-Grueso et al. suggested the extreme procedure of pharyngostomy [7]. Moreover, the EVT cost is twice as high as that of the stents, and the repeated inpatient sedation and endoscopy costs are a major concern, although the largest part of the costs results from the longer ICU stay [137].

4.5. Endoscopic Internal Drainage—EID

According to current knowledge, but also common sense, it is of great importance to thoroughly check the fluid/purulent collection next to the ruptured anastomosis line. If the leak opening is large enough, the endoscope must be passed through the leak to inspect the cavity to debride and to thoroughly lavage it prior to stenting or drainage. If the opening is small, it is preferable to dilate it a little so the endoscopist can get a clear view of the cavity [3,120].

The latest option is to then insert one or more pigtail plastic stents across the leak orifice, the number, length, and diameter of which will be decided after the inspection of the residual cavity. These pigtail plastic stents significantly help to internally drain any

fluid collection and obstruct the leak orifice, thus allowing early oral intake and to induce mechanical re-epithelization of the fistula tract [3,66,67].

In 2012, Pequignot et al. [65] first described the use of a double pigtail or naso-biliary drain across a leak orifice in order to guide drainage toward the GI lumen and promote healing while favoring leak orifice closure [3].

The pigtail plastic stents are then exchanged every six weeks until resolution of the abscess cavity. According to Larsen et al. [120], pigtail stents are better tolerated than esophageal stents and also exhibit a lower migration rate [138]. For bariatric surgery-related leaks, they are easier to insert throughout the anatomically disturbed GI tract, as after a Roux-en-Y bypass, by using an enteroscope if needed. Indeed, this technique has greatly improved since being applied in patients subjected either to sleeve gastrectomy or to RYGB surgery [66,139].

This technique has both advantages and disadvantages, with an overall success rate of 75%. One of the main advantages is the low cost of the procedure and the limited rate of complications, making it a cheap and safe method. On the other hand, the biggest disadvantage is the need for frequent catheter changes due to occlusion from debris and the fairly high percentage of late development of stenosis due to the overproduction of granulation tissue [3,34]. Despite all the advantages (and being the most friendly option for the patient other than esophageal stents), Rodrigues-Pinto E et al. [101] suggest endoscopic internal drainage as ideal for leaks up to 2 cm; from there on, endo-vacuum therapy is advised along with stents or OTSC depending on whether the leak is intrathoracic or intraabdominal.

4.6. Vac-Stent Technique

A promising endoscopic approach for treating esophageal leaks is the use of the novel Vac-Stent. It is a unique construction aiming to combine the advantages of an expandable metal stent and EVT in one device while maintaining the free luminal passage [68,70].

At present, there is very limited experience with this device: Chon et al. [68] published the largest series, with 20 patients and 24 endoscopic Vac-Stent implantations. They reported a 100% technical success and a 60% clinical success, with no severe adverse events. No stent migration was reported, probably due to the suction power applied to the sponge and thus to the mucosa, while the drainage tube, which is fixed at the nose, helps to some degree to prevent migration by acting as an anchor. Nevertheless, there are some restrictions for its application: it is not fit for defects larger than 5 cm in length, as the sponge is only 5 cm; the presence of a contaminated extraluminal cavity must be assessed in case an alternative available treatment is required; and, finally, as with every type of stent, defects within 2 cm of the upper esophageal sphincter must be excluded [70].

Regarding the suction pressure applied, interestingly, equal tissue granulation has been achieved with a continuous negative pressure of 65 mmHg in relation to the 125 mmHg used in a previous preliminary study [69]. On the other hand, oral feeding, which was the expected advantage when the device was designed, failed in all patients due to the clogging of the suction tube [68].

Another problem related to stent expansion is also reported. When fully extended, the Vac-Stent forms a 'dumbbell' shape which helps to prevent stent migration. Nevertheless, an incomplete expansion of the middle part of the Vac-Stent was observed, frequently occurring with the all-nitinol self-expandable stents, but an additional etiology for which may be the thickness of the sponge itself (10 mm), which counteracts the radial expansion force. However, with the present device, this may have a serious impact on its function: when it takes one to two days to fully expand and the exchange with a new one must be performed after three to five days, the stent functions properly for only a brief period before the device needs to be exchanged again [140]. A longer replacement interval might be an idea that seriously reduces the cost of the whole treatment and alleviates patient discomfort from repeated endoscopic interventions, but, based on previous experience from other vacuum devices, contamination and clogging of the sponge is frequent. An alternative

suggestion is the exertion of a pressure of 125 mmHg on the first day, then a decrease in suction to 75 mmHg [70].

Removal of the Vac-Stent can be challenging and may lead to complications such as perforations or bleeding [141]. To reduce this risk, it is advised that a continuous negative pressure of only 65 mmHg is applied, that the vacuum pump is switched off 2 h before extraction, and that the sponge is moistened. Although the Vac-Stent seems a promising endoscopic approach, further clinical research is needed to establish its possible advantages over the previous, and more studied, Eso-sponge and EVT techniques or to propose an efficient stepwise combination of more than one treatment.

4.7. Endoluminal Suturing

Endoluminal suturing techniques have been made possible with the OverStitch device, a minimally invasive endoscopic technique with interesting results in the management of leaks and fistulas, since it allows true, full-thickness closure. However, it is still a very complex procedure that should only be applied by expert hands after proper training. Placing sutures may be particularly useful where the endoluminal space is tight, as in the esophago-gastric confluence after a sleeve gastrectomy suture line leakage, or in cases where the suture machine cannot be located opposite the suture line gap, but only tangentially [3]. However, its use is still limited to some referral centers.

The largest multicenter study to date, by Sharaiha et al., refers to 122 patients, only 20 of whom were treated for an anastomotic leak [142]. Endoluminal suturing should be performed only in patients with very recent defects and in aseptic wound conditions [3]. In a very recent study [28], authors conclude that there are very few studies explicitly examining the effectiveness of endoscopic suturing on anastomotic malformations and stapler line leaks after bariatric surgery; therefore, further prospective studies are needed to determine its overall efficacy and safety in closing anastomotic dehiscence.

4.8. Stem Cells

The use of autologous stem cell transplantation for sealing anastomotic leaks by means of endoscopy seems to be a very promising technique, for which there is already quite a lot of experience in various fields of medicine. Mesenchymal stem cells, exhibiting well known immune-modulatory and anti-inflammatory effects, should open a new era in the salvage of anastomotic dehiscence in the near future since (i) the technology of the adipose tissue emulsification already exists and is rapidly evolving to be fully automated, thanks to a harvest set from Tulip Medical, San Diego, CA and possibly also others, and (ii) the adipose tissue—the raw material—is autologous, so it is easy to find, easy to obtain, with no restriction on its use, and, theoretically, no foreign body reactions.

However, what really makes this technique promising is the simplicity of its endoscopic application: a 6Fr lumen catheter is required, such as that used for injection of contrast medium during ERCP, and a 22Fr endoscopic needle. Both pieces of equipment are cheap and available in every endoscopic unit and, above all, can be used through the working channel of a common endoscope, while at the same time there is no need for a qualified endoscopist.

4.9. Modification of Lumenal Microbiome

In a wild-type mouse model, in which a uniform colonic mucosal trauma was performed by means of an endoscope, the abundance of anaerobic Akkermansia spp. bacteria were found to be substantially increased in the regenerative mucosa. When Akkermansia muciniphilia was applied intra-rectally, the mice showed an improvement in wound closure and an increased proliferation of enterocytes in relation to controls. Although this effect was found to be directly dependent on the presence of the Fpr1 gene, encoding a G protein which mediates the response of neutrophils to pathogen invasion, it is most likely that, by means of the appropriate bacteria, meticulously chosen, tissue healing capacity substantially increased [143].

In clinical practice, patients, before undergoing colorectal resection and anastomosis and for 15 days post-operatively, received a four-probiotic formulation (n = 84) or placebo (n = 80) in a randomized, double-blind allocation. The probiotic formulation—consisting of Lactobacillus acidophilus, Lactobacillus plantarum, Bifidobacterium lactis, and Saccharomyces boulardii—resulted in 1.2% anastomotic rupture versus 8.8% in the placebo group. The study was prematurely stopped due to the high efficacy of the treatment. However, the gene expression of SOCS3 was found to be positively related with the gene expression of TNF-a and of circulating IL-6 in the probiotic group. This finding clearly suggests a reduction in the inflammatory process, prominent in the initial phase of healing after probiotic treatment, and it is well known that prolongation of healing time leads to chronicity [95].

Recently, it has been experimentally demonstrated that anastomotic healing improved in mice after feeding on a low-fat/high-fiber diet in relation to animals fed with a Western-type diet, the second group being found to have an increase in the abundance of collagenolytic Enterococcus faecalis bacteria [144].

All of the above treatments greatly support the possibility of reducing the likelihood of anastomotic leakage by manipulating the gut microbiome by enriching it with the appropriate beneficial bacteria. If the abundance and diversity of beneficial bacteria is found to steadily increase with routine administration of probiotics, this could establish a new strategy to prevent anastomotic leakage rather than to close the leak. Furthermore, the reality of an altered microbiome being involved in anastomosis ruptures—that is to say, the absence of some microbiota species—make us believe that the replacement of such bacteria to restore the microbiota population will become a kind of future treatment, alone or in combination with another technique, to improve anastomotic gap closure; however, further studies are needed in the near future.

5. Conclusions

The rapid development of interventional endoscopy in terms of techniques and devices allowing safe and quick closure of anastomotic dehiscence has elevated it from a supplementary tool to the primary tool for the handling of leaks and perforations, allowing patients to almost totally avoid re-operation.

Comparison between different techniques is absolutely impossible due to the lack of comparative, randomized controlled studies. Furthermore, the same management is not necessary to exert the same result due to the heterogeneity of leaks, the clinical condition of each patient, the availability of the equipment and devices, and the general skills and expertise of the endoscopist, as well as his/her familiarity with an aforementioned modality. Therefore, it is only possible to outline pros and cons rather than attempt a standardized therapeutic algorithm.

Each treatment needs to be tailored to the individual patient, not excluding the stepwise application of different techniques, always taking into account what should not be perfomed. Clips can be used only in small defects of less than 2 cm; glues can be used only for small defects with no fluid collections extraluminally; stents have no contraindication but need to perfectly fit the lumen to seal the gap; vacuum therapies must be used either intraluminally or intracavitarily, while pigtail stents used intracavitarily for purulent wound cavities need changes every three to, at most, five days, resulting in a large increase in the cost of treatment and the need for repeated endoscopies; suturing techniques should only be applied by experts and to recent and aseptic defects. We must keep in mind that changing therapeutic schedules is not a problem for the endoscopist, since multimodal therapies seem to shorten the treatment period through conversion of one treatment to another.

Finally, submucosal mesenchymal stem cell injections and modification of the luminal microbiome by means of probiotics to improve healing are in development. Until this moment arrives, the DECIDE approach, proposed by Buttar [145], must be kept in mind and applied to each case: debridation of the necrotic tissue, evacuation of the extraluminal collections, closure of the leak in a tension-free way, control of infection by internal or

external drainage, diversion of noxious contents by overcoming distal obstruction, and the ensuring of luminal continuity for peroral intake or distal feeding.

Author Contributions: A.M. performed the literature review and drafted the manuscript; G.T. and G.S. performed a critical revision, A.D.S. performed language editing, drafted, and critically revised the manuscript; K.K. conceived the original idea, performed the literature review, drafted, and critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: No need for ethics committee approval.

Informed Consent Statement: Not applicable.

Data Availability Statement: All articles used in bibliography are available in PubMed.

Conflicts of Interest: The authors declare no conflict of interest.

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