Endotherapy of leaks and fistula

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Abstract
Perforations, leaks and fistula involving gastrointestinal (GI) tract are increasingly recognized in our day to day practice. While these patients were earlier managed by surgical interventions, more and more such patients are now considered for endoscopic therapy. Endotherapy for GI leaks include endoclips (through the scope and over the scope), covered stents, fibrin glue, suture devices and more recently introduced endoscopic vacuum therapy using bioactive sponge. Since the experience with these modalities is limited, there are hardly any clear guidelines to treat these difficult patients. This review article deals with endotherapy of GI leaks and fistula and presents an updated experience as well some guidance to select appropriate modality.

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INTRODUCTION

Gastrointestinal (GI) leaks and fistula constitute disruption of GI wall. GI leaks and fistula can be either spontaneous due to GI pathology or may be iatrogenic. There seems to be increase in prevalence of GI leaks and fistula. While majority of these complicated patients were managed by surgery 15-20 years back, non-operative treatment including endoscopy presently constitute the primary modality of therapy. There is evidence to suggest that this changing paradigm in form of endoscopic therapy is associated with improved outcome and shortened length of hospital stay. This review deals with endoscopic techniques and their present status in the management of GI leaks and fistula.

DEFINITION AND ETIOLOGY

Perforation, fistula and leaks are terms, which are often used interchangeably. However, in strict terms, they are somewhat different. Perforation refers to acute full thickness defect in GI tract. Leaks are defined as disruption of surgical anastomosis resulting in a fluid collection. The term fistula usually means an abnormal communication between two epithelialized surfaces. Table 1 enumerates the causes of GI leaks and fistula, while Table 2 distinguishes the underlying etiology for leaks and fistula. Table 3 details the endoscopic procedures associated with increased risk of perforation.

TOOLS AND TECHNIQUES

The two options for managing GI leaks and fistula include surgery and endotherapy. The choice between two is decided by size of disruption, location and accessibility of lesion, presence of contamination, time of diagnosis and availability of expertise. Whatever be the chosen option for repairing the disruption, the management needs to include bowel rest, institution of appropriate antibiotics, drainage of associated collection, pneumoperitoneum, pneumothorax and maintenance of nutrition. Proton pump inhibitors are instituted, if leaks are located in upper GI tract. As highlighted in a recently published Position Statement of European Society of Gastrointestinal Endoscopy, it is important to have a systematic approach for diagnosis and treatment of GI perforations. Endoscopist must record details of findings, attending physician must evaluate the clinical profile, necessary investigations which may include a CT scan and a blood picture should be carried out, a decision should then be taken whether to perform endotherapy or surgery and finally post endotherapy monitoring must be done to evaluate success or failure of the endotherapy. Table 4 lists the endoscopic modalities, which can be used for closure of GI leaks and fistula. Of these, endoclips and covered stents are the two modalities, which are most commonly used and have most consistent results.

Endoclips

Endoclips, which are more frequently used for arresting GI hemorrhage can also be used for closing the GI wall disruptions and work like surgical sutures or staples. First report of endoclipping for closure of GI perforation came from Germany. This report discussed successful endotherapy of a perforation after endoscopic removal of gastric leiomyoma. Endoclips can either be through the scope (TTS) clips, where clip applicator with loaded clip is introduced through the biopsy channel of the endoscope or recently available over the scope (OTS) clips, which are mounted over the scope tip like variceal band ligator device and released by a similar technique. TTS clips (Figure 1) are available in various designs and sizes: Quick clip

| Table 1  Etiology of gastrointestinal leaks and fistula |
|-----------------------------------------------|
| Diagnostic endoscopy including endoscopic ultrasound |
| Dilatation: bougie, balloon, achalasia |
| Polypectomy/EMR/ESD |
| Foreign body |
| Endoscopic variceal therapy including ligation |
| POEM |
| Anastomotic dehiscence |
| Boerhaave’s syndrome |
| Diverticulitis |
| Laser |
| PEG |
| Endoscopic sphincterotomy |
| Biliary stent migration |
| Ampullectomy |
| Appendicular abscess |
| Empyema |

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; POEM: Peroral endoscopic myotomy; PEG: Percutaneous endoscopic gastrostomy.

| Table 2 Causes of leaks and fistula |
|-----------------------------------|
| **Leaks** | **Fistula** |
| Iatrogenic (60%) | Malignant (50%) |
| Endoscopy | Benign |
| EVL | Stents |
| Dilatation | Tuberculosis |
| ESD/EMR | Crohn’s |
| POEM | Iatrogenic |
| Spontaneous | Trauma |
| Boerhaave’s | Surgical |
| Foreign body | AIDS |
| Surgical | |
| Trauma |

EVL: Endoscopic variceal ligation; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; POEM: Peroral endoscopic myotomy; AIDS: Acquired immune deficiency syndrome.
(Olympus, America Inc., Center Valley PA, United States), Resolution clip (Boston Scientific Inc., Natick, United States) and Instinct clip (Cook Medical Inc.; Bloomington, IN, United States). Some of these are rotatable and re-openable, making them convenient to appropriately align the disrupted tissue. Figure 2 shows an esophageal tear treated by TTS clips.

OTS clips (Figure 3) from Ovesco Endoscopy GmbH (Tuebingen, Germany) are nitinol, super elastic, biocompatible clips with teeth designed in the shape of a bear trap and can produce a full thickness closure. OTS clips are available in various shapes and sizes and selection of a particular size depends upon the size of the defect. For larger defect, one can use accessories like anchor and twin grasper, which can pull the defective mucosa into the OTS cylinder or reduce the gap of the defect respectively (Figure 3). One should carefully avoid capturing twin grasper or anchor while releasing the clip. Figure 4 illustrates the use of OTS clips in a patient with two defects in gastric wall located diagonally opposite one another following a Whipple’s surgery. Two OTS clips were placed with the help of anchor and twin grasper through a double channel endoscope. Follow-up CT scan confirmed the complete closure of defects.

In general, it is believed that OTS clips cover a larger defect and one OTS clip can be compared with results obtained with 5 TTS clips. In large defects, such as after Endoscopic Submucosal Dissection (ESD), multiple TTS clips can be used to fix an endoloop at the margin of the defect and then pulling the loop and closing it can obliterate the defect. There are case reports of OTS clips applied under laparoscopic control in order to achieve greater success\cite{21}.

Both TTS and OTS clips have been used to close fistula and leaks located in esophagus, stomach as
While closing a large leak, it may be worthwhile to attempt to include adjacent omental patch within the clip, akin to surgical practice. Because of possibility of leakage of air during the procedure, it may be a good idea to use CO\textsubscript{2} insufflation during endotherapy of leaks and fistula. In order to get best results, it is important to apply endoclips early after detection of leaks and perforations. There is no reported risk of peritoneal dissemination or tumor recurrence after endoclips used for perforations following ESD or EMR performed for early cancers.

Luminal stenting

A large variety of stents are available to close luminal defects (Figure 5). These stents are covered (at least partially), so as to seal the defect and avoid contamination of the disrupted area. Mostly these stents are self-expanding metallic stent except for a single design of plastic stent (Polyflex, Boston). Fully covered stents, because of their ease at removability, are generally preferred particularly in the setting of benign disease. Figure 6 shows a patient with leak following gastrojejunostomy done for distal duodenal obstruction. One of the major issues with use of covered stent for closing of the GI defects is the risk of migration in absence of any obstructive pathology. This can be reduced by using large sized stents (Mega stents by Niti or Danis stent by Ella). There is no reported risk of peritoneal dissemination or tumor recurrence after endoclips used for perforations following ESD or EMR performed for early cancers.

In general clips are preferred over stents, if the leak is located in proximal esophagus or in distal most esophagus as well as for stomach and right colon. While TTS clips are effective for leaks smaller than 10 mm, OTS clips are preferred if defect is larger than 20-30 mm. Prior ablation at edges of defect to make it raw, may help in clip placement. While closing a large leak, it may be worthwhile to attempt to include adjacent omental patch within the clip, akin to surgical practice. Because of possibility of leakage of air during the procedure, it may be a good idea to use CO\textsubscript{2} insufflation during endotherapy of leaks and fistula. In order to get best results, it is important to apply endoclips early after detection of leaks and perforations. There is no reported risk of peritoneal dissemination or tumor recurrence after endoclips used for perforations following ESD or EMR performed for early cancers.

Stents have been used mostly in esophagus, duodenum and colon. Van Boeckel et al reported the

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Figure 3 Over the scope clips (ovesco) (A) clip, (B) clip mounted on the endoscope, (C) anchor, (D) twin grasper.
and gastric iatrogenic perforation respectively. As shown most of the series with gastric perforation have used clips, while both clips and stents have been used for esophageal perforation.

Bariatric surgery is not uncommonly complicated by leaks and fistula. In a retrospective study, over a period of 6 years involving 1499 bariatric surgery, Spyropoulos et al. reported a 2% incidence of luminal leak. Leaks were noted in sleeve itself, at staple line or at anastomosis site (gastrojejunostomy or enteroenteral). Of the 30 patients with leak, stents were used in 9, while surgery was performed in 3 patients and conservative approach was followed in 18 patients. Another recent study by EI Mourad et al. reported success of stent to close leaks following bariatric surgery in 41 out of 47 patients. Mega stents with a diameter of 30 mm are best suited for these indications.

Results of 25 studies with luminal stent for iatrogenic esophageal leaks. In the cumulative data involving 267 patients, they reported a clinical success of 85% for closure of leak with no difference between plastic stent, fully covered or partially covered metal stents (84%, 85% and 86% respectively \( P = 0.097 \)). Overall complication rate was 34%. Migration rate was somewhat higher for plastic stents compared to fully covered and partially covered stents (31% vs 26% vs 12% respectively). There was however, no difference in other complications such as tumor in-growth or over-growth. Freeman et al. recently reported that factors associated with failure of leak closure with stent placement include leak at cervical esophagus and esophagogastric junction, injury greater than 6 cm and additional distal leak. Tables 5 and 6 gives details of results of case series with endotherapy in esophageal and gastric iatrogenic perforation respectively.

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Suturing and sealants

While suturing and use of sealants have been used to close GI leaks and fistula, results are mixed and experience is limited. Some of the suturing devices include EndoCinch suturing device (C.R. Bard, Inc, Boston, Mass, United States) Sefestitch (SafeStitch, Medical Inc, Miami, Florida), Medical Power System (Power Medical Interventions, Longtrome, Pennsylvania), ESD Flexible Endoscopic Suturing devices by Wilson-Cook Medical (Winston- Salem, North Carolina) and Eagle Claw (Olympus Corporation, Tokyo, Japan)[59]. All these devices are either being still investigated or have not stood the test of time. Apollo Overstitch system (Figure 10) introduced recently, has been shown to have encouraging results[60,61]. This device is front-loaded onto a double-channel endoscope and allows continuous or interrupted stitches to be made with a cinching device. The merits of this approved device include the ability to reload the device inside the body eliminating the need to remove it between stitches as well as predictability of tissue needle penetration due to it being not suction based. Moreover, the device allows one endoscopic channel to be free to allow passage of grasping forcep for better tissue apposition[61].

Sealants which have been used to obliterate GI leaks and fistula include Cyanoacrylate and Fibrin glue[62,63].

Figure 5  Stents for gastrointestinal leaks/fistula.

Figure 6  Leak after duodeno-jejunostomy managed by luminal stenting. A: Contrast introduced through the surgical drain site shows the leak (arrow); B: Stent being deployed; C: Fully deployed covered stent; D: Contrast through the surgical drain shows the closure of the leak.
clips, since the bigger insertion diameter can lead to iatrogenic perforations\[22\].

**RECENT DEVELOPMENTS**

Some of the recent techniques used to close GI leaks and fistula include Endovac therapy, Plugs and grafts, Biodegradable stents and Cardiac septal occluder. Endoscopic vacuum assisted closure sponge or Endovac therapy has been used in setting of leaks associated with infections (Figure 11)\[66–69\]. Ahrens et al\[68\] reported 5 patients with post esophageal surgery anastomotic leaks treated by endovac therapy. Polyurethane sponges with a drainage tube fixed to it allowing continuous suction was positioned endoscopically in the wound cavity and sponge was changed at regular interval. All 5 patients had closure of leak after a median of 9 sponge changes, median duration of drainage being 28 d. Two patients did require bougie dilatation for esophageal stenosis and one of them had fatal outcome due to aortoanastomotic fistula after dilatation. Loske et al\[67\] reported success in 13 out of 14 patients with esophageal leaks treated by Endovac therapy with sponge being placed in the esophageal lumen (intraluminal method) or in the extraluminal

**LIMITATIONS AND COMPLICATIONS**

While endotherapy is exciting and results are encouraging, it has limitations in situations such as large perforation, difficult endoscopic position, fibrosis at the edge of the defect, evidence of abscess or fecal contamination etc\[64\]. Additional procedures or surgical alternatives should be considered in these circumstances. It is important to identify patients with failed clip closure as surgery should be promptly instituted in these patients in order to avoid sepsis and its consequences\[65\]. Monitoring should therefore be done by clinical profile and repeated blood counts. While endotherapy is safe if performed judiciously, complications such as perforation and bleeding are known. In particular, one must be careful while introducing endoscopes loaded with OTS.
success in 28 out of 29 patients.

Plugs and grafts used include Vicryl plug and Surgisis. Surgisis soft tissue graft (Cook Biotech Inc, West Lafayette, Ind) is an acellular bioactive prosthetic biomatrix produced from sheep intestinal submucosa.

In contrast to synthetic prosthetic material which has inherent risk of foreign body reaction, sepsis and secondary fistula formation, surgisis has been shown successful in 28 out of 29 patients.

Table 5 Result of endotherapy for iatrogenic esophageal perforation

| Ref.                  | Type of treatment | Patients (n) | Technical success (%) | Complications (%) |
|-----------------------|-------------------|--------------|-----------------------|-------------------|
| Freeman et al[43]     | SEPS              | 19           | 100                   | 24                |
| Vallböhmer et al[44]  | SEPS              | 12           | 100                   | 8                 |
| van Heel et al[45]    | SEPS/SEPS/clip    | 31           | 100                   | 33                |
| Schimdt et al[46]     | SEPS/SEPS         | 22           | 100                   | NA                |
| Swinnen et al[47]     | SEPS/SEPS         | 15           | 95                    | 13                |
| D’Cunha et al[48]     | 12               | 100          | Stents ± clip         |
| Biancari et al[49]    |                   |              |                       |
|                      |                   |              |                       |

Table 6 Result of endotherapy for iatrogenic gastric perforation

| Ref.                  | n  | Additional procedures | Success rate (%) |
|-----------------------|----|-----------------------|------------------|
| TTS                   |    | Omental patch         | 100              |
| Fujishiro et al[50]   | 11 | -                     | 100              |
| Minami et al[51]      | 121| > 1 cm: omental patch | 98.3             |
| Shi et al[52]         | 20 | Endoloop              | 100              |
| Zhong et al[53]       | 14 | Endoloop              | 100              |
| OTS                   |    |                       |                  |
| Kirschner et al[54]   | 7  | -                     | 100              |
| Voermans et al[55]    | 6  | -                     | 100              |
| Nishiyama et al[56]   | 7  | -                     | 86               |

Only studies with 5 or more patients are included. All studies were retrospective except Voermans et al[55]; 13 OTS clips were placed in 7 patients.

Only studies with 10 or more patients have been included; Study design was prospective, rest were all retrospective. NA: Not available; OTSC: Over-the-scope clip; SEMS: Self-expandable metal stent; SEPS: Self expandable plastic stent.

wound cavity (intracavitary method). Similar technique has also been used for colonic anastomotic leaks with
to be safe in contaminated tissues. It has been used successfully to treat complicated infected fistula after surgical resections including bariatric surgeries\cite{71-73}. Vicryl mesh in combination with fibrin glue (covering the mesh as well as injected into the submucosa at the edge of the defect) used by Böhm et al\cite{74} has also shown success in 13 out of 15 patients with leaks or fistula in upper GI tract following surgery for cancer. One to four sessions were used for this purpose.

Biodegradable stents have been used in a small series of 5 patients with esophageal leaks\cite{75}. Four out of these 5 patients responded, inspite of 3 stents migrating during follow up. Cardiac septal occluder (Amplatzer Occluder, AGA Medical Corp, Plymouth, MN) used for cardiac septal defects have been used successfully by Repici et al\cite{76} to close esophageal - tracheal fistula. More data is however, required with these modalities before they are included in routine clinical practice.

**CONSERVATIVE TREATMENT**

While majority of patient with GI wall disruptions are candidates for either surgery or endotherapy, a small selected group of patients with iatrogenic perforation can be managed by conservative approach\cite{18}. This subset includes stable patients who have perforations in cervical esophagus or a small number of patients with gastric or duodenal perforation, which are diagnosed late (> 12 h), are asymptomatic, have no signs of peritonitis and do not show free fluid or contrast extravasation at CT scan\cite{19}. Somatostatin and its analogue octreotide, which decrease intestinal secretions, have also been used to improve the results of this conservative approach both in adults as well as children\cite{77-79}. However, their role has been primarily considered for post-operative dehiscence, particularly after pancreatic surgery\cite{78,79}.

In conclusion, leaks and fistula involving GI tract are increasingly encountered in our routine practice. In a small select group of patients, there is a scope for conservative treatment of perforation and leaks. However, majority of patients are treated by surgery or endoscopic therapy. Techniques such as Endoclips (TTS and OTS) and covered metal stents have made endotherapy a preferred method to treat GI leaks and fistula. In general small leaks (< 10 mm) can be managed by traditional TTS clips, larger leaks require covered stents or OTS clips.Leaks and fistula associated with luminal strictures should be managed by luminal stenting. Recent developments with use of Endovac, Plugs and Graft and Biodegradable stents are encouraging. In particular, use of Endovac in the setting of sepsis seems promising. In view of multiple endoscopic modalities available with us, an algorithm based on location, size and associated features need to be developed to use these techniques judiciously.
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