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Current endoscopic closure techniques for the management of gastrointestinal perforations

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***Abstract*:** Acute gastrointestinal perforations occur either from spontaneous or iatrogenic causes. However, particular attention should be made in acute iatrogenic perforations as timely diagnosis and endoscopic closure prevent morbidity and mortality. With the increasing use of diagnostic endoscopy and advances in therapeutic endoscopy worldwide, the endoscopist must be able to recognize and manage perforations. Depending on the size and location of the defect, a variety of endoscopic clips, stents, and suturing devices are available. This review aims to prepare and guide the endoscopist to use the right tools and techniques for optimal patient outcomes.

Keywords: clip, perforation, stent

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Introduction

Acute gastrointestinal perforation after diagnostic or therapeutic endoscopy of the gastrointestinal tract is a rare but potentially life-threatening complication. Gastrointestinal perforations are full-thickness mural defects caused by spontaneous or iatrogenic means. Spontaneous perforations may occur due to inflammation,[1] weakened tissue from medication or infection, connective tissue disorders,[2] or from severe straining and vomiting (Boerhaave syndrome).[3] Iatrogenic perforations result from instrumental injury during endoscopy and are defined by the presence of air or luminal contents outside of the gastrointestinal tract.[4] Perforation rates vary widely depending on occuring location more frequently in injury-prone sites such as the duodenum, ampulla, sigmoid colon, rectum, and post-EMR in the right colon.[5–7] However, mortality rates vary widely: evidenced by low mortality of 0.019% in colonic perforations, and up to 13% in oesophageal perforations due to infective sequalae.[8,9] Diagnostic endoscopies have an incidence of iatrogenic perforations between 0.01% and 0.6%.[8,10,11] Despite the relatively low perforation rate, absolute numbers are significant. For example, in Australia between 2016 and 2017 nearly 1 million colonoscopies were conducted, corresponding to 100 to 6000 potential perforations during this period.[12] Moreover, it can be assumed that the absolute number of iatrogenic perforations is increasing worldwide due to the implementation of screening programmes and the expansion of indications for therapeutic endoscopic procedures.[13] For example, the literature reports a perforation rate of roughly 1% to 3% for endoscopic mucosa resection (EMR) and is estimated to be 0.5% for endoscopic retrograde cholangiopancreatography (ERCP).[14–16] Now, with the increasing use of third-space endoscopic procedures such as per oral endoscopic myotomy (POEM) and endoscopic submucosal dissection (ESD), endoscopists must effectively manage complications at the time of injury. With the introduction of ESD, it is possible to perform R0 resection of mucosal tumours to achieve complete remission; however, ESD is technically difficult and perforation rates are reported between 2% and 20%.[17–19] Full-thickness perforations can also occur in POEM but are rare in experienced hands with an estimated pooled average between 0.2% and 0.9%, both during and postprocedure.[20] Early diagnosis

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Table 1. Sydney classification of deep mural injury following endoscopic mucosal resection (adapted from Burgess *et al.*[5]).

Type	
0	Normal defect. Blue mat appearance of obliquely oriented intersecting submucosal connective tissue fibres.
I	Muscularis propria visible, but no mechanical injury.
II	Focal lass of the submucosal plane raising concern for rendering the muscularis propria defect uninterpretable.
III	Muscularis propria injured, specimen target sign or defect target sign identified
IV	Actual hole within a white cautery ring, no observed contamination
V	Actual hole within a white cautery ring, observed contamination

by recognizing, understanding, and interpreting perforations with the involvement of a multidisciplinary team are key factors that lead to good outcomes.

Diagnosis of gastrointestinal perforations

Recognizing iatrogenic perforations immediately during endoscopy

Recognition of significant bowel wall injury and perforations during endoscopy prevents the delayed diagnosis of perforations, which generally occurs after the procedure in a non-hospital setting and can be life-threatening. Hospital presentations in this fashion strip the endoscopist of the opportunity to repair the defect and often require surgical management. To allow for timely endoscopic intervention, the target sign has been proposed as a simple means of identifying injury to the muscularis propria layer.[21] In 2017, the Sydney classification of deep mural injury (DMI) was developed to assess depth of injury as well as diagnose perforations in the setting of endoscopic mucosal resection of colonic polyps. Types 0 to V have been described (Table 1). Type-I injuries do not require clip placement, whereas type-II (focal loss of submucosal plane) injuries should ideally be clipped. DMI type-III (injury to muscularis propria) – V (full thickness injury) require closure of the injured muscularis propria.[5]

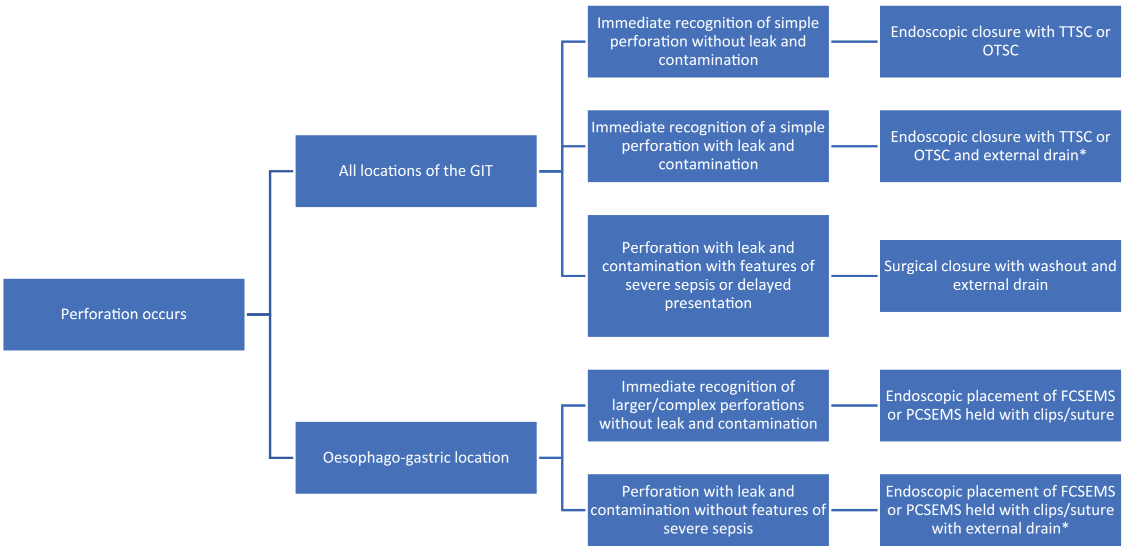
Recognizing postendoscopic (within 24 h) and delayed perforations (after 24 h)

Despite increased awareness, not all iatrogenic perforations are recognized at endoscopy. A retrospective study over a period of 10 years of patients with iatrogenic perforations showed that only 68% of perforations were identified within the first 24 hours.[22] Therefore, a perforation should be the priority diagnosis if patients present post-endoscopy with symptoms of abdominal pain with or without distension, chest pain, shortness of breath. Further concerns of contamination should be raised in the setting of a systemic inflammatory response including fevers, hypotension, and altered mental state or with subcutaneous emphysema. A computed tomography (CT) should be performed if there is any question of a perforation to prevent delay in diagnosis and clarify the presence of gas or fluid collections.[23] Conventional chest and abdominal X-rays are considered inferior compared to CT and should not be used as a primary diagnostic modality.[24]

The approach

Patients with uncontaminated perforations can be treated with direct closure with clips for smaller defects (<10 mm) anywhere in the gastrointestinal tract or using endoscopic self-expanding metal stents to close larger and complex defects within the oesophago-gastric tract.[25–29] In the event of a perforation associated with leak and contamination, management is dependent on the degree of the leak, location of the perforation and patient anatomy (Flowchart 1).

Perforations associated with large leaks may be approached in two ways. Traditionally, primary surgical closure and washout with or without external drain placement was the preferred modality, however was found to be associated with high morbidity and mortality rates of up to 36% and 10%, respectively.[30,31] This correlates to the severe



Flowchart 1. Approach to perforations in relation to size, location, and degree of contamination.
*External drain placement may be performed laparoscopically or under radiological guidance.

sequalae of gastrointestinal perforations and surgery may still be the only option in delayed presentations (>24-48 h) with purulent peritonitis. Recently, endoscopic closure of perforations with these large leaks with a SEMS combined with external drainage[32] (percutaneously or laparoscopically placed) have been used with success rates reaching up to 89%;[33] however, most experiences with stenting have been limited to the oesophago-gastric area. Regardless, endoscopic intervention allows for the potential of complete closure without need for surgery and minimizes duration of hospital stay.[5] Endoscopic closure should therefore be considered as the primary method and priority over surgery or conservative management.[25]

Other general considerations during endoscopic treatment

During endoscopic management of perforations, carbon dioxide (CO2) should be used due to its proven superior properties compared to room air due to lower rates of pain and abdominal distension.[34] This is due to its rapid absorptive properties of being absorbed 160 times faster than nitrogen, the major gaseous constituent of air and has been standardized as the choice gaseous agent in endoscopy units worldwide.[35] Thus, the use of CO2 reduces the potential risk of tension pneumothorax and abdominal compartment syndrome in the event of a perforation.[25] After endoscopic closure, gastrointestinal contents must be drained using a nasogastric or nasoduodenal tube within the stomach and duodenum to minimize the risk of ongoing leaks and prevent aspiration.[25] In addition to these measures, intravenous broad-spectrum antibiotics must be initiated to control sepsis even without overt features of abdominal contamination.[27] Choice and duration of antibiotics should be in line with local expertise and guidelines. These principles, as well as endoscopic closure techniques featured below may also be applied to spontaneous perforations.

Endoscopic closure techniques

The primary goal of endoscopic closure of perforations is to prevent the passage of gastrointestinal contents into the extraluminal space to avoid potentially life-threatening peritonitis or mediastinitis. Management of gastrointestinal perforations depends on their location and size. Several methods available are described below.

Through the scope-clips

Endoscopic clip placement was first described in 1975 by Hayashi *et al.* for achieving gastrointestinal bleeding haemostasis.[36] Since then, the application of through the scope clips (TTSCs) have evolved for a wide variety of indications including iatrogenic gastrointestinal perforations and are generally indicated for defects <10 mm in size.[37] Over the years, multiple TTSCs have been produced by different

Table 2. Clip types from respective brands, rotation capabilities, and opening width.

Through the scope clip	Rotation	Open width (mm)
Resolution clip (Boston Scientific)	Endoscopist	11 mm, 17 mm (ultra)
Sureclip (Microtech)	Assistant	8 mm, 11 mm, 16 mm, 17mm
Duraclip (Conmed)	Assistant	11 mm, 16mm
Quick clip (Olympus)	Assistant	11mm
Instinct clip (Cook medical)	Assistant	16mm
Hemoclip (Jiuhong medical)	Assistant	11 mm, 13mm

manufacturers with opening widths ranging from 8 to 17 mm with varying ease of rotation, open/close precision and closure strength (Table 2).[38] The opening width of the clip jaws remains the limiting factor as well as the grasping depth of superficial layers as successful closure requires the perforation edges to be in stable apposition.[39]

Nevertheless, clips have shown proven efficacy in animal studies with successful healing of perforations, leak proof sealing, and prevention of peritonitis.[40,41] Multiple human studies have also reported the effectiveness of closure of gastrointestinal perforations in different locations.

In the oesophagus, small case series in addition to a pooled analysis containing 17 patients have shown 100% closure of perforations.[26,42] Endoscopic closure succeeded in 98.3% of patients with gastric perforations[28] and a large series of 7598 colonoscopies revealed a technical success rate and clinical success rate of 96.3% and 92%, respectively.[43] A recent systematic review included 17 studies containing over 350 patients with iatrogenic perforations in varying gastrointestinal tract locations treated with TTSCs had clinically successful closure of 90.2%.[44] Techniques to promote successful closure include gentle air suction leading to deflation of the gastrointestinal lumen, thus bringing mucosal borders of the perforation into apposition as well as initiating clip closure distally (Figure 1) and proceeding towards the proximal end and the placement of multiple clips in a zipper fashion (Figure 2(a)–(d)).[45] Therefore, TTSCs are user friendly, widely available and effective in endoscopic closure of perforations generally ⩽10 mm in size.

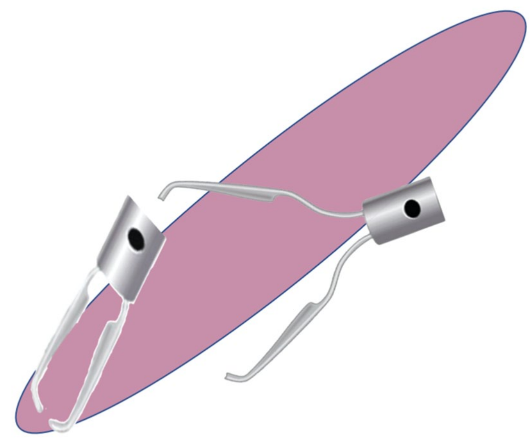


Figure 1. Through the scope clip approach. Gentle air suction and deflation to bring mucosal borders of the perforation into apposition and initiating clip closure distally.

Over the scope clips

In contrast to the TTSC, the over the scope clip (OTSC) is not applied through the working channel of the endoscope but is stretched on an applicator cap over the tip of the endoscope. This novel closure technique has the advantage of an application aid (anchor or twin grasper) which can be inserted through the working channel of the endoscope allowing the perforation edges to be grasped and pulled into the cap. The clip itself is made of nitinol (a biocompatible, MRI-safe material) and is released off the cap with a hand wheel allowing compression and closure around the drawn-in tissue like a bear trap (Video 1). The OTSC was approved for clinical use in 2009 by Conformite European certification in Europe and in 2010 by the US Food and Drug Administration. The most commonly used OTSC system is OVESCO (Ovesco Endoscopy AG, Tuebingen, Germany) which is available in four different sizes (mini, 11, 12, and 14) and can be fitted on diagnostic and therapeutic gastroscopes as well as colonoscopes. There are three different tooth geometries for different clinical scenarios; blunt

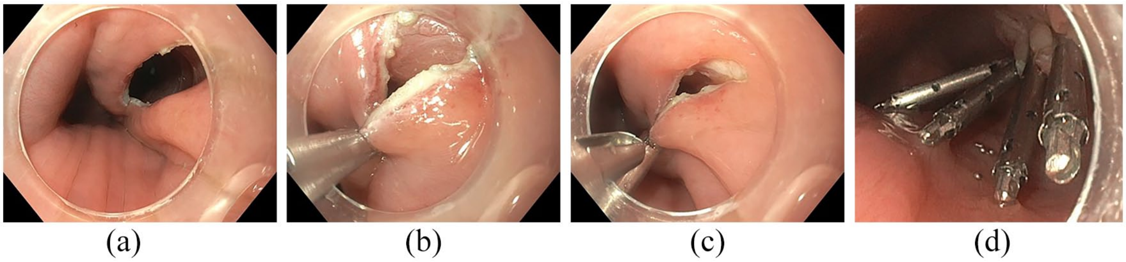


Figure 2. Through the scope clips clipping technique: (a) defect in oesophagus, (b) suction and deflation, starting to clip distally, (c) getting second clip in position close to the first one, and (d) defect closed in a zipper fashion technique.

teeth (type-a) for haemorrhagic lesions, teeth with small spikes (type-t) for thin-walled gastrointestinal lumen, and elongated teeth with spikes (type-gc) for the thick stomach wall.[46] Compared to the TTSC, the OTSC buries into the mucosa engaging deeper wall layers which may lead to a lower rate of leakage.[29,47] Another advantage is that the perforation can be closed in one step, saving time compared to sequential closure with multiple TTSCs.[48] Reports of clinical success of OTSC have also been reported for larger perforations up to 3 cm.[25] Furthermore, a benefit of this system over TTSCs involves the opposition of serosal surfaces causing fusion by fibrosis and thus a complete seal.[49,50]

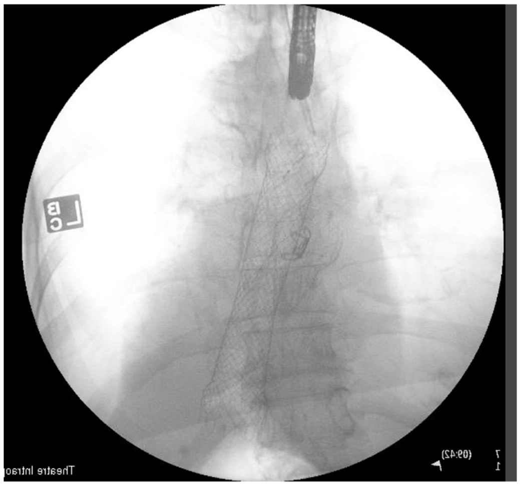
Various studies and a meta-analysis report the clinical success rates of OTSC for treatment of perforation to be between 64% and 92%.[46,51–53] However, in the instance of successful closure of a perforation associated with a leak using a OTSC, the contaminated cavity must be accessed with an external drain percutaneously under radiologic or laparoscopic guidance to drain the septic focus.[25,53] Over the scope clip when used correctly is effective, easily performed, and safe and therefore should be readily used for gastrointestinal perforations between 10 and 30 mm.

Stents

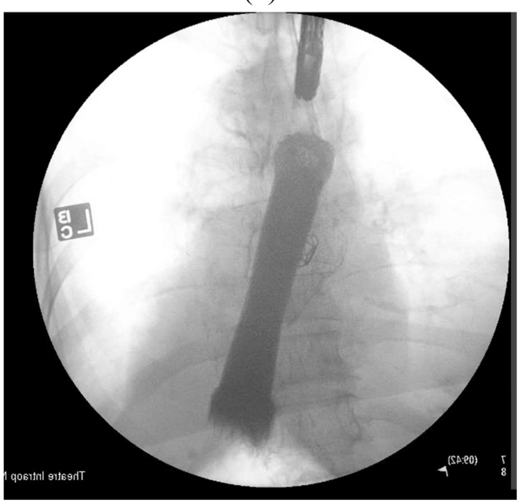
Larger and complex perforations in the oesophagogastric region may not be suitable for closure with the clips mentioned above.[25] Rather, self-expanding metal stents are required in such scenarios for the treatment of mid and lower esophageal perforations (deployment across the upper oesophagus is often not well tolerated). These stents prevent leakage and subsequent mediastinitis by covering the defect, promote re-epithelialization, and allows for early oral nutrition.

Theoretically, three main types of stents are available in the management of perforations: self-expandable plastic stents (SEPS), fully covered self-expandable metal stents (FCSEMS), and partially covered self-expandable metal stents (PCSEMS). The regular use of SEPS has diminished owing to a cumbersome setup and deployment system. In contrast, metal stents are quick and safe to place, and have excellent outcomes. Evidence points towards high technical and clinical success ranging from 91% to 100 % and 82% to 91%, respectively.[54–57] A systematic review showed similar clinical success rates of 85%, however higher stent migration rates of 26% was reported for FCSEMS compared with a 12% rate for PCSEMS.[58] Hence, stent migration is a common problem and various techniques have been investigated to anchor the stent to the esophageal wall. Proximal fixation of the stent has been reported with TTSC[59] and OTSC[60] have shown promising results. Notably, a multicenter study demonstrated a lower migration rate when fully-covered metal stents were anchored using an OTSC in comparison to stent placement alone (7.7% *vs* 26.9%, respectively, $P = .004$).[60]

Metal stents are available in different diameters and lengths. As a guide, the covered length of the stent should preferably be at least 2 cm longer than the proximal and distal end of the defect with deployment using a guide-wire under fluoroscopic and endoscopic vision. After successful placement, the absence of a leak should be confirmed with contrast (Figure 3(a) and (b)). The optimal duration of stent occupation ranges from 4 to 6 weeks and should be removed subsequently to prevent stent embedment.[61] Larger defects may require more than 6 weeks to achieve complete closure and stent replacement should occur at 6 weeks.[62]



(a)



(b)

Figure 3. Metal stent for treatment of an oesophagus perforation: (a) metal stent after placement and (b) closure control with contrast.

The choice of the right metal stent in treatment of esophageal perforations remains undefined, as no randomized controlled studies have directly compared the efficacy or FCSEMS against PCSEMS; however, current experiences favour stent fixation regardless of fully or partially covered stent types.[33] In addition to clips, stent fixation may also be performed with an endoscopic suturing device (Video 2).

Endoscopic suture devices

A novel technique for perforation closure that has emerged in recent years is endoscopic suturing. This modality has mainly been facilitated by the development of an over the scope suturing device, the OverStitch® (Apollo Endosurgery, TX, USA) (Figure 4). This endoscopic suturing device consists of a curved suturing needle that is placed on the tip of the endoscope, a catheter-based suture anchor and an operating handle attached to the neck of the instrument channel of the endoscope. Multiple full thickness sutures can be applied without requiring scope withdrawal and both, running and interrupted stitches can be deployed. On average, only 1 to 3 sutures are needed to permanently close defect 3 to 4 cm in size and the procedural time ranges from 5 to 15 minutes.[63–65] Other over the scope suturing devices, such as Endomina (Endo Tools Therapeutics, Brussels) have since come on the market, however has primarily used in endoscopic suture gastroplasty.[66,67] A retrospective, single-centre study, showed promising results of colonic closures with suturing devices. Of 21 patients with iatrogenic colonic perforations 5 (24%) were closed with TTSCs and 16 (76%) with an endoscopic suturing device. In the TTSC group, all patients had clinical deterioration and needed either surgical intervention (4 patients) or a rescue colonoscopy with endoscopic suturing closure (1 patient). In contrast, in the endoscopic suturing device group 93% (15 patients) required no rescue surgery or laparoscopy.[63] Successful use of this system for the closure of esophageal and gastric-wall defects have been reported in retrospective studies and case reports.[68–70] In addition, a recent meta-analysis including 19 studies with a mean perforation size of 34 mm (46% of these within the colon) reported a clinical success rate of 98.6% with endoscopic suturing.[71] Two limitations for endoscopic suture devices should be acknowledged. First, a double-channel endoscope is required as thread and anchor have to be inserted separately. Second, the user has to be familiar with instrument as well

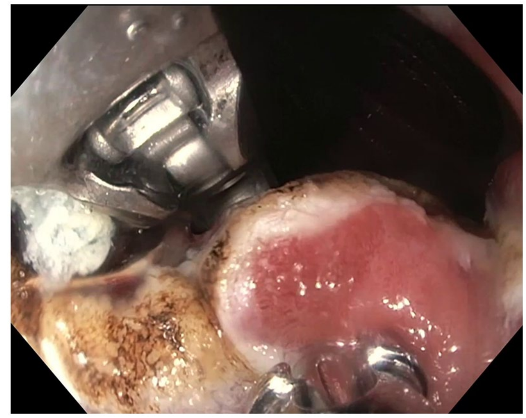


Figure 4. Endoscopic suturing device (OverStitch®).

as the suturing technique. The learning curve varies but competency is achieved quickly by endoscopists familiar with advanced and interventional endoscopy.[72] Although larger randomized controlled trials are needed to assess this technique against other endoscopic closure methods, there is good reason to believe that endoscopic suturing plays an important role in closure of perforations from emerging experience and data. Further long-term and prospective studies of stent fixation techniques are also required to choose suturing over clipping.

Endoscopic vacuum-assisted closure

Initially described by Wedemeyer *et al.* and Loske *et al.*, endoscopic vacuum-assisted closure (EVAC) was successfully reported to close oesophageal anastomotic leaks refractory to surgical and endoscopic stenting in two patients.[73,74] In brief, a cylindrical open-pore polyurethane sponge is fixed by suture on the distal end of a 14-Fr nasogastric tube and placed into or over the upper gastrointestinal defect.[75] The sponge is either placed directly into the cavity with forceps or is placed adjacent within the lumen of the oesophagus in smaller defects. Once the sponge is in position, a continuous high intensity vacuum is applied at 125 mmHg. The sponge is exchanged every 3 to 5 days.[76] With diminishing defect size, the sponge should be changed from the intracavity position to the intraluminal position. There are currently no head-to-head prospective studies comparing EVAC to other modalities of perforation closure. A systematic review on the use of EVAC in various upper gastrointestinal defects included a total of 210 patients and reported a combined closure success rate 90% (range: 70%-100%) over a median duration of 17 days.[77]

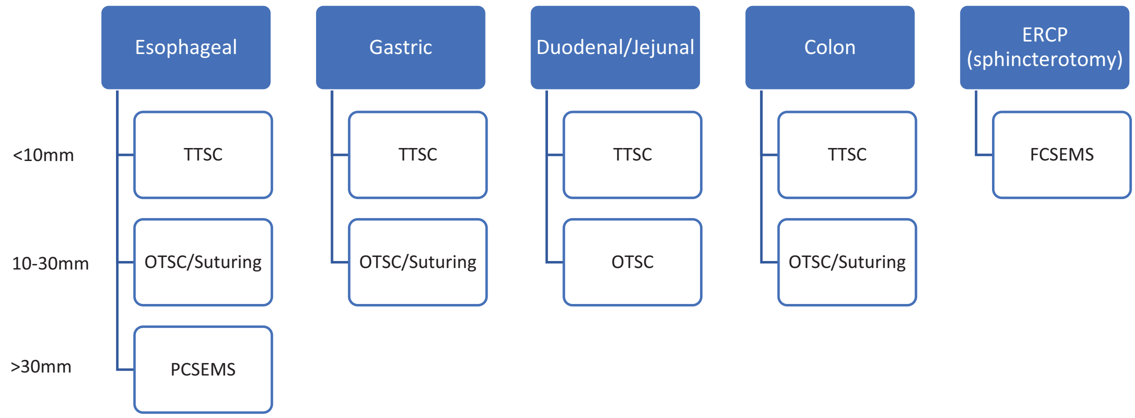
Most available literature reports experiences in the upper gastrointestinal tract; however, anastomotic leaks although rectal EVAC has successfully been reported (Weidenhagen).[78] EVAC should be used in experienced centres as an option for refractory cases to primary closure methods outlined above.

ERCP-related perforation

Endoscopic retrograde cholangiopancreatography-associated perforations are uncommon, however, is widely feared due to reported high-mortality rates of up to 13%, reaching up to 27% in those that require surgery.[44] Perforations can occur in different locations and treatment is based on the Stapfer classification.[79,80] Type I (perforation of duodenal wall) defects traditionally required surgery; however, small perforations have been successfully closed with through the scope and over the scope clips.[53] Injuries around the ampulla and ducts including type-II (retroperitoneal duodenal perforation due to peri-ampullary injury), type-III (pancreatic or bile duct perforation), and type-IV (retroperitoneal microperforation) can be managed with stents and biliary drainage.[27] A large study including 7471 ERCPs with sphincterotomy with 0.33% (25 patients) type-II perforations compared conservative management of endoscopic nasobiliary drainage against the placement of a biliary FCSEMS. The stent group had less postprocedural symptoms of pain during the follow-up period ($P = .005$), lower white blood cell counts ($13{,}218 \pm 4410 \times 10$ *vs* $8714 \pm 3270 \times 10 (P = .029)$), shorter hospital stay (15.77 ± 5.21 *vs* 11.7 ± 3.19 days ($P = 0.053$)), and none of the patients needed surgery or died.[81] Another study identified 15 patients out of 4860 ERCP procedures with post-sphincterotomy perforations who were all treated with a FCSEMS showed immediate resolution of the perforation and none required surgical intervention.[82] Therefore, in the presence of free-wall duodenal injury, concern for sphincterotomy-related perforations or contrast leak on cholangiopancreatogram, close inspection, and appropriate endoscopic therapy will prevent morbidity and mortality.

Discussion

Surgery has traditionally been the standard of care for the treatment of gastrointestinal perforations however is associated with significant morbidity and mortality,[32,33] safe and effective endoscopic closure negates the need for invasive surgery intervention. Until high-quality evidence is available, current guidelines are based on low-quality evidence supported by expert opinion.[27] However, real-world data experiences support the early diagnosis, adequate endoscopic closure with respective closure techniques in experienced hands. Our recommendations are that closure of defects less than 10 mm should be closed with TTSC in all areas of the gastrointestinal tract unless caused by sphincterotomy during ERCP. We propose the use of OTSC or endoscopic suturing (if technical expertise is available) for larger defects between 10 and 30 mm. Finally, we suggest most ERCP-related perforations (Types II-IV) be treated with biliary stenting, whereas most oesophagus perforations are should be managed with FCSEMS (Flowchart 2). Hospital admission, initiation of broad-spectrum antibiotics as per local guidelines, and surgical



Flowchart 2. Suggested approach for endoscopic closure of gastrointestinal perforations.

consultation are also required. Patients should be kept nil-by-mouth until review 24 hours later.

Looking forward, consecutive series and comparative studies should aim to delineate what size of perforation in which location of the gastrointestinal tract is best suited for a specific method of closure. However, realistically due to the low incidence of iatrogenic perforations, recruiting patients and obtaining consent in an acute perforation setting makes such studies difficult to execute. Future direction should be also be emphasized on innovative closure techniques such as endoscopic suturing and endoscopic vacuum assisted closure techniques.

Author contributions

Dominic Staudenmann: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.
Kevin Kyung Ho Choi: Conceptualization; Data curation; Formal analysis; Project administration; Writing – original draft; Writing – review & editing.
Arthur John Kaffes: Conceptualization; Methodology; Supervision; Writing – review & editing.
Payal Saxena: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – review & editing.

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Supplemental material

Supplemental material for this article is available online.

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