Diagnosis and management of iatrogenic endoscopic perforations: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement

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Institutions

Institutions are listed at the end of article.

Bibliography
DOI http://dx.doi.org/10.1055/s-0034-1377531
Published online: 21.7.2014
Endoscopy 2014; 46: 693–711

ISSN 0013-726X

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This Position Paper is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It addresses the diagnosis and management of iatrogenic perforation occurring during diagnostic or therapeutic digestive endoscopic procedures.

Main recommendations

1 ESGE recommends that each center implements a written policy regarding the management of iatrogenic perforation, including the definition of procedures that carry a high risk of this complication. This policy should be shared with the radiologists and surgeons at each center.

2 In the case of an endoscopically identified perforation, ESGE recommends that the endoscopist reports: its size and location with a picture; endoscopic treatment that might have been possible; whether carbon dioxide or air was used for insufflation; and the standard report information.

3 ESGE recommends that symptoms or signs suggestive of iatrogenic perforation after an endoscopic procedure should be carefully evaluated and documented, possibly with a computed tomography (CT) scan, in order to prevent any diagnostic delay.

4 ESGE recommends that endoscopic closure should be considered depending on the type of perforation, its size, and the endoscopist expertise available at the center. A switch to carbon dioxide insufflation, the diversion of luminal content, and decompression of tension pneumoperitoneum or tension pneumothorax should also be done.

5 After closure of an iatrogenic perforation using an endoscopic method, ESGE recommends that further management should be based on the estimated success of the endoscopic closure and on the general clinical condition of the patient. In the case of no or failed endoscopic closure of the iatrogenic perforation, and in patients whose clinical condition is deteriorating, hospitalization and surgical consultation are recommended.

Abbreviations:

CI	confidence interval
CT	computed tomography
DBE	double-balloon enteroscopy
EGD	esophagogastroduodenosocpy
EMR	endoscopic mucosal resection
ERCP	endoscopic retrograde cholangiopancreatography
ESD	endoscopic submucosal dissection
EUS	endoscopic ultrasound
ESGE	European Society of Gastrointestinal Endoscopy
OTSC	over-the-scope clip
PICO	participants, interventions, comparators, outcomes
RCT	randomized controlled trial
SEMS	self-expandable metal stent
SEPS	self-expandable plastic stent
TTS	through-the-scope

Introduction

Iatrogenic perforation of the gastrointestinal tract related to diagnostic or therapeutic endoscopy is a rare but severe adverse event, associated with significant morbidity and mortality. The absolute number of iatrogenic perforations is likely to increase [1], because of the widespread implementation of endoscopic screening programs and the expansion of the indications for therapeutic

endoscopy. Improvements in the endoscopic and surgical treatments of iatrogenic perforations might substantially reduce the associated morbidity and mortality, underlining the importance of correct diagnosis and management of these events [2]. Because of the lack of high quality studies, mainly due to the rarity of these adverse events, clinical/radiological/surgical strategies to deal with iatrogenic perforation are unclear. The clinical outcome of the patients depends on the timing and efficacy of such interventions, so that the lack of well-defined strategies may by itself be responsible for a suboptimal outcome.
In this Position Statement, ESGE aimed to define the main risk factors for iatrogenic perforations as well as clear diagnostic and therapeutic algorithms for their management. ESGE issues these recommendations as a position statement rather than a guideline because of the scarcity of high quality studies.

Methods

ESGE commissioned this Position Statement. The development process included meetings and online discussions among members of the committee during December 2012 and November 2013. Subgroups were formed, each in charge of a series of clearly defined key questions. The guideline committee chairs (G.P., C.H., J.M.D.) worked with the subgroup leaders (A.R., M.B., J.M.D., S.M., B.S.) to identify pertinent search terms that included: iatrogenic perforations, endoscopy, clips, surgery, as well as terms pertinent to specific key questions. For ease of literature searching, key questions were formulated using PICO (participants, interventions, comparators, outcomes) methodology [3].
Searches were performed on Medline (via Pubmed) and the Cochrane Central Register of Controlled Trials up to October 2013. Articles were first selected by title; their relevance was then assessed by reviewing full-text articles, and publications with content that was considered irrelevant were excluded. Because of the lack of well-designed studies on the diagnosis and management of iatrogenic perforations, quality of evidence and strength of recommendations were not formally graded [4].
Each subgroup developed draft proposals that were presented to the entire group for general discussion during a meeting held in December 2013 (Frankfurt, Germany). Further details on the methodology of ESGE guidelines have been reported elsewhere [4].
In April 2014, a draft prepared by G.P. was sent to all group members. After agreement on a final version, the manuscript was reviewed by two experts selected by the ESGE Governing Board and it was sent to all ESGE individual members and societies for comments/endorsement. It was then submitted to the journal Endoscopy for publication.
This Position Paper was issued in 2014 and will be considered for update in 2018. Any interim updates will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

Recommendations and statements

Evidence statements and recommendations are stated in italics. For ease of clinical use general recommendations and statements are given first followed by in the recommendations and statements for specific organs. A summary of the recommendations and statements is presented in **Table 1**.

General policy

ESGE recommends that each center implements a written policy regarding the management of iatrogenic perforations, including the definition of procedures that carry a high risk of this complication. This policy should be shared with the radiologists and surgeons at each center.
Iatrogenic perforations are associated with a high risk of morbidity and mortality. Such risks can probably be reduced by using an evidence-based algorithm for diagnosis and management. As outlined below, awareness of the risk factors, prompt availability of adequate radiological imaging, as well as clinical, endoscopic and surgical competence may be expected to substantially improve patient outcome. Because of its complexity, this condition is better managed by a multidisciplinary approach, including endoscopic, radiological, and surgical competences that need to be readily available.
In particular, the existence of a clear policy may prevent a situation where iatrogenic perforation has catastrophic consequences because of the non-availability of appropriate clinical, radiological, or surgical expertise. Although iatrogenic perforation is relatively rare, it is not a completely unpredictable adverse event. Some procedures appear to carry a relatively high risk, allowing a simple stratification between low risk and high risk procedures. It is reasonable to assume that implementation of policies before and not after the introduction of the procedure would by itself minimize the morbidity and mortality risk associated with endoscopic perforation. For instance, the simple awareness that a particular procedure is at high risk of esophageal perforation should indicate that the procedure should not be performed unless a surgeon with adequate thoracic competence is available. Similarly, lack of training with or non-availability of dedicated endoscopic devices would unnecessarily expose patients with iatrogenic perforations to surgical risks. Moreover, failure to use computed tomography (CT) instead of plain film radiography to detect subtle perforations may result in diagnostic delay. Thus the management team for iatrogenic perforations seems to resemble that of stroke and gastrointestinal bleeding units, where prompt collaboration and availability of required competences has led to better clinical outcomes [5, 6]. The availability of dedicated protocols may also represent a structural quality indicator for the health system.

Reporting

In the case of an endoscopically identified perforation, ESGE recommends that the endoscopist reports: its size and location with a picture; endoscopic treatment that might have been possible; whether carbon dioxide or air was used for insufflation; and the standard report information.
Acute iatrogenic perforation during endoscopy is defined as the presence of gas or luminal contents outside the gastrointestinal tract [7]. The timing of diagnosis is critical for management and patient outcome [8–10]. Endoscopy shows a high sensitivity and specificity for diagnosis of iatrogenic perforation [11]. Concerns that air insufflation associated with endoscopy may worsen the extraluminal contamination associated with perforation have not been conclusively demonstrated in any recent study; therefore such concerns should not prevent adequate reporting of the perforation characteristics and should not prevent possible treatment. In the case of an endoscopically recognized perforation, a

Table 1 Iatrogenic endoscopic perforations: summary of recommendations from the European Society of Gastrointestinal Endoscopy (ESGE).

- *ESGE recommends that each center implements a written policy regarding the management of iatrogenic perforation, including the definition of procedures that carry a high risk of this complication. This policy should be shared with the radiologists and surgeons at each center.*
- *In the case of an endoscopically identified perforation, ESGE recommends that the endoscopist reports: its size and location with a picture; endoscopic treatment that might have been possible; whether carbon dioxide or air was used for insufflation; and the standard report information.*
- *ESGE recommends that symptoms or signs suggestive of iatrogenic perforation after an endoscopic procedure should be carefully evaluated and documented, possibly with a computed tomography (CT) scan, in order to prevent any diagnostic delay.*
- *ESGE recommends that endoscopic closure should be considered depending on the type of perforation, its size, and the endoscopist expertise available at the center. A switch to carbon dioxide insufflation, the diversion of luminal content, and decompression of tension pneumoperitoneum or tension pneumothorax should also be done.*
- *After closure of an iatrogenic perforation using an endoscopic method, ESGE recommends that further management should be based on the estimated success of the endoscopic closure and on the general clinical condition of the patient. In the case of no or failed endoscopic closure of the iatrogenic perforation, and in patients whose clinical condition is deteriorating, hospitalization and surgical consultation are recommended.*
- *ESGE suggests that endoscopic dilations, mucosal resection/submucosal dissection, and foreign body removal should be considered to carry an increased risk of esophageal or gastric perforation.*
- *ESGE recommends endoscopic treatment for esophageal and gastric perforations using clips or other devices, especially for perforations < 10 mm. Temporary stent placement is particularly useful for large esophageal perforations. For gastric perforation > 10 mm, use of over-the-scope clips (OTSCs) or omental patching, or the combined technique using an endoloop and through-the-scope (TTS) clips are recommended. If such treatment is unfeasible or fails, or in the case of clinical deterioration, hospitalization and surgical consultation are recommended. General principles of management also include nil-by-mouth regimen, with intravenous administration of proton pump inhibitors, broad spectrum antibiotics, fluids, and on-demand pain medication.*
- *The most common causes of perforations related to endoscopic retrograde cholangiopancreatography (ERCP) are sphincterotomy (56 %) and guidewire manipulation (23 %). ESGE suggests that precut, Billroth II gastrectomy, and biliary stricture dilation should be considered to entail increased risk for biliopancreatic perforation.*
- *The majority of ERCP-related ductal or periampullary duodenal perforations can be managed nonsurgically. The indications for surgery are a major contrast medium leak, severe sepsis despite nonsurgical management, severe peritonitis, and fluid collections or unsolved problems (e. g., retained hardware) that cannot be solved by nonsurgical means. After careful patient selection, nonsurgical management is successful in more than 90 % of patients.*
- *For the nonsurgical management of ERCP-related ductal or periampullary duodenal perforation, ESGE recommends antibiotics and nasogastric or nasoduodenal aspiration in all patients; stenting of the perforated duct (or of the biliary duct in the case of periampullary perforation) on a case-by-case basis; and total parenteral nutrition in undernourished patients as well as in patients in whom adequate enteral feeding is presumed not to be feasible for ≥ 7 days. Cross-sectional imaging should be performed during follow-up and, if a liquid collection is disclosed, percutaneous drainage should be considered. The efficacy of TTS clips in closing periampullary perforations is unknown.*
- *ESGE suggests that altered anatomy, stricture dilation in Crohn's disease, dilation of gastrojejunal stricture after gastric bypass, endoscopic submucosal dissection (ESD) and, in patients with altered anatomy, double-balloon enteroscopy (DBE) are risk factors for duodenal and small-bowel perforation.*
- *In type I (i. e. nonperivaterian) duodenal perforations, ESGE recommends endoscopic treatment if the iatrogenic perforations is recognized immediately and, in the case of failure of endoscopic treatment, immediate surgery. If the duodenal perforation is diagnosed later (> 12 h), management should be surgical in the case of contrast medium extravasation or of persistent large fluid collection at CT scan, or if the patient's condition deteriorates. If the patient is in good condition without extravasation of contrast medium or persistent large fluid collection seen at CT, the patient should be treated conservatively without intervention. For iatrogenic perforations in the small bowel, the ESGE recommends surgical treatment although some iatrogenic perforations caused by dilation of a stricture at a gastrojejunal anastomosis (GJA) may be treated conservatively.*
- *ESGE recommends that complex endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and balloon dilation procedures should be considered to carry increased risk of colorectal perforation. Older age, co-morbidity, inflammatory colonic disease, use of hot biopsy forceps, and endoscopist inexperience are other significant risk factors for iatrogenic perforations at colonoscopy.*
- *ESGE recommends the use of TTS endoclips for small holes and OTSCs for larger ones. Adequate colon preparation is an important factor when contemplating endoscopic treatment of iatrogenic perforations. All patients treated conservatively should be watched closely by a multidisciplinary team in the immediate post-procedure period. Immediate surgical repair is required in the case of larger perforations or where endoscopic closure has failed or where the patient's clinical condition is deteriorating.*

comprehensive and clear written report is critical in driving further management. Thus, incomplete reporting – that may be dictated by the fear of future medicolegal litigation – may expose patients to needless diagnostic or therapeutic delays and cause a suboptimal outcome. A clear report stating that the endoscopic therapy applied to the iatrogenic perforation was effective is likely to represent by itself an indication not to proceed to surgery, whilst a report of failure to close a perforation may warn against any delay in surgical treatment. Awareness about the use of carbon dioxide or air may be critical in the interpretation of endoscopic and clinical findings. In order to simplify surgical access, an accurate description of the size and location of the iatrogenic perforations is also required [12]. The availability of photographic documentation of the perforated area may be useful for the multidisciplinary approach, and also for legal considerations.

ESGE recommends that symptoms or signs suggestive of iatrogenic perforation after an endoscopic procedure should be carefully evaluated and documented, possibly with a computed tomography (CT) scan, in order to prevent any diagnostic delay.

Iatrogenic perforations are not always recognized at endoscopy. For instance, in a study spanning 10 years of practice, only 68 % of colonoscopy-related perforations were diagnosed within 24 hours [13], so that a high level of suspicion for perforation is required when evaluating some post-endoscopy symptoms, especially following procedures with a high risk of perforation. Early diagnosis has been shown to substantially impact the post-perforation outcome, mainly because it allows potential surgical intervention in an uncontaminated setting [14]. An early search for iatrogenic perforations should be prompted by unusual abdominal pain with distension, chest pain, subcutaneous emphysema, or shortness of breath, while iatrogenic perforation at a later stage is associated with more severe symptoms or signs, such as systemic inflammatory response, hypotension, and mental confusion.

Chest and abdominal plain film radiography are considered to be suboptimal compared with CT scanning [15]. The advantages of CT over plain film radiography include the ability to detect small

amounts of gas in the peritoneum, retroperitoneum or mediastinum, as well as the ability to use luminal contrast to evaluate the efficacy of endoscopic perforation closure.
CT also has a higher sensitivity than plain film radiography for the detection of extraluminal liquids or small pneumothorax. In detail, CT imaging has the higher accuracy for showing small quantities of free air, fluid collections, or empyema in the mediastinum and/or pleural or peritoneal cavity and it provides better definition of adjacent structures [15]. The ingestion of water-soluble contrast prior to CT adds accuracy because it may display the site of extravasation [16].
After endoscopic resection, small air bubbles caused by transmural injection may be seen in the absence of actual iatrogenic perforation [9, 17]. Pneumomediastinum or pneumoperitoneum, without any endoscopic evidence of perforation, can be shown by CT scans in 31 % – 63 % of all gastroesophageal endoscopic submucosal dissection (ESD) procedures [18, 19]. Thus, radiologic findings should always be interpreted in conjunction with endoscopic and clinical findings.

Treatment

ESGE recommends that endoscopic closure should be considered depending on the type of the perforation, its size, and the endoscopist expertise available at the center. A switch to carbon dioxide endoscopic insufflation, the diversion of luminal content, and decompression of tension pneumoperitoneum or tension pneumothorax should also be done.
Randomized controlled studies performed in animal models have shown that the endoscopic closure of iatrogenic perforations is feasible, prevents peritonitis and, compared with surgery, limits adhesions [20, 21]. Thus, it may be decisive in influencing patient outcome, and need for surgery following iatrogenic perforation. Different devices may be applied, mainly according to the size of the iatrogenic perforation. It is unlikely, however, that holes larger than 3 cm may be endoscopically treated.
Clean contents of the gastrointestinal lumen and adequate expertise of the endoscopist are prerequisites for successful endoscopic closure of iatrogenic perforations. Nasogastric or nasoduodenal tubes should be used for diversion of gastrointestinal fluids, as appropriate. Although early involvement of the surgeon is advisable, his/her presence is not required for the endoscopic treatment of the iatrogenic perforation, as the endoscopist usually has more experience than the surgeon in endoscopic closure of iatrogenic perforations.
In the case of hemodynamic or breathing disorders caused by air under tension, decompression should be done as an emergency measure [22]. In a Japanese series, half of the patients underwent successful peritoneal decompression during the procedure [23] (**Video e1**, available online).
Carbon dioxide insufflation is generally recommended during long gastrointestinal endoscopy procedures in patients without severe underlying pulmonary disease [24]. Switching from air to carbon dioxide for insufflation in the case of unexpected iatrogenic perforation may prevent tension-pneumothorax, tension-pneumomediastinum, or tension-pneumopericardium, and the abdominal compartment syndrome, although supporting data are lacking [24, 25].

After closure of an iatrogenic perforation using an endoscopic method, ESGE recommends that further management should be based on the estimated success of the endoscopic closure and on the general clinical condition of the patient. In the case of no or failed endoscopic closure of the iatrogenic perforation, and in patients whose clinical condition is deteriorating, hospitalization and surgical consultation are recommended.
In the case of iatrogenic perforation, hospitalization is nearly always required. However, selected patients with asymptomatic iatrogenic perforation treated endoscopically may be discharged, but close follow-up should be considered [26].
All patients admitted to the hospital should be treated with general supportive measures including intravenous antibiotics, nothing by mouth, and close multidisciplinary follow-up. Parenteral nutrition is recommended in undernourished patients or in well-nourished patients with expected non-alimentation for ≥ 7 days [27]. Close clinical multidisciplinary monitoring (by endoscopists, surgeons, and intensive care physicians) is required, with special attention to signs of sepsis and peritonitis that could lead to urgent surgical management.
Early surgery is generally to be preferred in patients with large perforations, generalized peritonitis, ongoing sepsis, deteriorating clinical condition, after failure of percutaneous drainage, or with an active leak or with presence of a definite amount of free fluid detected at CT that cannot be drained percutaneously.
Iatrogenic perforations that are diagnosed late (particularly duodenal iatrogenic perforations) also require surgical drainage, which carries a high morbidity and mortality [8, 9, 14, 28, 29].

Gastroesophageal perforations

High risk gastroesophageal procedures

ESGE suggests that endoscopic dilations, mucosal resection/submucosal dissection and foreign body removal should be considered to carry an increased risk of esophageal or gastric perforation.

Esophagus: high risk procedures

Most esophageal perforations are associated with therapeutic endoscopic maneuvers, and occur in the thoracic part of the esophagus [30, 31]. Iatrogenic perforation is the most frequently reported major complication of esophageal dilation [30]. The risk is low (0.09 % – 2.2 %) for simple ring or peptic strictures [30], and much higher for strictures that are complex (angulated, multiple, or long), caustic, or radiation-induced [32, 33]. The perforation rate in pneumatic dilation for achalasia has been reported to range broadly between 0.4 % and 14 %, and it seems to be lower if a 30-mm balloon is used first with an interval, stepwise approach [34, 35].
Endoscopic resections have also been associated with esophageal perforations: retrospective series on endoscopic mucosal resection (EMR) (mostly for Barrett's esophagus) have reported perforation rates between 0 % and 3 % [36, 37].

Video e1

Inoue & Fockens draining a pneumoperitoneum

Online content including video sequences viewable at: www.thieme-connect.de

Comparably low rates of perforation (2.4%) have been reported by Japanese authors for endoscopic submucosal dissection (ESD) of squamous cell cancer [38]; these have been confirmed by limited European series [39, 40].
Finally, regarding foreign bodies, a large, irregular, or sharp shape, impaction in the esophagus for a very long duration, and a history of repeated intentional foreign body ingestion are all risk factors for esophageal perforation [41]. Passage of transesophageal echocardiography probes has also been associated with iatrogenic perforation.

Stomach: high risk procedures

Iatrogenic gastric perforations are most often related to therapeutic procedures, including: gastroenteric anastomosis dilation (2%) [42]; overdistension during argon plasma coagulation or cryotherapy (< 0.5%); standard snare polypectomy; EMR (0.5%) and, more frequently, ESD [43]. Additional risk factors during EMR and ESD are: the presence of an ulcer or unhealthy (e.g. irradiated) tissues [44], age > 80 years, large tumor size, location of the lesion in the thinner upper region, and long duration of the resection [43, 45, 46].

Treatment of gastroesophageal perforations

ESGE recommends endoscopic treatment for esophageal and gastric perforations using clips or other devices, especially for perforations ≤ 10 mm. Temporary stent placement is particularly useful for large esophageal perforations. For gastric perforations > 10 mm, use of over-the-scope clips (OTSCs) or omental patching, or the combined technique using an endoloop and through-the-scope (TTS) clips are recommended. If such treatment is unfeasible or fails, or in the case of clinical deterioration, hospitalization and surgical consultation are recommended. General principles of management also include nil-by-mouth regimen, with intravenous administration of proton pump inhibitors, broad spectrum antibiotics, fluids, and on-demand pain medication.

Esophagus: treatment

Some of the prerequisites or conditions that favor successful general and endoscopic management include: early recognition and treatment (< 24 hours) of the perforation; small size of the defect (< 1 cm for through-the-scope [TTS] clips, < 2 cm for OTSCs); a clean esophagus with little or no passage of its content into the mediastinum; lack of patient co-morbidities, and absence of clinical instability following perforation; treatment by an experienced interventional endoscopist; and management by an experienced multidisciplinary team [9, 16, 47 – 49]. A perforation located in the cervical esophagus has more potential for successful conservative management because of anatomical factors; the fascial planes of the neck reduce the risk of contamination of the mediastinal organs [16, 48]. Generally, if the patient is unstable after perforation then surgery is indicated. If recognition of the perforation is late (> 24 hours) and radiology shows free perforation and/or important fluid collections in the mediastinum/pleural cavity, or if the patient has co-morbidities, then surgery is indicated [9, 48, 50]. Similarly, surgery must be advocated when there is no local endoscopic expertise in advanced therapeutic maneuvers or when there is evidence of leak persistence after previous endoscopic treatment.
The main endoscopic management options for esophageal perforations include closure with clips, and diversion of enteral contents with stents, or endoscopic vacuum therapy (**Table 2**). In a systematic review, TTS clips were reported as a successful method (in all cases) for closing esophageal perforations ranging from 3 to 25 mm (median size 10 mm) [51]. A limitation of TTS clips is their restricted ability to close large defects because of their limited wingspan; moreover TTS clips cannot approximate perforation edges when there is scarring or inflammation in cases of late treatment or previous unsuccessful attempts [52]. Larger esophageal perforations may be treated using the OTSC. In a recent European multicenter cohort study, enrolling 36 consecutive cases of iatrogenic perforation, [2] all of 5 esophageal perforations were successfully closed endoscopically, using a combination of OTSC and TTS clips (n = 3) or OTSCs only (n = 2) to close the defect. Temporary stent placement has also been proposed for the treatment of mid and lower esophageal perforations [53]. **Table 2** summarizes the outcome after treatment, with partially covered self-expandable metal stents (PC-SEMSs), or fully covered self-expandable metal stents (FC-SEMSs), as well as self-expandable plastic stents (SEPSs). In perforations spanning the gastroesophageal junction, the use of PC-SEMS is preferred because of the migration risk of FC-SEMS, particularly in the absence of stricture. Stents are deemed particularly useful for treatment of large esophageal perforations [54, 55], and in cases of malignancy-associated perforation where they also contribute to relief of dysphagia [56].
Vacuum therapy enhances the formation of granulation tissue and healing by secondary intention, by reducing bacterial contamination, secretions, and edema. Endoscopic vacuum therapy is achieved using a sponge attached to the tip of a nasogastric tube that is placed on the site of perforation under endoscopic guidance [57, 58].
Oral intake must be interrupted for an adequate period (i. e., at least 5 days). The patient should be treated with intravenous broad spectrum antibiotics, proton pump inhibitors, and fluid reconstitution. On-demand pain medication should be administered intravenously. Partial diversion of the luminal content may be achieved by insertion of a nasogastric tube, which, when possible, should be placed under endoscopic vision and left with continuous controlled suction [9, 59]. Placement of a nasogastric tube in a patient with a small perforation that has been correctly sealed is not recommended because of the risk of dislodging the clips. Nasogastric tubes have not been used after the placement of self-expandable metal stents (SEMSs) for esophageal fistula sealing [60].
If radiologic investigations show fluid collection and/or the formation of empyema in the mediastinum and/or pleural cavity, percutaneous drainage is indicated.
Mortality after esophageal perforation is high despite any definitive surgical or conservative strategy. Analysis of 75 studies showed a pooled mortality of 11.9% (95% confidence interval [95%CI] 9.7 – 14.3; 75 studies with 2971 patients) with a mean hospital stay of 32.9 days (95%CI 16.9 – 48.9; 28 studies with 1233 patients) [61].

Stomach: treatment

When the perforation is diagnosed during or within 12 hours of endoscopy, endoscopic closure has been associated with good patient outcome. If the perforation is asymptomatic and recognized later than 12 hours, the approach may be conservative. In a recent retrospective series [62], 38 patients with perforations were initially treated nonoperatively. The majority showed neither clinical evidence of peritonitis nor required interventions

Table 2 Efficacy of endoscopic treatment for esophageal iatrogenic perforation.

First author, year	Study design	Type of treatment	Patients, n	Technical success, %	Clinical success, %	Complications, %	Mortality, %
Eroglu, 2009 [78]	Retrospective	SEMS	4	100	n.a.	0	0
Freeman, 2009 [79]	Prospective	SEPS	19	100	89	24	0
Salminen, 2009 [80]	Retrospective	SEMS	8	100	75	25	37.5
Amrani, 2009 [81]	Prospective	SEMS	2	100	100	0	0
Leers, 2009 [82]	Prospective	SEMS	9	100	n.a.	n.a.	< 6
Kiernan, 2010 [83]	Retrospective	SEMS	8	100	75	n.a.	12
Vallböhmer, 2010 [59]	Retrospective	SEMS	12	100	n.a.	8	0
Van Heel, 2010 [55]	Prospective	SEMS/SEPS	31	100	97	33	21
Schimdt, 2010 [84]	Retrospective	SEMS + endoclip	21 + 1	100	n.a.	n.a.	< 13.3
Swinnen, 2011 [85]	Retrospective	SEMS	23	100	n.a.	n.a.	n.a.
Làzàr, 2011 [86]	Retrospective	Endoclip	1	100	100	0	0
Dai, 2011 [87]	Prospective	SEPS	5	n.a.	83	n.a.	n.a.
D'Cunha, 2011 [88]	Retrospective	SEMS/SEPS	15	95	60	13	6.7
Baron, 2012 [71]	Retrospective	Novel OTSC	1	100	100	0	0
Lin, 2014 [89]	Retrospective	Mesh-covered stents	9	100	n.a.	4	55.6
Biancari, 2013 [90]	Retrospective	Unspecified stents + endoclips	11 + 1	100	n.a.	25	46
Wilson, 2013 [91]	Retrospective	SEMS	7	100	n.a.	n.a.	n.a.
Wahed, 2013 [92]	Retrospective	Unspecified stent	2	100	0	n.a.	100
Voermans, 2012 [2]	Prospective, multicenter	OTSC	5	100	100	0	0
Schweigert, 2013 [93]	Retrospective	SEMS/SEPS	13	100	15	85	15
Sato, 2013 [94]	Retrospective	Endoclip	1	100	100	0	0
Heits, 2014 [95]	Prospective	Vacuum therapy	10	100	90	20	10
Hadj, 2012 [96]	Retrospective	OTSC + SEMS	1	100	100	0	0
Biancari, 2014 [97]	Retrospective	SEMS/endoclips	67	100	15	34	19.4

n.a., not available; OTSC, over-the-scope clip; SEMS, self-expandable metal stent; SEPS, self-expandable plastic stent

beyond conservative management and only 18 % required surgery. The only factors associated with failure of nonoperative treatment were free fluid or contrast extravasation seen on CT scan (75 % vs. 23 %, $P < .005$, and 33 % vs. 0 %, $P = .047$], respectively). The morbidity in operated patients after initial nonoperative management was equivalent to that observed in patients who underwent initial operative management (63 % vs. 61 %; P value not significant); however mortality was greater in those who underwent operative management after failed endoscopic treatment than in those who underwent initial operative management (43 % vs 21 %, $P = 0.09$).

In the case of late recognition of perforation, conservative management may be attempted after a CT scan evaluation that confirms the absence of peritoneal effusion and with close monitoring for signs of sepsis. Late recognition of gastric perforations with septic symptoms is generally associated with peritonitis due to leak of intra-abdominal fluid. These patients generally require surgical management (**Fig. 1**).

Endoscopic treatment for small gastric defects (< 10 mm)

In the case of perforations smaller than 10 mm (the opening width of TTS clips) with a linear shape, endoscopic clipping is an acceptable method and should be attempted [63]. Sometimes, the clip placement may be difficult because of the location of the perforation. In such cases, the recently described band ligation technique [64] can be an interesting alternative. In the literature there are only a few papers on acute endoscopic iatrogenic perforations of the stomach, with to date a total of 145 patients having been treated with endoclips [65]. In detail, eight studies on acute iatrogenic perforations after EMR or ESD procedures have been reported and TTS clips were used in all these studies. Pooling these studies, the overall success rate using TTS clips was > 99 % (**Table 3**).

Endoscopic treatment for large gastric defects (> 10 mm)

TTS clips alone are not recommended for perforations > 10 mm. In the case of perforations measuring 10 – 30 mm, the OTSC system has been the most evaluated technique and it has demonstrated its efficacy in clinical studies for the management of postoperative leaks or fistulas [66 – 69]. Regarding acute gastric perforations, four relevant papers have highlighted the efficacy of OTSC (**Table 4**) [2, 70 – 72] with a total success rate of more than 95 % (22 patients). All of these experimental and clinical studies recommend OTSCs for the management of gastric defects between 10 and 30 mm in diameter, with or without the use of grasping devices to place them. However, perforations > 20 mm are challenging to manage endoscopically, requiring experience and the availability of surgery in case of failure. If the OTSC technique is unavailable, the combined technique using TTS clips plus endoloop can be recommended [73 – 75]. When the omentum is visible through the defect, the omental patch technique may be recommended [63, 76], especially if the defect is very large (**Table 5**). The use of the new suturing devices must be restricted to expert centers and/or the setting of clinical trials.

Finally, the nonsurgical treatment of gastric perforations may include the use of removable fully covered self-expandable metal stents (FC-SEMSs) or self-expandable plastic stents (SEPSs); these stents are indicated for perforations caused by dilation of a gas-

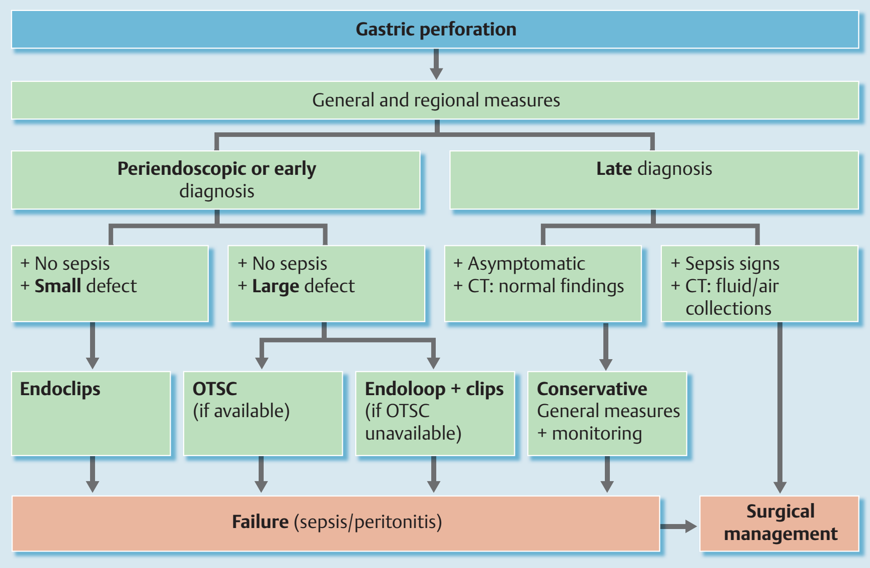

Fig. 1 Algorithm for the management of gastric iatrogenic perforations. CT, computed tomography; OTSC, over-the-scope clip.

Table 3 Results of endoscopic management of gastric perforation with through-the-scope (TTS) clips.

First author, year	Type	n	Pathologies	Technique	Success rate	Others
Binmoeller, 1993 [98]	Case report	1	Leiomyoma	TTS clipping	100 %	–
Albuquerque, 2004 [99]	Case report	1	Adenoma	TTS clipping	100 %	–
Katsinelos, 2004 [100]	Case report	1	Adenoma (HGD)	TTS clipping	100 %	–
De Caro, 2009 [101]	Case report	1	Adenocarcinoma in situ	TTS clipping	100 %	–
Kim, 2000 [102]	Case report	1	Adenocarcinoma in situ	TTS clipping	100 %	–
Tsunada, 2003 [76]	Retrospective, case series	7	Early gastric cancer	TTS clipping (6) Omental patch (1)	100 %	1 large defect
Fujishiro, 2006 [18]	Retrospective, case series	11	Early gastric cancer	TTS clipping	100 %	Mean discharge time 12.1 days
Minami, 2006 [63]	Retrospective	121	Early gastric cancer	– < 1 cm: TTS clipping – > 1 cm: omental patch	98.3 %	2 surgeries
Total	–	144		–	> 99 %	For defects < 10 mm

HGD, high grade dysplasia

Table 4 Results of endoscopic management of gastric perforation with over-the-scope clips (OTSCs).

First author, year	Type	n	Perforation cause	OTSCs, n	Success rate	Size
Baron, 2012 [71]	Retrospective	2	Iatrogenic	2	100 %	–
Kirschniak, 2011 [70]	Retrospective	7	Iatrogenic (1 ESD)	7	100 %	–
Voermans, 2012 [2]	Prospective	6	Iatrogenic: ESD, EMR, EUS	6	100 %	< 30 mm
Nishiyama, 2013 [72]	Retrospective	7	Iatrogenic: ESD, scope/ulcer	13	86 % (6/7)	Mean diameter 30 mm 1 failure, 50 mm
Total		22	Iatrogenic	28	95 %	For 10-mm to 30-mm defects

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound.

Table 5 Results of endoscopic management of gastric perforation with omental patch, band ligation, or the combined technique using endoclips plus endoloop

First author, year	Type	n	Perforation cause	Method	Success rate	Size
Minami, 2006 [63]	Retrospective	121	Iatrogenic perforations (ESD/EMR)	Omental patch	98.3 %	> 10 mm
Tsunada, 2003 [76]	Case report	1	After EMR procedure	Omental patch	100 %	Large perforation
Han, 2013 [64]	Case series	5	After ESD (3), EMR (1), biopsy (1)	Band ligation	100 %	5 to 11 mm
Shi, 2013 [103]	Retrospective	20	Full-thickness resections of tumors	Endoloop + endoclips	100 %	Median size 15 mm (0.4 – 30)
Zhong, 2012 [104]	Retrospective	14	Full-thickness resections of tumors	Endoloop + endoclips	100 %	0.6 to 30 mm

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection

troenteric anastomosis, or dilation of an antral stricture, or related to cystogastrostomy [77].

The nonsurgical treatment of gastric perforations should include placement of a nasogastric tube under endoscopic control. It should be connected to suction for 1 day after the treatment of the perforation [63].

Perivaterian (periampullary) and biliopancreatic ductal perforation

High risk procedures: ERCP-related perforations

The most common causes of perforations related to endoscopic retrograde cholangiopancreatography (ERCP) are sphincterotomy (56 %) and guidewire manipulation (23 %). ESGE suggests that precut, Billroth II gastrectomy, and biliary stricture dilation should be considered to entail increased risk for biliopancreatic perforation.

In a review of studies that reported on ERCP-related complications of any type in a total of 16 855 patients, amongst whom 50 % – 100 % had undergone a therapeutic procedure depending on individual studies, perforation was reported in 101 patients (0.6 %, 95 % confidence interval [CI] 0.48 – 0.72) with a perforation-related mortality of 9.90 % (95 % [CI] 3.96 – 15.84) [105]. Other studies listed in **Table 6** reported ERCP-related perforations in any location and in the periampullary area/biliopancreatic ducts in 0.43 % (95 %CI 0.37 – 0.59) and 0.33 % (95 %CI 0.28 – 0.48), respectively, of 115 747 patients.

The causes of perforation were endoscopic sphincterotomy, guidewire manipulation, stricture dilation, and stent insertion or migration in 56 %, 23 %, 4 %, and 3 % of cases, respectively; perforations were located in the periampullary area, the bile ducts and the pancreatic ducts in 65 %, 25 %, and 1.4 % of cases, respectively (**Table 7**).

Independent risk factors for ERCP-related perforations include precut, Billroth II gastrectomy, intramural injection of contrast medium, procedure duration, sphincter of Oddi dysfunction, a dilated common bile duct, and biliary stricture, as identified in two studies [106, 107].

ESGE recommends that ERCP-related perforations be described according to the classification by Stapfer et al.: type I, lateral or medial wall duodenal perforation; type II, perivaterian injuries; type III, distal bile duct injuries; type IV retroperitoneal air alone [108].

Treatment: ERCP-related perforations

The majority of ERCP-related ductal or periampullary duodenal perforations can be managed nonsurgically. The indications for surgery are a major contrast medium leak, severe sepsis despite nonsurgical management, severe peritonitis, and fluid collections or unsolved problems (e.g., retained hardware) that cannot be

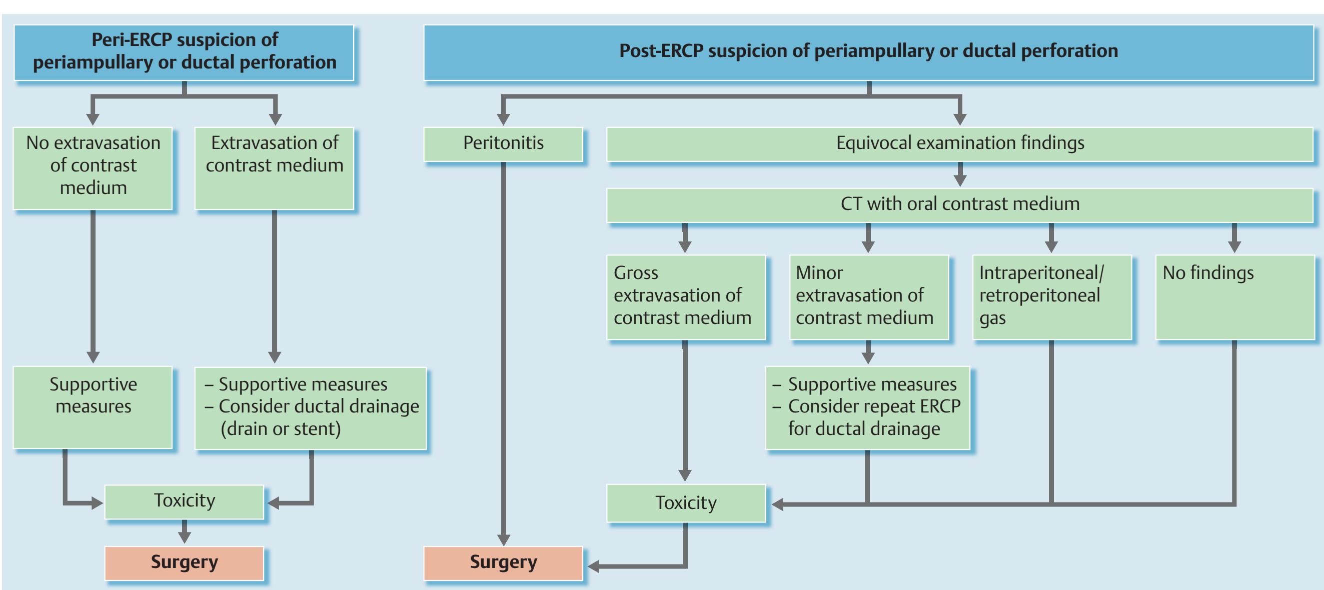

Fig. 2 Algorithm for the management of iatrogenic perforations (types II, III, IV, according to Stapfer et al. [108]) related to endoscopic retrograde cholangiopancreatography (ERCP).

Table 6 Incidence of perforations related to endoscopic retrograde cholangiopancreatography (ERCP), and requirement for surgery.

First author, year	Study design	n	Perforation		Type II, III, IV[1]		Surgery required in types II, III, IV, n
			n	%	n	%	
Assalia, 2007 [120]	Prospective	3 104	22	0.70	20	0.64	1
Avgerinos, 2009 [121]	Retrospective	4 358	15	0.34	6	0.13	5
Dubecz, 2012[122]	Retrospective	12 232	11	0.08	4	0.03	1
Enns, 2002 [106]	Retrospective	9 314	33	0.35	28	0.30	3
Fatima, 2007 [28]	Retrospective	12 427	75	0.60	67	0.53	15
Howard, 1999 [110]	Retrospective	6 040	40	0.66	36	0.59	1
Kayhan, 2004 [115]	Retrospective	3 124	17	0.54	15	0.48	4
Kim, 2011 [123]	Retrospective	7 638	13	0.17	9	0.11	4
Kim, 2012 [124]	Retrospective	11 048	68	0.61	55	0.49	Not reported
Knudson, 2008 [116]	Retrospective	4 919	32	0.65	26	0.52	8
Kwon, 2012 [125]	Retrospective	8 381	53	0.63	32	0.38	1
Mao, 2008 [126]	Retrospective	2 432	9	0.37	9	0.37	3
Morgan, 2009 [127]	Retrospective	12 817	24	0.18	12	0.09	0
Polydorou, 2011 [12]	Retrospective	9 880	44	0.44	37	0.37	6
Stapfer, 2000 [108]	Retrospective	1 413	14	0.99	9	0.63	4
Wu, 2006 [128]	Retrospective	6 620	30	0.45	25	0.37	7
Total		115 747	500	0.43	390	0.33	63 (18.8 %)[2]

[1] According to Stapfer's classification [108] (type I, lateral or medial wall duodenal perforation; type II, perivaterian injuries; type III, distal bile duct injuries, type IV retroperitoneal air alone).
[2] Percentage was calculated after exclusion of the results reported by Kim et al. [124].

Table 7 Assumed etiology of 405 type II, III, IV[1] perforations related to endoscopic retrograde cholangiopancreatography (ERCP).

First author, year	Endoscopic sphincterotomy, n	Guidewire, n	Dilation of strictures, n	Other instruments, n	Stent insertion or migration, n	Unknown, n
Alfieri, 2013 [112]	15	1	–	–	–	8
Assalia, 2007 [120]	17	2	–	–	1	–
Avgerinos, 2009 [121]	3	–	–	3	–	–
Dubecz, 2012 [122]	3	1	–	–	–	–
Enns, 2002 [106]	13	13	2	–	–	–
Fatima, 2007 [28]	11	24	5	9	7	11
Howard, 1999 [110]	22	14	–	–	–	–
Kayhan, 2004 [115]	15	–	–	–	–	–
Kim, 2011 [123]	3	4	–	2	–	–
Kim, 2012 [124]	25	23	–	2	–	–
Knudson, 2009 [116]	11	–	–	–	3	8
Kwon, 2012 [125]	24	2	6			–
Mao, 2008 [126]	9	–	–	–	–	–
Morgan, 2009 [127]	12	–	–	–	–	–
Polydorou, 2011 [12]	30	2	2	3	–	–
Stapfer, 2000 [108]	6	3	–	–	–	–
Wu, 2006 [128]	11	7	–	–	–	7
Total	230 (56 %)	96 (23 %)	15 (3.7 %)	19 (4.6 %)	11 (2.7 %)	34 (8 %)

[1] According to Stapfer's classification (type I, lateral or medial wall duodenal perforation; type II, perivaterian injuries; type III, distal bile duct injuries, type IV retroperitoneal air alone) [108]

solved by nonsurgical means. After careful patient selection, nonsurgical management is successful in more than 90 % of patients.
An algorithm (**Fig. 2**) summarizes ESGE's recommendations on how to select the most individually appropriate management of ductal or periampullary duodenal ERCP-related perforation. In patients initially managed nonsurgically following ductal or periampullary ERCP-related perforation, the morbidity and mortality rates were 7 % and 3 %, respectively; surgery was eventually required in approximately 6 % of cases. These figures were calculated for the 220 patients included in seven studies (**Table 8**). No significant difference was found between patients with type II vs. type III perforation, after initial nonsurgical management, in terms of final requirement for surgery, morbidity, or mortality.

A recent review of duodenal, periampullary, and ductal ERCP-related perforations found that nonsurgical management, applied in 62 % of patients, was successful in 92.9 % of those patients [109]. In 335 patients with ductal or periampullary perforation and final outcome detailed in **Table 6**, surgery was required in 19 % of the cases.
Early diagnosis and prompt treatment are vital for a better outcome [110, 111]. The choice between surgical vs. nonsurgical management should be guided by the site and degree of the leak and by the patient's condition [106, 109, 111 – 114]. Suspected ductal and periampullary perforations should be assessed by an early contrast medium study, during ERCP or using CT scan, and documentation should be retained for medicolegal purposes.

Table 8 Outcome after initial nonsurgical management of type II, III, IV[1] perforations related to endoscopic retrograde cholangiopancreatography (ERCP) in selected series.

First author, year	Type II					Type III					Type IV				
	n	Standard treatment[2]	Surgery[3], n (%)	Morbidity, n (%)	Mortality, n (%)	n	Standard treatment[2]	Surgery[3], n (%)	Morbidity, n (%)	Mortality, n (%)	n	Standard treatment[2]	Surgery[3], n (%)	Morbidity, n (%)	Mortality, n (%)
Assalia, 2007 [120]	20	Antibiotics Nasogastric/nasoduodenal aspiration	2 (10)	0	1 (5)	2	Antibiotics Nasogastric/nasoduodenal aspiration	0	0	0	1	Antibiotics Nasogastric/nasoduodenal aspiration	0	0	0
Enns, 2002 [106]	13	Antibiotics Nil-by-mouth regimen	2 (16)	0	0	14	Antibiotics Nil-by-mouth regimen	1 (7)	2 (14)	0	1	Antibiotics Nil-by-mouth regimen	0	0	0
Fatima, 2007 [28]	15	Antibiotics Nasogastric/nasoduodenal aspiration Percutaneous/endoscopic biliopancreatic drainage[2]	0	0	1 (7)	32	Antibiotics Nasogastric/nasoduodenal aspiration Percutaneous/endoscopic biliopancreatic drainage[2]	0	0	2 (6)	6	Antibiotics Nil-by-mouth regimen	0	0	0
Howard, 1999 [110]	22	Antibiotics Nasogastric/nasoduodenal aspiration Biliary stent or nasobiliary drainage	3 (14)	3 (14)	1 (5)	14	Antibiotics Nasogastric/nasoduodenal aspiration Biliary stent or nasobiliary drainage	0	3 (21)	0	0	–	–	–	–
Kwon, 2012 [125]	24	Antibiotics Total parenteral nutrition	0	5 (21)	1 (4)	8	Antibiotics Total parenteral nutrition	1 (13)	1 (13)	0	0	–	–	–	–
Morgan, 2009 [127]	12	Antibiotics Nasogastric/nasoduodenal aspiration	0	1 (8)	0	0	–	–	–	–	0	–	–	–	–
Polydorou, 2011 [12]	29	Antibiotics Total parenteral nutrition	5 (17)	1 (3)	0	5	Antibiotics Nasogastric/nasoduodenal aspiration	0	2 (40)	0	2	Antibiotics Nasogastric/nasoduodenal aspiration	0	0	0
Total	135		12 (9)	10 (7)	4 (3)	75	–	2 (3)	6 (8)	2 (3)	10		0	0	0

[1] According to Stapfer's classification [108]; figures were extracted for each type of perforation as accurately as possible from published data.
[2] Where appropriate
[3] Surgery describes operations performed to treat the perforation itself and/or its complications, not the primary disease for which ERCP was performed.

Major periampullary or ductal contrast medium leaks are usually recognized as an indication for immediate surgery [109, 111].

For the nonsurgical management of ERCP-related ductal or periampullary duodenal perforation, ESGE recommends antibiotics and nasogastric or nasoduodenal aspiration in all patients; stenting of the perforated duct (or of the biliary duct in the case of periampullary perforation) on a case-by-case basis; and total parenteral nutrition in undernourished patients as well as in patients in whom adequate enteral feeding is presumed not to be feasible for ≥ 7 days. Cross-sectional imaging should be performed during follow-up and, if a liquid collection is disclosed, percutaneous drainage should be considered. The efficacy of TTS clips in closing periampullary perforations is unknown.

Modalities available for the nonsurgical management of ERCP-related ductal or periampullary duodenal perforation include:

- Antibiotics and nasogastric or nasoduodenal aspiration, used in most case series.
- Stenting, consistently used by some authors to divert fluids from the perforation site, [110, 112] but on a case-by-case basis by others (e.g., in 12 [48 %] of 25 patients treated nonoperatively by Enns et al.), with no significantly different results [106]. Another concern about stenting is the impact of abandoning scheduled ERCP tasks because of recognition of perforation during the ERCP procedure. Following ERCP-related perforation, a significant proportion of patients may refuse ERCP and prefer surgery although repeat ERCP has been reported to succeed in treating the primary biliopancreatic disease in up to 100 % of patients [106, 115].
- Total parenteral nutrition, mentioned in a single study [12], is recommended in European guidelines for postoperative parenteral nutrition if complications impede adequate enteral feeding for at least 7 days and in undernourished patients [27]. Using mean duration of hospital stay as a proxy for the fasting period following ERCP-related perforation, we conclude that total parenteral nutrition is required in a minority only of well-nourished patients who are successfully treated nonoperatively.
- Abdominal fluid collections are commonly drained percutaneously in the first place; this was performed in 13 (6 %) of the 209 patients listed in **Table 8** with wide variations between studies (0 to 20 %). Endosonography-guided transenteric stenting has been proposed as an alternative for draining bilomas [113].
- TTS clips have been used by some authors in an attempt to close perforations, but in the absence of controlled trials the true efficacy of this measure is unknown [28, 112, 116].
- Somatostatin has not been tested in patients with a peri-ERCP pancreatic duct perforation. It improves closure of postoperative enterocutaneous fistulas compared with placebo [117 – 119].

Duodenal and small bowel perforation

High risk procedures: duodenum and small bowel

ESGE suggests that altered anatomy, stricture dilation in Crohn's disease, dilation of gastrojejunal stricture after gastric bypass, endoscopic submucosal dissection (ESD) and, in patients with altered anatomy, double-balloon enteroscopy (DBE) are risk factors for duodenal and small-bowel perforation.

Duodenum: high risk procedures

In a retrospective case series of 72 iatrogenic perforations following esophagogastroduodenoscopy (EGD), the incidence of perforation was 0.033 % (25 were in the duodenum, for an incidence of 0.01 %) [62].

Perforations of the lateral or medial wall of the duodenum caused by the endoscope itself (type I in Stapfer's classification) are usually large and carry a high mortality (28 % in the study by Merchea et al.) [62, 108]. The main risk factor for this type of perforation is Billroth II gastrectomy [124].

Among therapeutic procedures, ESD has a particularly high risk of perforation, with a perforation rate of 35.7 % reported in a retrospective study of 14 patients [129]. Delayed perforation after ESD is more frequent in the duodenum (14 %) than after gastric (0.45 %) and colorectal ESD (0.3 % – 0.7 %) [130 – 132]. The high incidence of delayed perforations may be due to the thinness of the duodenal wall, coupled with proteinolysis or chemical irritation by pancreatic enzymes and bile juice. However, endoscopic mucosal resection (EMR) seems to be safe in the duodenum. No case of perforation was reported in two studies evaluating 47 cases in total [133, 134].

Small bowel: high risk procedures

DBE-related perforations in the small bowel are rare. In a German prospective study of 2245 DBE examinations, only 3 perforations were observed (incidence 0.1 %), with 2 of these occurring after polypectomy (1.5 % of 137 polypectomies) [135]. A large retrospective study of DBE complications in nine US centers showed a iatrogenic perforation rate of 0.4 % with a significantly higher incidence of iatrogenic perforations in patients with altered surgical anatomy (3 %) [136]. In the last 5 years there have been three case reports describing capsule endoscopy in patients with Crohn's disease leading to retention and perforation [137 – 139]. One perforation is reported in a small prospective case series (n = 13) of DBE with stricture dilation in Crohn's disease [140]. Dilation of gastrojejunal anastomotic strictures after gastric bypass surgery carries an iatrogenic perforation rate of between 0 and 4.5 % [141].

Treatment: duodenum and small bowel

In type I (i. e. nonperivaterian) duodenal perforations, ESGE recommends endoscopic treatment if the iatrogenic perforation is recognized immediately and, in the case of failure of endoscopic treatment, immediate surgery. If the duodenal perforation is diagnosed later (> 12 h), management should be surgical in the case of contrast medium extravasation or of persistent large fluid collection at CT scan, or if the patient's condition deteriorates. If the patient is in good condition without extravasation of contrast medium or persistent large fluid collection seen at CT, the patient should be treated conservatively without intervention.

For iatrogenic perforations in the small bowel, ESGE recommends surgical treatment although some iatrogenic perforations caused by dilation of stricture at a gastrojejunal anastomosis (GJA) may be treated conservatively.

Duodenum: treatment

In the case of immediate recognition of perforation, an endoscopic closure should be attempted. This is effective in a minority of cases only (17 [22 %] of 76 cases listed in **Table 9**). In the 76 cases listed in **Table 9** endoscopic closure was possible in 18

Table 9 Reports of treatments of duodenal iatrogenic perforation (type I) since September 2008[1]

First author, year	n	Procedure	Endoscopic closure, n (system used)	Surgery, n	Conservative, n	Standard treatment	Mortality, n (%)
Avgerinos, 2009 [121]	9	ERCP		9	–	–	0
Palanivelu, 2008 [144]	1	ERCP		1	–	Broad spectrum antibiotics + Nil-by-mouth regimen + Nasoduodenal aspiration + Parenteral nutrition	0
Ahlawat, 2009 [145]	1	EUS	1 (endoclips)	–	–	Broad spectrum antibiotics + Nil-by-mouth regimen	0
Honda, 2009 [146]	2	ESD	1 (endoclips)	1 (delayed perforation)	–	–	0
Nakagawa, 2010 [147]	1	ERCP	1 (endoclip + endo-loops)	–	–	Broad spectrum antibiotics + Nil-by-mouth regimen + Parenteral nutrition + Proton pump inhibitor	0
Farhat, 2011 [148]	1	ESD	1 (endoclips)	–	–	–	0
Lee, 2010 [149]	4	ERCP	4 (endoclips)	–	–	Broad spectrum antibiotics + Parenteral nutrition + Proton pump inhibitor	0
Polydorou, 2011 [12]	7	ERCP	–	6	1	–	2 (29)
Ercan, 2012 [150]	17	ERCP	–	17		Broad spectrum antibiotics + Nil-by-mouth regimen + Nasoduodenal aspiration	8 (47)
Kim, 2012 [124]	9	ERCP	–	8	1	Broad spectrum antibiotics	Not reported
Fanning, 2012 [151]	1	ERA	1 (endoclips)			Broad spectrum antibiotics	0
Samarasena, 2012 [152]	1	ERA	1 (endoclips, endo-loop, and fibrin glue)	–	–	Broad spectrum antibiotics + Nil-by-mouth regimen + Nasoduodenal aspiration	0
Hadj Amor, 2012 [96]	1	EMR	(OTSC, endoclips, and stent)	–	–	–	0
Gubler, 2012 [153]	2	ERA	2 (OTSC)		–	Broad spectrum antibiotics + Nil-by-mouth regimen	0
Matsumoto, 2013 [154]	3	ESD	–	2	1	–	0
Rabie, 2013 [155]	10	ECRP	–	3	7	–	1 (10)
Nishiyama, 2013 [72]	1	ESD	1 (OTSC)	–	–	–	–
Jung, 2013 [129]	5	ESD	3 (endoclips)	2	–	Nasoduodenal aspiration	–
Summary	76		17	49	10	–	11 (16)

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; ESD, endoscopic submucosal dissection; ERA, endoscopic resection of adenomas; EMR, endoscopic mucosal resection; OTSC; over-the-scope clip.
[1] Several reports fail to inform about standard treatment and the management of the perforation.

(24 %) cases and it was successful in 17 (clinical success rate after successful endoscopic closure of duodenal perforation, 94.4 %). In the 17 cases with successful endoscopic closure, 11 perforations with a maximum diameter of 13 mm were successfully treated with TTS clips, 2 perforations of 10 mm and 30 mm were treated with a combination of TTS clips and endoloops, and 4 perforations with a maximum diameter of 28 mm were treated with an OTSC. The dimensions of the lesion are rather unclear in the articles but in most cases the number indicates the maximum lesion size. Immediate endoscopic closure is believed to be technically easier compared with a delayed attempt because the perforation margins are soft, not yet being involved by inflammation [72]. A successful therapeutic ERCP following treatment with an OTSC for acute duodenal perforation that occurred during diagnostic endoscopic ultrasonography (EUS) has been reported [142].

If the iatrogenic perforation is diagnosed several hours after the endoscopy and the patient shows symptoms of generalized peritonitis and/or sepsis, the only option is surgery. Avgerinos et al. found in a retrospective review of 15 cases of duodenal iatrogenic perforations that mortality dramatically increases with late (> 24 h) surgical management [121]. These authors described a clinicoradiographic test to choose between a surgical or a conservative treatment for ERCP-related duodenal iatrogenic perforation. If an abdominal radiograph showed free intraperitoneal air, an abdominal CT scan with oral water-soluble contrast was carried out. Extravasation of contrast in the intra-abdominal cavity or the presence of extradigestive fluid indicated surgical exploration, whereas nonsurgical treatment was possible in the absence of these factors (**Fig. 3**) [121].

Small bowel: treatment

Table 10 summarizes the case reports on treatments of small-bowel iatrogenic perforations published since September 2008. Out of 32 patients with small-bowel iatrogenic perforations, 19 underwent surgery, 5 patients were treated conservatively, 1 laceration was closed with an OTSC and in 7 cases the management was not reported. All of the 5 patients who were treated conservatively had iatrogenic perforations following endoscopic dilation of a GJA.

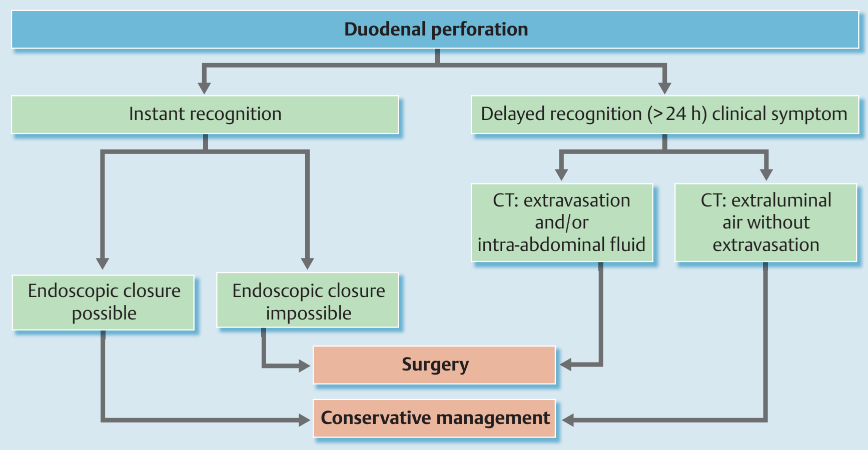

Fig. 3 Algorithm for the management of duodenal iatrogenic perforations (type I). CT, computed tomography.

Table 10 Reports of treatments of small-bowel perforation since September 2008.

First author, year	n	Procedure	Endoscopic closure, n (system used)	Surgery, n	Conservative, n	Standard treatment[1]	Mortality (%)
Um, 2008 [139]	1	Capsule endoscopy	–	1	–	–	0
Gerson, 2009 [136]	10	DBE	–	10	–	–	1 (10)
Despott, 2009 [140]	1	DBE	–	1	–	–	0
Teruel, 2009 [156]	1	Colonoscopy	–	1	–	–	0
Möschler, 2011[1] [135]	3	DBE	–	–	–	–	0
Campos, 2012[1] [157]	14	Dilation of GJA	–	5	5	Broad spectrum antibiotics + Nil-by-mouth regimen	0
Yitzhak, 2012 [138]	1	Capsule endoscopy	–	1	–	–	0
Balmadrid, 2013 [143]	1	SBE–PEJ	OTSC	–	–	Broad spectrum antibiotics	0
Summary	32		1	19	5	–	1 (3)

DBE, double-balloon enteroscopy; GJA, gastrojejunal anastomosis; SBE-PEJ, single balloon enteroscopy-percutaneous endoscopic jejunostomy
[1] No description of the management of all perforations.

Until recently surgery has been the only choice for management and only one case report, as mentioned above, describes an endoscopic closure, using the OTSC system, of a small-bowel laceration near the ligament of Treitz [143].
Surgery should still be the first choice in the management of small-bowel iatrogenic perforations.

Colorectal perforations

High risk procedures in the colorectum

ESGE recommends that complex EMR, ESD, and balloon dilation procedures should be considered to carry increased risk of colorectal perforation.
Older age, co-morbidity, inflammatory colonic disease, use of hot biopsy forceps, and endoscopist inexperience are other significant risk factors for iatrogenic perforations at colonoscopy.
Risk factors include female gender, presumably related to pelvic adhesions, major co-morbidities and greater age (weakened colonic wall tissues) [13, 158 – 160]. Risk may also be increased during surveillance colonoscopy in patients with colitis such as inflammatory bowel disease [161]; however, the colonoscopic surveillance for long-standing extensive ulcerative colitis has proved to be safe with no significant complications when biopsies are obtained with caution [162].

The sigmoid colon and the rectosigmoid junction are the most common sites of diagnostic perforation due to direct mechanical injury via shearing forces applied by the shaft or tip of the colonoscope during endoscope insertion [14, 163]. Pericolic adhesions (from previous gynecological surgery or abdominal inflammation) and severe diverticular disease may increase the risk of perforation, particularly when large-caliber instruments and excessive force are used [164]. Traumatic antimesenteric tears of the colonic wall are less common elsewhere but can occur at the flexures because of excessive tip force or in the rectum during retroflexion [165]. Cecal perforation can also occur because of barotrauma, particularly if gas is introduced above an area of stenosis [166]; barotrauma is probably less likely when carbon dioxide is used, compared with air, as the former is absorbed more quickly.
Iatrogenic perforation has been reported in 0.03 % – 0.8 % of diagnostic colonoscopies and flexible sigmoidoscopies in both the symptomatic and screening settings [167 – 169].
Therapeutic colonoscopy carries a small but significant risk of perforation (up to 5 %), particularly following advanced polypectomy. However, high risk procedures such as endoscopic balloon dilation, applied to treat ileocolonic anastomotic strictures as in Crohn's disease, may entail perforation rates up to 11 % [170]. Regarding the use of SEMSs in the setting of acute malignant colonic obstruction, retrospective studies demonstrate a perforation rate

of 5%–9% [171,172]. The British Society of Gastroenterology (BSG) audit of colonoscopy demonstrated that the risk of perforation at diagnostic examinations was 1:923 compared with 1:460 following polypectomy [173]. The Munich Polypectomy Study reports a risk of 1.1% for colorectal perforation when polyps were larger than 10mm in the right colon or 20mm in left colon or when there were multiple polyps [174]. Equivalent results were reported by a French national survey, reporting a perforation rate of 3.6% after EMR polypectomy in the lower gastrointestinal tract [175].

For piecemeal EMR of polyps larger than 20mm, two experienced centers reported acceptably low perforation rates of 1.3% and 0.003% [176,177]. Conversely, the perforation rate for colorectal ESD is higher but varies depending on the experience of the operator. Predictive risk factors for iatrogenic perforations during colorectal ESD such as submucosal fibrosis and tumor size should be also considered because they may complicate ESD, being associated with a higher perforation incidence of 20.4% [178]. Early Japanese experience with ESD showed a perforation risk of 5%–10%, although current literature demonstrates a lower perforation risk ranging from 1.9% to 4.7% [179, 180]. An early multicenter report of colorectal ESD from France reported a high perforation rate (18.1%) [148]; but more recently other centers have described more acceptable perforation rates of 2%–12%, in line with the early experience from Japan [181].

In the past, hot biopsy forceps have been applied to destroy small polyps but recent animal studies demonstrate a potential hazard for deep thermal injury with transmural necrosis found in a high proportion of cases [182]. Anecdotal reports of delayed hemorrhage and perforation following hot biopsy have led many centers to abandon the use of this technique particularly in the right colon.

The risk of iatrogenic perforation appears to be operator-dependent; non-gastroenterologist endoscopists and endoscopists who perform only a low number of cases being associated with an increased risk of iatrogenic perforation [1,159].

Investigations such as abdominal plain film radiography or CT scan are commonly performed in the case of clinically suspected or diagnosed perforation to verify the presence of air or fluid collections or injected contrast material. Abdominal CT is the most sensitive examination for detecting gas or liquid leaks [183]; water-soluble contrast enema per rectum is seldom used to detect concealed perforation.

Treatment in the colorectum

ESGE recommends the use of TTS endoclips for small holes and OTSCs for larger ones. Adequate colon preparation is an important factor when contemplating endoscopic treatment of iatrogenic perforations. All patients treated conservatively should be watched closely by a multidisciplinary team in the immediate post-procedure period. Immediate surgical repair is required in the case of larger perforations or where endoscopic closure has failed or where the patient's clinical condition is deteriorating.

Air or gas entry into the peritoneal cavity is a hallmark of iatrogenic perforation but does not necessarily cause infective peritonitis unless egress of luminal contents occurs. The recognition of colorectal wall tears may be immediate at the time of the procedure or can be delayed for up to 3 days [184,185].

A conservative strategy is possible when a perforation site is recognized early, enabling an urgent closure without the spillage of gut contents. Rapid endoscopic intervention with clip placement and the use of carbon dioxide may limit the volume of extraluminal insufflation and subsequently the need for surgery [186, 187]. When there is no evidence of intraperitoneal contamination by fecal contents, free air may either resolve spontaneously within a week or progress to a compartment syndrome [188]. In this case, a tension pneumoperitoneum develops requiring an immediate release of trapped intraperitoneal air. However, if fecal contents are present, then the optimal management is surgery.

The decision to attempt endoscopic closure of an iatrogenic perforation depends on multiple factors, including the size and the cause of iatrogenic perforation, the endoscopist's experience and the accessories available at the time. With immediate endo-

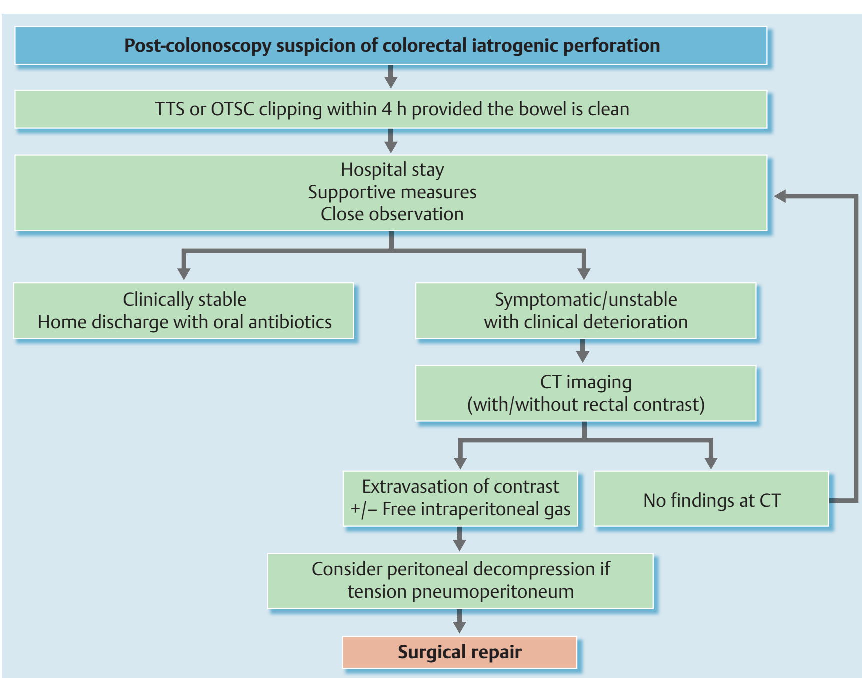

Fig. 4 Algorithm for the management of colonic iatrogenic perforations. TTS, through-the-scope; OTSC, over-the-scope clip; CT, computed tomography.

scopic closure of the defect, superficial apposition of the mucosa and submucosal layers seems sufficient to obtain adequate wound healing at the perforation site and to achieve a good non-surgical outcome [189].

Early endoscopic closure of an iatrogenic perforation smaller than 20 mm, using either TTS clips or OTSC, is likely to be effective, with overall technical and clinical success rates of 93 % and 89 % respectively [2, 190, 191]. Electrocautery injury may induce colorectal perforations which are amenable to both TTS clip and OTSC clipping, in particular during ESD where there is a high risk of microperforation [68, 178]. It has been reported that TTS clipping is more effective for closure of therapeutic perforations that are less than 10 mm than for diagnostic perforations where defects are blunter and larger in size [192, 193]. Recent systematic reviews based mainly on case series, report that the OTSC technique is also a safe, easy to handle, and efficacious method for treating both diagnostic and therapeutic colorectal perforations [194, 195]. Band ligation has been reported as a salvage therapy after failed clipping [196].

An early endoscopic sign, during the post-polypectomy examination of the resected polyp, is the "target sign" showing full-thickness muscle tissue surrounded by submucosa [26]. In this case, an iatrogenic perforation is strongly suspected and immediate endoscopic clipping is indicated. Occasionally, a perforation is diagnosed post-procedurally and if preparation is still adequate (within 4 hours after the procedure) endoscopic therapy may also be considered (**Fig. 4**).

Concomitant administration of intravenous fluids, broad spectrum antibiotics and close monitoring of vital signs are always recommended in each suspected or diagnosed colorectal perforation, to prevent clinical deterioration. Empirical medical treatment should possibly be undertaken promptly, prior to confirmation of perforation by appropriate radiological means.

A clear indication for surgery is a complicated or failed endoscopic closure with an ongoing leak that is causing feculent peritonitis [197]. Minimally invasive laparoscopic treatment of perforations has become the preferred surgical option and is now widely accepted and practiced [198]. Preliminary data have demonstrated that the laparoscopic approach resulted in decreased morbidity and length of hospital stay as well as reduced abdominal wall scarring [199].

Conclusions

Despite the lack of high quality studies, there is substantial evidence, particularly in the colorectum, that a few simple risk factors may be used to stratify the risk of iatrogenic perforation for each organ, allowing anticipation of higher probability of iatrogenic perforation. Moreover, there is compelling evidence that endoscopic treatment by means of clipping or stenting is effective in the management of iatrogenic perforations, especially for small breaches. Additionally, the wide implementation of CT allows early diagnosis of iatrogenic perforations in subtle cases, preventing harmful delays in conservative or surgical management. All these factors support the implementation of proactive policies to minimize the morbidity and mortality related to iatrogenic perforation. There is an urgent need for high quality studies to clarify the efficacy and safety of the proposed policies. The main issues to be addressed are reported in **Table 11**.

Table 11 Main issues for research

– What is the long-term morbidity of iatrogenic perforations successfully treated with clips?
– What is the necessity of carbon dioxide use during ESD?
– What is the feasibility of combined techniques (endoclips + endoloop) in closing large defects?
– What training is required for inserting OTSCs in the case of iatrogenic perforations?

ESD, endoscopic submucosal dissection; OTSC, over-the-scope clip

ESGE guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations. ESGE guidelines are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

Competing interests: None

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