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Thieme

Endoscopic management of gastrointestinal motility disorders – part 1: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

ESGE

Authors

Bas L. A. M. Weusten[1,2], Maximilien Barret[3], Albert J. Bredenoord[4], Pietro Familiari[5], Jan-Michel Gonzalez[6], Jeanin E. van Hooft[4], Sauid Ishaq[7], Vicente Lorenzo-Zúñiga[8], Hubert Louis[9], Suzanne van Meer[1,2], Helmut Neumann[10], Daniel Pohl[11], Frederic Prat[3], Daniel von Renteln[12], Edoardo Savarino[13], Rami Sweis[14], Jan Tack[15], Radu Tutuian[16], Jan Martinek[17]

Institutions

1 Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht University, The Netherlands
2 Department of Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, The Netherlands
3 Department of Gastroenterology and Digestive Oncology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris and University of Paris, Paris, France
4 Department of Gastroenterology, Amsterdam University Medical Centers, University of Amsterdam, The Netherlands
5 Digestive Endoscopy Unit, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
6 Department of Gastroenterology, Hôpital Nord, Marseille, France
7 Department of Gastroenterology, Dudley Group NHS Foundation Trust and Birmingham City University, Birmingham, UK
8 Endoscopy Unit, University Hospital La Fe, Valencia, Spain
9 Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
10 Department of Medicine I, University Medical Center Mainz, Mainz, Germany
11 Department of Gastroenterology, University Hospital Zurich, Zurich, Switzerland
12 Division of Gastroenterology, Montréal University Hospital (CHUM), Montréal, Canada
13 Department of Surgery, Oncology and Gastroenterology, DiSCOG, University of Padua, Padua, Italy
14 Department of Gastroenterology, University College London Hospital, London, UK
15 Department of Gastroenterology, University Hospitals Leuven, Leuven, Belgium
16 Department of Gastroenterology, University Clinic for Visceral Surgery and Medicine, Bern University Hospital, Bern, Switzerland
17 Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Corresponding author

Bas L.A.M. Weusten, MD, PhD, Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Internal mail no F02.618, P.O. Box 85500, 3508 GA UTRECHT, The Netherlands
b.l.a.weusten@umcutrecht.nl

Appendix 1s – 3s
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MAIN RECOMMENDATIONS

ESGE recommends the use of a graded pneumatic dilation protocol in achalasia, starting with a 30-mm dilation and followed by a 35-mm dilation at a planned interval of 2–4 weeks, with a subsequent 40-mm dilation when there is insufficient relief, over both a single balloon dilation procedure or the use of a larger balloon from the outset.
Strong recommendation, high quality of evidence, level of agreement 100%.

ESGE recommends being cautious in treating spastic motility disorders other than achalasia with peroral endoscopic myotomy (POEM).
Strong recommendation, very low quality of evidence, level of agreement 87.5%.

ESGE recommends against the routine use of botulinum toxin injections to treat patients with non-achalasia hypercontractile esophageal motility disorders (Jackhammer esophagus, distal esophageal spasm). However, if, in individual patients, endoscopic injection of botulinum toxin is chosen, ESGE recommends performing injections into four quadrants of the lower esophageal sphincter and in the lower third of the esophagus.
Strong recommendation, low quality of evidence, level of agreement 78.6%.

ESGE recommends that endoscopic pylorus-directed therapy should be considered only in patients with symptoms suggestive of gastroparesis in combination with objective proof of delayed gastric emptying using a validated test, and only when medical therapy has failed.
Strong recommendation, very low quality of evidence, level of agreement 100%.

ESGE recommends against the use of botulinum toxin injection in the treatment of unselected patients with gastroparesis.
Strong recommendation, high quality of evidence, level of agreement 92.9%.

ESGE recommends consideration of gastric peroral endoscopic myotomy (G-POEM) in carefully selected patients only, because it is an emerging procedure with limited data on effectiveness, safety, and durability. G-POEM should be performed in expert centers only, preferably in the context of a clinical trial.
Strong recommendation, low quality of evidence, level of agreement 100%.

SOURCE AND SCOPE
This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It provides guidance on the endoscopic management of achalasia and gastroparesis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

1 Introduction

Therapeutic gastrointestinal (GI) endoscopy is rapidly evolving. Its role in the management of motility disorders of the digestive tract is increasing. The purpose of this guideline is to provide guidance on various aspects of the endoscopic management of GI motility disorders. This first of two parts of the guideline is dedicated to achalasia and gastroparesis. The second part of this guideline will be published separately and focuses on Zenker's diverticulum, gastroesophageal reflux disease (GERD), intractable constipation, and Ogilvie's syndrome.

2 Methodology

The ESGE commissioned this Guideline (Guideline Committee chair, J.v.H.) and appointed a Guideline leader (B.W.), who identified six clinical conditions of abnormal GI motility in which therapeutic endoscopy is one of the treatment possibilities: Zenker's diverticulum, achalasia, GERD, gastroparesis, intractable constipation, and Ogilvie's syndrome. These six areas were at a later stage agreed on by the Guideline committee members.

In March 2018, an email was sent out to several key opinion leaders in the field of therapeutic endoscopy to identify potential Guideline committee members. Individual ESGE members were informed about this Guideline and were asked to apply if they were interested in participating with this Guideline. Three individual members (V.L.-Z., H.L., and F.P.) were selected based

ABBREVIATIONS

CRP	C-reactive protein
CT	computed tomography
EGJ	esophagogastric junction
ESGE	European Society of Gastrointestinal Endoscopy
ESNM	European Society of Neurogastroenterology and Motility
GERD	gastroesophageal reflux disease
GCSI	gastroparesis cardinal symptom index
GI	gastrointestinal
G-POEM	gastric peroral endoscopic myotomy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IRP	integrated lower esophageal sphincter relaxation pressure
IT-knife	Insulated Tip knife
LES	lower esophageal sphincter
LHM	laparoscopic Heller myotomy
OTSC	over-the-scope clip
POEM	peroral endoscopic myotomy
PPI	proton pump inhibitor
RCT	randomized controlled trial
SEMS	self-expandable metal stent
TT-knife	Triangle Tip knife
UEG	United European Gastroenterology

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on their expertise and scientific output. In addition, the European Society of Neurogastroenterology and Motility (ESNM) was approached for collaboration and scientific input. As a result, the ESNM appointed on request four Guideline committee members who were regarded as experts in the field of GI motility and therapy (D.P., E.S., J.T., and R.T.). Finally, a Guideline committee was formed comprising of 18 members, and covering the six areas of this guideline. Six task forces were created, based on the six clinical conditions. Each task force had one or two task force leaders, and each group member was assigned to one or more task forces (**Appendix 1s**, see online-only Supplementary Material). The kick-off meeting for this Guideline was held during United European Gastroenterology (UEG) Week, on 21 October 2018, in Vienna.

During a teleconference in November 2018, clinical questions were formulated for the six clinical conditions. Subsequently, these clinical questions were translated into research questions (**Appendix 2s**). The questions followed the PICO format (P, population in question; I, intervention; C, comparator; and O, outcomes of interest) wherever appropriate. Subsequently, systematic literature searches were done using MEDLINE, Embase, and the Cochrane library.

Evidence levels and recommendation strengths were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [1]. Further details on the methodology of ESGE guidelines have been reported elsewhere [2]. The results of data extraction are presented in **Appendix 3s**.

Available literature, draft recommendations, and strength of evidence were discussed during a face-to-face meeting with all group members at Schiphol Airport, Amsterdam on 12 April 2019.

In order to establish consensus-based recommendations, a modified Delphi process [3] was organized using an online voting platform (www.surveymonkey.com). Voting was based upon a five-point Likert scale (1, strongly disagree; 2, disagree; 3, neither disagree nor agree; 4, agree; 5, strongly agree). A recommendation was approved if >75% of the members agreed (reflected by a Likert score of 4–5). In total, three iterations of the online voting process were needed to reach the final document.

In January 2020, a draft prepared by B.W. was sent to all group members. After the agreement of all group members had been obtained, the manuscript was reviewed by the ESGE Guideline Committee Chair (J.v.H.) and two external reviewers, and was sent for further comments to the ESGE national societies and individual members. After this, it was submitted to *Endoscopy* for publication.

3 Achalasia and other primary esophageal motility disorders

Idiopathic achalasia is a rare disease and affects individuals of both sexes and all ages. The annual incidence is estimated to be between 1.07 and 2.2 cases per 100 000 individuals, with prevalence rates estimated between 10 and 15.7 per 100 000 individuals [4, 5]. Achalasia is a primary esophageal motility dis-

order characterized by insufficient relaxation of the lower esophageal sphincter (LES) in combination with absent peristalsis, which leads to symptoms of dysphagia, regurgitation, chest pain, or weight loss [6]. Besides achalasia, other primary esophageal motility disorders, such as absent contractility, distal esophageal spasm, and hypercontractile (Jackhammer) esophagus, are also recognized [7].

Parallel to the development of the current ESGE guideline, an achalasia-specific guideline was written by a joint UEG and ESNM endeavor [8]. Before this, it was agreed that general research questions regarding types of treatment for achalasia would be covered by the UEG/ESNM guideline and that the ESGE guideline would focus on the technical aspects, as far as the endoscopic treatment was concerned, and that statements would be cross-referenced when appropriate. ▶ **Table 1** summarizes the relevant recommendations of the UEG/ESNM guideline. For supportive evidence, please refer to the original paper [8]. The current ESGE guideline should be considered as complementary to the UEG/ESNM guideline.

3.1 Peroral endoscopic myotomy (POEM)

Peroral endoscopic myotomy (POEM) as a treatment modality for achalasia was first described in humans by Inoue et al. [9]. In short, after creating a mucosal entry, the endoscope is advanced through the submucosal space. Subsequently, a myotomy of the muscle layer of the esophagus including the LES is carried out, which is protected by the overlying intact mucosa. On completion, the mucosal entry is closed.

3.1.1 Use of CO_2

> **RECOMMENDATION**
> ESGE recommends performing POEM using low-flow CO_2 insufflation.
> Strong recommendation, low quality of evidence, level of agreement 100%.

CO_2 insufflation was used for POEM in the vast majority of published series [9–12]. CO_2 is reabsorbed more quickly than room air, and its use reduces the risk of gas-related complications, including pneumoperitoneum, pneumomediastinum, pneumothorax, abdominal compartment syndrome, and subcutaneous emphysema.

In a large retrospective cohort study of complications after POEM, a very high incidence of major gas-related complications (27.8%) was reported, especially during the first year when insufflation of room air was used during POEM [13]. The major complication rate declined to 1.9% after the introduction of CO_2 insufflation and seemed to plateau after 3.5 years at around 1%.

Gas-related adverse events may also occur with CO_2. When deterioration in circulatory and/or respiratory function is observed during POEM, the procedure should be temporarily stopped. When a high-pressure (tension) pneumoperitoneum occurs as a result of excessive CO_2 insufflation through the sub-

► **Table 1** Summary of relevant recommendations on achalasia from the European Guideline on Achalasia by UEG and ESMN [8].

Recommendations	Strength	Certainty of evidence
We recommend that, in the treatment of achalasia, symptom relief should be regarded as the primary treatment aim	Expert opinion	
We recommend that improvement of objectively measured esophageal emptying should be regarded as an important additional treatment aim	Expert opinion	
Botulinum toxin therapy can be considered an effective and safe therapy for short-term symptom relief in esophageal achalasia	Conditional recommendation	Moderate
Graded pneumatic dilatation is an effective and relatively safe treatment for esophageal achalasia	Strong recommendation	Strong
Peroral endoscopic myotomy is an effective and relatively safe treatment for esophageal achalasia	Conditional recommendation	Moderate
Laparoscopic Heller myotomy (LHM) combined with an antireflux procedure is an effective and relatively safe therapy for achalasia	Conditional recommendation	Moderate
We suggest age and manometric subtype be taken into account when selecting a therapeutic strategy	Conditional recommendation	Moderate
Treatment decisions in achalasia should be made based on patient-specific characteristics, the patient's preference, possible side effects and/or complications, and a center's expertise. Overall, graded repetitive pneumatic dilation, LHM, and POEM have comparable efficacy	Strong recommendation	Moderate
Botulinum toxin therapy should be reserved for patients who are too unfit for more invasive treatments, or in whom a more definite treatment needs to be deferred	Conditional recommendation	Moderate
We suggest treating recurrent or persistent dysphagia after LHM with pneumatic dilation, POEM, or redo surgery	Conditional recommendation	Very low
We suggest treating recurrent or persistent dysphagia after POEM with either re-POEM, LHM, or pneumatic dilation	Conditional recommendation	Very low
We recommend follow-up endoscopy to screen for GERD in patients treated with myotomy without an antireflux procedure If reflux symptoms occur in the absence of reflux esophagitis, TBE, empiric PPI therapy, and/or 24-hour esophageal pH-(impedance) monitoring can be considered PPIs are the first-line treatment of GERD after achalasia treatment. We recommend lifelong PPI therapy in patients with esophagitis > grade A	Expert opinion	

LHM, laparoscopic Heller myotomy; POEM, peroral endoscopic myotomy; GERD, gastroesophageal reflux disease; TBE, timed barium esophagogram; PPI, proton pump inhibitor.

mucosal tunnel, an abdominal puncture with a needle is a simple but effective solution to decompress the abdomen and release the tension. The use of "low flow" or "very low flow" CO_2 insufflation decreases the incidence of tension pneumoperitoneum, compared with the use of "mid flow" or "high flow" inflation [11].

3.1.2 Perioperative use of antibiotics

RECOMMENDATION
ESGE recommends the prophylactic perioperative use of antibiotics when performing POEM. The choice and duration of antibiotics should be adapted according to national or local protocols.
Strong recommendation, very low quality of evidence, level of agreement 100%.

Perioperative antibiotics are recommended during "clean-contaminated" surgery [14]. Because POEM can be analogized to clean-contaminated supra-mesocolic digestive surgery, current guidelines for antibiotic prophylaxis during clean-contaminated surgery should apply. A first- or second-generation cephalosporin aimed at meticillin-sensitive *Staphylococcus aureus*, *Escherichia coli*, and enterobacteriae is a standard recommendation for this type of surgery, but adaptations can be implemented along national guidelines or as discussed with local infection control teams depending on local bacteriological ecology. A single-dose injected intravenously between 1 hour before and the induction of anesthesia is generally considered appropriate, with the assumption that the intervention duration generally does not exceed 2 hours [15].

With regard to antibiotics during POEM, only three randomized studies including very small patient samples have been published, none of them as a full paper. One study showed no benefit of perioperative antibiotics over preoperative antibiotics only, but found a significant inflammatory response and probable microbial translocation in both groups, therefore sup-

porting the need for antibiotic prophylaxis [16]. Another study found a reduced need for postoperative antibiotics in the group receiving preoperative antibiotic prophylaxis, although no difference existed in the number of documented infections [17]. The last study found no additional clinical benefit from preoperative antibiotics over postoperative antibiotics alone for the prevention of infection after POEM [18].

3.1.3 Location of submucosal tunnel

> **RECOMMENDATION**
> ESGE recommends that POEM can be performed on either the anterior (12–3 o'clock in supine position) or posterior (5–7 o'clock) side.
> Strong recommendation, high quality of evidence, level of agreement 100%.

In contrast to laparoscopic Heller myotomy (LHM), POEM may be performed on any side of the esophagus. Anterior myotomy (also lesser curvature myotomy, 12–3 o'clock in the supine position) was the first approach implemented. This approach is considered to preserve the posterior sling fibers alongside the angle of His. In 2013, anterior myotomy was the preferred approach among the majority of centers performing POEM [19]. Posterior myotomy (5–7 o'clock in the supine position) was introduced later, and several centers adopted this approach as standard because of some theoretical advantages, such as the easier myotomy owing to the perpendicular axis of the knife towards the circular muscle fibers.

A total of four studies (only two published as full papers) have compared these two approaches in terms of efficacy, safety, and post-POEM reflux. In the first randomized study, there were no significant differences between anterior and posterior POEM with regard to efficacy and overall safety, the occurrence of mucosal injuries was higher in the anterior myotomy group and acid exposure was higher with the posterior myotomy approach [20]. Tan et al. found no significant differences between patients with anterior vs. posterior POEM in terms of treatment success, physiological parameters, such as integrated LES relaxation pressure (IRP), and post-POEM reflux [21]. Both studies included small numbers of patients and may have been underpowered to detect real differences between the two approaches. Moreover, the follow-up was short (less than 2 years). In a recent single-blind randomized trial comprising 150 patients, no differences were found in efficacy, safety, and post-procedural reflux between the anterior and the posterior approach [22]. A recent systematic review concluded that anterior and posterior myotomy are equally effective, without significant differences in post-procedural GERD [23].

One study demonstrated that POEM on the side of the greater curvature is also feasible and effective [24]. Therefore, if required (fibrosis, previous POEM and/or LHM, or diverticula), POEM may be performed on the side of the greater curvature; however, no comparative data exist for greater curvature POEM vs. anterior or posterior POEM.

There are no comparative data on the preferred myotomy side in patients undergoing POEM after failed LHM or in patients undergoing redo-POEM. The tunneling and myotomy should avoid the site of the previous laparoscopic myotomy because of scarring and fibrosis and should therefore be done on the posterior side (5–7 o'clock) or on the side of the lesser curvature (2–3 o'clock) [25–29].

Redo-POEM (POEM after failed POEM) is normally (and logically) undertaken on the opposite side to the index procedure in order to avoid submucosal fibrosis. Thus, in patients who had an anterior POEM, redo-POEM should be performed on the posterior side, and vice versa. Therefore, a report should always mention at which site POEM was performed. There are no comparative data examining the outcomes of anterior vs. posterior procedures in patients undergoing redo-POEM. An international multicenter retrospective study reported the short-term (3 months) clinical success of redo-POEM to be 85% [30].

3.1.4 Distal extension of myotomy

> **RECOMMENDATION**
> ESGE recommends in POEM extending the length of the myotomy 2–3 cm into the gastric side of the cardia.
> Strong recommendation, low quality of evidence, level of agreement 100%.

In the vast majority of open-label series of POEM and in all randomized controlled trials (RCTs), a 2–3-cm extension of the myotomy into the cardia has been described [31–33]. This practice was initially undertaken to replicate the extension of the myotomy into the cardia during the laparoscopic and open Heller myotomy procedures, although the supportive evidence for this practice during surgery was also weak. Per-procedural distensibility data with Endoflip show that further extension beyond 2–3 cm does not increase distensibility further, thereby suggesting that a 2-cm extension is sufficient [34]. It has been proposed that limiting the myotomy to 2 cm into the cardia might lead to less reflux, but the evidence for this is weak and indirect [35]. All published POEM outcome data, including efficacy, complications, and reflux risk, are based on implementing a myotomy extension of 2–3 cm into the cardia, so this technique is now considered to be the standard reference method.

3.1.5 Circular versus full myotomy

There are three retrospective cohorts comparing full-thickness myotomy with myotomy targeting only the circular muscle layers [36–38]. The efficacy with regards to subjective and objective measures seems similar; however, it has been suggested that full myotomy is associated with shorter procedure times and circular myotomy potentially with lower reflux rates. Because direct comparisons from prospective studies with appropriate methodology are lacking, full myotomy is the most used and described technique, and most clinical trials have used full myotomy, it is considered the current reference technique.

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3.1.6 Closure of tunnel entry

In most series and trials, the mucosal entry is closed with simple clips, but other techniques such as a multi-firing clip device, endoscopic suturing, and the over-the-scope clip (OTSC) device (Ovesco, Tübingen, Germany) have been described. Closure of the mucosal entry seldom results in complications such as re-opening and it therefore seems unlikely that a comparative trial on complications following closure as an end point will ever be performed.

There are two comparative studies on closure techniques, but no randomizations were performed, both had small sample sizes, and there is a suspicion of considerable bias [39, 40]. Neither study found a difference between single clips vs. multi-firing clips or single clips vs. endoscopic suturing. A retrospective description of two cases in which closure of the mucosal entry was not possible with standard clips described the successful use of the OTSC device for this purpose [41]. Owing to the lack of evidence on efficacy and safety, no recommendation is made on this aspect of management.

3.1.7 Antibiotic lavage of the tunnel

> **RECOMMENDATION**
> ESGE does not recommend lavage of the submucosal tunnel with antibiotics.
> Strong recommendation, low quality of evidence, level of agreement 93.8 %.

Lavage of the submucosal tunnel has been performed in several centers in order to decrease the risk of infectious complications; however, a negligible risk of infectious adverse events has consistently been reported across centers that both do and do not perform lavage. As such, lavage is not universal, and in fact several centers have changed their practice because infectious complications are exceedingly rare. The only study addressing this issue is a single-center retrospective analysis, which demonstrated no difference in terms of infectious complications between patients who did and did not undergo gentamicin lavage [42]. Although patients who had lavage had a lower post-POEM serum C-reactive protein (CRP) level and lower white blood cell count, the differences were not clinically relevant.

3.1.8 Knives and electrosurgical settings

Any needle-knife can be used for POEM; the decision should be made according to the preference and experience of the endoscopist. It is unlikely that the type of needle-knife used will affect the safety profile or efficacy of the procedure.

Inoue's original technique involved the use of the Triangle Tip knife (TT-knife; KD-640 L, Olympus) for mucosal incision, submucosal dissection, and myotomy [9]. In the vast majority of published series, the TT-knife was the device of choice.

The group of Zhou and colleagues from Shanghai first described the use of the T-type HybridKnife (ERBE, Tübingen, Germany) for POEM [43]. Indeed, the HybridKnife is now widely used in many centers, even if published series are lacking. In addition, the HookKnife (KD-620LR, Olympus) is also used by several centers.

Two studies have compared the TT-knife and HybridKnife [43, 44]. An RCT by Cai et al. on 100 patients and a case–control study by Tang et al. on 67 patients found that the HybridKnife was associated with a significantly shorter procedure time and fewer minor procedural bleeding episodes compared with the TT-knife. In both studies, complication rates, success rates, and efficacies were comparable.

Recently, a new TT-knife equipped with injection facilities was introduced into clinical practice (the TT-knife J; KD-645 L, Olympus). A study by Nabi et al. retrospectively compared the traditional TT-knife with the new TT-knife J in 193 patients [45]. No difference was observed in technical success. The procedural time was significantly shorter in the TT-knife J group as compared with the TT-knife group. Significantly fewer uses of coagulation forceps and exchanges of accessories were required in the TT-knife J group.

The settings for the electrosurgical generator vary between the different brands and models, as well as between the assortment of devices and needle-knives. Therefore, the specific electrosurgical generator settings should be manufacturer and knife specific. In the published studies, the vast majority of authors used an ERBE (Tübingen, Germany) electrosurgical generator, the most commonly used being the VIO300 D. For the mucosal incision, the preferred settings were "Dry cut mode, 50 W, effect 3," "Endocut Q mode, effect 2," or "Endocut I mode, effect 2." For the submucosal dissection and myotomy, when a TT-knife was used, the preferred setting was "Spray coagulation mode, 50 W, effect 2"; when a HybridKnife was used, the preferred settings were "Spray coagulation mode, 50 W, effect 2," "Swift coagulation mode, 35 – 50 W, effect 3 – 5," "Endocut Q, effect 2." "Soft coagulation mode, 80 W, effect 5" was most often used for hemostasis with coagulation forceps.

3.1.9 Postoperative care

With regard to the postoperative care of patients after POEM, no specific recommendations can be deduced from the analysis of the current literature. However, after the procedure, patients should be carefully monitored in order to recognize possible complications. Chest and abdominal pain are common during the first 24 hours after POEM, but usually respond promptly to mild analgesic therapy (i.e. paracetamol 1000 mg intravenously, 3 – 4 times a day). Mild opioids (i.e. tramadol 100 mg) can be used if the first-line analgesic therapy fails, although intravenous or subcutaneous morphine may also be required for a short period.

A chest radiograph or a computed tomography (CT) scan should be considered only in the context of a suspected perforation or pleural effusion, or to exclude other more serious complications. In some preliminary studies, a CT scan was routinely performed after POEM, revealing a high prevalence of pneumoperitoneum, pneumomediastinum, or pneumothorax [9, 13,46,47]. However, the vast majority of such events are asymptomatic and require no interventions. Furthermore, there is no significant correlation between the occurrence of

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pneumomediastinum and/or pneumoperitoneum on CT scan and the development of severe complications, including delayed hemorrhage, esophageal perforation, and retroperitoneal abscess [48]. The use of a post-procedure CT scan in asymptomatic patients should therefore be avoided.

As a routine, a Gastrografin or barium esophagram was performed the day after POEM in several studies to confirm the mucosal integrity before oral feeding. Other authors preferred an endoscopy on the day after POEM to rule out mucosal complications, including ulceration, hematoma, dehiscence, or ischemia, before the resumption of oral feeding [10 – 12]. However, major or significant complications and adverse events are rare and, if they do occur, they are rarely asymptomatic, while minor mucosal injuries do not tend to alter the postoperative course [49]. Therefore, the routine use of a Gastrografin or barium esophagram or an endoscopy after POEM is maybe an excessive prophylactic measure and of debatable value.

No studies have compared or analyzed the optimal dietary regimen after POEM. Nevertheless, it seems reasonable to keep the patients fasting for at least 24 hours after the procedure to prevent the early dislodgment of the clips used to close the mucosal incision and to avoid complications. Patients should be fed with liquids only on the day after the procedure, and with a soft diet for the following 1 – 2 weeks. In two series, patients developed major complications related to non-adherence to the recommended dietary restrictions within the immediate (1 – 2 days) following POEM [13, 49].

Finally, double-dose proton pump inhibitors (PPIs) are usually prescribed for 2 – 4 weeks after POEM to facilitate the healing of the traumatized mucosa and to prevent symptoms of gastroesophageal reflux [10 – 12, 47, 50]. Thereafter, gastroesophageal reflux should be treated, usually with long-term PPIs, in all patients with typical reflux symptoms and/or reflux esophagitis grade B or higher.

3.1.10 POEM for spastic esophageal motility disorders other than achalasia

> **RECOMMENDATION**
> ESGE recommends being cautious in treating spastic motility disorders other than achalasia with POEM.
> Strong recommendation, very low quality of evidence, level of agreement 87.5 %.

There are no comparative studies that address the treatment of spastic and hypercontractile disorders with POEM or alternative therapies. Also, owing to the nature of the intervention (POEM), none of the published series can incorporate blinding, with considerable bias therefore being inevitable. All of the reports present small series of cases with unknown or short-term follow-up [51 – 69]. A subset of these series reports only subjective results, some using non-validated questionnaires. It is uncertain if safety can be assessed using the literature, as considerable publication bias is suspected.

Two RCTs compared endoscopic botulinum toxin injections in the esophagus with sham injections. The first study showed some effect of botulinum toxin on symptoms over and above that of the sham injection, but a second study showed no more effect for botulinum toxin than for the sham injection, with a benign natural history reported in both cohorts [70, 71]. It thus seems questionable whether an invasive treatment such as POEM is justified in patients with spastic motility disorders, given this benign natural history and lack of evidence on efficacy and safety from methodologically sound studies. In exceptional cases, however, for instance in patients with persisting severe dysphagia with profound manometric abnormalities combined with weight loss, POEM might be appropriate given the lack of effectiveness of the other (medical) therapeutic options available.

3.2 Botulinum toxin injection
3.2.1 Technicality and dosing

> **RECOMMENDATION**
> ESGE recommends that botulinum toxin injection should be performed using 100 units* of the toxin diluted in preservative-free saline that is injected in aliquots of 0.5 – 1 mL using an injection needle in forward view just above the squamocolumnar junction in at least four quadrants. Strong recommendation, high quality of evidence, level of agreement 100 %.

The standard approach is to inject 100 units* of the toxin, usually diluted in preservative-free saline and injected in aliquots of 0.5 – 1 mL, using an injection needle just above the squamocolumnar junction in at least four quadrants [72]. An alternative approach, with similar safety, involves the injection of botulinum toxin aliquots of 0.5 mL into four quadrants of the LES with the endoscope in a retroflexed position and then into each quadrant from direct vision [73].

Although the initial (1 month) response rate is high (> 75 %), the therapeutic effect of repeated treatments substantially reduces over time and about half of patients required further injections at intervals of 6 – 24 months [73 – 80]. Moreover, there is some evidence that multiple treatments with botulinum toxin injection can induce an inflammatory and subsequently fibrotic reaction, which in turn might compromise the efficacy of subsequent surgical or endoscopic treatment [80 – 86]. In contrast, recent retrospective studies suggest that prior botulinum toxin treatment does not influence the results of POEM [27, 87]. Serious side effects are uncommon, although there is a 16 % – 25 % rate of developing chest pain and rare complications, such as mediastinitis and allergic reactions related to egg protein.

In a multicenter randomized trial, injection of 50, 100, and 200 units of botulinum toxin did not result in different short-

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* Dosing based on Botox. Other brands might require an adjusted dosing as the units are not equivalent between the brands.

term responses when assessing symptoms or LES pressure 1 month after injection [77]. However, performing two injections of 100 units 1 month apart led to the best long-term clinical response, with 68 % of patients being in clinical remission after 2 years. In addition, in a systematic review, a dose of 100 units of botulinum toxin was used most frequently [88]. Therefore, we recommend using a dose of 100 units of botulinum toxin, as there appears to be no benefit from injecting higher doses.

3.2.2 Botulinum toxin in type III achalasia

> **RECOMMENDATION**
> ESGE does not suggest the routine injection of botulinum toxin in the esophageal body, in addition to injection in the LES, for patients with type III achalasia.
> Weak recommendation, very low quality of evidence, level of agreement 78.6 %.

In type III achalasia, botulinum toxin is the treatment modality with by far the worst outcomes (overall 21 %) according to the most recent meta-analysis published by Andolfi and colleagues [89]. Indeed, different retrospective studies evaluating the role of botulinum injection in type III achalasia observed a success rate ranging from 0 to 73 % [90 – 93]. In particular, Marjoux and co-workers found that clinical response was similar whether botulinum toxin was injected in the LES alone (n = 6), in the distal esophagus alone (n = 5), or at both locations (n = 5) [93]. However, the numbers from such studies are small and might not be representative.

3.2.3 Botulinum toxin in spastic esophageal motility

> **RECOMMENDATION**
> ESGE recommends against the routine use of botulinum toxin injections to treat patients with non-achalasia hypercontractile esophageal motility disorders (Jackhammer esophagus, distal esophageal spasm). However, if, in individual patients, endoscopic injection of botulinum toxin is chosen, ESGE recommends performing injections into four quadrants of the LES and in the lower third of the esophagus.
> Strong recommendation, low quality of evidence, level of agreement 78.6 %.

Most studies on the use of botulinum toxin in esophageal motility disorders other than achalasia are retrospective in nature and describe a 33 % – 72 % clinical response rate [93 – 95]. In a recent sham-controlled trial, however, manometric improvement occurred at 3 months in about 6/10 patients in the sham group, therefore suggesting there is an unpredictable disease course in hypercontractile esophageal motility disorders [70].

Two RCTs involving botulinum toxin for hypercontractile esophageal motility disorders have been performed. Vanuytsel et al. found a significant clinical and manometric improvement following injection of 100 units of botulinum toxin at 2 and 7 cm above the LES in a population of patients with dysphagia [71]. The more recent RCT by Mion et al. mentioned previously found a similar 30 % clinical improvement in both the treated and sham groups with chest pain being the predominant symptom [70].

Hence, the evidence supporting the use of botulinum toxin injection as a treatment for non-achalasia esophageal motility disorders is inconsistent. However, if botulinum toxin is used for this indication, dysphagia is probably the target symptom and there are data to advocate injection into the distal esophagus in conjunction with botulinum toxin injection into the LES [71, 96].

3.3 Balloon dilation
3.3.1 Technical aspects

Dilation is a frequently used treatment option for symptomatic patients with achalasia. In the vast majority of published series, an air-filled balloon is used (pneumatic dilation) [76, 97 – 106]. A relatively low pressure is usually required for the gentle, safe, and gradual dilation of the LES. There are no data to suggest that the use of water- or contrast-filled balloons can offer more reliable, safe, or effective dilations [107].

Published dilation protocols vary substantially in terms of balloon pressure targets, stepwise insufflation, and duration of inflation [108]. Commonly, balloons are initially inflated with a low pressure (e. g. 3 psi) across the esophagogastric junction (EGJ). When a waist is seen, the balloon is further inflated until a pressure of 6 – 12 psi is reached or until the waist at the midpoint of the balloon is effaced. Studies have also described variable minimum duration inflation times, ranging between 6 and 180 seconds [108]. An RCT, using 30-mm balloons, compared two dilation protocols: 60 seconds at 10 psi vs. 6 seconds at 10 psi [105]. No differences with regard to outcome and perforation rate were observed between the two groups. In the European Achalasia Trial, balloons were dilated at 5 psi for 1 minute and then again at 8 psi for an additional minute [99]. A recent systematic review and meta-analysis confirms that inflation time and pressure do not seem to influence the treatment efficacy or perforation risk [108].

In view of the lack of clarity in the literature, we suggest slowly inflating balloons at least until the disappearance of the waist on fluoroscopy, but that the maximum nominal pressure should not be exceeded.

The accurate positioning of the pneumatic device across the EGJ is essential and should be carefully reaffirmed during the procedure because, during inflation, the balloon can easily migrate above or below the junction, making the procedure inefficacious and risking unnecessary trauma. The achalasia balloons have radiopaque markers to control their positioning during fluoroscopy. Under fluoroscopic guidance, accurate positioning of the dilator during the inflation can also be assured by observing the temporary appearance of a waist in the balloon that corresponds to the position of the EGJ. In

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some series, however, dilation was performed under direct endoscopic vision rather than under fluoroscopic guidance [109, 110]; the endoscope is passed alongside the pneumatic balloon catheter to ensure its accurate positioning. These non-randomized studies report results that are similar to fluoroscopic-guided pneumatic dilation techniques. However, in line with the recent RCTs and the largest case series and comparative trials, and to ensure adequate effacement of the waist, we recommend that the fluoroscopic technique should be the preferred method.

3.3.2 Dilation protocol

> **RECOMMENDATION**
> ESGE recommends the use of a graded pneumatic dilation protocol in achalasia, starting with a 30-mm dilation and followed by a 35-mm dilation at a planned interval of 2 – 4 weeks, with a subsequent 40-mm dilation when there is insufficient relief, over both a single balloon dilation procedure or the use of a larger balloon from the outset.
> Strong recommendation, high quality of evidence, level of agreement 100 %.

Comparative and cohort trials have shown repeatedly that a single dilation leads to an improved symptom profile and that progressing to a larger diameter balloon can salvage many of the patients who have persistent or recurrent symptoms [106, 111 – 114]. It became apparent that, the bigger the balloon, the better the outcome [115, 116]. On the other hand, the use of bigger balloons, particularly during the initial dilation, is associated with higher perforation rates. In an RCT, Boeckxstaens et al. found that, when dilations began at 35 mm, the perforation rate was as high as 31 % (4 of the first 13 patients) but, when the initial diameter was reduced to 30 mm, followed a few weeks later by the next level diameter, the perforation rate dropped to 4 % overall (4/95 patients) [117]. In the subsequent follow-up study of the same cohort at 5 years, the perforation rate was defined as 2 % per procedure [118]. A very recent meta-analysis, evaluating 10 high quality studies including 643 patients, showed that perforations occurred most often during initial dilations and significantly more often using a 35-mm balloon than using a 30-mm balloon (3.2 % vs. 1.0 %) [108]. A subsequent 35-mm dilation was safer than an initial dilation to 35 mm (0.97 % vs. 9.3 % perforations). We therefore recommend always starting with an initial 30-mm dilation in a previously untreated patient.

In a comparative trial, Vela et al. showed that at 6 months and 6 years after therapy, when compared with surgery, outcomes following a single dilation were clearly inferior. On the other hand, with graded dilation, whereby the procedure was repeated with a bigger diameter balloon at a planned subsequent interval, symptomatic outcomes became equivalent to surgery [119]. The aforementioned study by Boeckxstaens et al. confirmed the equivalent efficacy of graded balloon dilation and LHM [117, 118]. Of note, in this study, 25 % of patients required a repeat dilation series within 5 years [118].

It is therefore now clear that, where dilations are considered as a therapeutic option, unless there is a contraindication, graded dilations should be the recommended regimen, beginning at 30 mm then 35 mm, and then eventually 40 mm if symptoms persist, at a planned interval of 2 – 4 weeks. Furthermore, as long as symptoms do not recur within the same year, repeating the dilation series over subsequent years should not be considered a failure of therapy, but part of the course of the disease management.

3.3.3 Postoperative care

There is variability in the published series with regard to the postoperative care after pneumatic esophageal dilation. Older published series described the routine use of a Gastrografin esophagram a few hours after the procedure to rule out immediate complications [76, 109, 111]. Subsequent publications advocated the use of the esophagram only in patients with suspected perforation [104, 107]. An esophagogastroduodenoscopy performed immediately after the balloon dilation, when the patient is still sedated, is likely to be the most practical and useful method to rule out possible immediate complications and guarantee the safety of early oral feeding [106].

Perforation is the most common adverse event that can occur after pneumatic dilation. The presentation varies and therapy should be customized according to the clinical needs [108]. Conservative management, including fluid replacement, antibiotics, and nil-per-os prescription, can be proposed as the initial management in stable patients. When there is a large full-thickness breach, rapid deterioration in the clinical status, or evidence of fluid collections or gas on CT scanning, surgery should be considered [103]. Standard clips and OTSCs, as well as fully covered self-expandable metal stents (SEMSs), have been used for the management of perforations in some case series and can be proposed as an alternative to surgery if there are no large collections on cross-sectional imaging and the breach is recognized immediately [103, 120].

No recommendations can be made with regard to the use of acid-reducing therapy following dilation. Furthermore, the literature does not help determine the most appropriate timeline to resume oral intake. In the majority of publications, liquid diet was allowed 2 – 8 hours after dilation [98, 101, 103]. We recommend that, in asymptomatic patients in whom there is no suspicion of a full-thickness tear, a soft/normal diet can be initiated on the same day or the day after the procedure.

Immediate or delayed bleeding is a very rare complication after pneumatic dilation and, in the majority of cases, tends to terminate spontaneously and does not require additional endoscopic intervention or other treatments [107, 109]. Careful observation, fluid replacement, and clinical support are advisable.

3.4 Deciding on treatment options for achalasia

To date, in achalasia, studies have not found any of the three primary definitive treatment options (repeated series of pneumatic dilations, LHM, or POEM) to be clearly superior.

The European Achalasia Trial, an RCT comparing pneumatic dilation and LHM, showed graded dilation to be equivalent to LHM at 2 and 5 years [117, 118]. To reduce the likelihood and severity of reflux, a partial Dor (anterior) or Toupet (posterior) fundoplication almost always follows LHM [121, 122]. By doing this, an overall reflux risk of 15 % and 23 % was observed in patients following pneumatic dilation and LHM, respectively (P = 0.28) [117]. It should be stressed that, in this trial, re-dilation was allowed if there was symptom recurrence and thus multiple dilation series were compared with, and were equivalent to, a single LHM.

Studies have suggested POEM to be on a par with both graded dilation series and LHM in terms of outcomes and complication rates [123, 124], albeit with a predilection to reflux disease [10, 123, 125, 126]. On the other hand, POEM appears to be superior to LHM for treating type III achalasia, with success rates of 98 % vs. 80 %, respectively [127]; however, an RCT proving this benefit is lacking.

Two recent RCTs assessed the outcomes following POEM in myotomy-naïve patients with achalasia. The first trial, comparing POEM to pneumatic dilation, showed in terms of subjective response (Eckardt score ≤ 3) that POEM was much more effective than a single series of pneumatic dilations after 2 years (92 % vs. 54 %; P < 0.01) [31]. On the other hand, reflux esophagitis was more likely in the POEM group than in those treated by pneumatic dilation (41 % vs. 7 %, respectively; P = 0.002); following POEM, 49 % of patients had reflux esophagitis at 1 year, with the majority of them having grade A esophagitis when tested off PPIs. It should be noted that this study showed markedly reduced outcomes following pneumatic dilation when compared to other comparative and randomized studies [117 – 119], likely because the dilation protocol was less aggressive.

The second RCT compared POEM with LHM [33]. This study showed that at 2 years there was no difference in the subjective outcome (Eckardt score ≤ 3) following either POEM or LHM (83 % vs. 81.7 %). While reflux esophagitis 2 years after the procedure was evident in 44 % of patients following POEM and 29 % following LHM; grade C/D esophagitis was seen in only 5 % of patients following POEM and 7 % following LHM. Furthermore, most patients with reflux symptoms following achalasia therapy respond very well to acid-reducing therapy [128].

Both comparative and randomized studies thus far imply that therapy decisions should be based on local/operator expertise and patient choice. Caveats however are that: (i) pneumatic dilation is undertaken in a graded fashion as routine and further pneumatic dilation is permitted in subsequent years if required, so patients should be informed that this approach implies multiple treatments over the course of years; (ii) acid-reducing therapy is permitted for those post-POEM who might have an increased risk of reflux, albeit this is mild in the majority of patients; and (iii) in type III achalasia, there might be a preference for POEM over pneumatic dilation or LHM.

4 Gastroparesis

Gastroparesis is a syndrome defined as delayed gastric emptying in the absence of mechanical obstruction in patients with symptoms that include early satiety, postprandial fullness, nausea, vomiting, bloating, and abdominal pain. Patients may also show weight loss and poor nutritional status. The most common etiologies of gastroparesis include idiopathic, diabetic, and post-surgical; other causes comprise neurological, infectious, and infiltrative disorders. Multiple pathophysiological factors may play a role in the development of gastroparesis, such as abnormal function of the gastric smooth muscle, enteric and extrinsic autonomic nerves, and the interstitial cells of Cajal. Traditionally, gastroparesis has been considered to be a disorder principally caused by gastric hypomotility. Besides hypomotility, pylorospasm is recognized as another significant pathophysiological factor. Endoscopic treatments targeting the pyloric muscle in order to open up the pylorus may provide a therapeutic effect.

In patients with refractory gastroparesis, in whom conservative measures have not been effective, endoscopic therapies may be considered. Although antral hypomotility might play a role in patients with symptomatic gastroparesis, endoscopic therapies are only able to target the pyloric sphincter. Endoscopic methods include intrapyloric botulinum toxin injection, balloon dilation, stenting, and gastric peroral endoscopic myotomy (G-POEM). G-POEM is a novel endoscopic method based on the principle of submucosal tunneling. At present, indications for pylorus-targeted therapies have not been clearly defined because a validated and widely accessible method for assessing pyloric function is missing. Measurement of pyloric distensibility (Endoflip technology) may be a promising diagnostic approach in the near future.

4.1 Indications for pylorus-directed endoscopic therapy

> **RECOMMENDATION**
> ESGE recommends that endoscopic pylorus-directed therapy should be considered only in patients with symptoms suggestive of gastroparesis in combination with objective proof of delayed gastric emptying using a validated test, and only when medical therapy has failed.
> Strong recommendation, very low quality of evidence, level of agreement 100 %.

Endoscopic pylorus-targeted therapies should only be considered in patients with symptomatic gastroparesis documented by a validated gastric emptying test (gastric scintigraphy, breath test, motility capsule). Symptoms should have been refractory to conservative measures (diet) and medical therapy for at least 6 months.

At present, there is no generally accepted method for the diagnosis of pylorospasm. Assessment of the pyloric tonus during diagnostic endoscopy alone (widely opened pylorus, pin-

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point pylorus, resistance to passing the endoscope through the pylorus) is subjective, and there are no data to support that endoscopists can reliably assess "pylorospasm" based on these endoscopic features.

Four prospective studies, including a limited number of patients (20–35), are currently available and report the use of the new Endoflip system to assess pyloric distensibility in patients with gastroparesis. Three of them assessed the distensibility before (and one study also after) treatment by balloon dilation, botulinum toxin injection, or G-POEM [129–132]. These four studies concur in showing a correlation between pyloric distensibility at 40 and 50 mL and the symptom score, and an improved clinical success when treating patients with impaired pyloric distensibility, defined as <10 mm^2/mmHg at 40 mL in sedated patients. However, no prospective validation of this cutoff value has been performed, and ESGE considers these data to be preliminary. Future studies are needed before pyloric distensibility measurement can be advised to select patients for pylorus-directed therapy.

Antral hypomotility is usually present in patients with gastroparesis and may be diagnosed by antroduodenal manometry [133, 134]. However, ESGE does not recommend this test for the selection of patients for pylorus-directed therapies as there are no data on its ability to predict response to therapy. Moreover, antroduodenal manometry is not widely available [135]. Electrogastrography is not a reliable method for diagnosing pylorospasm. ESGE therefore does not recommend it for selecting patients for pylorus-targeted therapies [135].

4.2 Intrapyloric botulinum toxin

> **RECOMMENDATION**
> ESGE recommends against the use of botulinum toxin injection in the treatment of unselected patients with gastroparesis.
> Strong recommendation, high quality of evidence, level of agreement 92.9 %

Although most retrospective studies have suggested a clinical benefit of intrapyloric botulinum toxin injection in patients with refractory gastroparesis (50 %–77 % short-term clinical improvement [136]), the clinical improvement was not different to that seen with placebo treatment (saline injection) in two well-conducted RCTs, whichever dose of botulinum toxin was used (100 or 200 units*) [137, 138]. Of note, no adverse events associated with intrapyloric botulinum toxin injection were reported in either of the two studies, and several experts feel that a subset of patients with gastroparesis might respond favorably to this treatment, albeit temporarily. Hence, if intrapyloric botulinum toxin injection is considered, based on an individual decision, a dose of 100 units should be used, because

the results of the two RCTs do not support the use of higher doses of botulinum toxin.

> **RECOMMENDATION**
> ESGE recommends against the use of botulinum toxin injection as the screening test to select patients for endoscopic pyloromyotomy or for other pylorus-directed therapies.
> Strong recommendation, low quality of evidence, level of agreement 94.1 %.

Only one small retrospective study has assessed the role of botulinum toxin injection as a predictor for treatment success after endoscopic pyloromyotomy [139]. Patients responding to botulinum toxin tended to respond better to G-POEM: of five patients who responded to botulinum toxin injection, three (60 %) responded to G-POEM, whereas of three patients not responding to botulinum toxin injection, only one (33 %) responded to G-POEM. Other studies have used a similar approach by selecting patients for endoscopic pyloromyotomy based on their response to botulinum toxin injection [140, 141]. Although they showed significant improvement in post-procedural symptom score (gastroparesis cardinal symptom index [GCSI]) and gastric emptying, the overall clinical response rate was similar to other studies where the selection of patients was not based on the effect of botulinum toxin injection. Moreover, there was no direct comparison of patients who received botulinum toxin injection vs. those who did not.

Taking into account that: (i) botulinum toxin injection carries (at least theoretically) risk of submucosal fibrosis (making the subsequent endoscopic pyloromyotomy more difficult); (ii) the benefit of botulinum toxin injection for treatment of gastroparesis is controversial (see above); and (iii) there are no data reliably documenting the predictive role of botulinum toxin injection to select patients for pylorus-directed therapies, this approach cannot be recommended.

4.3 Endoscopic pyloric balloon dilation

> **RECOMMENDATION**
> ESGE suggests not to use balloon dilation in the treatment of unselected patients with gastroparesis.
> Weak recommendation, very low quality of evidence, level of agreement 94.1 %.

Balloon dilation of the pylorus has been mostly reported in retrospective series. Pylorospasm following esophagectomy or pylorus-preserving gastrectomy was diagnosed by endoscopy or radiology in patients with symptoms suggestive of gastroparesis [142–147]. Pyloric dilation was safe and symptomatic improvement was observed in the majority of patients in the short term, and dilation was repeated if recurrence occurred.

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* Dosing based on Botox. Other brands might require an adjusted dosing as the units are not equivalent between the brands.

Bae et al. showed a satisfactory clinical effect in 73 % of patients after almost 2 years [145].

Only one prospective study has assessed the efficacy of hydraulic balloon dilation (2-cm balloon inflated at 6 atm) in 10 patients with gastroparesis and with low pyloric compliance (<10 mm^2/mmHg) [130]. The follow-up after dilation was very short (10 days). At this point after pyloric dilation, fasting pyloric compliance had increased in all patients (from 7.4 ± 0.4 to 20.1 ± 4.9 mm^2/mmHg), gastric emptying half-time had accelerated in 7/8 patients, and quality of life score had improved. No prospective data with long-term outcomes are available with regard to pyloric balloon dilation.

If balloon dilation is considered for patients with gastroparesis/pylorospasm, preferably post-surgical, both hydraulic dilation with through-the-scope 20-mm balloons and pneumatic dilation with a 30-mm balloon (Rigiflex) can be used following the manufacturer's instructions [130, 143, 144, 146, 147]. Inflation should be slow (2 minutes) and dilation should last for 1 – 2 minutes. In the study by Maus et al., pneumatic dilation using the 30-mm Rigiflex balloon was associated with a reduced need for redilation when compared with hydraulic dilation with a 20-mm balloon, with no differences in adverse events [146]. However, available data are retrospective and therefore insufficient to favor any type of balloon.

4.4 Transpyloric stenting

> **RECOMMENDATION**
> ESGE recommends against the use of transpyloric stenting in the treatment of gastroparesis.
> Strong recommendation, low quality of evidence, level of agreement 100 %.

A total of 33 patients with gastroparesis have been treated by transpyloric placement of fully covered esophageal SEMSs in one retrospective study and in one small retrospective case series [148, 149]. Most of the stents were anchored to the gastric wall using clips or endoscopic sutures. Symptomatic relief was present in 75 % of patients and a considerable proportion of patients had normalized or at least improved gastric emptying studies. Stents remained in situ for a mean of 67 days and stent migration (either proximal or distal) occurred following 59 % of the procedures (100 % in patients without anchoring, 48 % in patients with anchoring using endoscopic sutures).

Given the merely temporary effect, need for stent removal, potential risk of adverse events (especially distal migration with the risk of intestinal obstruction), very high rate of migration, lack of prospective data, and availability of other pylorus-directed therapies, ESGE recommends against transpyloric stenting as a therapeutic option for patients with gastroparesis/pylorospasm.

4.5 Gastric peroral endoscopic myotomy (G-POEM)

> **RECOMMENDATION**
> ESGE recommends consideration of G-POEM in carefully selected patients only, because it is an emerging procedure with limited data on effectiveness, safety, and durability. G-POEM should be performed in expert centers only, preferably in the context of a clinical trial.
> Strong recommendation, low quality of evidence, level of agreement 100 %.

G-POEM seems a promising method but data on its effectiveness and safety are very limited with only one prospective study published so far [129]. Only patients with pylorospasm should logically be good candidates for the procedure and, as reliable methods to differentiate between patients with gastroparesis, with or without a pylorospasm, are hitherto lacking, optimal patient selection is hampered. Endoflip technology might be a tool for the selection of appropriate patients in the future, but more research is needed.

Short-term clinical success at 3 months (defined as a significant improvement in GCSI) has been reported in 73 % – 90 % of patients with refractory gastroparesis undergoing G-POEM [150]. Long-term data are missing and the recurrence rate is not known. Some studies have reported a longer follow-up and the effect seemed to wane in time [151]. In one study, the success rate was lower in patients with diabetic gastroparesis compared with other etiologies [152], most of the studies, however, did not find differences among the varying etiologies. G-POEM seems safe, serious adverse events are rare, and no mortality has been reported so far. Only one case of gastric perforation necessitating surgery has recently been described [153]. Nevertheless, care should be taken with regard to serosal perforation (leak of gastric content) and post-procedural ulcers. G-POEM appears safer compared with laparoscopic pyloroplasty [154].

4.5.1 Use of antibiotics and CO_2

> **RECOMMENDATION**
> ESGE recommends the use of prophylactic antibiotics during G-POEM. The choice and duration of antibiotics should be adapted according to national or local protocols.
> Strong recommendation, very low quality of evidence, level of agreement 88.2 %.

No articles have specifically addressed the use of perioperative systemic antibiotics during G-POEM. G-POEM can potentially induce translocation of bacteria from the digestive tract to the peritoneal space, especially if a serosal perforation occurs during myotomy. ESGE therefore recommends the pro-

phylactic administration of systemic antibiotics prior to G-POEM because it should be considered a potentially septic intervention. The choice of antibiotics should be guided by the current national/local guidelines for gastric or abdominal surgery.

> **RECOMMENDATION**
> ESGE recommends against local application of antibiotics prior to the procedure (stomach, esophagus, and/or oral cavity) or during the procedure (submucosal tunnel).
> Strong recommendation, low quality of evidence, level of agreement 94.1%.

G-POEM seems very safe in terms of infectious complications. The majority of studies did not use either gastric (or esophageal/oral cavity) lavage or lavage of the submucosal tunnel with antibiotics. Local antibiotics have been used in only two published studies [139, 155]. Therefore, such a lavage seems unnecessary, even though no study has specifically addressed this issue. As the principle of G-POEM is similar to POEM, one retrospective study may serve as the only available piece of evidence against a meaningful role of gentamicin submucosal lavage: in this retrospective study examining patients undergoing POEM for achalasia [42], no differences were found between patients with and without antibiotic lavage in terms of infectious complications (see Section 3.1.7).

G-POEM should always be performed with CO_2 insufflation. The lowest possible insufflation force should be used to prevent CO_2-related adverse events; however, in contrast to POEM, only a few patients have required puncture of a capnoperitoneum.

4.5.2 Mucosal incision and closure

> **RECOMMENDATION**
> ESGE recommends the submucosal tunnel created during the G-POEM procedure should be at least 3 cm in length to secure a safe overlap of the myotomy site by intact mucosa.
> Strong recommendation, low quality of evidence, level of agreement 92.9%.

Mucosal incisions are usually 1.5 – 2 cm in length and may be longitudinal or transverse. Most endoscopic pyloromyotomies have been performed using the posterior or greater curvature approaches. There are no data about the advantages or disadvantages of different locations (posterior vs. anterior vs. greater curvature vs. lesser curvature) and shapes (transverse vs. longitudinal) of tunnel entry. The submucosal tunnel should not be too short in case mucosal tearing occurs at the site of the mucosal incision (longitudinal in particular), meaning the mucosa might not protect the myotomy site and leakage of gastric contents through the stomach wall could occur.

Closure of the mucosal entry may be performed using endo-clips or a suturing device. At present, there are no published studies comparing different closure methods but one prospective study is ongoing [156]. No major problems with closure have been reported so far.

4.5.3 Length of myotomy

> **RECOMMENDATION**
> ESGE suggests the length of myotomy should be 2 – 3 cm and should include the pyloric muscle up to its termination in the duodenal bulb.
> Strong recommendation, low quality of evidence, level of agreement 100%.

There are no data assessing the effectiveness and safety of G-POEM in terms of myotomy length. No clinical study has compared different myotomy lengths. Most studies have reported the mean length of pyloromyotomy, with the length varying between 1 and 3 cm. However, no study has specifically described the method for how the length was measured. Therefore, these data should be taken into consideration with care. A longer myotomy (more than 3 cm) might hypothetically lead to a worsening of antral hypomotility and should be avoided. A shorter myotomy (less than 2 cm) might not be sufficient to provide a good effect.

One experimental ex vivo study on a porcine ex vivo stomach assessed the appropriate length of pyloromyotomy [157]. Four myotomy lengths (1, 2, 3, and 4 cm) were compared in terms of pyloric distensibility. The most appropriate myotomy length was 3 cm in the large stomach (similar to an adult's) and 2 cm in the small stomach (pediatric equivalent). The authors found that the change in the mean distending pyloric diameter was significantly larger after the 3-cm and 4-cm incisions compared with the 1-cm incision, but there was no statistically significant difference between the 3-cm and 4-cm myotomies.

4.5.4 Knives and electrosurgical settings

Different knives are used for G-POEM (HybridKnife, TT-knife, Insulated Tip knife [IT-knife], HookKnife). There is no evidence for the superiority of any of these knives in terms of effectiveness or safety. Selection of a knife should reflect the endoscopist's experience and preference.

Most of the studies used Endocut Q mode (ERBE VIO electrosurgical unit) for incision and spray coagulation mode for tunneling and myotomy. Other settings (dry cut, swift or soft coagulation) have also been used. For electrosurgical units from other manufacturers, the recommended settings according to the indications for use should be followed

4.6 Postoperative care

There are no guideline recommendations on follow-up after gastroparesis treatment. If the pylorus-directed therapy is performed in an ambulatory setting (botulinum toxin injection, dilation), a post-interventional clinical examination should be

performed immediately after the intervention to exclude adverse events (perforation). Surveillance with monitoring for signs of perforation and vital parameters for at least 1 hour is recommended. A routine radiographic check is not recommended after dilation of the pylorus because the rate of adverse events is quite low [158]. The same monitoring is also recommended in patients who are hospitalized after the intervention (usually dilation). Fluids can be given orally, 2–4 hours after the procedure, and a soft diet can start the following day.

G-POEM should be performed in hospitalized patients because the risk of severe complications cannot be ruled out. Prior to G-POEM, an upper GI endoscopy should be performed to exclude an ulcer and clean the stomach of food residues. On postoperative day 1, a routine upper GI fluoroscopy (with a water-soluble contrast) or an endoscopy can be considered to exclude a leak or confirm secure closure of an incision, but evidence from the literature is lacking. If no complications occur, patients may be discharged on postoperative day 1 and slowly restart feeding (liquid diet on postoperative day 1, soft diet starting on postoperative day 2). Treatment with a PPI is necessary during and after G-POEM to prevent ulceration. Prior to and during the procedure, PPIs should be given intravenously, after restarting oral intake, they can be administered orally twice daily for at least 4 weeks.

After G-POEM, being the most invasive yet still experimental therapy, proper documentation of all relevant parameters – preferably in the context of an Institutional Review Board (IRB)-supervised study protocol – is crucial. Idiopathic and diabetic gastroparesis should be studied separately. Symptoms (before, as well as after the procedure) should be assessed using a validated symptom score, and this is an indispensable requirement for all clinical studies. The GCSI is widely used and has been validated [159]. The GCSI is a component of the Patient Assessment of Upper Gastrointestinal Symptom Severity (PAGI-SYM) score, which is a self-reported instrument for patients suffering from gastroparesis, dyspepsia, and GERD [160].

To evaluate the change of gastric emptying after endoscopic intervention, given the paucity of data with regard to all types of endoscopic therapy (botulinum toxin, dilation, G-POEM), we advocate a validated gastric emptying test (scintigraphy, breath test, motility capsule) 3–6 months after a pylorus-directed therapy. In patients with pre-procedural pyloric distensibility testing, a post-procedural measurement may also be recommended to further document the pathophysiological effect of these interventions.

Disclaimer

The legal disclaimer for ESGE guidelines [2] applies to this Guideline.

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Competing interests

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CORRECTION

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In the above-mentioned article, the institution of Daniel Pohl has been corrected.

This was corrected in the online version on June 19, 2020.